# AZEPINES—PART 2

*This is the forty-third volume in the series*

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER AND EDWARD C. TAYLOR

*Editors*



# AZEPINES
## Part 2

*Authors:*

**Jeffrey W. H. Watthey**
CIBA-GEIGY CORPORATION
ARDSLEY, NEW YORK

**James Stanton**
CIBA-GEIGY CORPORATION
ARDSLEY, NEW YORK

**Norton P. Peet**
THE DOW CHEMICAL COMPANY
INDIANAPOLIS, INDIANA

*Editor:*

**Andre Rosowsky**
DANA-FARBER CANCER INSTITUTE
BOSTON, MASSACHUSETTS

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# The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

ARNOLD WEISSBERGER

*Research Laboratories*
*Eastman Kodak Company*
*Rochester, New York*

EDWARD C. TAYLOR

*Princeton University*
*Princeton, New Jersey*

# Preface

Heterocyclic systems with seven atoms, once considered chemical oddities, are today just as easily obtained as their five- and six-membered cousins, thanks to the very substantial advances in synthetic art that have been made in this field over the past 20 years. In a previous volume of the *Heterocyclic Compounds* (Volume 26), seven-membered oxygen ring systems (oxepins) and sulfur ring systems (thiepins) were reviewed. The present two-part volume extends this coverage to the seven-membered nitrogen heterocycles (azepines).

As with the oxepins and thiepins, interest in the azepines encompasses a broad spectrum of theoretical and applied disciplines. At the theoretical level, chemists are fascinated by these compounds from the molecular orbital standpoint. Of particular importance in this regard are the azulenoid cyclopentazepine ring systems, the bridgehead nitrogen benz[*a*]azepinium cation, the bridged annulene system 11-azabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene (''1,6-azirino[10]annulene''), and the still unknown cycl[4.4.3]azine. At the ''applied'' end of the spectrum, one hardly need be reminded of the enormous amount of research that has been conducted in pharmaceutical laboratories since the early 1960s on tranquilizers, antidepressants, and other psychotropic drugs of the benzodiazepine and dibenzazepine class. Probably more than any other factor, the vast commercial success of these medicinal agents and their benefit to society have caused the chemistry of condensed azepines to evolve into a major area of research in heterocyclic chemistry. One of the consequences of this effort has been the appearance, on the chemical scene, of a host of new ring systems which collectively form a dazzling array of structural types. It is the purpose of this two-part volume to give an account of the current state of knowledge concerning the synthesis, chemical reactions, and physical properties of some—though by no means all—of these systems, with particular emphasis on those facets that pertain to the ''seven-memberedness'' of the azepine ring.

Part 1 consists of two chapters. Chapter I (Renfroe and Harrington) is devoted to tricyclic systems containing an azepine ring along with two other other rings that can be either carbocyclic or heterocyclic. This category includes no fewer than 150 different heterocyclic systems, ranging from oxireno[*d*][2]benzazepines (a 3,6,7-system) to benzo[*e*]cyclooct[*b*]azepines (a, 6,7,8-system). The largest single family, the dibenz [*b,f*]azepines, has as its most famous members the antidepressant imipramine and its congeners, such as carbamazepine. Other dibenzazepines of pharmaceutical interest are the dibenz[*c,e*]azepines, a number of which possess hypotensive activity. Certain tricyclic azepine ring systems are also noteworthy because they appear in natural products. Here may be cited certain alkaloids of the rheadan family (1,3-dioxolo[4,5-*h*][3]benzazepines) and at least three groups of indole

alkaloids, the erythroidine and tuberostemonine family (azepino[3,2,1-*hi*]indoles), the naucladerine family (azepino[4,5-*b*]indoles), and the ergot family (azepino[5,4,3-*cd*]indoles). Additionally, fused tricyclic azepine systems have been generated from tricyclic terpene ketones (e.g., santonin) via ring enlargement. The identification and characterization of the products from these reactions have played an important role in increasing our understanding of the mechanism of the Schmidt and Beckmann rearrangements and in providing model systems for the synthesis of ring-enlarged azasteroid analogues.

Chapter II (Proctor) presents a review of the chemistry of bicyclic, as opposed to tricyclic, azepine derivatives. Here again a substantial number of fused, bridged, and spiran systems are covered, with emphasis being placed again on the seven-membered ring. Among these compounds the 1-, 2-, and 3-benzazepines are of interest because of their potential psychopharmacologic activity. A novel class of antiviral agents also cited in this chapter consists of compounds belonging to the bridged 1,6-azirino[10]annulene ring system. The development of these compounds represents an intriguing blend of "pure" and "applied" heterocyclic chemistry.

Part 2 also consists of two chapters. Chapter I (Watthey and Stanton) covers the tricyclic diazepine systems, a number of which have attracted attention because of the pharmaceutical importance of some of their members. Here may be cited anxiolytic agents such as benzazepam, oxazolam, and triazolam; antidepressants such as dibenzopin; and antipsychotic agents such as clozapine. All these tricyclic azepine derivatives have contributed in a major way to the modern treatment of mental illness. Another example of a biologically important class of tricyclic azepine derivatives is provided by the anthramycin antibiotics (pyrrolo[2,1-*c*][1,4]benzodiazepines), which have shown impressive activity as antineoplastic agents.

The practical importance of azepine derivatives is by no means limited to medical applications. For example, among the ring systems discussed in Chapter II (Peet) are the 1,2,5-triazepines, some of which have found use in the agricultural field as pesticidal plant protectants. Other triazepines, of the 1,3,5-type with *N*-nitro substituents, have been investigated as high explosives.

In summary, the two-part volume for which this Preface is written bears witness to the fact that seven-membered heterocyclic compounds are no longer the esoteric species they were once considered to be. Quite to the contrary, the pace of research and development in this area is accelerating, and there seems to be virtually no limit to the number of interesting ring systems that can be created in the laboratory by a combination of ingenuity and perseverance. The future should bring rich rewards not only in terms of new academic knowledge but also in terms of practical applications that will benefit us all, chemists and nonchemists alike. I wish to gratefully thank the several authors who have joined me in preparing this review. Their thoroughness and limitless patience cannot be sufficiently praised. Thanks

are due, as well, to Drs. Arnold Weissberger and Edward C. Taylor for their encouragement and support of the project, and to the capable staff at John Wiley & Sons for their expeditious handling of these chapters.

ANDRE ROSOWSKY

*Boston, Massachusetts*
*January 1984*

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CHAPTER I

# Dibenzodiazepines and Other Tricyclic Diazepine Systems

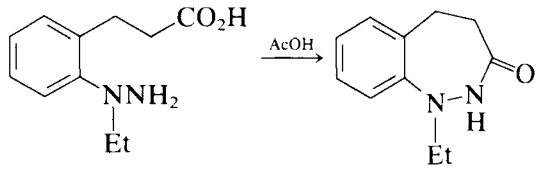
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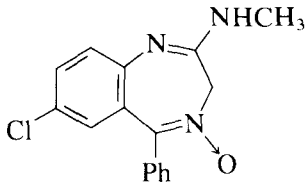
## I. INTRODUCTION

The earliest known diazepine (**1**), the synthesis of which was reported in 1883 by Fischer, was prepared by cyclization of **2** in acetic acid (Eq. 1) (1). Since then the chemistry of diazepines has flourished (2–5). This chapter focuses on the preparation and reactions of fused tricyclic diazepines (6). Although compounds of this type have been of interest for a wide variety of reasons, most of the work in the field derives its inspiration from the discovery of the important pharmacologic properties of benzodiazepines, of which two well-known examples are the minor tranquilizers chlordiazepoxide (**3**) and diazepam (**4**) (7).

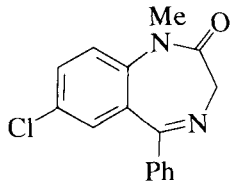
The discovery that fusion of a third ring to the diazepam skeleton maintains or enhances anxiolytic activity led to extensive investigations of tricyclic heterocyclic ring-fused derivatives. These studies culminated in the development of several clinically active substances, including triazolam (**5**), oxazolam (**6**), and bentazepam (**7**).



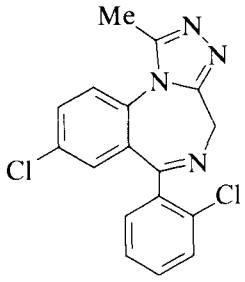

**2** **1** (1)



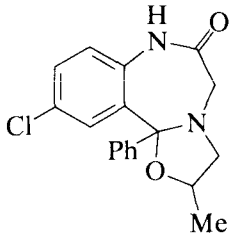
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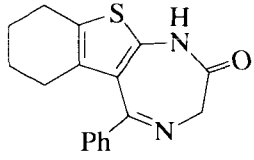
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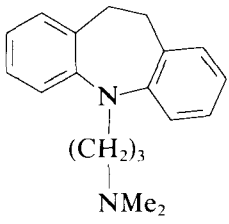
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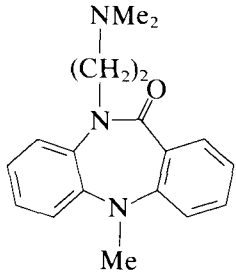
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Another medicinally important group of compounds reviewed in this chapter consists of analogs of imipramine (**8**), the first antidepressant to be used widely in the clinic (8). An important example of these analogs is the dibenzodiazepine antidepressant dibenzepin (**9**) (9). More extensive structural modification led to the development of the important antipsychotic agent clozapine (**10**) (10).

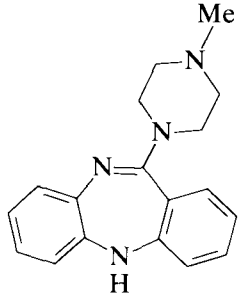
The order of appearance of each ring system follows the rules of the Ring Index of *Chemical Abstracts*. The chapter includes all fused tricyclic diazepines appearing in the chemical literature through Volume 86 of *Chemical Abstracts*. The Addendum includes publications through Volume 93. Highlights of significant new chemistry are included in the Addendum for ring



8



9

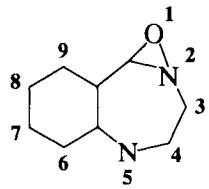


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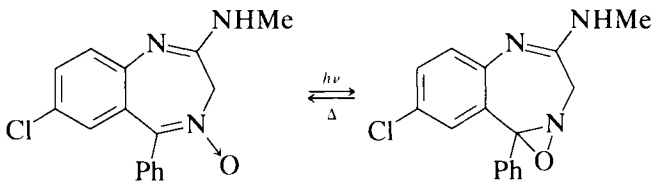
systems also reviewed in the main portion of the chapter. Those ring systems appearing for the first time in the Addendum are indicated by having their ring skeleton drawn out and numbered, and these systems are reviewed comprehensively.

## II. 3,6,7-SYSTEMS

### 1. Oxazirino[2,3-*d*][1,4]benzodiazepines (see Section XI.1)




In 1962 Sternbach and co-workers (11) reported that chlordiazepoxide (**11**) could be converted in 65% yield to the isomeric oxaziridine **12** by exposing the substance in isopropanol solution to diffuse daylight for 12 days (Eq. 2).



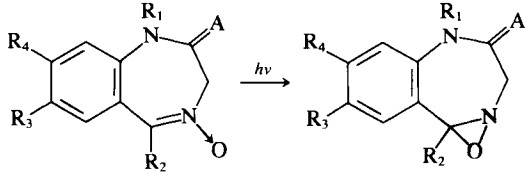

**11** **12** (2)

The structure of the photoisomer was deduced from its oxidizing properties (liberation of iodine from potassium iodide solution), its ultraviolet spectrum, and its facile reconversion to **11** on heating at its melting point of 167–170°C or in refluxing isopropanol, or on treatment with dilute hydrochloric acid at room temperature.

Numerous additional oxazirino[2,3-*d*][1,4]benzodiazepine derivatives have been obtained using this procedure or by irradiation of the starting material in tetrahydrofuran solution with a medium-pressure mercury lamp. These substances are listed in Table 1 (12–16).

Despite the successful preparation cited above, the oxaziridine derivatives are not photostable. Irradiation of **12** using a medium-pressure mercury lamp led to the formation of the benzo[*g*]-1,3,6-oxadiazocine **13** and the dihydro-

TABLE 1. OXAZIRINO[2,3-*d*][1,4]BENZODIAZEPINES FROM IMINE OXIDES



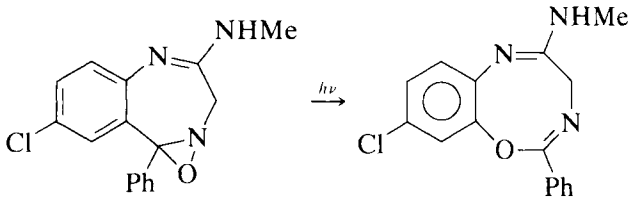

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | A | Method | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|---|---|
| CHO | O | Cl | H | $H_2$ | A[a] | | 150–152 | 12 |
| $COCH_3$ | O | Cl | H | $H_2$ | A | | 161–163 | 12 |
| H | O | Cl | H | O | B[b] | 79 | 136 | 13 |
| Me | O | Cl | H | O | B | 74 | 99–100 | 14 |
| H | O | H | H | O | B | 96 | 159 | 14 |
| Me | 2-$ClC_6H_4$ | Cl | H | O | B | 61 | 119–121 | 14 |
| $CH_2Ph$ | O | Cl | H | O | B | 63 | 148–150 | 14 |
| H | O | Me | Me | O | B | 87 | 163 | 14 |
| H | O | $CF_3$ | H | O | B | 80 | 128–131 | 14 |
| H | 2-$FC_6H_4$ | Cl | H | O | B | 80 | 139 | 14 |
| H | 2-$ClC_6H_4$ | Cl | H | O | B | 55 | 127 | 14 |
| H | 2-$FC_6H_4$ | $SCH_3$ | H | O | B | 96 | 126 | 14 |
| H | Ph | $SO_2CH_3$ | H | O | B | 88 | 165 | 14 |
| H | Ph | $SCH_3$ | H | O | B | 82 | 128 | 13 |
| Me | Ph | Cl | H | $H_2$ | B | | 97–100 | 16 |
| H | 2-Pyridyl | Br | H | O | B | | 142–143 | 16 |

[a]Irradiation with diffuse daylight (reverts to starting material on heating at 165°C).
[b]Irradiation with medium-pressure mercury lamp.

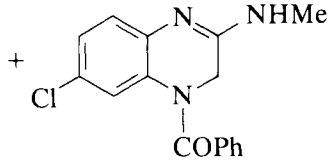
quinoxaline **14** (17), while analogous products were obtained from the lactones **15** and **16** (13) (Eq. 3).

It was later found (12) that oxazirino[2,3-*d*][1,4]benzodiazepine derivatives could also be obtained in good yield by oxidation of acylated 2,3-dihydrobenzodiazepines with peracetic acid (Table 2). This process could be reversed by treating the oxaziridines with aqueous acidic potassium iodide or with hydroxylamine in tetrahydrofuran (16). Substances prepared in this manner are listed in Table 3.

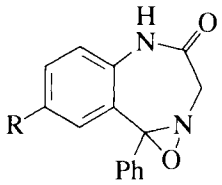
Sternbach and co-workers (18) have studied the interaction of various nucleophiles with some oxazirino[2,3-*d*][1,4]benzodiazepinones. Treatment of the lactam **15** with methanol or ethanol at room temperature gave the dihydroquinazolinones **17** (Eq. 4). The structure of the methanol addition product was confirmed by its preparation from 2-amino-5-chlorobenzophenone and methoxymethyl isocyanate. The formation of **17** was considered to proceed via ring closure of the imino isocyanate **18** to a species such as **19** and final alcohol addition. This mechanism is supported by the observations that the reaction was accelerated markedly by base and that the *N*-methyl lactam corresponding to **15** did not undergo the reaction. Also accommodated



12 13 (3)



14

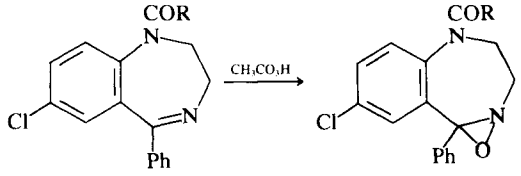


15, R = Cl
16, R = MeS

by the mechanism is the conversion of **15** to the quinazolinone **20** in aqueous tetrahydrofuran at room temperature (Eq. 5).

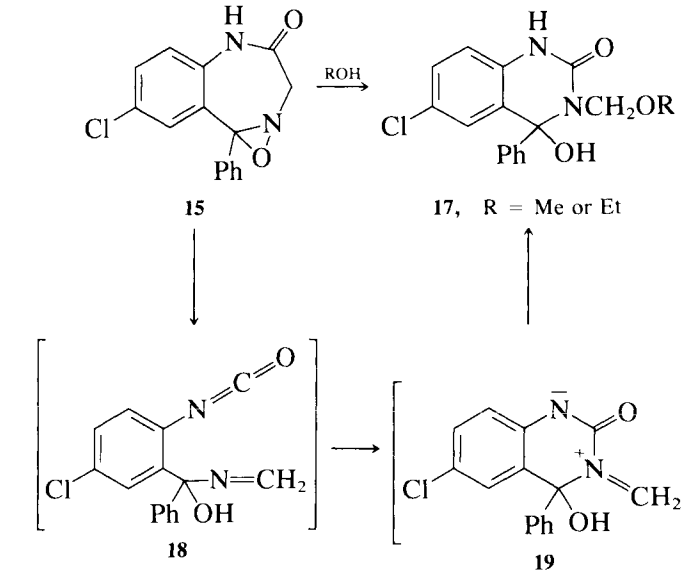
Reactions with amines (19) did not give products analogous to those obtained with alcohols. Treatment of **15** with ethylamine in tetrahydrofuran at room temperature gave the ring-opened derivative **21** (Eq. 6). The reaction appears to proceed via removal of the proton $\alpha$ to the carbonyl group of **15**,

TABLE 2. OXAZIRINO[2,3-*d*][1,4]BENZODIAZEPINES FROM IMINES[a]



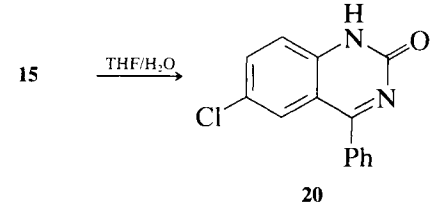
| R | Yield (%) | mp (°C) |
|---|---|---|
| H | 63 | 150–152 |
| Me | 83 | 161–163 |

[a]Ref. 12.



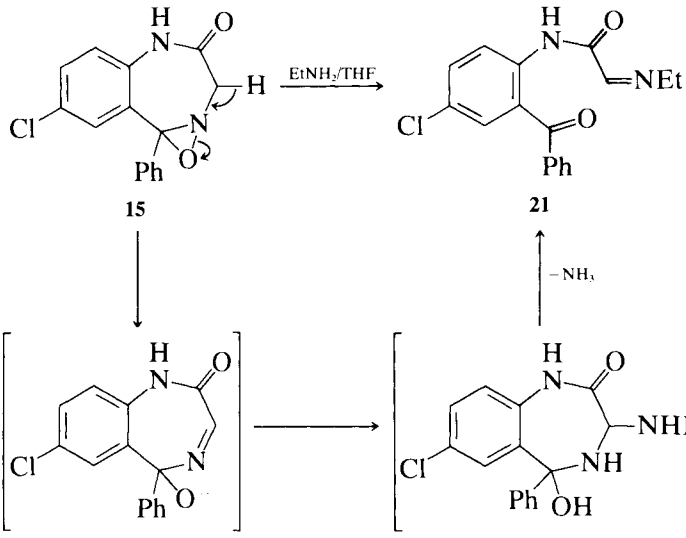

15 17, R = Me or Et 18 19

(4)




15 20

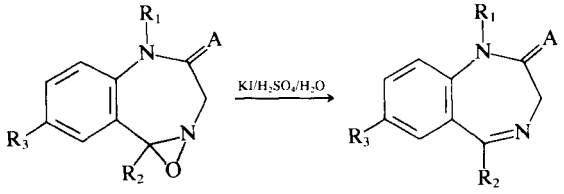
(5)




15 21

(6)

TABLE 3. DEOXYGENATION PRODUCTS OF OXAZIRINO-[2,3-*d*][1,4]BENZODIAZEPINES[a]

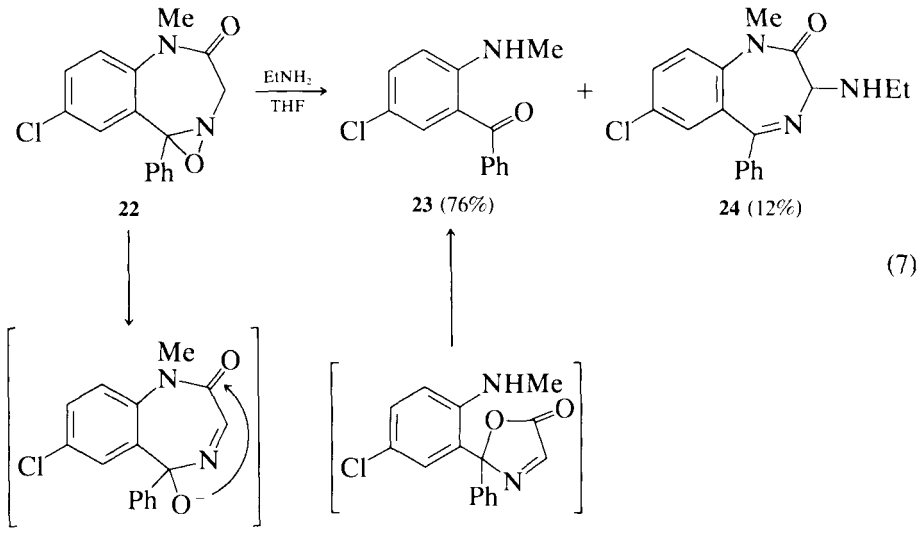



| $R_1$ | $R_2$ | $R_3$ | A | Yield (%) | mp (°C) |
|---|---|---|---|---|---|
| H | Ph | Cl | O | 78[b] | 216–218 |
| Me | Ph | Cl | O | | 129–131 |
| Me | Ph | Cl | $H_2$ | | 99–100 |
| H | 2-Pyridyl | Br | O | | 239–240 |

[a]Ref. 16.
[b]Also prepared from the oxaziridine with hydroxylamine in tetrahydrofuran.

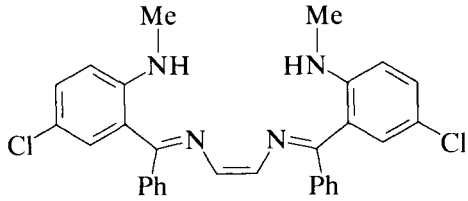
followed by addition of ethylamine to the resulting imine, to give an intermediate that can readily lose ammonia.

Reaction of the *N*-methyl lactam **22** with ethylamine under the same conditions gave products **23** and **24** (19), as indicated in Eq. 7. As before, deprotonation $\alpha$ to the carbonyl group was considered to be the first step, followed in this case by cyclization. This process apparently was inhibited in the desmethyl series because the lactam function could be protected by deprotonation. The minor product **24** was considered to arise by addition of ethylamine to the deprotonated intermediate, followed by elimination of



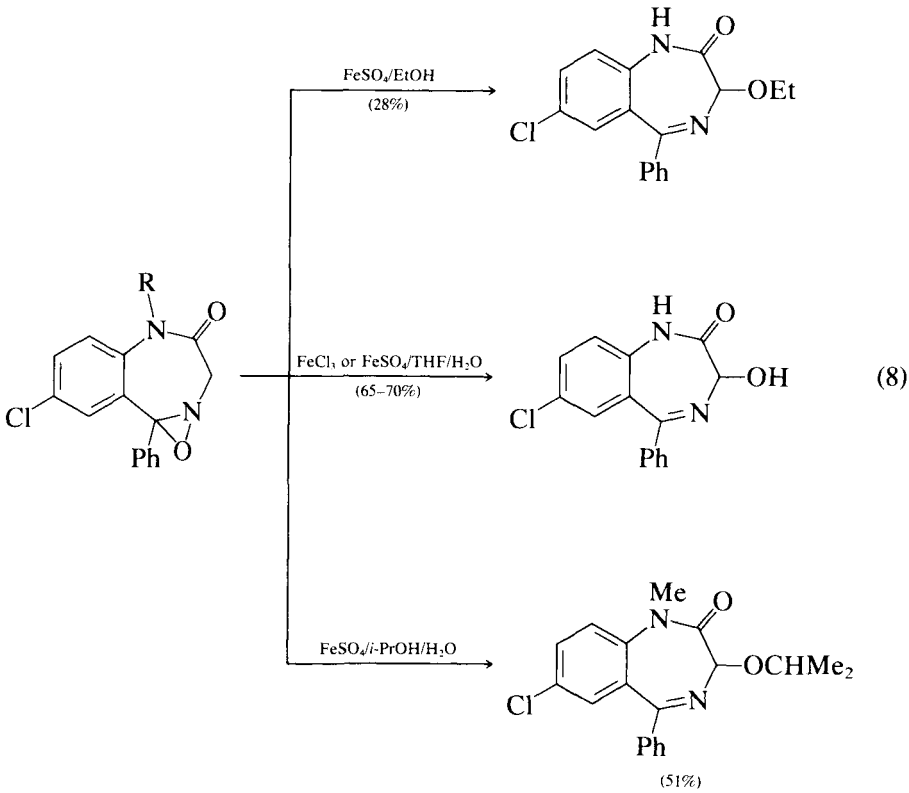

(7)

water. Treatment of **22** with triethylamine in pyridine at room temperature gave the dimeric imine **25.** The *cis* geometry of the central double bond was demonstrated by X-ray crystallography (19).



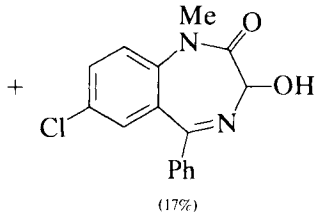
**25**

When the lactams were treated with ferrous sulfate or ferric chloride in alcohol or aqueous tetrahydrofuran solution, products reminiscent of the minor ethylamine addition product **24** were obtained (20) (Eq. 8). Sedative, muscle relaxant, and anticonvulsant activities have been claimed for certain oxazirino[2,3-*d*][1,4]benzodiazepine derivatives (14).



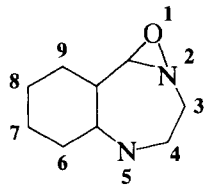

(8)

(*see next page*)

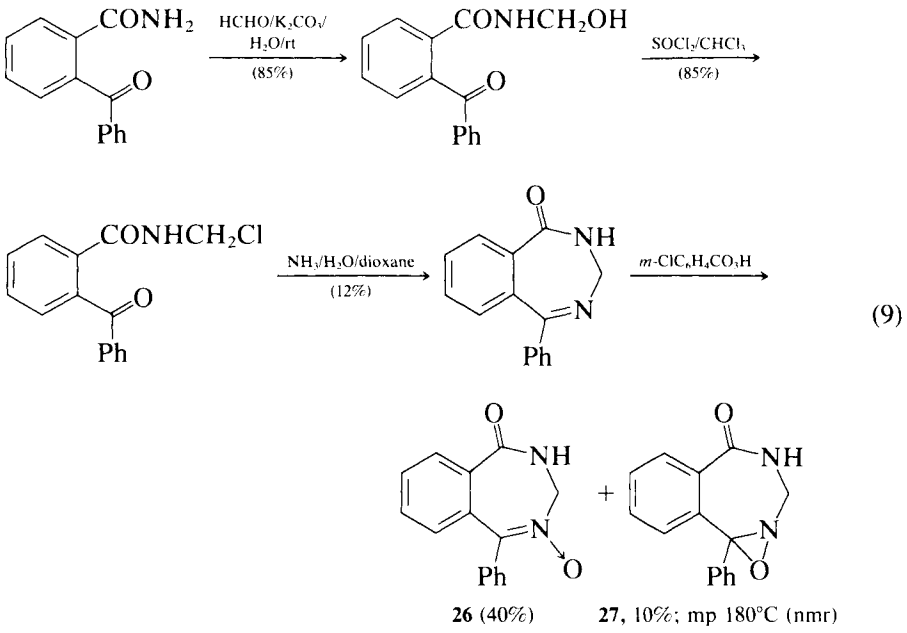



(17%) (8 *cont'd*)

## 2. Oxazirino[3,2-*a*][2,4]benzodiazepines




The sole example of the oxazirino[3,2-*a*][2,4]benzodiazepine ring system was obtained by Golik (21) as a by-product in the preparation of the isomeric 2,4-benzodiazepin-1-one $N^4$-oxide **26** by oxidation of the corresponding imine. The synthesis of the imine from *o*-benzoylbenzamide is given in Eq. 9. The oxaziridine **27** was identified on the basis of its oxidizing properties (liberation of iodine from potassium iodide solution).

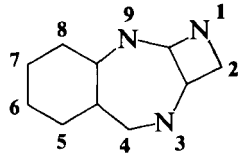



(9)

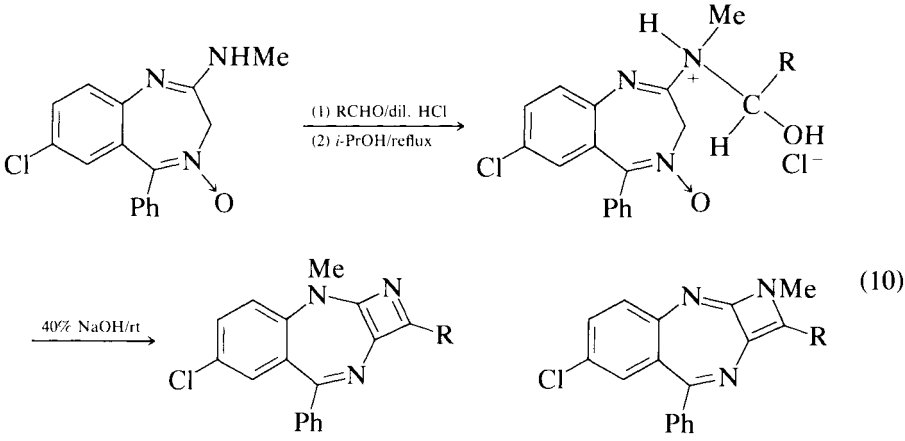
**26** (40%) **27**, 10%; mp 180°C (nmr)

# III. 4,6,7-SYSTEMS

## 1. Azeto[2,3-*b*][1,4]benzodiazepines



The synthesis of certain azeto[2,3-*b*][1,4]benzodiazepine derivatives has been claimed in a patent (22) (Eq. 10). Since no analytic data other than microanalyses were provided, structures **28a,b** must be regarded as tentative. The isomeric structure **29** would appear more likely on mechanistic grounds and also on the basis of the predictable lack of stability of **28**.

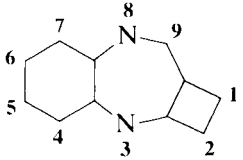



(10)

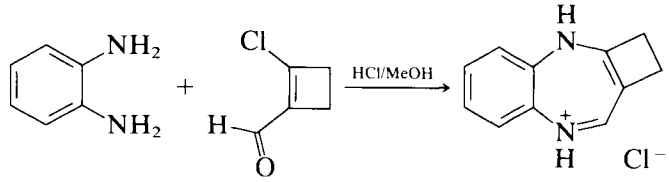
**28a,** R = Et; mp 194–195°C (HCl salt, mp 189–190°C)
**28b,** R = *n*-Pr; mp 179–180°C (HCl salt, mp 183–184°C)

**29,** R = Et, Pr

## 2. Benzo[*b*]cyclobuta[*e*][1,4]diazepines

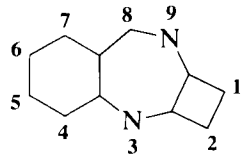


In a study of the condensation of β-chlorovinyl aldehydes with *o*-phenylenediamine, it was found that addition of a methanolic hydrochloric acid solution of 1-chloro-2-formylcyclobutene (**30**) to *o*-phenylenediamine (Eq. 11) at 0°C produced the bluish green diazepine hydrochloride **31** (mp 145–146°C) (23). The compound had a characteristic ultraviolet absorption maximum at 538 nm (24) and could be transformed into its perchlorate salt (mp 171–172°C) by treatment with 70% perchloric acid. As is typical for 2,4-substituted 1,5-diazepines (25), these salts were sensitive to hydrolysis, and the free base could not be prepared.

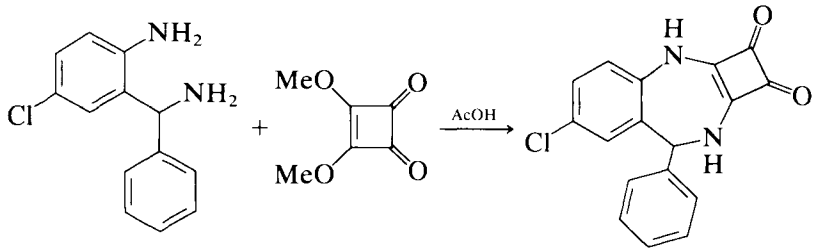



**30** **31** (11)

### 3. Benzo[*e*]cyclobuta[*b*][1,4]diazepines



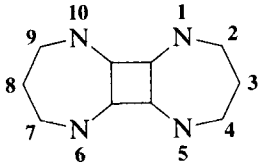

Condensation of benzhydrylamine **32** with squaric acid dimethyl ester in refluxing acetic acid generated diazepine **33** (mp 298°C) in 87% yield (Eq. 12). The structure assigned to this product was supported by infrared and nmr spectral evidence (26).



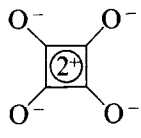

**32** **33** (12)

## IV. 4,7,7-SYSTEMS

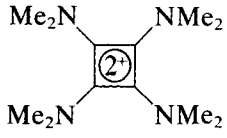
### 1. Cyclobuta[1,2-*b*:3,4-*b'*]bis-1,4-diazepines (see Section XIII.1)




Erhardt and Hünig (27) studied the synthesis of derivatives of the cyclobuta[1,2-*b*:3,4-*b'*]bis-1,4-diazepine ring system with the aim of generating a

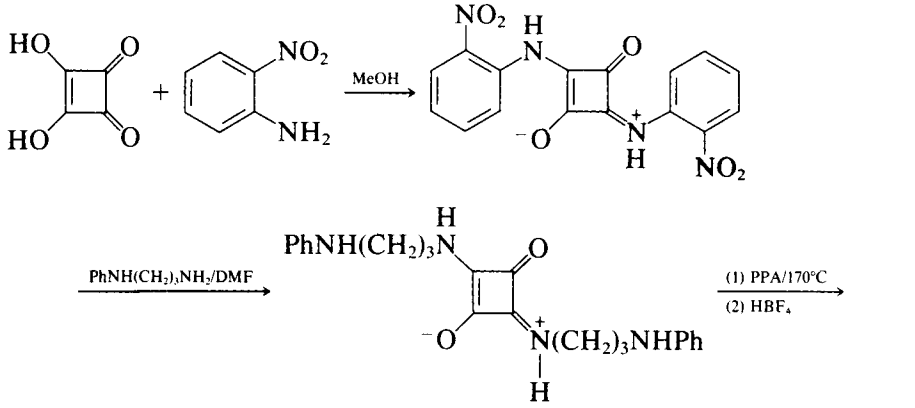


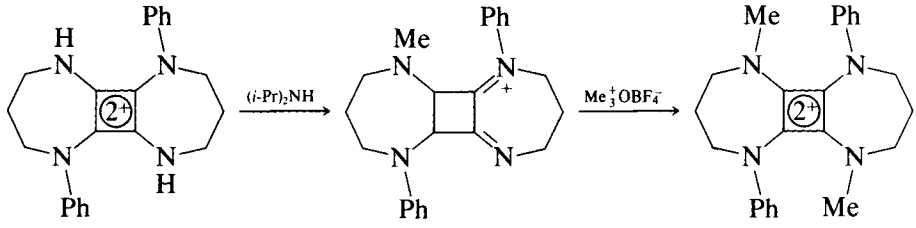

34




35

stable analog of the squaric acid dianion (**34**) in which all four oxygen atoms would be replaced by nitrogen atoms, thus giving a dication (**35**). Their




2BF₄⁻ BF₄⁻ 2BF₄⁻

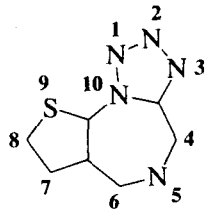
36 37 38

**Figure 1**

synthesis is shown in Fig. 1. Squaric acid was converted to the bis(2-nitroanilino) derivative by the method of Gauger and Manecke (28). Amine exchange gave the 1,3-diamide, which on treatment with polyphosphoric acid at 170°C gave the desired squaric acid bisamidinium salt, isolated as the colorless bis(tetrafluoroborate) **36**. This substance gave the orange-yellow monotetrafluoroborate with diisopropylamine, and subsequently was methylated with trimethyloxonium fluoroborate to give **37**. This, in turn, was further alkylated using the same procedure in order to obtain the fully substituted squaric acid bisamidinium bis(tetrafluoroborate) **38**. Ultraviolet, $^{1}$H- and $^{13}$C-nmr, and field desorption mass spectral data were provided for **38**. In particular, the intense, relatively long wavelength ultraviolet absorption was appropriate for the desired $\pi$-system, while the $^{13}$C-nmr spectrum excluded the possibility of a bicyclobutane structure. Polarographic reduction of **38** resulted in the formation of an unstable cation radical, but further reduction to the cyclobutadiene could not be achieved.

## V. 5,5,7-SYSTEMS

### 1. Tetrazolo[1,5-*a*]thieno[3,2-*f*][1,4]diazepines




Tetrazolo[1,5-*a*]thieno[3,2-*f*][1,4] diazepines are patented as minor tranquilizers with only weak ataxia-inducing action. Their synthesis is outlined in Fig. 2. Diazepinone **39** was converted to thione **40** by treatment with phosphorus pentasulfide. This intermediate was then treated with hydrazine to give the 2-hydrazinodiazepine **41**, which exists in equilibrium with its tautomeric hydrazone **41a**. Treatment of **41** with sodium nitrite in 2 *N* hydrochloric acid gave the tetrazole **42**. Specific tricyclic tetrazoles prepared by this process are listed in Table 4 (29).

These compounds undergo hydrolytic cleavage of the imine bond to give the thiophenes **43**, which are claimed to have sedative, anxiolytic, and anticonvulsant properties. Thus treatment of **42** with hydrochloric acid leads

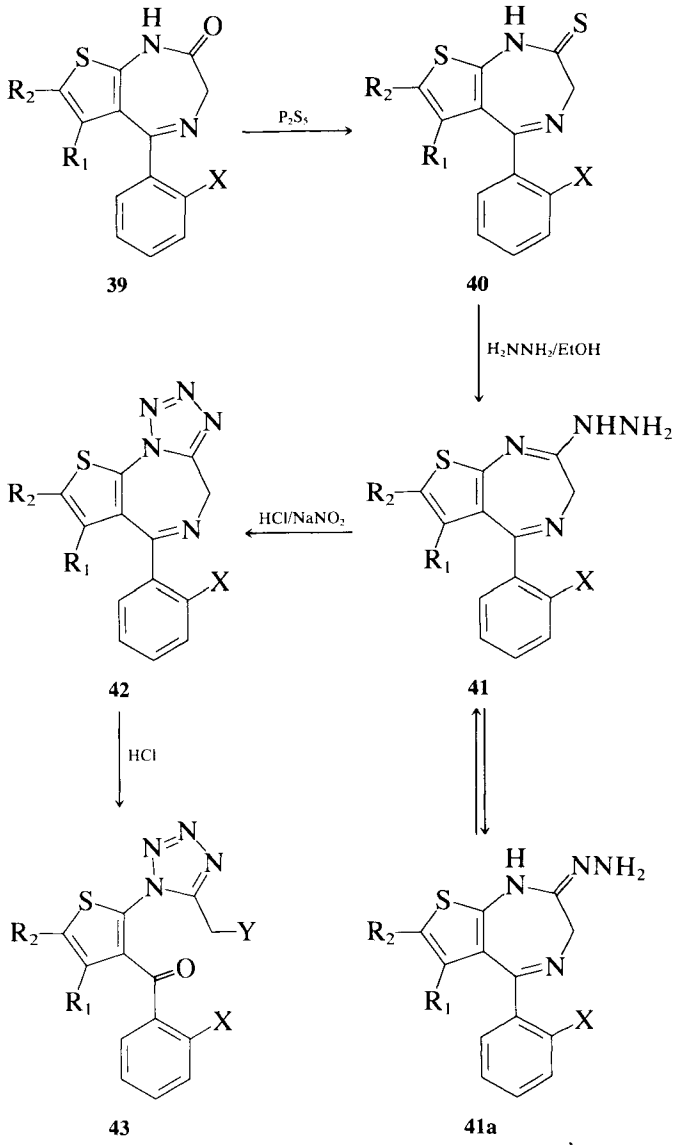



**Figure 2**

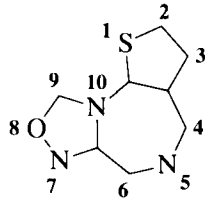
to primary amines **43** (Y = $NH_2$), which can in turn be converted *in situ* to the corresponding chlorides by addition of sodium nitrite. Subsequent addition of substituted amines gives **43** (Y = $NR_1R_2$). The synthesis of **43** (Y = $NMe_2$) can also be achieved directly from **42** under Eschweiler–Clarke conditions (30).

TABLE 4. TETRAZALO[1,5-*a*]THIENO[3,2-*f*][1,4]DIAZEPINES

| Structure | $R_1$ | $R_2$ | X | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| **42** | H | Et | Cl | 80 | 135–136 | 29 |
| **42** | H | Me | Cl | 77 | 122–123 | 29 |
| **42** | Me | Me | Cl | | 149–150 | 29 |
| **43** (Y = $NMe_2$) | H | Et | Cl | 77 | 170–171[a] | 30 |
| **43** (Y = $NMe_2$) | Me | Me | Cl | | 189–190[a] | 30 |

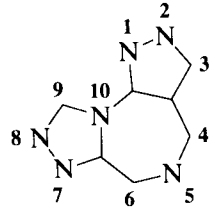
[a]Oxalate.

## 2. [1,2,4]Oxadiazolo[4,3-*a*]thieno[3,2-*f*][1,4]diazepines

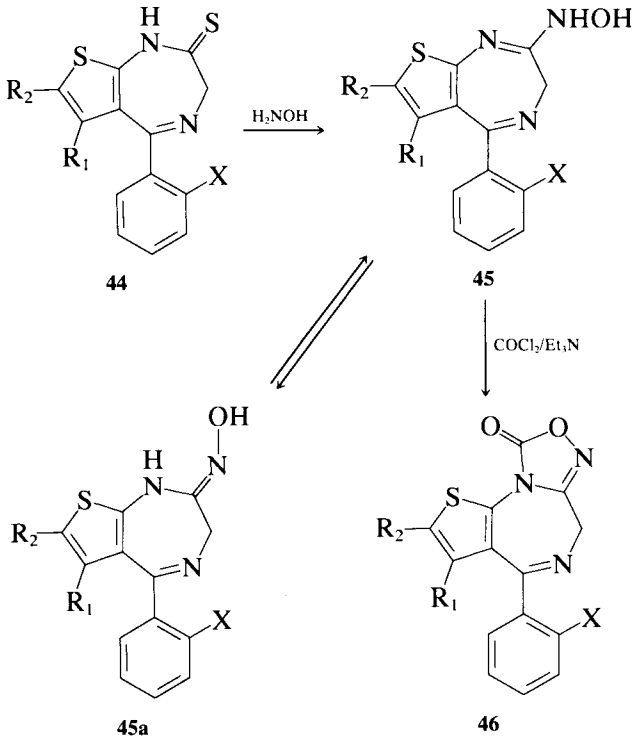



[1,2,4]Oxadiazolo[4,3-*a*]thieno[3,2-*f*][1,4]diazepines were prepared as shown in Eq. 13. Reaction of thione **44** with hydroxylamine led to the 2-hydroxyamino derivative **45**, in equilibrium with its 2-hydroxyimino tautomer **45a**. Treatment of **45** with phosgene in the presence of triethylamine led to the target oxadiazole **46.** Specific compounds prepared in this manner are listed in Table 5. These compounds were identified as minor tranquilizers (29).

## 3. Pyrazolo[4,3-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepines

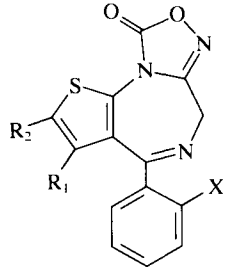



Reaction of the pyrazolo[3,4-*e*][1,4]diazepines **47a–d** with acetohydrazide initially at 160°C at atmospheric pressure and then at 185–200°C/10 torr gave



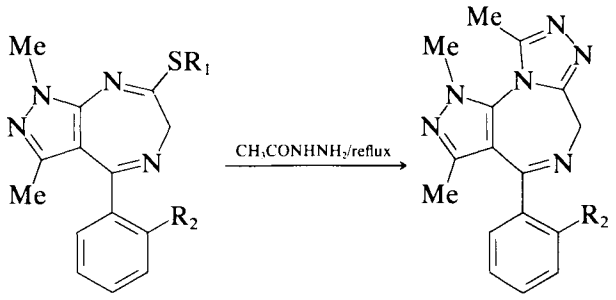

(13)

TABLE 5. [1,2,4]OXADIAZOLO[4,3-*a*]THIENO[3,2-*f*][1,4]DIAZEPINES



| $R_1$ | $R_2$ | X | Yield (%) | mp (°C) |
|---|---|---|---|---|
| H | Et | Cl | 68 | 132–133 |
| H | Me | Cl | 55 | 154–156 |
| H | Et | H | — | 191–192[a] |
| Me | Me | Cl | — | 136–138 |

[a]HCl salt.



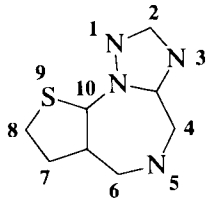

(14)

**47a**, $R_1$ = Me, $R_2$ = Cl
**47b**, $R_1$ = H, $R_2$ = Cl
**47c**, $R_1$ = Me, $R_2$ = H
**47d**, $R_1$ = Me, $R_2$ = F

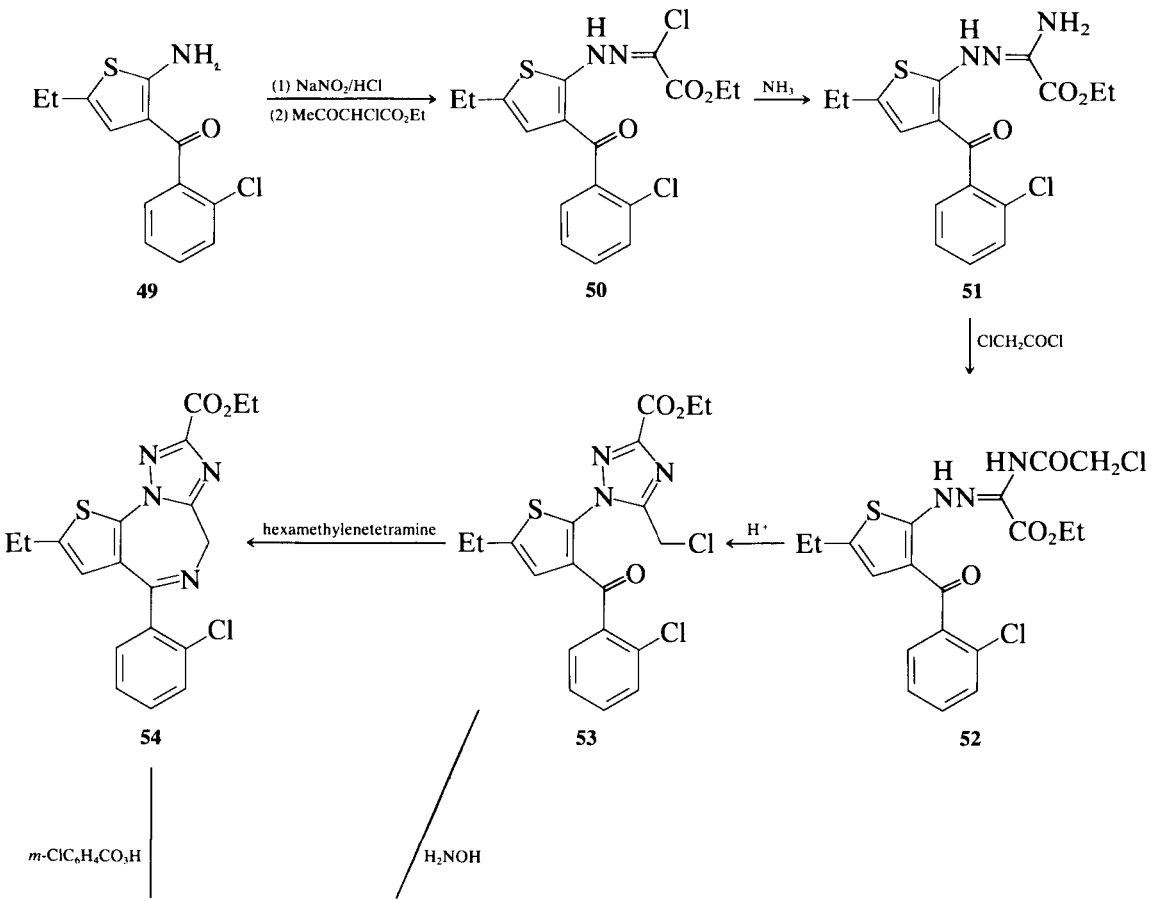
**48a**, $R_2$ = Cl; mp 236–237°C
**48c**, $R_2$ = H; mp 319–320°C
**48d**, $R_2$ = F; mp 254–256°C

the triazole derivatives indicated in Eq. 14 (31). Purification involved alumina chromatography, recrystallization, sublimation, and preparation of the hydrochloride salts.

## 4. Thieno[3,2-*f*][1,2,4]triazolo[1,5-*a*][1,4]diazepines (see Section XIV.4)




Thieno[3,2-*f*][1,2,4]triazolo[1,5-*a*][1,4]diazepines were prepared as depicted in Fig. 3. Diazotization of **49** followed by addition of ethyl 2-chloroacetoacetate led to azo compound **50**. Addition of ammonia to **50** followed by reaction with chloroacetyl chloride generated **52**. Acid-catalyzed cyclization of **52** to give **53** completed the synthesis of the triazole. Ring closure of **53** to diazepine **54** was effected with hexamethylenetetramine. Use of methanolic ammonia led to concomitant formation of the corresponding carboxamide. Treatment of **54** with *m*-chloroperbenzoic acid led to the $N^4$-oxide **55**, which could also be prepared directly from **53** by reaction with hydroxylamine (32,33). Amine oxide **55** was converted to amide **56** by standard methods and the latter was subjected to acetic anhydride to yield the rearranged acetate **57**. Hydrolysis or methanolysis afforded the corresponding hydroxy and methoxy derivatives **58** and **59**, respectively. Compounds prepared by this route are listed in Table 6 (33).


(1) NaNO2/HCl
(2) MeCOCHClCO2Et
NH3
ClCH2COCl
hexamethylenetetramine
H+
m-ClC6H4CO3H
H2NOH
49
50
51
52
53
54

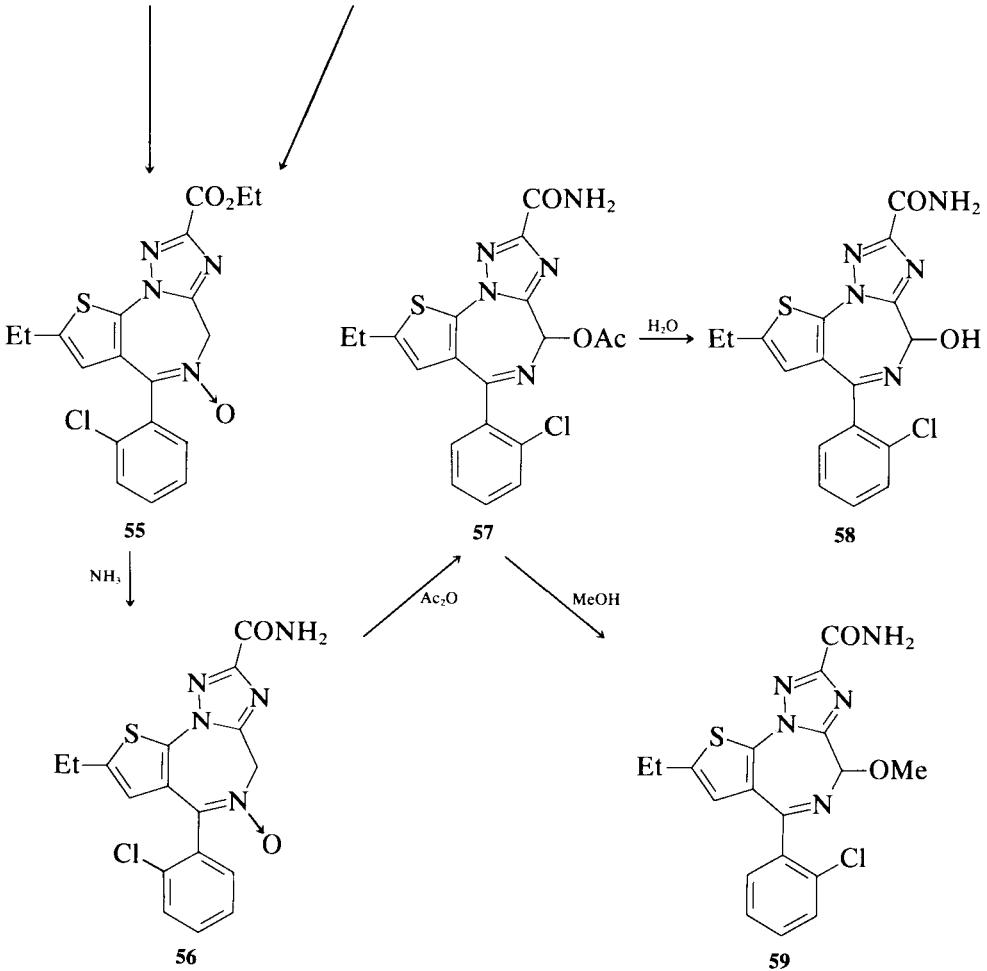
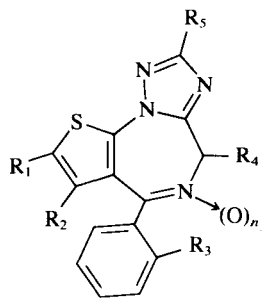
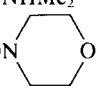
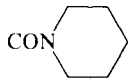
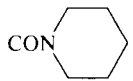
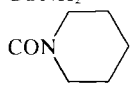
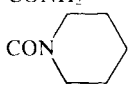
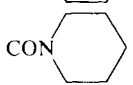

CO2Et
Et
S
N
N
N
N
O
Cl
55
NH3
CONH2
56
Ac2O
CONH2
OAc
57
H2O
MeOH
CONH2
OH
58
CONH2
OMe
59

**Figure 3**

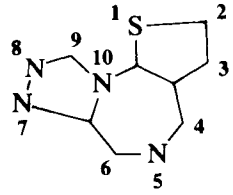
TABLE 6. THIENO[3,2-*f*][1,2,4]TRIAZOLO[1,5-*a*][1,4]DIAZEPINES




| *n* | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | mp (°C) | Refs. |
|---|---|---|---|---|---|---|---|
| 0 | Et | H | Cl | H | $CO_2Et$ | 147.5–148.5 | 32 |
| 0 | Et | H | Cl | H | $CONH_2$ | 232–233 | 32,33 |
| 0 | Et | H | Cl | H | COOH | 134–136 | 32,33 |
| 1 | Et | H | Cl | H | $CO_2Et$ | 193–194 | 32,33 |
| 1 | Et | H | Cl | H | CONHMe | 228–229 | 32 |
| 1 | Et | H | Cl | H | $CONH_2$ | 247–248 | 32,33 |
| 0 | Et | H | Cl | H | CONHMe | 214–215 | 32 |
| 0 | Et | H | Cl | H | $CONHMe_2$ | 122–123 | 32 |
| 0 | Et | H | Cl | H |  | 218–220 | 32 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 | Et | H | Cl | H | COOH | 224–226 | 32,33 |
| 1 | Et | H | Cl | H |  | 213–214 | 32,33 |
| 0 | Me | Me | H | H | $CO_2Et$ | 173–174 | 32,33 |
| 0 | Me | Me | H | H | COOH | 209–211 | 32,33 |
| 0 | Me | Me | H | H | $CONH_2$ | 251–252 | 32 |
| 0 | Me | Me | H | H |  | 178–179 | 32,33 |
| 1 | Me | Me | H | H | $CONH_2$ | 281–283 | 32,33 |
| 1 | Me | Me | H | H |  | 213–214 | 32 |
| 0 | Et | H | Cl | OAc | $CONH_2$ | 168–170 | 33 |
| 0 | Et | H | Cl | OH | $CONH_2$ | 228–231 | 33 |
| 0 | Et | H | Cl | OMe | $CONH_2$ | 200–201 | 33 |
| 0 | Me | Me | H | OAc |  | 168–169 | 33 |
| 0 | Me | Me | H | OMe |  | — | 33 |

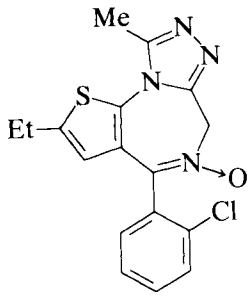
## 5. Thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepines (see Section XIV.5)



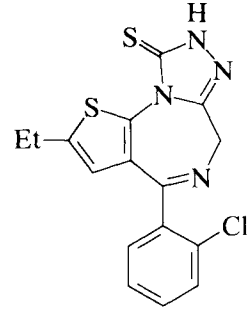

The thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine class of compounds was prepared for its potential anxiolytic properties on the basis of its bioisosteric relationship to the corresponding triazolobenzodiazepine series. The synthetic approach (Fig. 4) is similar to the literature route to triazolobenzodiazepines. Thus condensation of thiones **60** with acyl hydrazides afforded the triazoles **61**. Alternatively, **61** could be prepared by addition of ammonia to **64**. These compounds are listed in Table 7 (34–38). The related 6-pyridyl-substituted products were prepared similarly and are summarized in Table 8 (34,35,38). $N^5$-Oxides such as **67a** were prepared similarly.

An alternative synthetic approach to **61** is outlined in Eq. 15. Reduction of **68** with sodium borohydride, cyclization with base to form the oxazepine ring, and treatment with phosphorus pentasulfide led to **69**. Compound **70** was prepared under the usual conditions of triazole annelation, and then transformed to **71** by cleavage of the oxazepine ring to a diol, conversion to a dichloride, and recyclization with ammonia. Finally, **71** was dehydrogenated with manganese dioxide to yield **61** (37). The dihydrodiazepine products (such as **71**) are listed in Table 9.

The 1-oxo tricyclic ring system was also prepared from **60** by reaction with ethoxycarbonylhydrazine or by addition of hydrazine, followed by reaction with phosgene, to yield **62** (Fig. 4). Alkylation or acylation of **62** generated the 2-substituted derivatives **63**. These structures are included in Table 10. A 1-thione compound (**72**) was also prepared from **60** by sequential addition of hydrazine and thiophosgene (40–43).




**67a**




**72**, mp 236–237°C

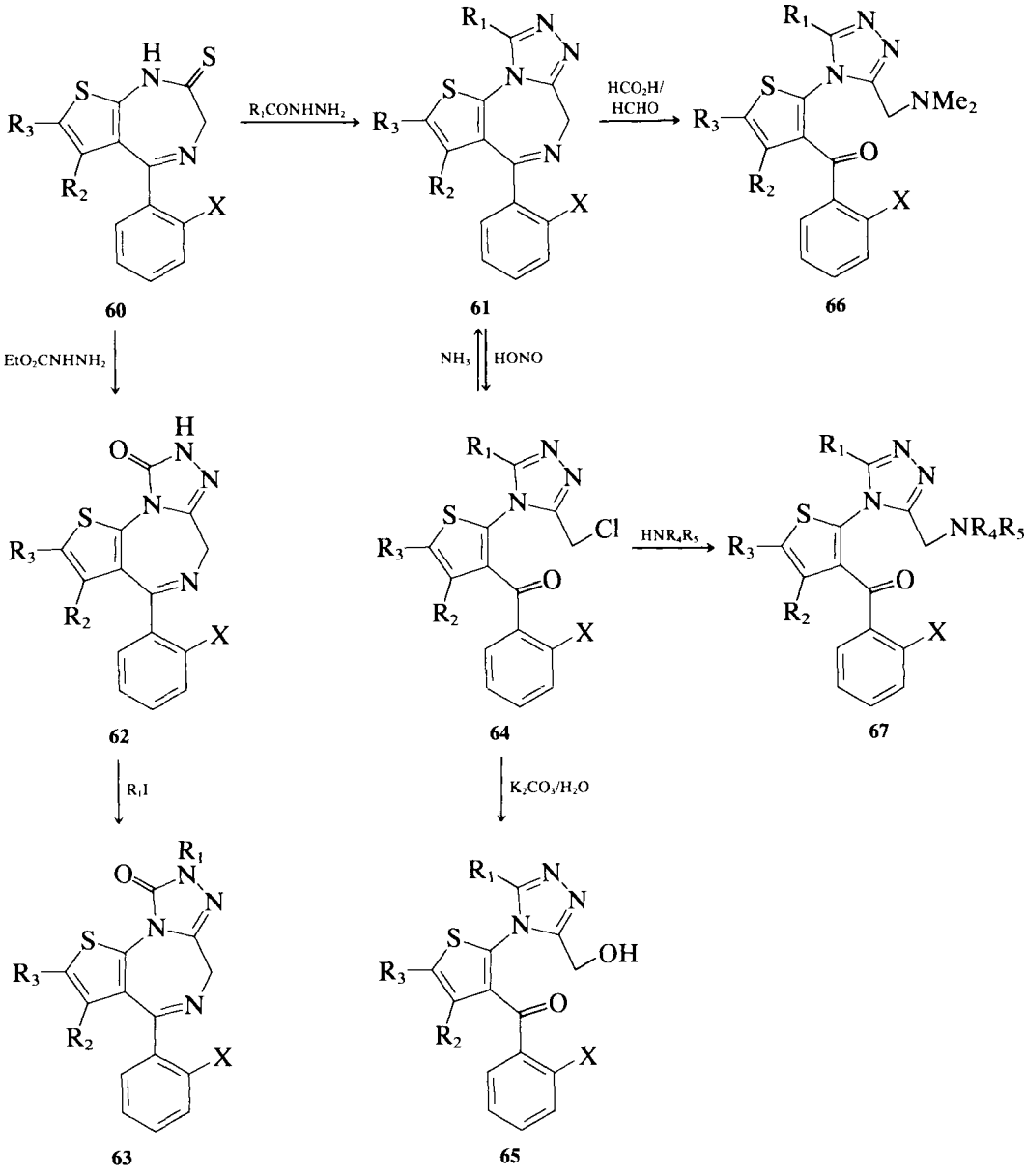
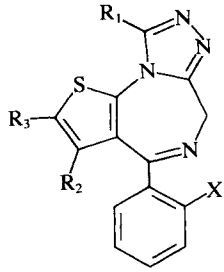

R1CONHNH2
HCO2H/
HCHO
NMe2
EtO2CNHNH2
NH3
HONO
HNR4R5
NR4R5
R1I
K2CO3/H2O
OH
60
61
66
62
64
67
63
65

**Figure 4**

TABLE 7. THIENO[3,2-*f*][1,2,4]TRIAZOLO[4,3-*a*][1,4]DIAZEPINES



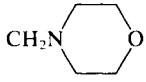
| $R_1$ | $R_2$ | $R_3$ | X | mp (°C) | Refs. |
|---|---|---|---|---|---|
| Me | H | Cl | Cl | 205–206 | 34,35,37 |
| Me | H | H | H | 224–226 | 34,38 |
| Me | H | Cl | $NO_2$ | 210–212 | 34 |
| Me | H | Cl | $CF_3$ | 193–195 | 34 |
| Me | H | $NO_2$ | Cl | 270–272 | 34 |
| Me | H | Cl | F | 187–189 | 34 |
| Me | H | H | $NO_2$ | 260–262 | 34 |
| Me | H | H | Cl | 221–223 | 34 |
| Me | H | Cl | *o*-$F_2$ | 185–187 | 34 |
| $CH_2OMe$ | H | Cl | $NO_2$ | 204–205 | 34 |
| $CH_2NMe_2$ | H | Cl | $NO_2$ | 234–236 | 34 |
| $CO_2Et$ | H | Cl | Cl | 180–182 | 34 |
| $CO_2Et$ | H | Cl | $NO_2$ | 143–145 | 34 |
| $CH_2CN$ | H | Cl | Cl | 217–220 | 34 |
| $OCH_3$ | H | Cl | Cl | 248–251 | 34 |
| $CH_2NH_2$ | H | Cl | Cl | 190–192 | 34 |
| $CH_2OH$ | H | Cl | Cl | 219–221 | 34 |
|  | H | Cl | Cl | 224–226 | 34 |
| $CH_2SMe$ | H | Cl | Cl | 200–202 | 34 |
| $CH_2Cl$ | H | Cl | Cl | 101–103 | 34 |
| $CH_2CHOHCH_3$ | H | Cl | Cl | 118–120 | 34 |
| H | H | Et | Cl | 153–154 | 30,35,36,38 |
| Me | H | Et | Cl | 147–148 | 35,37 |
| Me | H | Et | H | 166–167 | 35,36,38 |
| H | H | Et | H | 153–154 | 35,38 |
| H | —$(CH_2)_4$— | | Cl | 214–216 | 35,36,37,38 |
| Me | H | H | Cl | 120–124 | 35 |
| H | —$(CH_2)_4$— | | Cl | 222–223 | 35,36,38 |
| H | H | Me | Cl | 193–194 | 35,36,38 |
| H | Me | Me | H | 195–196 | 35,36,38 |
| Me | Me | Me | Cl | 197–198 | 35,36,38 |
| Et | H | Et | Cl | 143–145[a] | 35,36,38 |
| Ph | H | Et | H | 139–141 | 35 |
| H | H | Et | Me | 128–130 | 35,36,38 |
| H | H | Et | F | 156–157 | 35,36,38 |
| Me | H | Et | F | 195–196 | 35,36,38 |
| H | H | Et | Br | 158–159 | 35,36,38 |
| Me | H | Et | Br | 142–143 | 35,38 |

TABLE 7. (*Continued*)

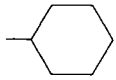
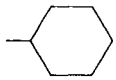
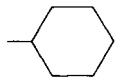
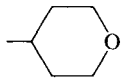
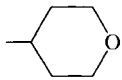
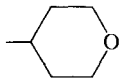
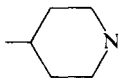
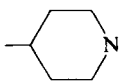
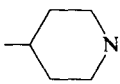
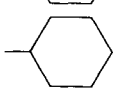
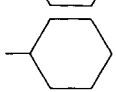
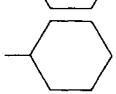
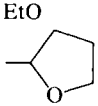
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|---|---|---|---|---|---|
| Me | H | COOEt | Cl | 232 | 46 |
| Me | H | $CO_2H$ | Cl | 302 | 46 |
|  | H | $CO_2Et$ | Cl | 220 | 46 |
|  | H | COOH | Cl | 300 | 46 |
|  | H | Br | Cl | 190–192 | 37,46,47 |
|  | H | $CO_2Et$ | Cl | 231 | 46 |
|  | H | $CO_2H$ | Cl | 302 | 46 |
|  | H | Br | Cl | 211–212 | 37,46 |
|  | H | $CO_2Et$ | Cl | 202 | 46 |
|  | H | $CO_2H$ | Cl | 300–303 | 46 |
|  | H | Br | Cl | 240–241 | 46 |
|  | H | $CO_2Et$ | Br | 204 | 46 |
|  | H | $CO_2H$ | Br | 295–297 | 46 |
|  | H | Br | Br | 190–191 | 46,47 |
| Me | H | $CO_2Et$ | Br | 212 | 38,46 |
| Me | H | $CO_2H$ | Br | 288 | 38,46 |
| Me | H | Br | Br | 204–206 | 37,46,47 |
| Me | H | Br | Cl | 211–213 | 37,47 |
| H | H | Br | Cl | 214–216 | 47 |
| Br | H | Br | Cl | 210–211 | 37,47 |
| MeO | H | Br | Cl | 198–200 | 47 |
| MeS | H | Br | Cl | 158–160 | 47 |
| EtO | H | Br | Cl | 144–146 | 47 |
|  | H | Br | Cl | 140–142 | 47 |

TABLE 7. (*Continued*)

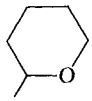
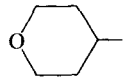
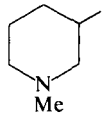
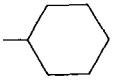
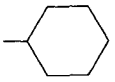
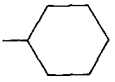
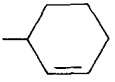
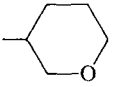
| $R_1$ | $R_2$ | $R_3$ | X | mp (°C) | Refs. |
|---|---|---|---|---|---|
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|  | H | Br | Cl | 257–258 | 37,47 |
|  | H | Br | Cl | 257–258 | 47 |
|  | H | Cl | Cl | 191 | 47 |
|  | H | Br | Cl | 212–213 | 28,47 |
| Cl | H | Br | Cl | 161–162 | 47 |
|  | H | Br | Cl | 190–191 | 47 |
|  | H | Br | Cl | 192–193 | 47 |
| Br | H | Cl | Cl | 170–172 | 47 |
| $C(CH_3)_3$ | H | Cl | Cl | 160–162 | 47 |
|  | H | Cl | Cl | 188–189 | 47 |
|  | H | Et | Cl | 128–129 | 47 |
|  | H | H | H | 178–180 | 47 |
| Br | H | H | Cl | 202–203 | 47 |
| $C(CH_3)_3$ | H | H | Cl | 184–185 | 47 |
| Br | H | Et | Cl | 175–176 | 47 |
| MeO | H | Et | Cl | Oil | 47 |
| MeO | H | H | H | 167–168 | 47 |
| Br | H | H | H | 197–199 | 47 |
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|  | H | Br | Cl | 187–188 | 47 |

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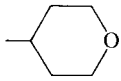
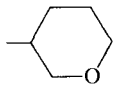
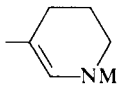
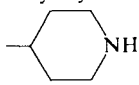
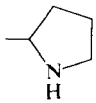
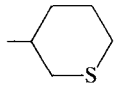
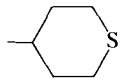
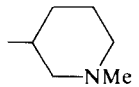
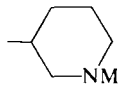
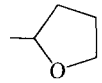
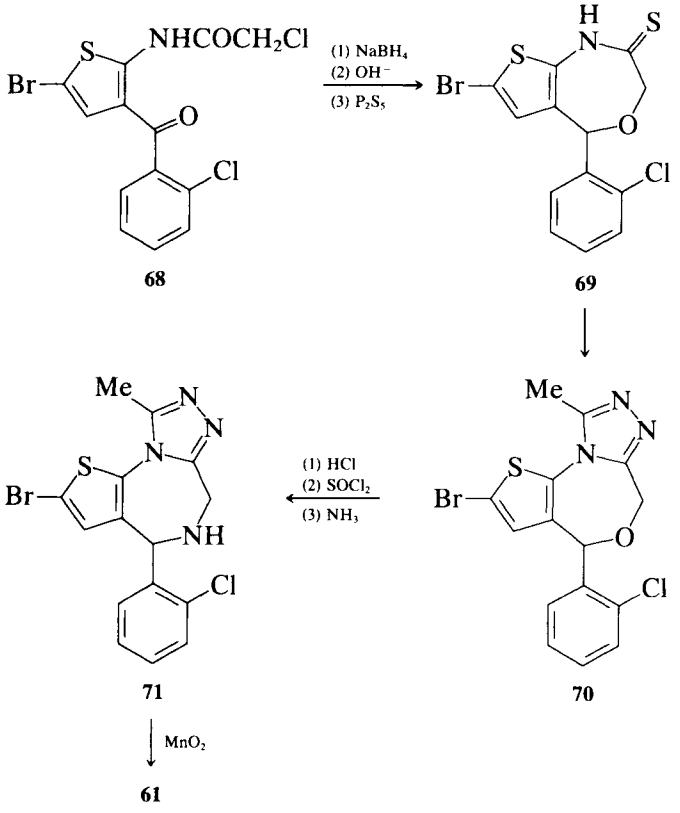
| $R_1$ | $R_2$ | $R_3$ | X | mp (°C) | Refs. |
|---|---|---|---|---|---|
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|  | H | Br | Br | 242 | 47 |
|  | H | Et | Cl | 174–175 | 47 |
|  | H | Br | Cl | 171–180 | 47 |
| 2-Pyridyl | H | Br | Cl | 260–262 | 47 |
|  | H | Br | Cl | 251–253 | 47 |
|  | H | Br | Cl | 223–225 | 47 |
|  | H | Br | Cl | 187–189 | 47 |
|  | H | Br | Cl | 231–233 | 47 |
|  | H | Br | Cl | 209–211 | 47 |
|  | H | Br | Cl | 260–261 | 47 |
|  | H | H | Cl | 98–100 | 47 |
|  | H | Et | Cl | 120–122 | 47 |
| Me | H | Br | F | 210 | 37,47 |
| Me | H | Br | H | 284 | 47 |
| H | H | Br | Cl | 216–218 | 37,47 |
| *i*-$C_3H_7$ | H | Br | Cl | 203–205 | 47 |
|  | H | Br | Br | 140–141 | 47 |
| Br | H | Br | Me | 205–206 | 37 |
| $CH_2OH$ | H | Br | Cl | 205–206 | 37 |

TABLE 7. (*Continued*)

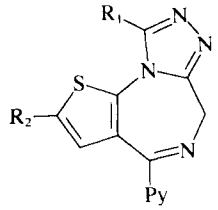
| $R_1$ | $R_2$ | $R_3$ | X | mp (°C) | Refs. |
|---|---|---|---|---|---|
| Me | H | Me | Cl | 158–159 | 36,38 |
| Me | H | Me | Br | 142–143 | 36 |
| Me | —$(CH_2)_4$— | | Cl | 120–124 | 36,38 |
| H | H | H | H | 199–200 | 36,38 |
| Me | H | Et | *p*-F | 171–172 | 38 |
| H | H | Et | MeO | 215–216[a] | 38 |
| H | H | F | *p*-MeO | 173–175 | 38 |
| H | Me | Me | Cl | 131–132 | 38 |
| Me | H | COMe | Cl | 231–232 | 38 |
| Me | F | Cl | Cl | 200–202 | 38 |
| H | H | H | Cl | 156–157 | 38 |
| H | H | Me | H | 252–253[b] | 38 |
| H | H | Et | *p*-Cl | 130–132 | 38 |

[a]2HCl salt.
[b]HCl salt.



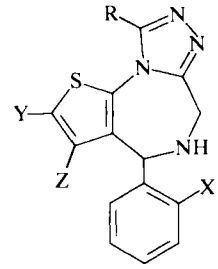

(15)

TABLE 8. 6-PYRIDYLTHIENO[3,2-*f*][1,2,4]TRIAZOLO[4,3-*a*][1,4]DIAZEPINES



| Pyridyl Position | $R_1$ | $R_2$ | mp (°C) | Refs. |
|---|---|---|---|---|
| 2 | Me | Cl | 174–176 | 34 |
| 2 | H | Et | 165–166 | 35,38 |
| 3 | H | Et | 166–167 | 35,38 |
| 3 | Me | Et | 196–197 | 35,38 |

TABLE 9. DIHYDROTHIENO[3,2-*f*][1,2,4]TRIAZOLO[4,3-*a*][1,4]DIAZEPINES[a]



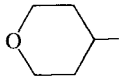
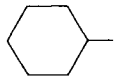
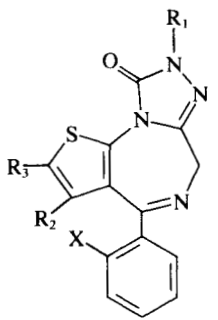
| R | X | Y | Z | mp (°C) |
|---|---|---|---|---|
| Me | Cl | Br | H | 160–162 |
|  | Cl | Br | H | 174–175 |
|  | Cl | Br | H | 190–192 |
| Me | Br | Br | H | 171–173 |
| Me | Cl | Cl | H | 131–133 |
| Me | F | Br | H | 180–182 |
| Me | Cl | Et | H | 120–122 |
| Me | Cl | —$(CH_2)_4$— | | 219–220 |
|  | Cl | Br | H | 156–158 |
| H | Cl | Br | H | 176–178 |
| $CH_2OH$ | Cl | Br | H | 205–206 |
| Br | Cl | Br | H | 135–137 |

TABLE 10. 1-OXOTHIENO[3,2-*f*][1,2,4]TRIAZOLO[4,3-*a*][1,4]DIAZEPINES



| $R_1$ | $R_2$ | $R_3$ | X | Salt | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| H | H | Et | Cl | | 199–200 | 40,41 |
| Me | H | Et | Cl | HCl | 186–188 | 40,41 |
| Me | H | Me | Cl | | 199–200 | 41 |
| MeNHCO | H | Et | Cl | | 193–194 | 40,42 |
| $Me_2NCH_2CH_2$ | H | Et | Cl | | 221–223 | 40,41 |
| H | H | Me | Cl | | 213–215 | 40,41 |
| H | H | Et | H | HCl | 276–278 | 40,41 |
| H | H | Et | Me | | 158–160 | 40,41 |
| H | H | Et | MeO | | 193–194 | 40,41 |

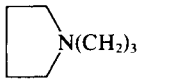
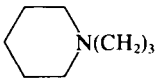
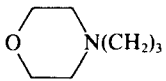
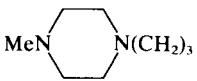
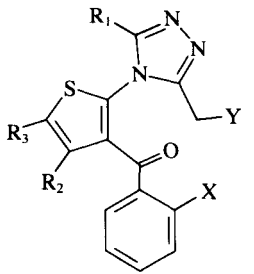
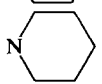
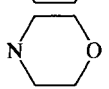
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| H | H | | Et | Br | | 219–220 | 40,41 |
| H | Me | | Me | Cl | | 212–214 | 40,41 |
| H | | —$(CH_2)_4$— | | Cl | | 252–254 | 40,41 |
| MeNHCO | H | | H | Cl | | 169–171 | 40,43 |
| $Me_2NCH_2CH_2$ | Me | | Me | Cl | HCl | 262–263 | 40 |
| $Me_2N(CH_2)_3$ | H | | Et | Cl | Oxalate | 125–126 | 40,42 |
|  | H | | Et | Cl | | 104–106 | 40,42 |
|  | H | | Et | Cl | | 124–125 | 40 |
|  | H | | Et | Cl | | 137–138 | 40,42 |
|  | H | | Et | Cl | Dioxalate | 199–200 | 40,42 |
| $Me_2NCH_2CH_2$ | | —$(CH_2)_4$— | | Cl | Oxalate | 146–148 | 40,42 |
| | | | | | | | 40,42 |
| MeNHCO | | —$(CH_2)_4$— | | Cl | | 223–225 | 40,43 |
| PhNHCO | H | | Me | Cl | | 223–224 | 43 |
| MeNHCO | H | | Me | Cl | | 185–187 | 43 |
| MeNHCO | H | | Et | H | | 165–167 | 43 |

TABLE 11. RING OPENED THIENO[3,2-*f*][1,2,4]TRIAZOLO[4,3-*a*][1,4]DIAZEPINES

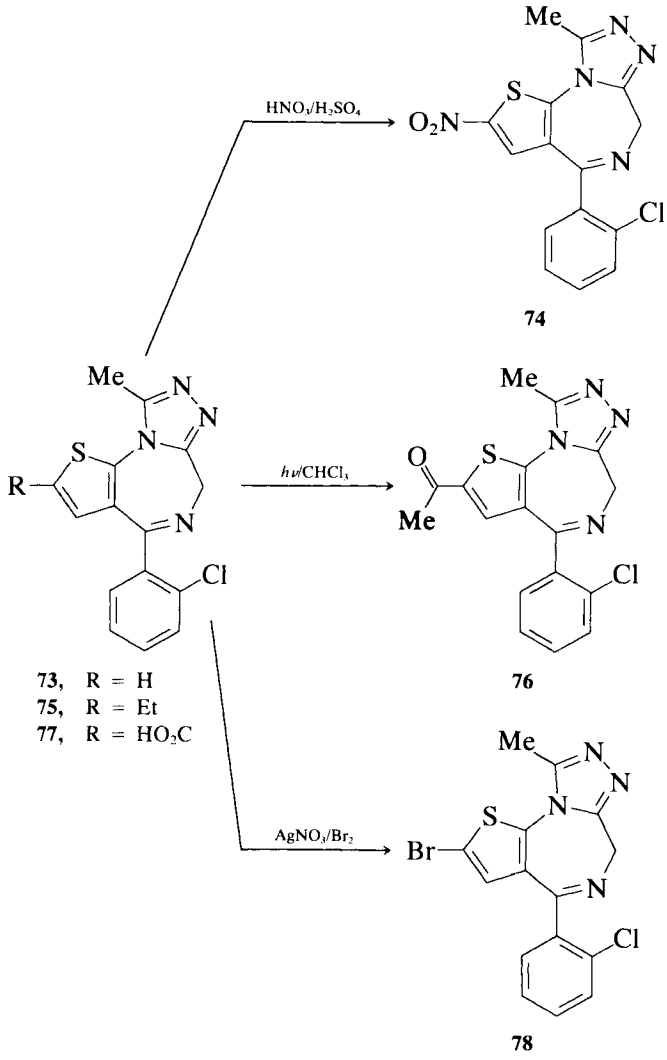


| $R_1$ | $R_2$ | $R_3$ | X | Y | Salt | mp (°C) | Other Data | Refs. |
|---|---|---|---|---|---|---|---|---|
| Me | H | Et | Cl | Cl | | 109–110 | | 30,44 |
| Me | H | Et | OH | Cl | | 140–141 | | 30,44 |
| Me | H | Me | Cl | Cl | | | $n_D^{20} = 1.6006$ | 30 |
| H | H | Et | Cl | Cl | | | $n_D^{20} = 1.5930$ | 30 |
| Me | H | Et | F | Cl | | | $n_D^{20} = 1.5868$ | 30,44 |
| Me | Me | Me | F | Cl | | | $n_D^{20} = 1.5942$ | 30,44 |
| H | —$(CH_2)_4$— | | Cl | Cl | | 128–130 | | 30,44 |
| Me | H | Et | Cl | $NH_2$ | 2TsOH | 167–170 | | 30 |
| H | H | Et | Cl | $NH_2$ | 2TsOH | 167–169 | | 30 |
| Me | H | Me | Cl | $NH_2$ | 2TsOH | 149–151 | | 30 |
| Me | Me | Me | H | $NH_2$ | 2TsOH | 163–165 | | 30 |
| Me | H | Et | Cl | $NMe_2$ | Oxalate | 172–175 | | 30 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| H | H | Et | H | $NM_2$ | Oxalate | 176–177 | | 30 |
| H | H | Et | Cl | $NMe_2$ | Oxalate | 166–167 | | 30 |
| Me | H | Me | Cl | $NMe_2$ | Oxalate | 174–176 | | 30 |
| Me | H | Et | Cl | $NMe_2$ | Oxalate | 150–152 | | 30 |
| Me | H | Et | Br | $NMe_2$ | Oxalate | 168–170 | | 30 |
| Me | H | Et | F | $NMe_2$ | Oxalate | 169–170 | | 30 |
| Me | H | Et | F | $NMe_2$ | | 107–108 | | 30 |
| Me | Me | Me | Cl | $NMe_2$ | | 145–146 | | 30 |
| Me | —$(CH_2)_4$— | | Cl | $NMe_2$ | Oxalate | 179–181 | | 30 |
| $HOCH_2$ | H | Et | Cl | $NMe_2$ | Oxalate | 144–146 | | 30 |
| Me | —$(CH_2)_4$— | | Cl | OH | | 183–202 | | 44 |
| H | H | Et | Cl | NHMe | Oxalate | 183–184 | | 30 |
| H | H | Et | Cl |  | 2HCl | 94–95 | | 30 |
| H | H | Et | Cl |  | 2HCl | 202–204 | | 30 |
| H | H | Et | Cl |  | Oxalate | 178–179 | | 30 |
| Me | H | Et | Cl | OH | | | $n_D^{20} = 1.5930$ | 44 |
| H | H | Et | Cl | Cl | | 108–109 | | 44 |
| Me | H | Et | F | OH | | 141–142 | | 44 |
| Me | Me | Me | Cl | OH | | 198–199 | | 44 |

Some reactions of **61** were also undertaken. Cleavage of the diazepine ring to **64** was accomplished with 10% aqueous hydrochloric acid followed by sodium nitrite. Reaction of **64** with amines led to the adducts **67**. On treatment with aqueous potassium carbonate, **64** was converted to alcohol **65**. In refluxing formic acid and formaldehyde, **61** was transformed to dimethylamino derivative **66**. Ring-opened compounds of this class are listed in Table 11 (30,44).

Other reactions of the basic tricyclic system (Eq. 16) included nitration of **73** to yield **74** (34) and photolysis of **75** to give the acetyl derivative **76** (38,45). In addition, the Hunsdiecker reaction with **77** led to bromothiophene



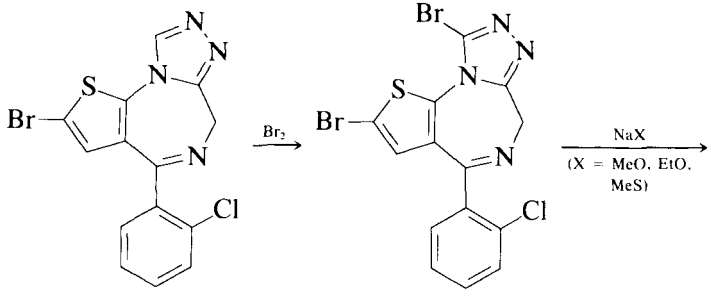

**73**, R = H
**75**, R = Et
**77**, R = $HO_2C$

**74** **76** **78**

(16)

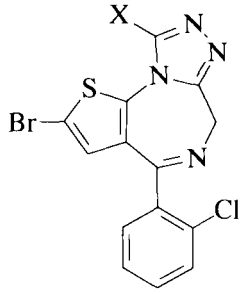
derivative **78**. Compounds synthesized by this process are included in Table 7 (46).

Turning to reactions at the 1-position (Eq. 17), addition of bromine to **79** afforded **80**. Displacement reactions on substrate **80** with methoxide, ethoxide, and methylmercaptide afforded the corresponding methoxy, ethoxy, and methylthio derivatives (**81**) (47).



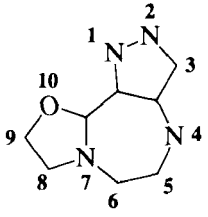

**79** **80**

(17)

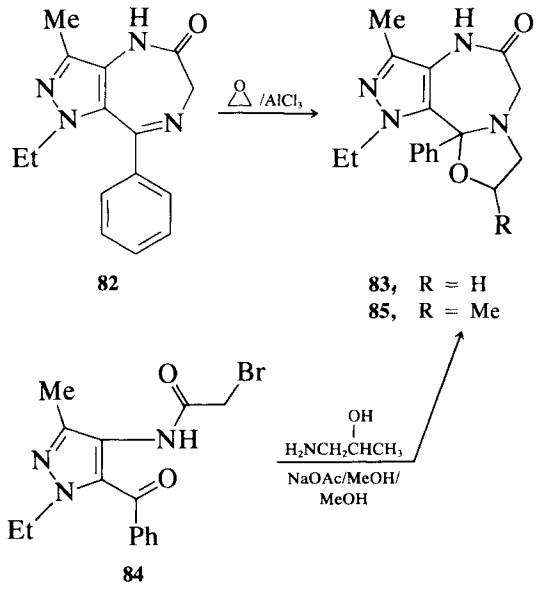



**81**

## 6. Oxazolo[3,2-*d*]pyrazolo[3,4-*f*][1,4]diazepines



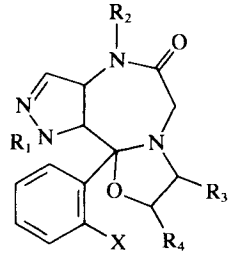

Oxazolo[3,2-*d*]pyrazolo[3,4-*f*][1,4]diazepines, patented as anticonvulsants, were prepared by two methods (Eq. 18). In one procedure, pyrazolodiazepine **82** was treated with ethylene oxide in the presence of aluminum




(18)

chloride to give **83**. The use of other epoxides with stannic chloride also led to oxazole ring annelation. An alternative approach to this ring system was achieved by cyclization of bromoacetamide **84** with 1-amino-2-propanol to yield **85**. Each of these methods appears to be general, and most of the products, listed in Table 12, were prepared by both procedures (48).

TABLE 12. OXAZOLO[3.2-*d*]PYRAZOLO[3,4-*f*][1,4]DIAZEPINES

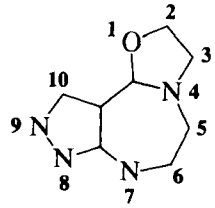



| $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | mp (°C) |
|---|---|---|---|---|---|
| Et | H | H | H | H | 204–205 |
| *n*-$C_3H_7$ | H | H | H | H | 181.5–183 |
| Me | H | H | H | 2,6-$F_2$ | 193–195 |
| Me | H | H | Me | H | 202–205.5 |
| Me | H | H | H | F | 211–215 |
| Et | H | H | Me | H | 149–179 |

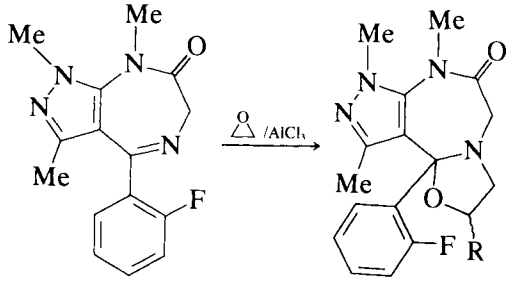
TABLE 12. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | mp (°C) |
|---|---|---|---|---|---|
| Et | H | H | Me | F | 199–201 |
| Me | H | H | Me | F | 208–210 |
| Et | H | H | H | F | 223.5–226 |
| Me | H | H | Me | 2,6-$F_2$ | 195–200 |
| Et | H | H | Me | 2,6-$F_2$ | 175–180 |
| Me | Me | H | Me | 2,6-$F_2$ | 183–186 |
| Et | Me | H | Me | H | 121–124 |
| Et | H | Me | H | H | 234–236.5 |
| Et | H | H | Ph | H | 195–196.5 |

## 7. Oxazolo[3,2-*d*]pyrazolo[4,3-*f*][1,4]diazepines




The oxazolo[3,2-*d*]pyrazolo[4,3-*f*][1,4]diazepine ring system, in the form of compounds **87a** and **87b**, was prepared by Lewis acid–catalyzed addition of ethylene oxide to diazepine **86** or by condensation of 1-amino-2-propanol with bromoacetamide **88** (Eq. 19). The products were claimed to have anticonvusant activity (49).

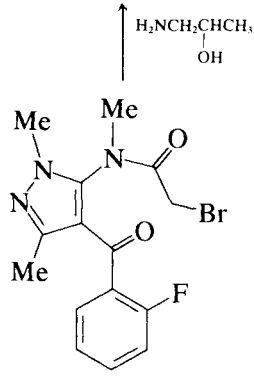



**86**

**87a**, R = H; mp 191–194°C
**87b**, R = Me; mp 156–158.5°C

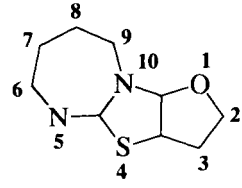
(19)

(*see next page*)

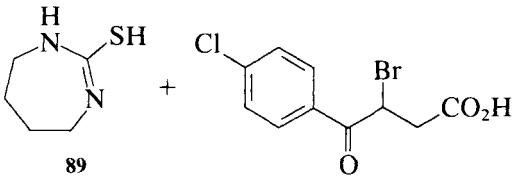



88 (19 *cont'd*)

## 8. Furo[2′,3′:4,5]thiazolo[3,2-*a*][1,3]diazepines



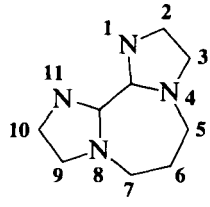

Treatment of mercaptodiazepine **89** with 3-bromo-3-(*p*-chlorobenzoyl) propionic acid and acetic anhydride led directly to the target structure **90** (Eq. 20). The transformation occurs by alkylation at sulfur, cyclization to a transitory carbinolamine, and lactonization. The product is patented for its central nervous system (CNS) depressant properties (50,51).



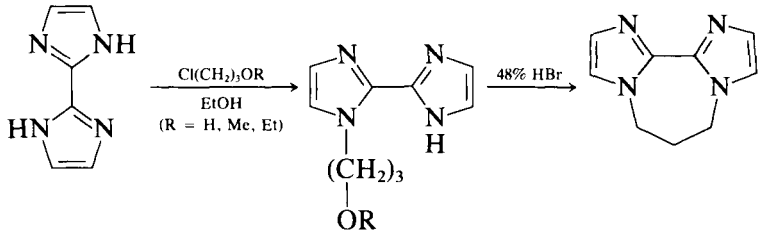

89 + (20)

**90**, mp 183–185°C (HBr)

## 9. Diimidazo[1,2-*a*:2',1'-*c*][1,4]diazepines




Examples of diimidazo[1,2-*a*:2',1'][1,4]diazepines have been prepared by a variety of related methods, starting with 2,2'-biimidazole **91** (Eq. 21)(52). Reaction of **91** with 3-chloropropanol in refluxing ethanol gave the 3-hydroxypropyl derivative **92**, which was cyclized in refluxing 48% hydrobromic acid (or with thionyl chloride in dioxane or dimethylformamide) to the diazepine derivative **93**.

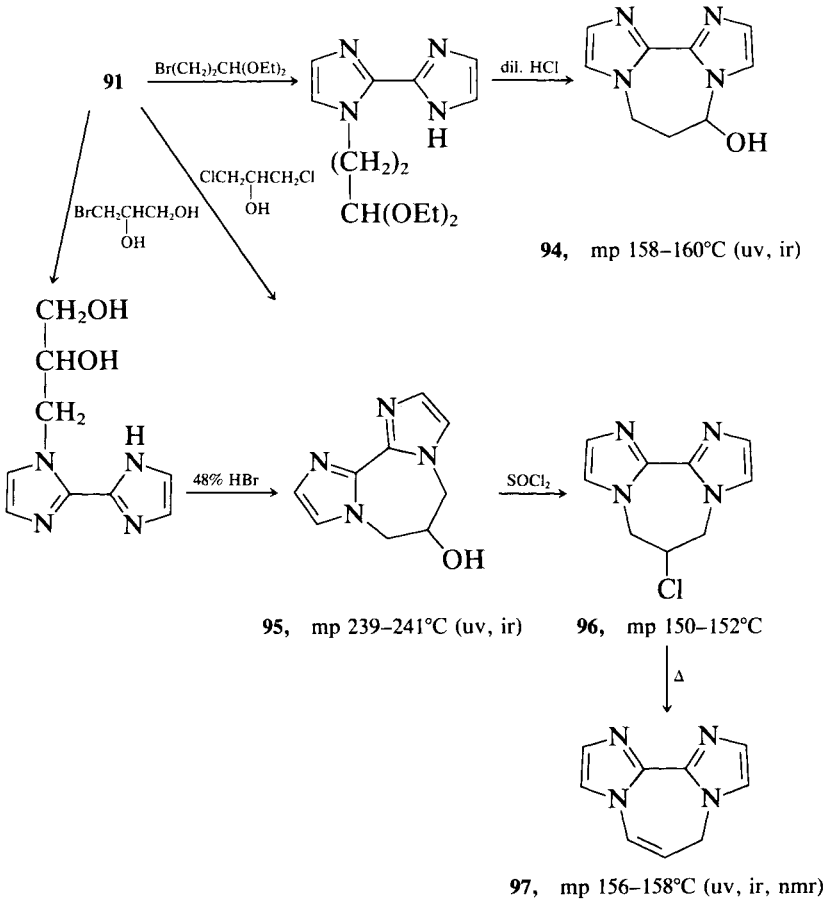



(21)

**91** **92** **93** (nmr, ir, uv)

Alternatively, 3-alkoxyhalides could be used instead of 3-chloropropanol. Again, cyclization was achieved with 48% hydrobromic acid. Reaction of **91** with 1-bromo-3-chloropropane and sodium hydroxide in dimethylformamide gave **93** directly. Substances functionalized on the 3-carbon bridge were prepared by analogous procedures (Fig. 5).

These studies were later extended to the preparation of nitro derivatives (53) (Eq. 22, Fig. 6). The pivaloate **101** was prepared from the hydroxy compound with pivaloyl chloride. The position of the double bond in **104** was determined on the basis of the nmr spectrum. Compounds **99** and **103** demonstrated significant antiprotozoal activity.



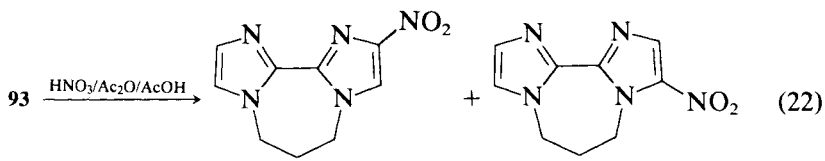

**94,** mp 158–160°C (uv, ir)

**95,** mp 239–241°C (uv, ir)

**96,** mp 150–152°C

**97,** mp 156–158°C (uv, ir, nmr)

**Figure 5**




(22)

**98,** mp 300°

**99,** mp 266–267°C

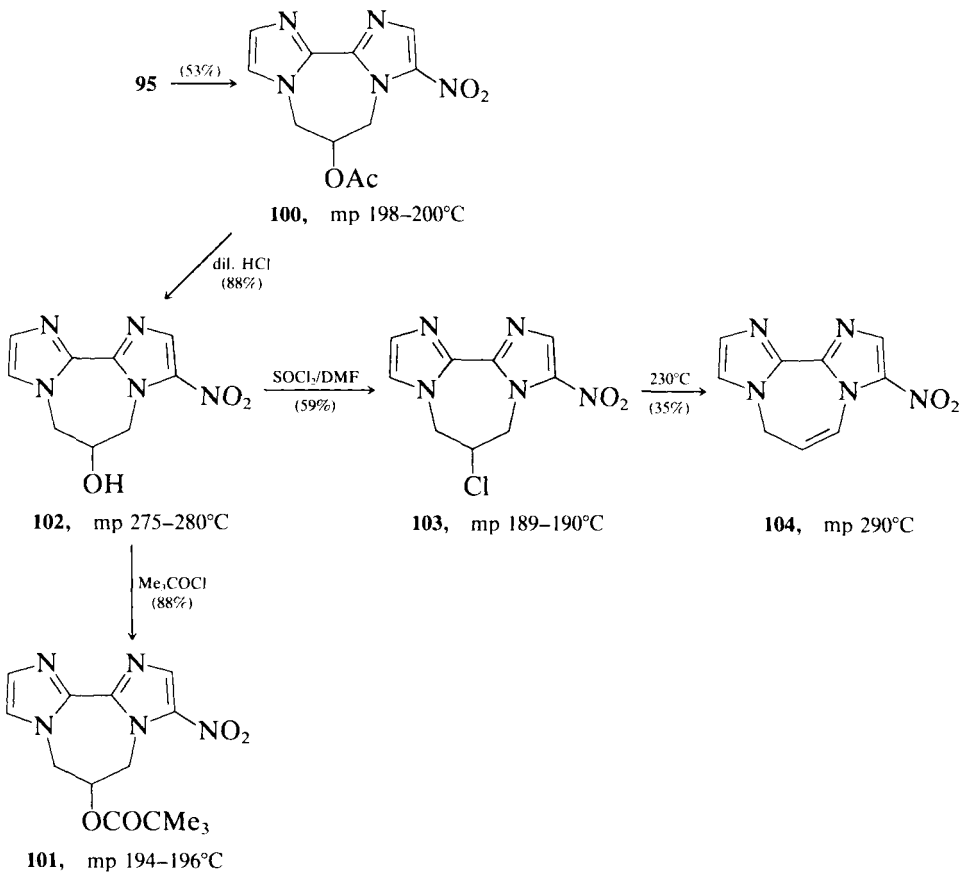
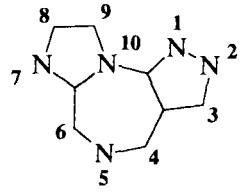


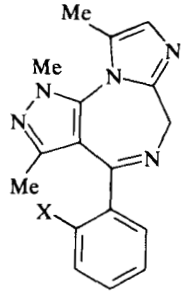

**Figure 6**

## 10. Imidazo[1,2-*a*]pyrazolo[4,3-*f*][1,4]diazepines (see Section XIV.6)

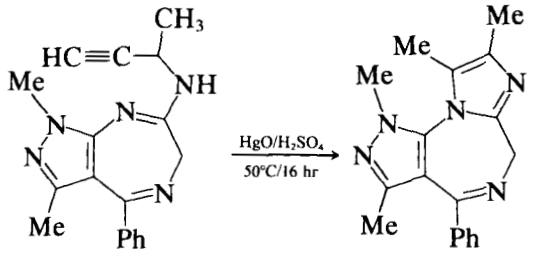



The imidazo[1,2-*a*]pyrazolo[4,3-*f*][1,4]diazepine ring system, related chemically and biologically to the corresponding imidazobenzodiazepines, was prepared by mercuric oxide–catalyzed cyclization of the propynylamidine **105** to **106** (Eq. 23). Additional examples are given in Table 13 (54).

TABLE 13. IMIDAZO[1,2-*a*]PYRAZOLO[4,3-*f*][1,4]DIAZEPINES

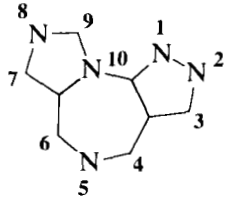


| X | mp (°C) |
|---|---|
| Cl | 189–190 |
| H | 224–226 |
| F | 169–171 |



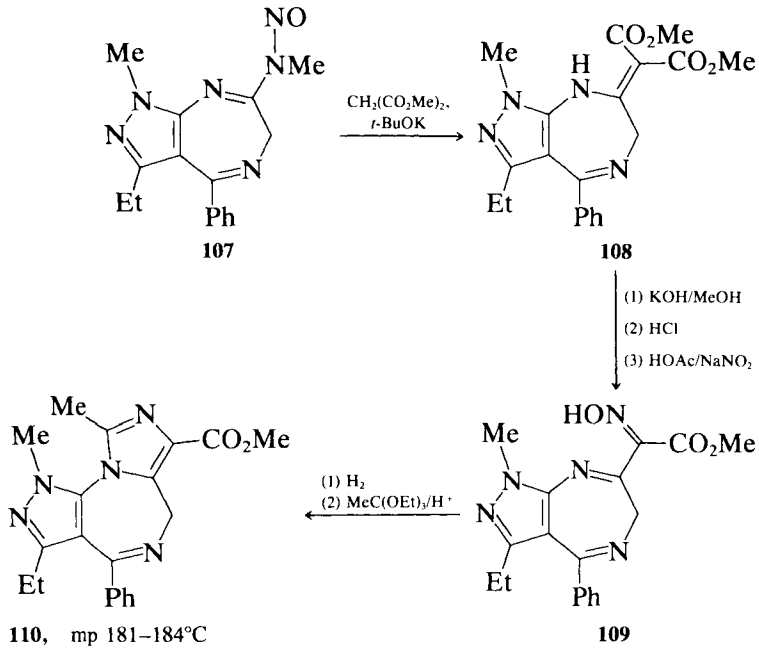

105 106 (23)

## 11. Imidazo[1,5-*a*]pyrazolo[4,3-*f*][1,4]diazepines (see Section XIV.7)



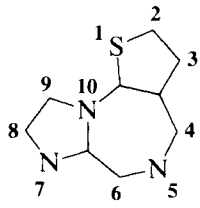
The imidazo[1,5-*a*]pyrazolo[4,3-*f*][1,4]diazepine ring system appeared as a minor part of a patent predominantly dealing with the corresponding imidazobenzodiazepine system. Its synthesis, analogous to that of imidazobenzodiazepines, is summarized in Eq. 24. Condensation of diazepine **107** with dimethyl malonate led to the adduct **108**. Decarbomethoxylation of **108**

followed by nitrosation afforded oxime derivative **109**. Hydrogenation of **109**, followed by acid-catalyzed condensation with triethyl orthoacetate, produced the tricyclic product **110** (55).

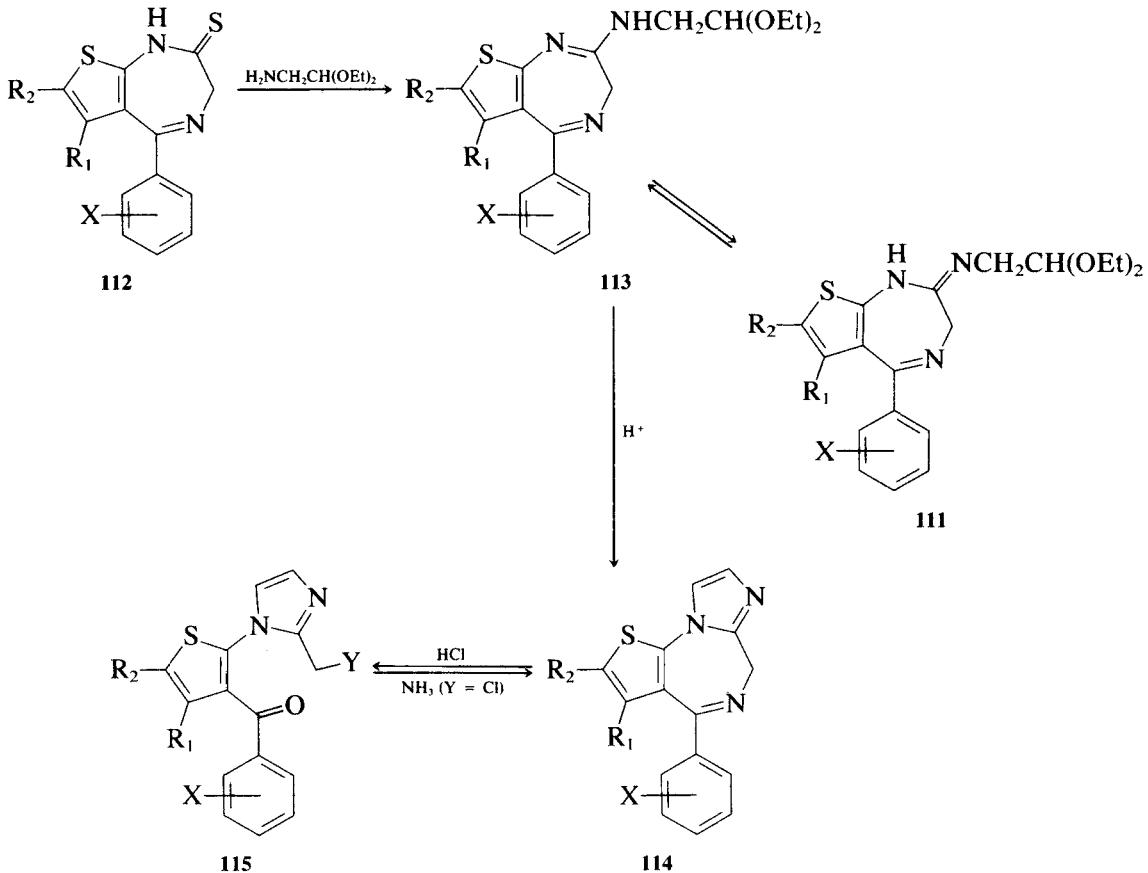



(24)

## 12. Imidazo[1,2-*a*]thieno[3,2-*f*][1,4]diazepines (see Section XIV.8)




Several syntheses of the imidazo[1,2-*a*]thieno[3,2-*f*][1,4]diazepine system have appeared. Reaction of thienodiazepine-2-thione **112** (a key intermediate also used in the preparation of the corresponding tetrazolo and oxadiazolo tricyclic diazepines) with 2,2-diethoxyethylamine led to the diazepine **113**, which was in equilibrium with its imino tautomer. Acid-catalyzed cyclization produced the tricyclic imidazole **114** as outlined in Eq. 25. Another systhesis


H
N
S
S
R2
R1
X
112
H2NCH2CH(OEt)2
NHCH2CH(OEt)2
113
NCH2CH(OEt)2
111
H+
HCl
NH3 (Y = Cl)
O
Y
115
114

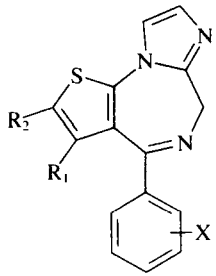
(25)

of **114** involved diazepine formation from imidazothiophene **115** (Y = Cl) by treatment with methanolic ammonia. The compounds prepared by these methods are summarized in Table 14 (29,30).

These diazepines undergo hydrolysis of the imine bond to give the substituted thiophenes **115** (Eq. 25). Hydrolysis with aqueous hydrochloric acid generated the intermediate amino ketones (**115**, Y = $NH_2$), which were converted directly to the corresponding chlorides (**115**, Y = Cl) by addition of sodium nitrite to the acidic reaction mixture. With sulfuric acid, the nitrite procedure converted **114** to the corresponding alcohols **115** (Y = OH). The chloride substituent in **115** (Y = Cl) could be displaced by a series of amines, including methylamine, pyrrolidine, and *N*-methylpiperazine. The hydrolysis of **114** could also be carried out directly to the dimethylamino compound **115** (Y = $NMe_2$) by refluxing in formic acid and formaldehyde. The ring-opened diazepines prepared under these conditions are listed in Table 15 (30,36).

The imidazo[1,2-*a*]thieno[3,2-*f*][1,4]diazepines (**114**) are classified as minor tranquilizers with strong anticonvulsant but weak ataxia-inducing effects. The amino-substituted hydrolysis products (**115**) are claimed to possess sedative, anxiolytic, and anticonvulsant activities.

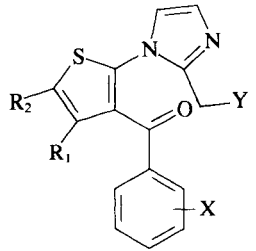
TABLE 14. IMIDAZO[1,2-*a*]THIENO[3,2-*f*][1,4]DIAZEPINES[a]

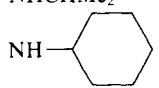
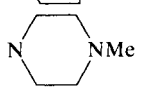
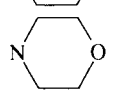



| $R_1$ | $R_2$ | X | Yield (%) | mp (°C) | Salt |
|---|---|---|---|---|---|
| H | H | *o*-Cl | | 124–127<br>243–245 | HCl |
| H | Et | H | 80 | 96–98 | |
| H | H | H | 78 | 156–157 | |
| H | Me | *o*-Cl | | 252–253 | |
| H | Et | *o*-Cl | | 180–182 | |
| H | Et | *o*-Br | | 237–238 | |
| H | Et | *o*-F | | 95–96 | |
| H | Et | *p*-F | | 116–117 | |
| H | Et | *o*-MeO | | 215–216 | 2HCl |
| H | Et | *p*-MeO | | 173–175 | |
| Me | Me | *o*-Cl | | 131–132 | |

[a]Refs. 29 and 30.

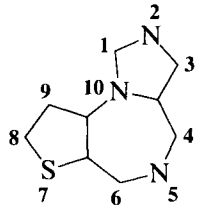
TABLE 15. RING-OPENED IMIDAZO[1,2-*a*]THIENO[3,2-*f*][1,4]DIAZEPINES[a]



| $R^1$ | $R_2$ | X | Y | Salt | mp (°C) | Other Data |
|---|---|---|---|---|---|---|
| H | Et | H | Cl | | | |
| H | Et | H | $NMe_2$ | | | $n_D^{20} = 1.5952$ |
| H | Et | *o*-Cl | Cl | | | $n_D^{20} = 1.6061$ |
| H | Et | *o*-Cl | $NMe_2$ | Oxalate | 150–152 | |
| H | Et | *o*-F | Cl | | | $n_D^{20} = 1.5952$ |
| Me | Me | *o*-Cl | Cl | | 128–129 | |
| H | Et | *o*-Cl | NHMe | Oxalate | 162–163 | |
| H | Et | *o*-Cl | $NHCHMe_2$ | Oxalate | 146–147 | |
| H | Et | *o*-Cl |  | Oxalate | 172–173 | |
| H | Et | *o*-Cl |  | Oxalate | 184–185 | |
| H | Et | *o*-Cl |  | Oxalate | 188–189 | |
| H | Et | *o*-Cl |  | Oxalate | 145–146 | |

[a]Refs. 30 and 36.

## 13. Imidazo[1,5-*a*]thieno[2,3-*f*][1,4]diazepines (see Section XIV.9)




The imidazo[1,5-*a*]thieno[2,3-*f*][1,4]diazepine structure appeared in a patent dealing mainly with the corresponding imidazobenzodiazepines, and the syntheses of the two systems are analogous. As outlined in Fig. 7, thienodiazepinone **116** was transformed into amidine **117** with methylamine and titanium tetrachloride. Conversion to *N*-nitroso compound **118** followed by displacement with nitromethane led to **119**, which was transformed to diamine **120** by catalytic hydrogenation. Cyclization with triethyl orthoacetate followed by aromatization with manganese dioxide afforded the target structure **121** (55).

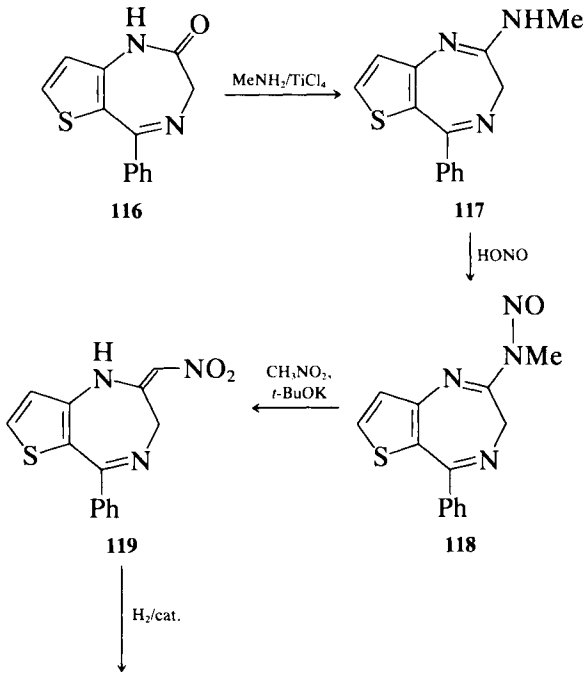
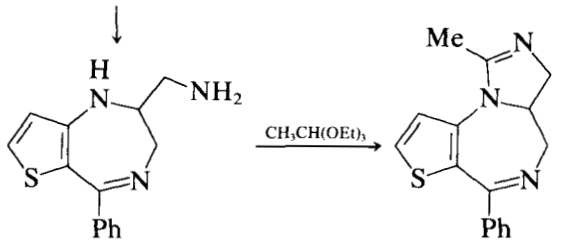


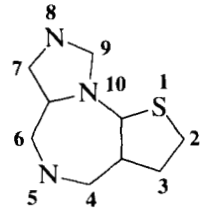

**Figure 7** (*cont'd on next page*)



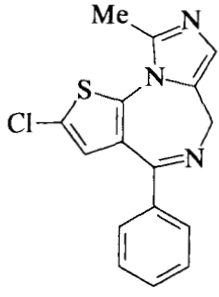

**121,** mp 223–225°C

**Figure 7** (*continued*)

## 14. Imidazo[1,5-*a*]thieno[3,2-*f*][1,4]diazepines (see Section XIV.10)

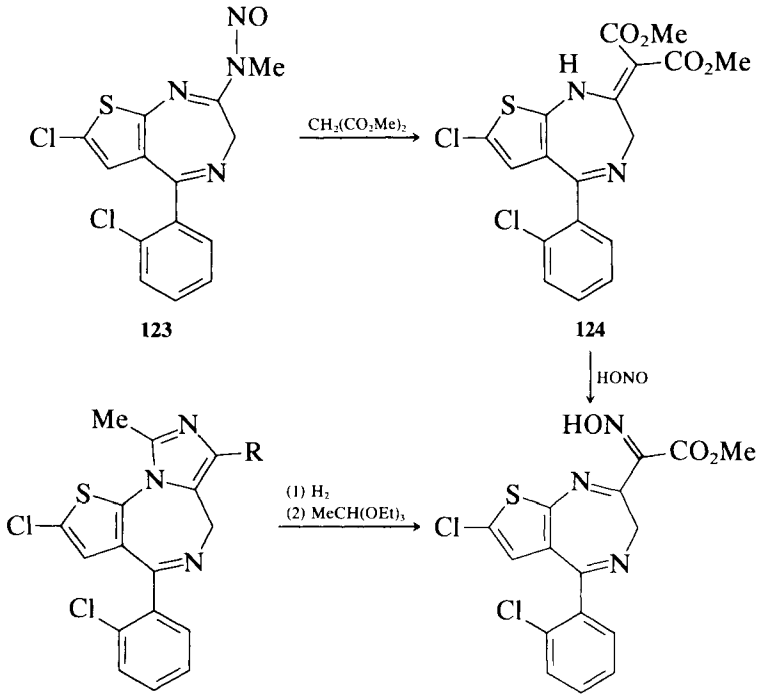



The synthesis of **122** follows the route described for the imidazo[1,5-*a*]-thieno[2,3-*f*][1,4]diazepine system. The 3-substituted derivatives were prepared by displacement of *N*-nitroso intermediate **123** with dimethylmalonate, which led to **124**. Conversion of **124** to imidazole **125** was achieved by nitrosation, reduction, and cyclization with triethyl orthoacetate (Eq. 26).




**122,** mp 168–170°C

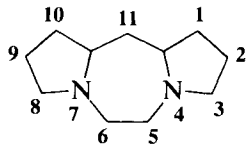
Variations at the 3-position of **125** were carried out using standard procedures (55).




123 124 (26)

| | R | mp (°C) |
|---|---|---|
| **125a** | $CO_2Me$ | 211–212 |
| **125b** | $CO_2H$ | 190–194 |
| **125c** | $CONH_2$ | 300–303 |
| **125d** | $CONMe_2$ | 197–200 |
| **125e** | $CH_2OH$ | 190–194 |

## 15. Dipyrrolo[1,2-*d*:2′,1′-*g*][1,4]diazepines




The only reported synthesis of a dipyrrolo[1,2-*d*:2′,1′-*g*][1,4]diazepine derivative is the work of Benary (56). As shown in Fig. 8, condensation of the aminocrotononitrile **126** with ethylenediamine gave the dinitrile **127**, which on treatment with chloracetyl chloride in pyridine led to the *C*-acylated derivative **128**. When **128** was treated with alcoholic ammonia, an unstable substance was formed which turned black on drying. This substance was

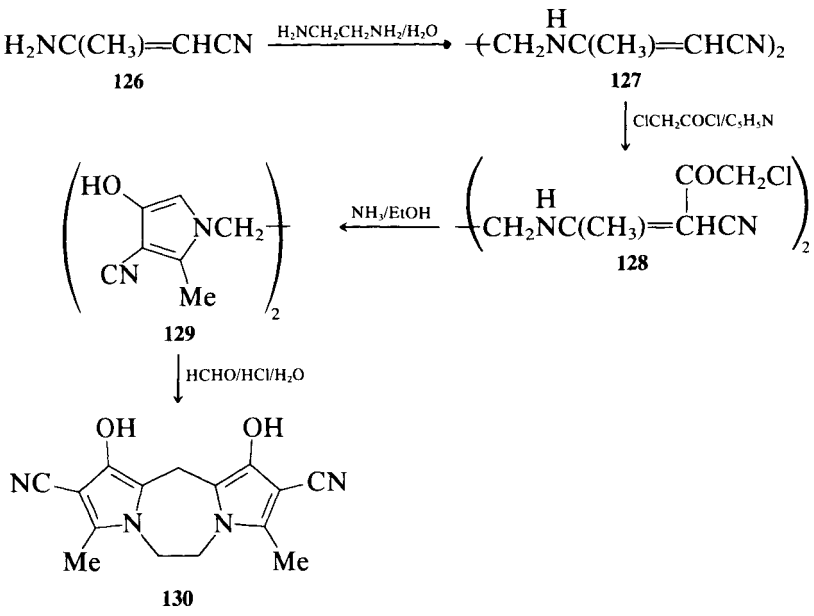
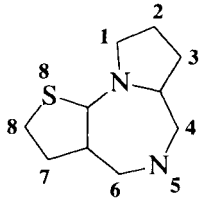



**Figure 8**

considered to be the dipyrrole **129**. Treatment of an aqueous solution of **129** with formaldehyde solution and dilute hydrochloric acid gave a red-brown precipitate which could not be recrystallized and was formulated as the tricyclic diazepine **130**. As no analytic data were provided for **129** and only a nitrogen analysis for **130**, the validity of this synthesis is obviously open to question.

### 16. Pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepines (see Section XIV.11)




The synthesis of this tricyclic system is outlined in Fig. 9. Phthalimidomethylfurans **131** were treated with bromine in methanol to give the dihydrofurans **132**. Hydrolysis followed by hydrogenation over Raney nickel afforded the 1,4-diketones **134**. Condensation of **134** with 2-amino-3-benzoylthiophenes **135** yielded the pyrrolylthiophenes **136**, which were fully characterized. Removal of the phthaloyl groups and ring closure with hydrazine in refluxing ethanol was accompanied by ring closure to the diazepines **137**. Tricyclic diazepines **137** prepared in this fashion (57) are listed in Table 16.

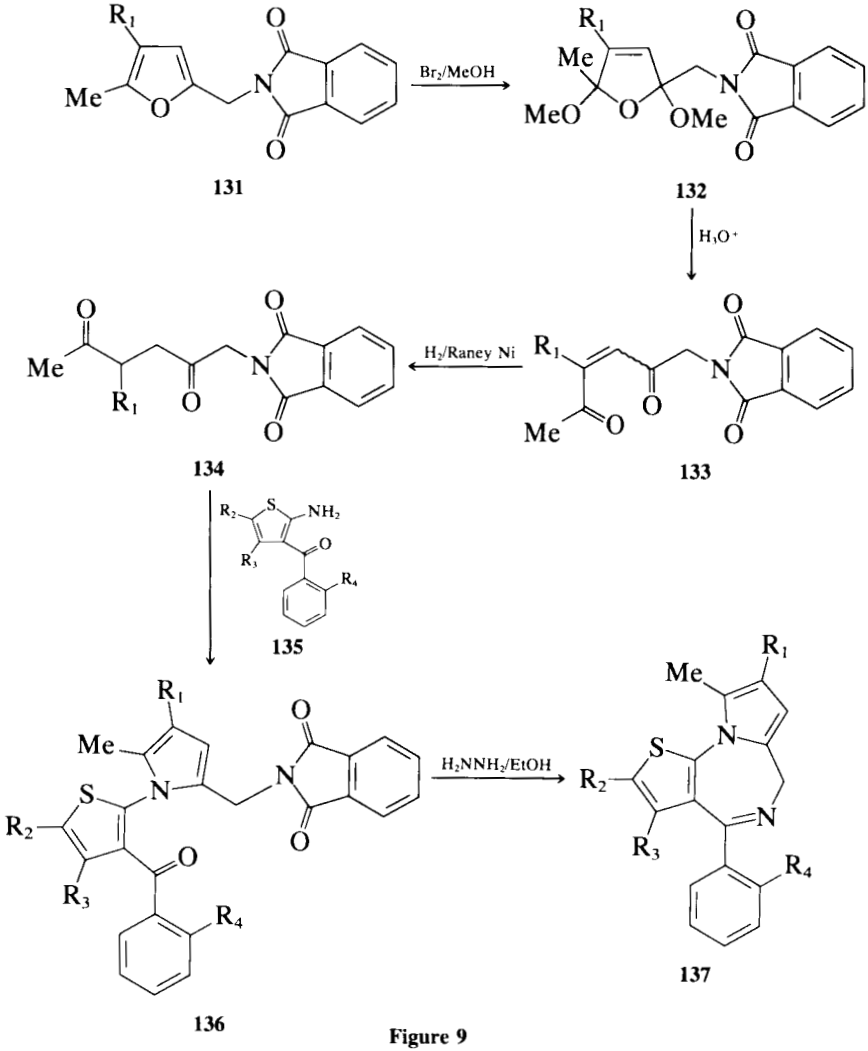
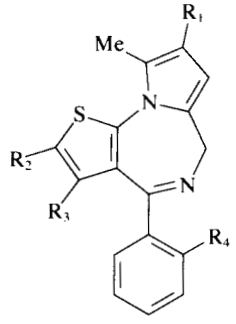



**Figure 9**

TABLE 16. PYRROLO[1,2-*a*]THIENO[3,2-*f*][1,4]DIAZEPINES

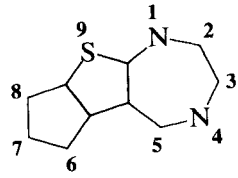


*(continued)*

TABLE 16. (*Continued*)

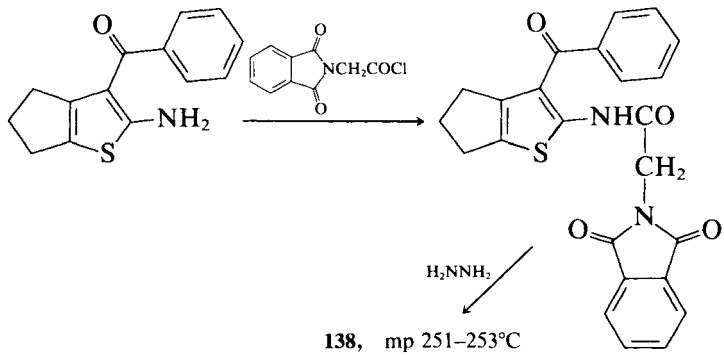
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | mp (°C) | Spectra |
|---|---|---|---|---|---|---|
| H | Me | Me | H | 84 | 154–155 | nmr, ms |
| H | Et | H | H | 79 | 103.5–104 | nmr, ms |
| Me | Me | Me | H | 65 | 173–174 | nmr, ms |
| Me | Me | Me | Cl | 57 | 125–127 | nmr, ms, ir |
| H | Me | Me | Cl | 54 | 151–152 | nmr, ms |

## 17. Cyclopenta[4,5]thieno[2,3-*e*][1,4]diazepines




Although only one cyclopenta[4,5]thieno[2,3-*e*]diazepine has been described in the literature, it has been prepared independently by two groups. The first synthesis (58) (Fig. 10) started with the preparation of the aminobenzoylthiophene by the Gewald procedure (59). This substance was converted to the aminoacetyl derivative either by condensation with benzyloxycarbonylaminoacetyl chloride followed by deprotection with hydrogen bromide in acetic acid, or by reaction with chloroacetyl chloride followed by treatment with ammonia in chloroform/methanol. Cyclization was achieved with acetic acid in pyridine/benzene under reflux.

The second synthesis (60) proceeded by way of very similar intermediates (Eq. 27). In this case the phthalimidoacetyl derivative was prepared from the corresponding acid chloride. Hydrazinolysis gave the cyclopentathienodiazepinone. The substance was reported to have marginal antianxiety and moderate anticonvulsant activity (60).




(27)

**138**, mp 251–253°C

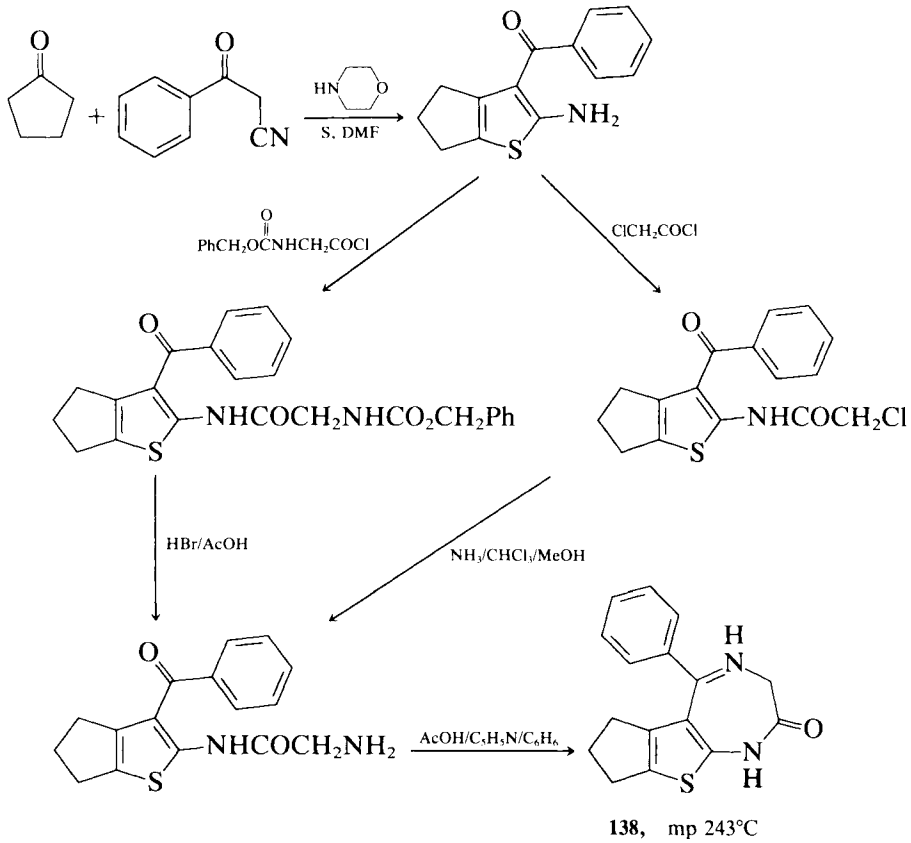
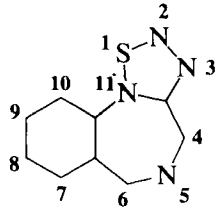



**Figure 10**

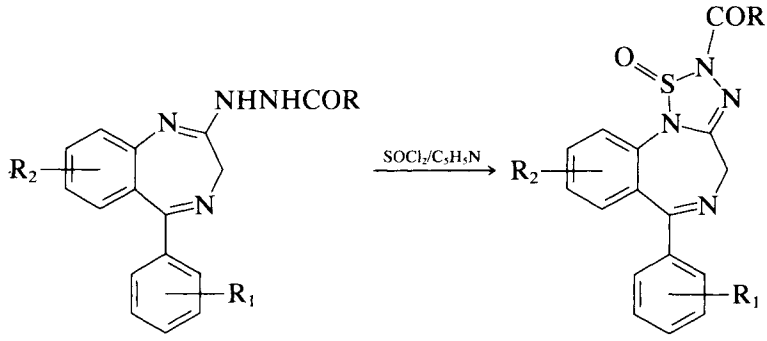
## VI. 5,6,7-SYSTEMS

### 1. [1,2,3,5]Thiatriazolo[5,4-*a*][1,4]benzodiazepines




Reaction of substituted benzodiazepin-2-yl hydrazides (**139**) with thionyl chloride (Eq. 28) produced the corresponding thiatriazolobenzodiazepines

(**140**), which are claimed to be useful as sedatives and tranquilizers. The starting acyl hydrazide was prepared by acylation of the hydrazine with acetic or propionic anhydride or by the reaction of 1,4-benzodiazepine-2-thiones with carboxylic acid hydrazides. The products are listed in Table 17 (61).

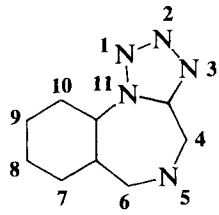



**139** **140** (28)

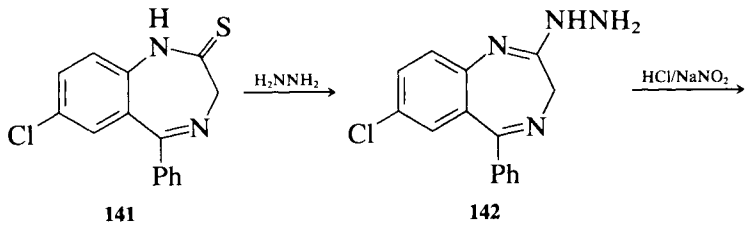
TABLE 17. [1,2,3,5]THIATRIAZOLO[5,4-*a*][1,4]BENZODIAZEPINES (**140**)

| $R_1$ | $R_2$ | $R_3$ | mp (°C) |
|---|---|---|---|
| Me | H | 8-Cl | 160.6–161.5 |
| Me | *o*-Cl | 8-Cl | 162–165 |

## 2. Tetrazolo[1,5-*a*][1,4]benzodiazepines

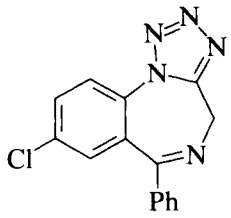


The synthesis of these tricyclic diazepines was achieved from the corresponding bicyclic benzodiazepines. As shown in Eq. 29, addition of hydrazine to thione **141** led to 2-hydrazinylbenzodiazepine **142**. Treatment of this hydrazine in dilute aqueous hydrochloric acid at 0°C with sodium nitrite led to nitrosation followed by cyclization to tetrazole **143** in 80% yield. Compounds of this class are claimed to have sedative, tranquilizing, and muscle relaxant effects (62).



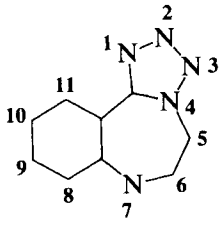

141 142

(29)



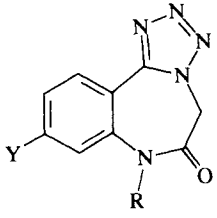

**143,** mp 178.5–180°C

### 3. Tetrazolo[1,5-*d*][1,4]benzodiazepines (see Section XV.2)



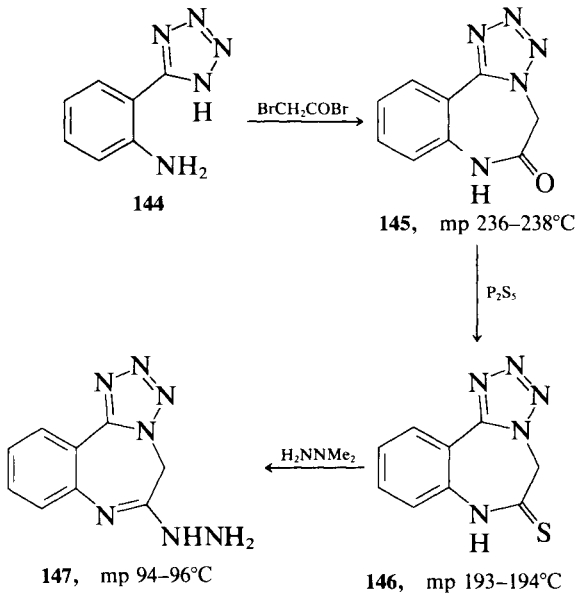

Tetrazolo[1,5-*d*][1,4]benzodiazepines were prepared as exemplified in Eq. 30. Reaction of *o*-aminobenzonitrile with sodium azide afforded tetrazole

TABLE 18. TETRAZOLO[1,5-*d*][1,4]BENZODIAZEPINES




| Y | R | Yield (%) | mp (°C) | Spectra |
|---|---|---|---|---|
| MeO | H | 20 | 239–241 | ir, nmr, ms |
| $CF_3$ | H | 25 | 266–277 | ir, nmr, ms |
| H | Ph | 68 | 176–179 | ir, nmr, ms |

**144**. Acylation of **144** with bromoacetyl bromide resulted in cyclization to the lactam **145**. Other, similarly prepared, members of this group are listed in Table 18. Benzodiazepine **145** was further elaborated to the dimethylhydrazino adduct **147** via thione **146** (63).




**144**

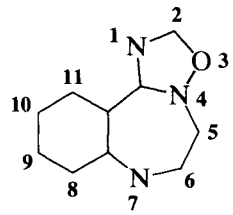
**145**, mp 236–238°C

**147**, mp 94–96°C

**146**, mp 193–194°C

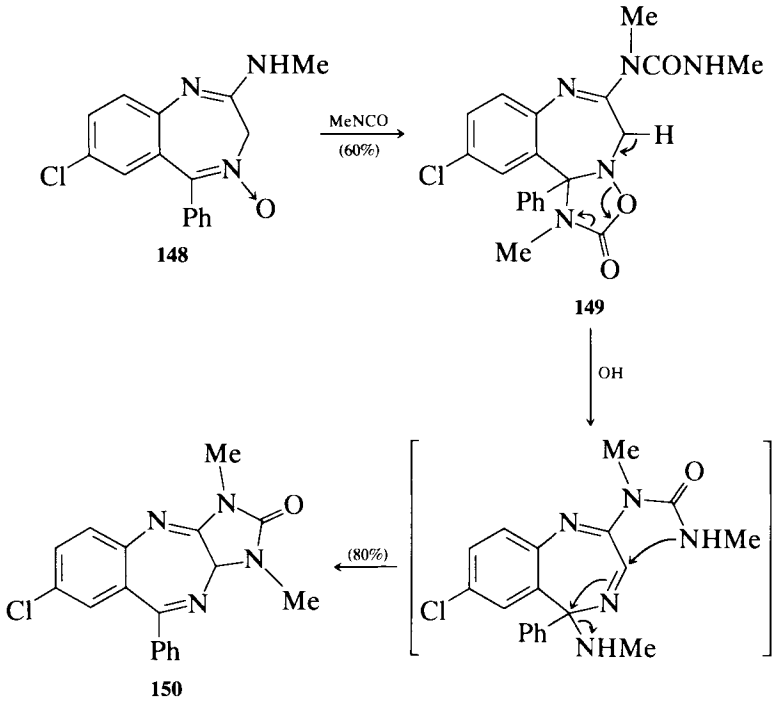
(30)

## 4. [1,2,4]Oxadiazolo[2,3-*d*][1,4]benzodiazepines



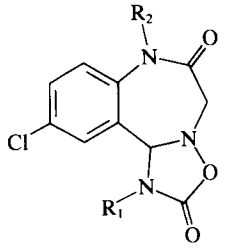

Addition of excess methyl isocyanate to chlordiazepoxide (**148**) led to facile 1,3-addition to the nitrone with simultaneous urea formation. The product, identified on the basis of spectral data as oxadiazole **149**, was unstable on standing or in the presence of base and rearranged to **150** with a net loss of carbon dioxide and methylamine (Eq. 31). Another possible mechanism, involving a Polonovski rearrangement with 7-chloro-3-hydroxy-2-*N*-methylamino-5-phenyl-3H-[1,4]-benzodiazepine as an intermediate, was ruled out by the independent synthesis of this compound and its subsequent reaction with methyl isocyanate, which failed to produce compound **150**.

To establish the generality of the oxadiazole ring formation of **149** and to characterize this class of products, several other 1,3-additions to similar nitrones were carried out. The products, listed in Table 19, were obtained in good yields and had consistent spectral properties (64).



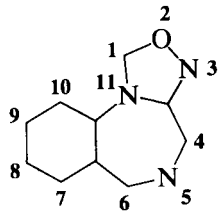

(31)

TABLE 19. [1,2,4]OXADIAZOLO[2,3-*d*][1,4]BENZODIAZEPINES

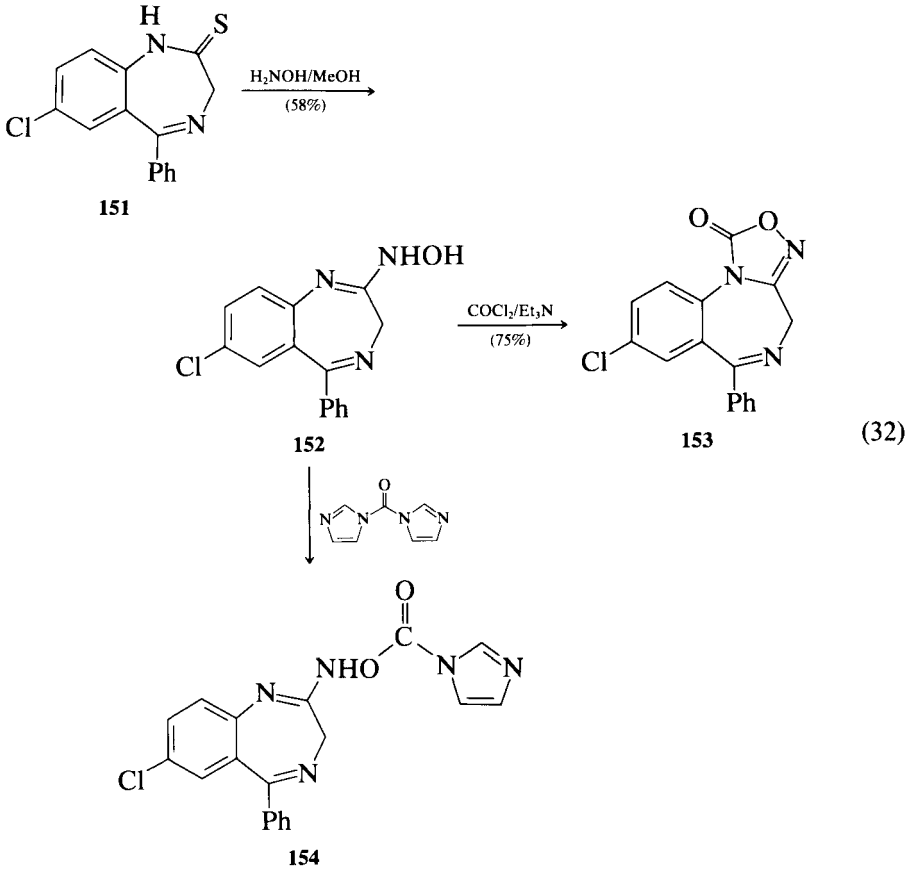



| $R_1$ | $R_2$ | Yield (%) |
|---|---|---|
| Me | H | 41 |
| Me | CONHMe | 50 |
| Me | Me | 97 |
| $CH_2CO_2Et$ | Me | 95 |

## 5. [1,2,4]Oxadiazolo[4,3-*a*][1,4]benzodiazepines



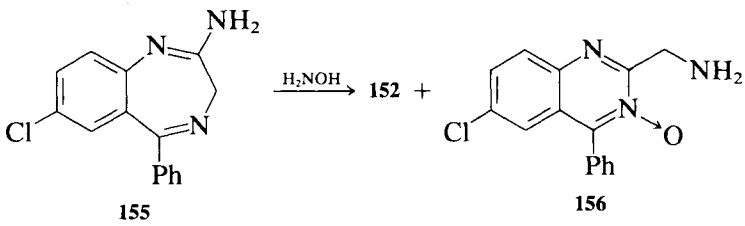

Hester (65,66) described the synthesis of [1,2,4]oxadiazolo[4,3-*a*]-benzodiazepines starting with thione **151.** The 2-hydroxyamino compound **152** (mp 126–130°C) was synthesized in 58% yield by treatment of **151** with hydroxylamine and sodium bicarbonate in refluxing methanol for 1.5 hr. Condensation of **152** with phosgene in the presence of triethylamine gave oxadiazole **153** (mp 191–192°C) in 75% yield (Eq. 32). The structure was




151 152 153 154 (32)

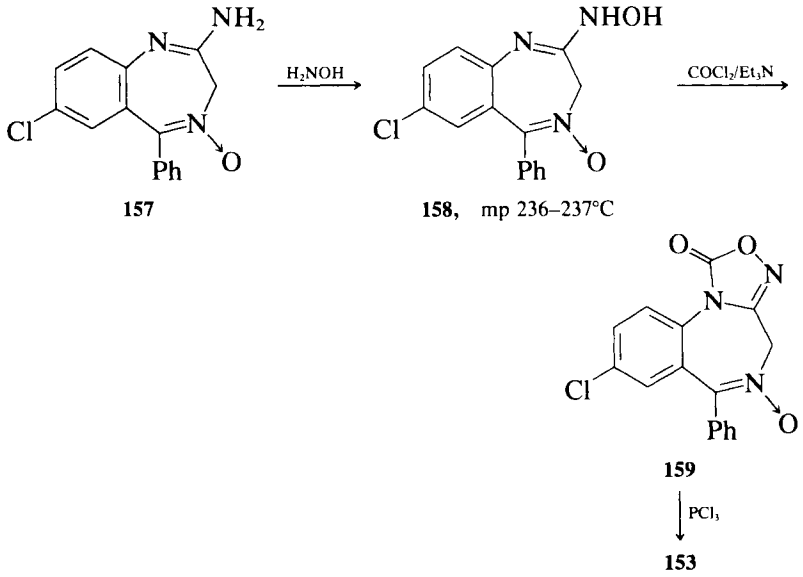
supported by ultraviolet ($\lambda_{max} = 226$ nm, $\epsilon = 31{,}200$), infrared (1795 (sh), 1770, and 1725 $cm^{-1}$), and nmr ($\delta$ 4.93, br s, 2, $C_4$) spectral data. Reaction of hydroxylamine **152** with carbonyldiimidazole in place of phosgene gave the uncyclized imidazole **154** instead of **153** (65,66).

Meguro et al. (67) also prepared hydroxylamine **152** while studying reactions of 2-amino[1,4]benzodiazepines with primary amines and hydroxylamines. Reaction of 2-amino derivative **155** with hydroxylamine at 0°C produced **152** in 70% yield (Eq. 33) as well as quinazoline oxide **156** as a minor product (10% yield).




**155** **156** (33)

The product to which Meguro et al. assigned structure **152** had a melting point of 136–138°C (instead of 126–130°C). The structure was verified by its mass spectrum ($M^+ = 285$), a positive ferric chloride test, and the formation of an *O*-acetate (ir peak at 1750 $cm^{-1}$). Reaction with *N*,*N*′-carbonylbis(2-methylimidazole) led to the tricyclic diazepine **153** in 69% yield. This compound had a melting point of 151–152°C (instead of 191–192°C). The infrared spectrum contained carbonyl absorption of 1775 $cm^{-1}$. Interestingly, Hester




**157** **158**, mp 236–237°C

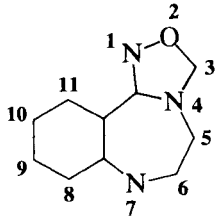
**159**

**153** (34)

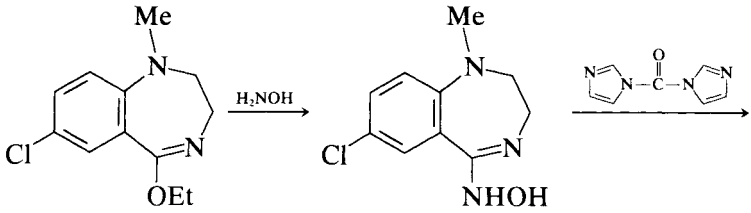
found no oxadiazole formation from **152** using carbonyldiimidazole. The discrepancies in melting point data for **152** and **153** appear to reflect the state of purity of the respective products.

When the same sequence of reactions was applied to the $N^4$-oxide **157**, the intermediate hydroxylamine **158** (Eq. 34) underwent cyclization with phosgene to the tricyclic compound **159** in 80% yield. Reduction of *N*-oxide **159** with phosphorus trichloride in refluxing chloroform for 20 min produced **153**, which by this route had a melting point of 145–147°C (67).

### 6. [1,2,4]Oxadiazolo[4,3-*d*][1,4]benzodiazepines

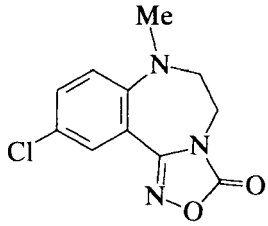



In a study of additions to $C_5$ of [1,4]benzodiazepines, nucleophiles were added to benzodiazepine **160,** which was available by alkylation of the corresponding amide with triethyloxonium fluoroborate. Addition of hydroxylamine to **160** (Eq. 35) in refluxing ethanol gave the 5-hydroxyaminobenzodiazepine **161**, which was condensed with carbonyldiimidazole in refluxing THF to give the oxadiazolobenzodiazepine **162.** The products were identified by elemental analysis as well as ir, uv, and nmr spectral data (68).



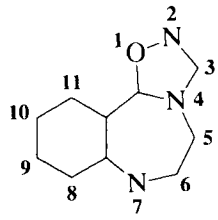

**160** **161,** mp 187–189°C

(35)

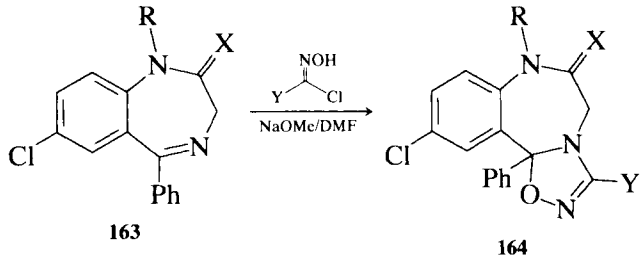



**162,** mp 190–191°C

## 7. [1,2,4]Oxadiazolo[4,5-*d*][1,4]benzodiazepines

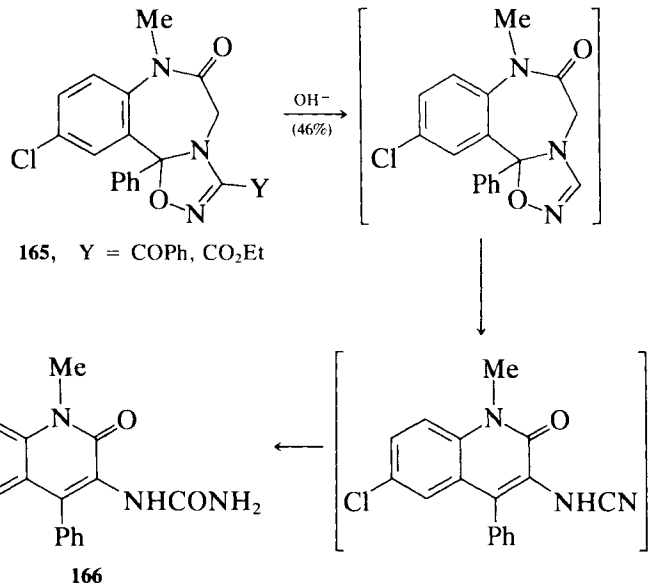


Diazepines of general structure **164** were prepared by 1,3-dipolar cycloaddition of nitrile oxides to 1,4-benzodiazepines (Eq. 36). In refluxing 1 *N* sodium hydroxide, compound **165** rearranged, as shown in Eq. 37, to quinoline **166.** Compound **167** could be reduced with 1.5 or 5 equivalents of



(36)

**163** **164**

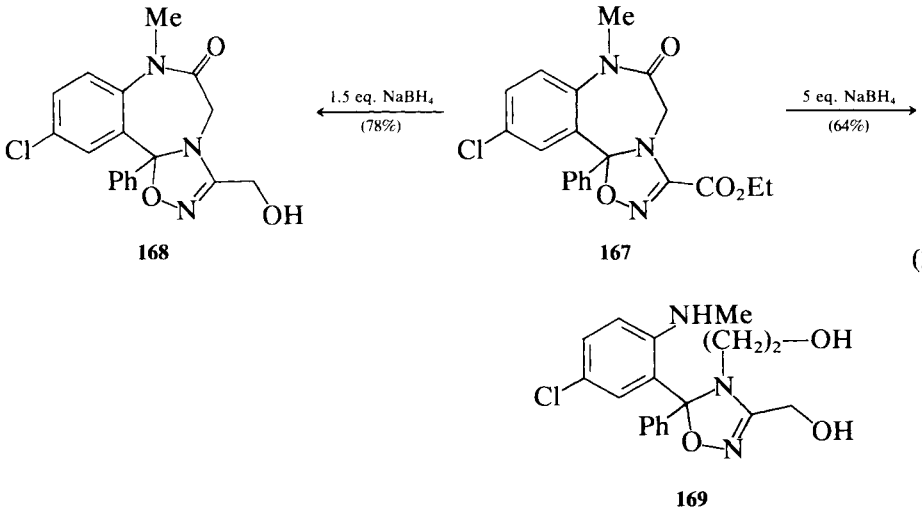


**165**, Y = COPh, $CO_2Et$

(37)

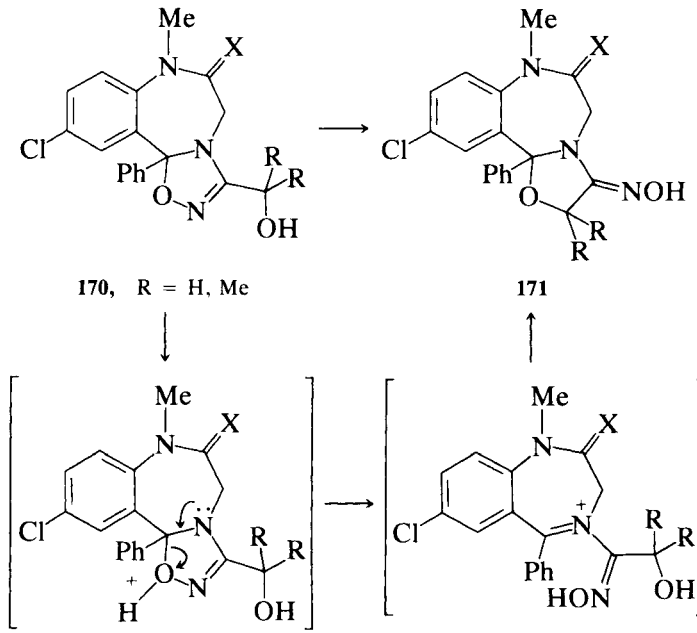
**166**

sodium borohydride to **168** or **169,** respectively (Eq. 38). Treatment of **170** with 2% sulfuric acid led to the rearranged oxazole derivative **171** (Eq. 39). Specific examples of this ring system are listed in Table 20 (69).



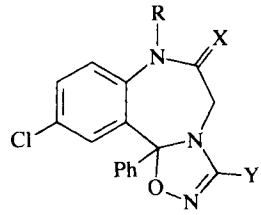

**168** **167** (38)

**169**



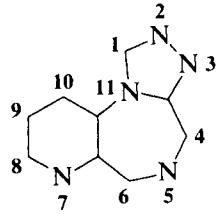

**170,** R = H, Me **171** (39)

TABLE 20. OXADIAZOLO[4,5-*d*][1,4]BENZODIAZEPINES

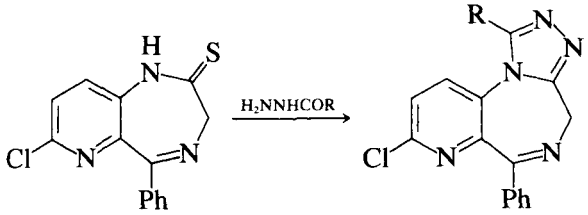


| R | X | Y | Yield (%) | mp (°C) |
|---|---|---|---|---|
| H | O | Ph | 53 | 245–247 |
| Me | O | Ph | 51 | 237–239 |
| Me | $H_2$ | Ph | 77 | 146–148 |
| H | O | COPh | 33 | 198–200 |
| Me | O | COPh | 44 | 193–195 |
| Me | $H_2$ | COPh | 73 | 135–137 |
| H | O | $CMe_3$ | 32 | 260–262 |
| Me | O | $CMe_3$ | 54 | 193–194 |
| H | O | $CO_2Et$ | 43 | 211–213 |
| Me | O | $CO_2Et$ | 59 | 178–180 |
| Me | $H_2$ | $CO_2Et$ | 55 | 92–94 |
| Me | O | $CH_2OH$ | 77 | 232–234 |
| Me | O | $CH_2OCOPh$ | 87 | 185–186 |
| H | O | $CH_2OH$ | 47 | 209–211 |
| H | O | $CH_2OCOPh$ | — | 169–171 |
| H | $H_2$ | $CH_2OH$ | 78 | 126–128 |
| H | $H_2$ | $CH_2OCOPh$ | — | 98–100 |
| Me | $H_2$ | $COHMe_2$ | 71 | 179–181 |
| Me | $H_2$ | CHOHPh | 83 | 165–169 |

## 8. Pyrido[2,3-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepines (see Section XV.5)



Pyrido[2,3-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepines, which are analogs of the extensively studied triazolobenzodiazepine system, were prepared by reaction of acyl hydrazides with thione **172** to give **173**, as shown in Eq. 40 (70).

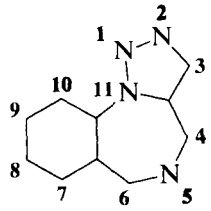



(40)

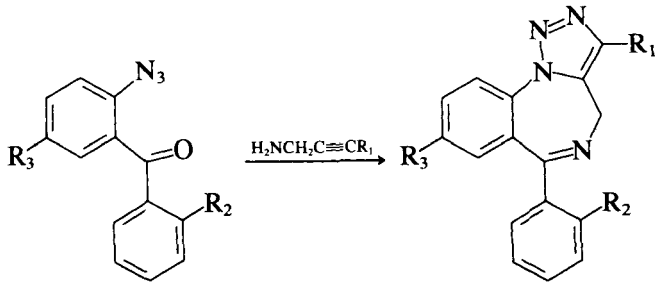
**172**

**173a**, R = Me; mp 258–260°C
**173b**, R = Ph; mp 246°C

## 9. [1,2,3]Triazolo[1,5-*a*][1,4]benzodiazepines



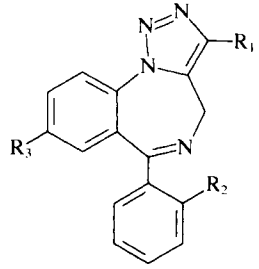

Several syntheses of [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepines, which are patented as tranquilizers, have been described. Compounds of general structure **175** were formed by treatment of 2-azidobenzophenones (**174**) with 1-amino-2-alkynes in the presence of acidic catalysts (Eq. 41). The reaction proceeds via imine formation and concomitant 1,3-cycloaddition of the azide to the alkyne. In this way triazolobenzodiazepines substituted at the 3-position with H, $CH_2OH$, $CH_2NH_2$, and $CH_2NMe_2$ were constructed (Table 21, Nos. 1–9). The hydroxymethyl compounds (Nos. 1, 6, and 8) were transformed further to the corresponding *N,N*-dimethylamides by oxidation of the alcohol to the aldehyde with manganese dioxide followed directly by




(41)

**174** **175**

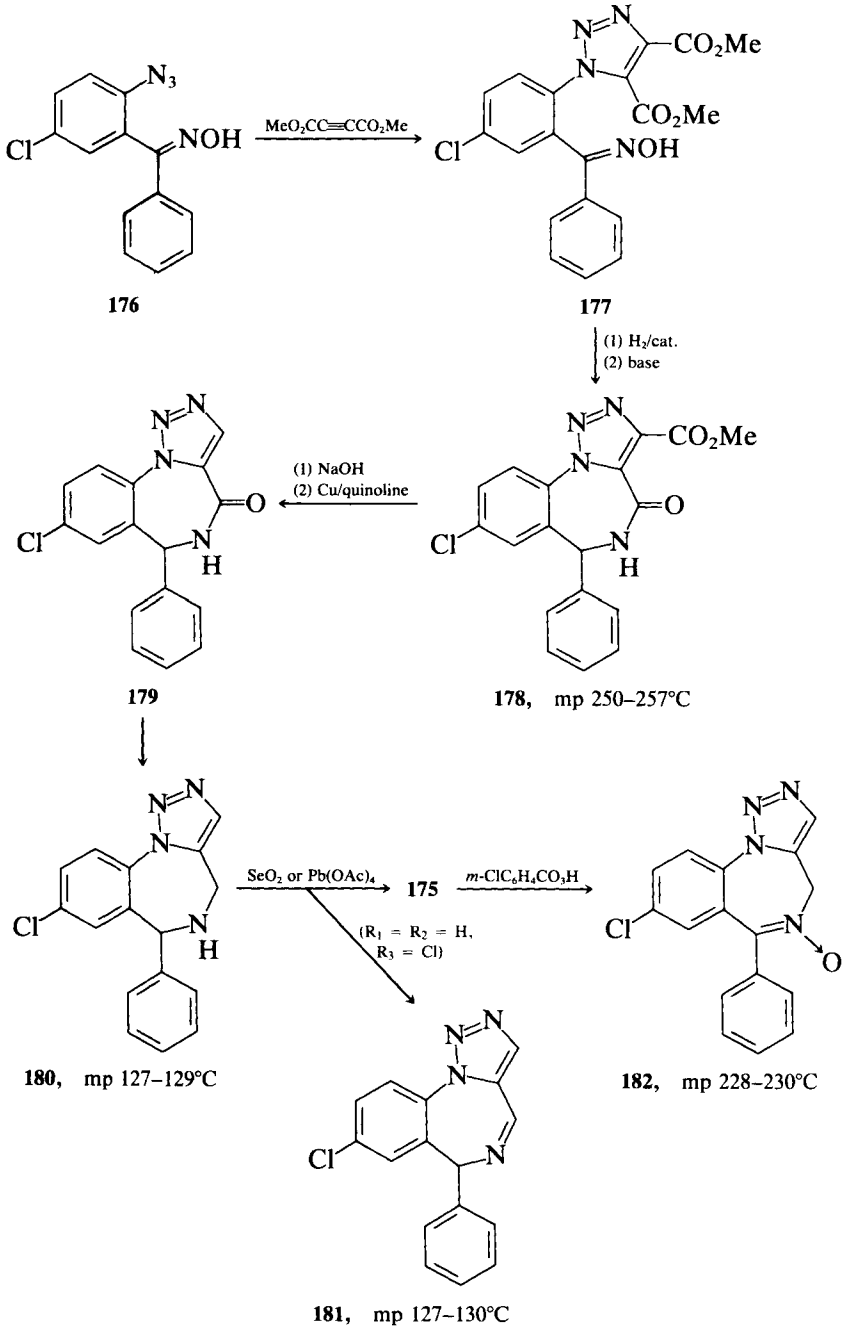
TABLE 21. [1,2,3]TRIAZOLO[1,5-*a*][1,4]BENZODIAZEPINES



| No. | $R_1$ | $R_2$ | $R_3$ | mp (°C) |
|---|---|---|---|---|
| 1 | $CH_2OH$ | H | Cl | 183–184 |
| 2 | H | H | Cl | 159–162 |
| 3 | $CH_2NH_2$ | H | Cl | 164–169 |
| 4 | $CH_2NMe_2$ | H | Cl | 150–152 |
| 5 | H | Cl | Cl | 196–198 |
| 6 | $CH_2OH$ | Cl | Cl | 144–148 |
| 7 | H | F | Cl | 194–196 |
| 8 | $CH_2OH$ | F | Cl | 172–173 |
| 9 | H | H | $NO_2$ | 204–207 |
| 10 | $CO_2Me$ | H | Cl | 205–207 |
| 11 | COOH | H | Cl | 178 |
| 12 | $CONMe_2$ | H | Cl | 208–210 |
| 13 | $CONMe_2$ | Cl | Cl | 178–180 |
| 14 | $CONMe_2$ | F | Cl | 183–185 |

reaction with sodium cyanide, manganese dioxide, and dimethylamine (Nos. 12–14). This transformation was also carried out in stepwise fashion by oxidation of the aldehyde to an ester, hydrolysis to the acid, reaction with thionyl chloride to give the acid chloride, and addition of dimethylamine.

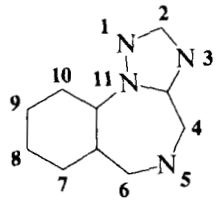
An alternative synthesis of this class of tricyclic diazepines is exemplified by cycloaddition of acetylene dicarboxylic acid dimethyl ester to 2-azidobenzophenone oxime (**176**), as shown in Fig. 11. The resulting triazole (**177**) was reduced with hydrogen (oxime to amine) and then cyclized with base to the triazololactam **178.** Decarboxylation of the triazolo ester to triazole **179** followed by lactam reduction led to amine **180.** Finally, dehydrogenation afforded the desired diazepine **175,** identical to the product synthesized by the previous route. Dehydrogenation to **175** was accomplished with selenium dioxide, manganese dioxide, sodium dichromate, or lead tetraacetate. In most instances the oxidation was not regiospecific and resulted in the 6H-diazepine **181** as well as the 4H-diazepine **175.** The mixture could be isomerized to the more stable 4H compound by treatment with DBN or potassium *t*-butoxide. In addition, diazepine **175** could be further oxidized to the $N^5$-oxide **182** by treatment with *m*-chloroperbenzoic acid (71).



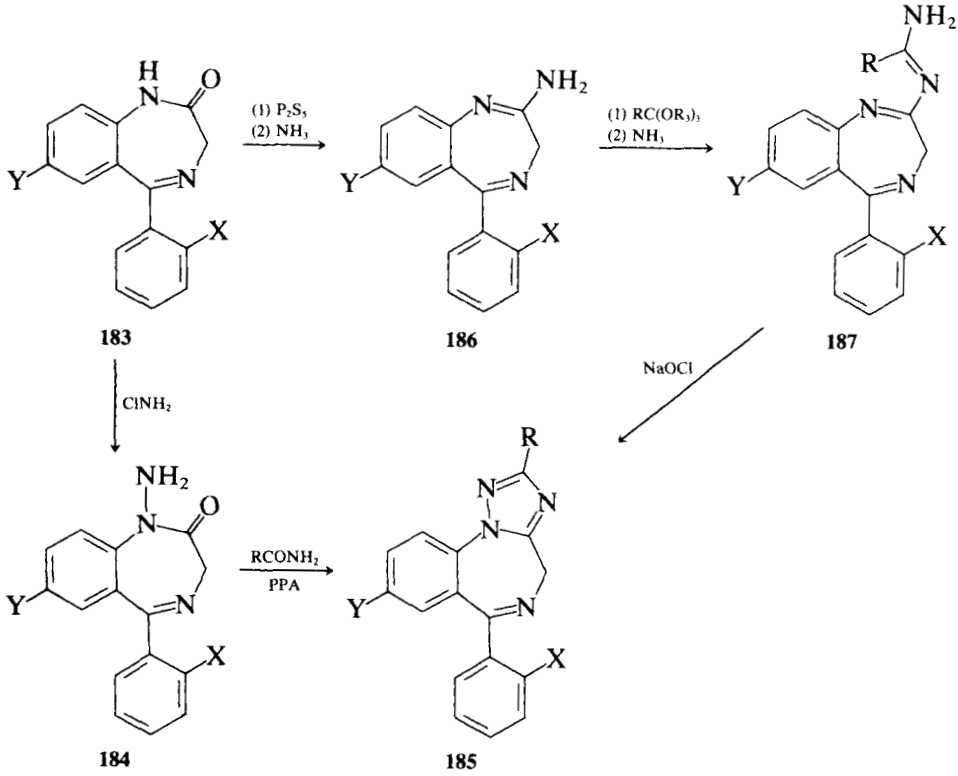

**176** **177** **179** **178,** mp 250–257°C **180,** mp 127–129°C **181,** mp 127–130°C **182,** mp 228–230°C

**Figure 11**

## 10. [1,2,4]Triazolo[1,5-*a*][1,4]benzodiazepines (see Section XV.6)




[1,2,4]Triazolo[1,5-*a*][1,4]benzodiazepines are patented for their sedative, muscle relaxant, anticonvulsant, and hypnotic effects. Several synthetic approaches to this ring system have appeared. One process (Eq. 42) involves fusion of the triazole ring to the benzodiazepine substrate **183** (72). Amination of **183** with sodium hydride and chloroamine yields **184,** which, in the presence of an acid catalyst, combines with amides to generate the triazole **185.** A related sequence converts 2-aminobenzodiazepine **186** to **187** by stepwise treatment with an orthoester and ammonia. Oxidative cyclization of **187** in the presence of lead tetraacetate or sodium hypochlorite yields **185.** Starting




(42)

with the $N^4$-oxide of **186** (X = H, Y = Cl) and trimethyl orthoacetate as the cyclization reagent, this route afforded the corresponding $N^5$-oxide of **185** (mp 220–221°C), which was converted to **185** (R = Me) by reduction with phosphorus trichloride (73).

Another pathway leading to this ring system is illustrated in Fig. 12 (74–

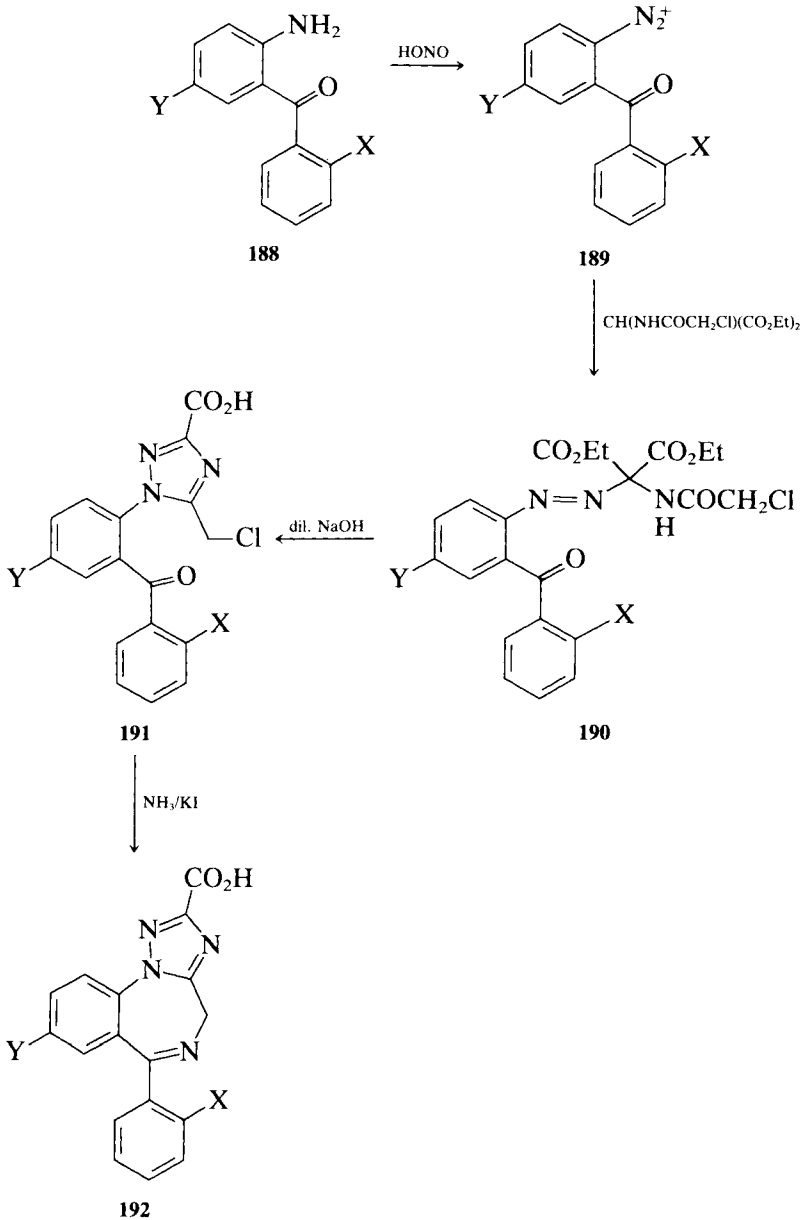



**Figure 12**

77). Conversion of benzophenone derivative **188** to the diazonium chloride **189,** followed by addition of diethyl chloroacetamidomalonate, produced the azo compound **190.** Ring closure of **190** to triazole **191** with simultaneous removal of one carbethoxy group was carried out with excess sodium hydroxide. During the reaction the remaining ester likewise underwent hydrolysis. However, if the reaction was carried out at room temperature with two equivalents of hydroxide, the remaining ester was not disturbed. The final cyclization of **191** to diazepine **192** was achieved with potassium iodide and ammonia.

Compound **192** proved to be a versatile intermediate for the synthesis of other 2-substituted derivatives (Fig. 13). Decarboxylation of **192** with cuprous oxide led to the unsubstituted triazole **185** (R = H) (72). Formation of the acid chloride of **192** followed by addition of sodium azide produced the corresponding acyl azide, which on thermolysis and aqueous workup afforded the 2-amino derivatives **193** (75). By conducting the Curtius reaction in the presence of an alcohol, the 2-carbamates **194** were formed (74). Re-

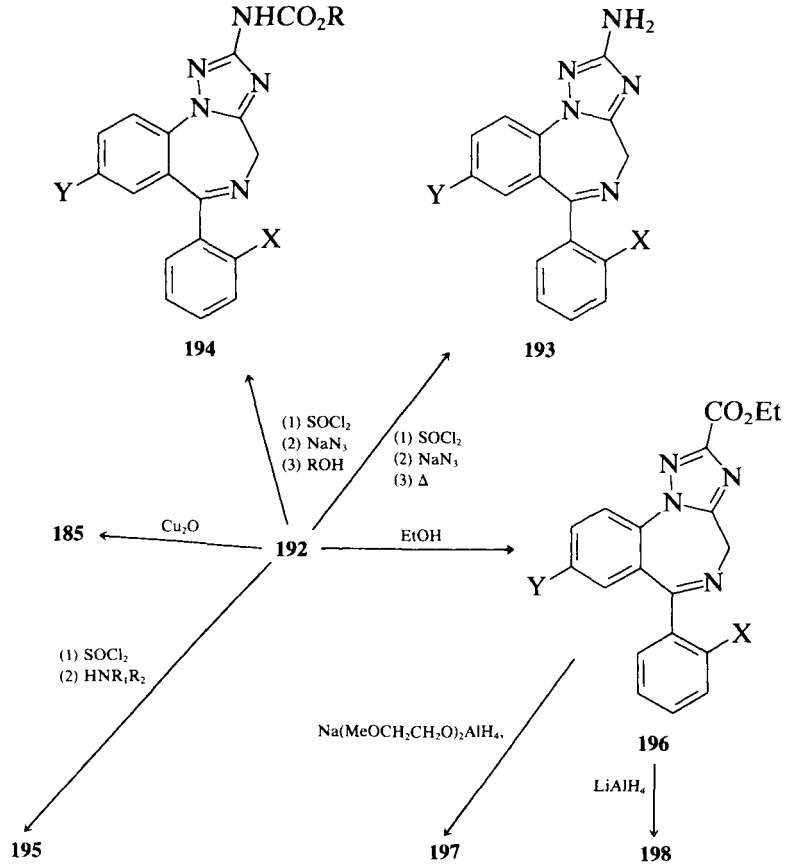



**Figure 13** (*cont'd on next page*)

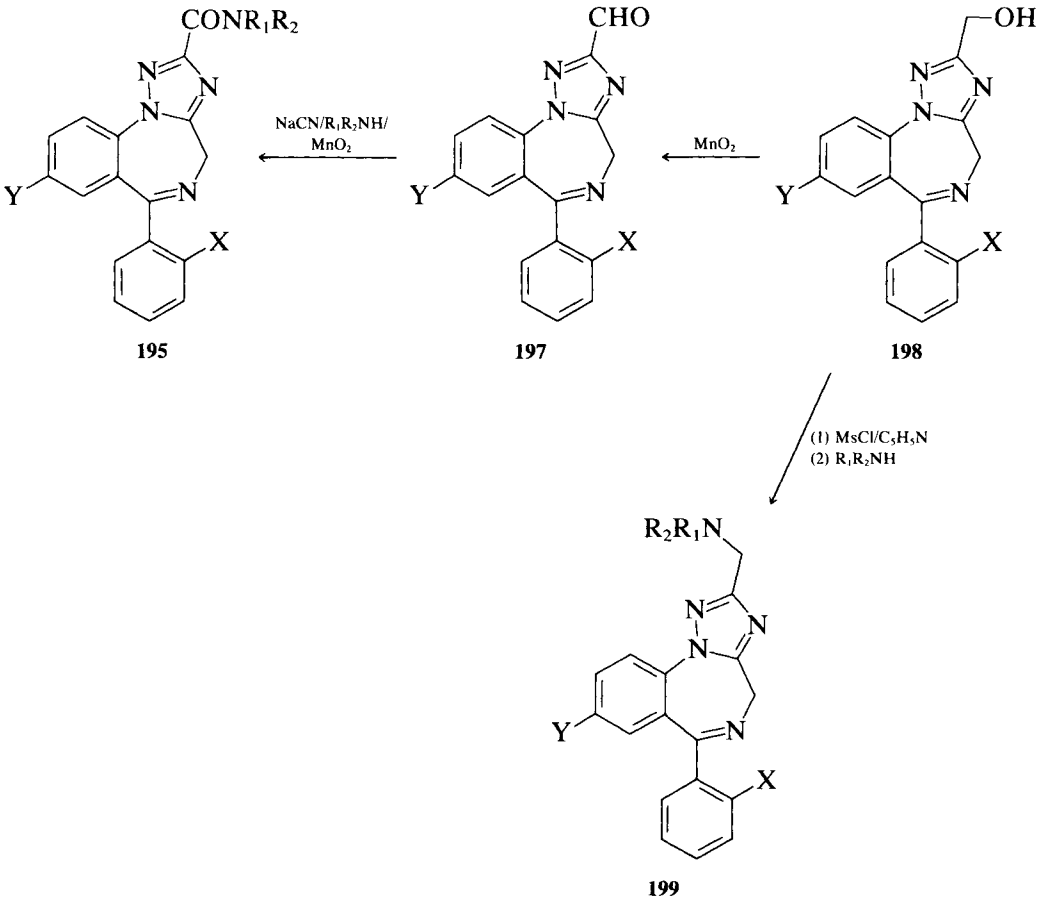
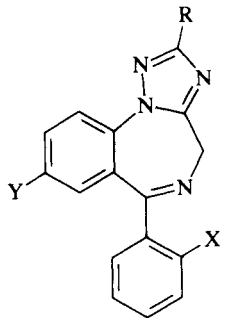



**Figure 13** (*continued*)

action of the acid chloride of **192** with amines generated the amides **195** (76). These amides could also be prepared via the 2-carboxaldehydes **197,** which were made directly from the esters **196** by reduction with sodium bis(ethoxymethoxy)aluminum hydride in toluene at −70°C for 15 min or in two steps by reduction of **196** with $LiAlH_4$ to alcohol **198** followed by oxidation with manganese dioxide to **197** (76,79). In the presence of sodium cyanide, an amine, and activated manganese dioxide, the aldehyde **197** was oxidized directly to amide **195.**

Apart from its conversion to aldehyde **197,** hydroxymethyl intermediate **198** was also transformed into aminomethyl derivatives **199.** The synthesis of primary amino derivatives was carried out by mesylate formation, displacement of the mesylate with azide, and reduction of the azide function with alkaline stannous chloride (80). Substituted amines were obtained directly by mesylate displacement (81). The compounds prepared by these methods are listed in Table 22.

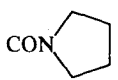
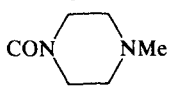
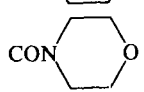
TABLE 22. [1,2,4]TRIAZOLO[1,5-*a*][1,4]BENZODIAZEPINES

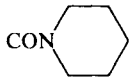
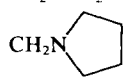
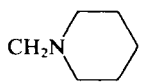
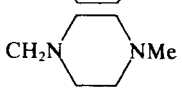
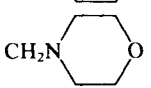



| R | X | Y | Salt | mp (°C) | Refs. |
|---|---|---|---|---|---|
| Me | H | Cl | | 164–166 | 72,73 |
| H | H | Cl | | 126–128 | 72,78 |
| H | Cl | Cl | | 175–177 | 72,78 |
| Me | H | $NO_2$ | | 170–171.5 | 73 |
| Me | H (*p*-MeO) | Cl | | 148–149 | 73 |
| COOH | H | Cl | | 170 | 74,75,78 |
| COOH | Cl | Cl | | 190–195 | 74 |
| COOH | F | Cl | | 179–182 | 74,77 |
| COOH | H | $CF_3$ | | 195 | 76 |
| COOH | H | $NO_2$ | | 208 | 76 |
| COOH | F | $NO_2$ | | 190 | 76 |
| $CO_2Et$ | F | Cl | | 177–179 | 74,77 |
| $CO_2Et$ | H | $CF_3$ | | 162–164 | 76 |
| $CO_2Et$ | H | $NO_2$ | | 145–147 | 76 |
| $CO_2Et$ | F | $NO_2$ | | 165–167 | 76 |
| $CO_2Et$ | Cl | Cl | | 211–213 | 76 |
| $CO_2Et$ | H | Cl | | 137–138 | 76 |

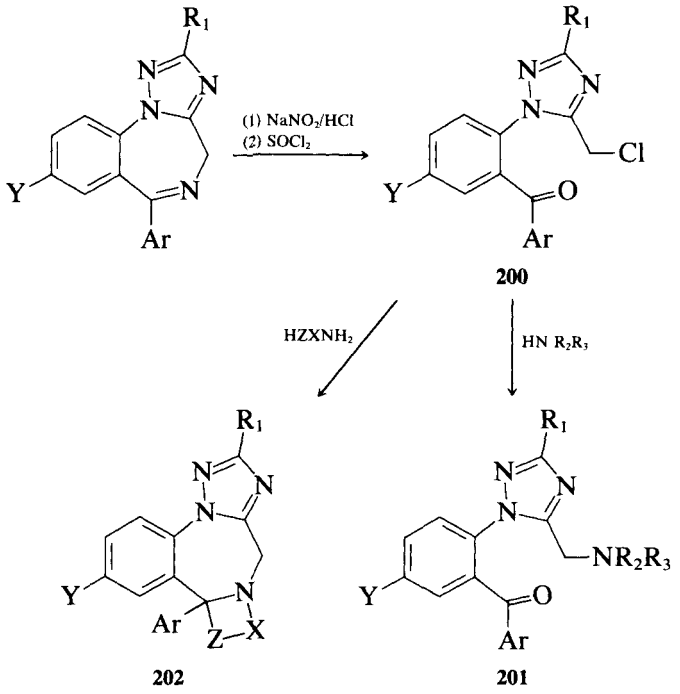
(*continued*)

TABLE 22. (*Continued*)

| R | X | Y | Salt | mp (°C) | Refs. |
|---|---|---|---|---|---|
| $CON_3$ | F | Cl | | 205–210 | 75 |
| $CON_3$ | Cl | Cl | | 144–148 | 75 |
| $NH_2$ | F | Cl | | 215–217 | 75 |
| $NH_2$ | Cl | Cl | | 183–188 | 75 |
| $NH_2$ | H | Cl | | 213–215 | 75 |
| $CON_3$ | H | Cl | | 130 | 75 |
| $CONH_2$ | H | Cl | | 252–254 | 76 |
| $CONMe_2$ | H | Cl | | 135–137 | 76 |
| $CONEt_2$ | H | Cl | | 175–177 | 76 |
| $CONH_2$ | Cl | Cl | | 283–285 | 76 |
| $CONMe_2$ | Cl | Cl | | 142–145 | 76 |
| CONHMe | Cl | Cl | | 211–213 | 76 |
| $CONEt_2$ | Cl | Cl | | 156–158 | 76 |
| $CONH_2$ | F | Cl | | 250–252 | 76 |
| $CONMe_2$ | F | Cl | | 180–182 | 76 |
| CONHMe | F | Cl | | 202–203 | 76 |
| $CONEt_2$ | F | Cl | | 200–202 | 76 |
| $CONMe_2$ | H | $CF_3$ | | 195–197 | 76 |
| $CONMe_2$ | H | $NO_2$ | | 209–211 | 76 |
| $CONMe_2$ | F | $NO_2$ | | 178–180 | 76 |
|  | F | Cl | | 202–204 | 76 |
|  | F | Cl | | 190–195 | 76 |
|  | F | Cl | | 180–182 | 76 |

| | | | | | |
|---|---|---|---|---|---|
|  | F | Cl | | 100–105 | 76 |
| CONHEt | F | Cl | | 232–234 | 76 |
| $CONHCH(CH_3)_2$ | F | Cl | | 255–258 | 76 |
| $CONHCH_2CH_2OH$ | F | Cl | | 236–240 | 76 |
| $CONH(CH_2)_3NMe_2$ | F | Cl | HCl | 160–165 | 76 |
| CHO | H | Cl | | 165–167 | 76 |
| $CH_2OH$ | H | Cl | | 185–186 | 76 |
| $CH_2OH$ | F | Cl | | 138–145 | 76 |
| $CH_2NH_2$ | H | Cl | | 69–75 | 76,80 |
| $CH_2NHMe$ | H | Cl | | 56–67 | 80 |
| $CH_2NH_2$ | Cl | Cl | Fumarate | 221–223 | 76 |
| $CH_2NHMe$ | Cl | Cl | Fumarate | 199–201 | 80 |
| $CH_2NH_2$ | F | Cl | HCl | 228–230 | 76 |
| $CH_2NHMe$ | F | Cl | HCl | 247–249 | 80 |
| NHCOMe | H | Cl | | 236–238 | 75 |
| $CH_2NMe_2$ | H | Cl | | 133–135 | 80 |
|  | H | Cl | | 53–63 | 80 |
|  | H | Cl | | 55–64 | 80 |
|  | H | Cl | | 162–163 | 80 |
|  | H | Cl | | 111–113 | 80 |

Several 6-(2-pyridyl) compounds were prepared as described above (Table 23). On treatment with sodium nitrite in 6 *N* HCl and subsequent reaction with thionyl chloride, these and several 6-phenyl derivatives yielded the chlorides **200.** Treatment of **200** with amines (Eq. 43) then gave the ring-cleaved products **201** (82). These compounds are listed in Table 24. The ring-opened chloride **200** could also be transformed into tetracyclic diazepine derivatives **202** by reaction with functionalized amines such as ethanolamine and ethylenediamine. The products are listed in Table 25 (83).




**200**

**202**

**201**

(43)

TABLE 23. [1,2,4]TRIAZOLO[1,5-*a*][1,4]BENZODIAZEPINES

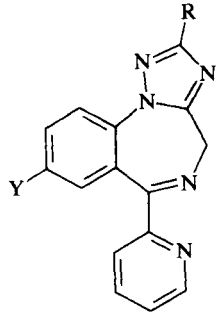
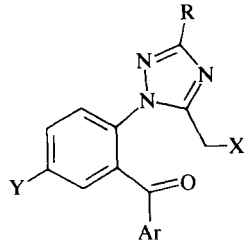
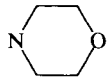
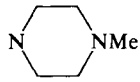


TABLE 23. (*Continued*)

| R | Y | mp (°C) | Refs. |
|---|---|---|---|
| Me | Br | 169–170 | 82 |
| Me | H | 143–144 | 82 |
| Et | Br | 164–166 | 82,83 |
| Me (*N*-oxide) | Br | 207–208 | 82 |
| Me (*N*-oxide) | H | 173–175 | 83 |
| Et (*N*-oxide) | Br | 204–205 | 83 |
| Me (*N*-oxide) | Br | 207–208 | 83 |

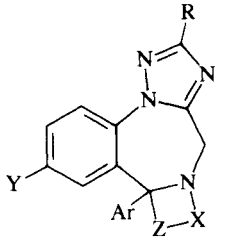
TABLE 24. RING-OPENED [1,2,4]TRIAZOLO[1,5-*a*][1,4]BENZODIAZEPINES[a]



| | Ar | X | Y | mp (°C) | Spectra |
|---|---|---|---|---|---|
| Me | Ph |  | Cl | 105–106 | |
| Et | 2-Pyridyl |  | Br | 130–131 | |
| Me | Ph | $NMe_2$ | Cl | 74–75 | |
| Et | 2-Pyridyl | $NMe_2$ | Br | | ir, nmr |

[a]Ref. 82.

TABLE 25. TETRACYCLIC [1,2,4]TRIAZOLO[1,5-*a*][1,4]BENZODIAZEPINES[a]



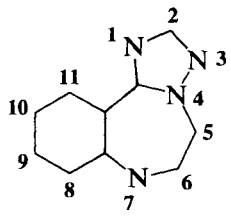
(*continued*)

TABLE 25. (*Continued*)

| R | Ar | Y | X | Z | mp (°C) |
|---|---|---|---|---|---|
| Me | Ph | Cl | $(CH_2)_2$ | O | 128–129 |
| Et | 2-Pyridyl | Br | $CH(CH_3)CH_2$ | O | 178–179 |
| Me | Ph | Cl | $CH_2CH_2$ | N | 159–161 |
| Me | Ph | Cl | $(CH_2)_3$ | O | 130–131 |
| Me | Ph | Cl | $CH(CH_3)CH_2$ | O | 168–170 |
| Et | 2-Pyridyl | Br | $CH_2CH_2$ | O | 148–149 |
| Et | 2-Pyridyl | Br | $(CH_2)_3$ | O | 119–120 |

[a]Ref. 83.

## 11. [1,2,4]Triazolo[1,5-*d*][1,4]benzodiazepines (see Section XV.7)




[1,2,4]Triazolo[1,5-*d*][1,4]benzodiazepines were prepared for their potential anxiolytic activity. One synthesis is portrayed in Fig. 14. Treatment of triazole **203** with bromoacetyl bromide led to **204,** which was cyclized to the diazepinone **205** in the presence of sodium ethoxide. Alkylation of **205** was also studied. Reaction of **205** (R = H, Y = Cl) with excess diazomethane for 18 hr afforded *N*-methylamide **206.** Alkylation of **205** with methyl iodide in the presence of sodium hydride was not specific and resulted in mixtures of **206, 207,** and **208.** Diazepinones that have been obtained by this sequence are listed in Table 26 (84).

Another entry into this ring system was achieved by starting from quin-

TABLE 26. [1,2,4]TRIAZOLO[1,5-*d*][1,4]BENZODIAZEPINES

| Structure | R | Y | mp (°C) | Refs. |
|---|---|---|---|---|
| **205** | H | Cl | 228–229 | 84,85 |
| **205** | H | H | 223–224 | 85 |
| **205** | Me | Cl | 255–258 | 84 |
| **206** | H | Cl | 140–144 | 84,85 |
| **206** | H | H | 212–216 | 85 |
| **206** | Me | Cl | 133–138 | 84 |
| **207** | H | Cl | 138–142 | 84 |
| **207** | Me | Cl | 130–135 | 84 |
| **208** | H | Cl | 173–174 | 84 |
| **208** | Me | Cl | 140–145 | 84 |

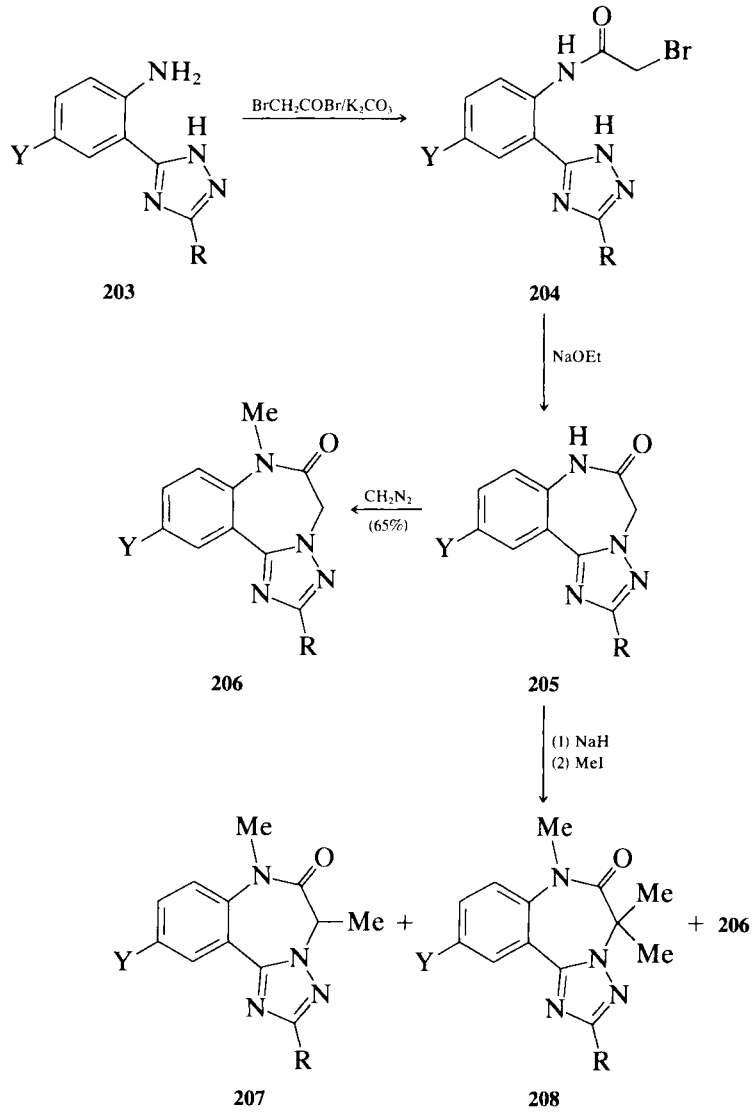



Figure 14

azoline **209.** Sequential treatment of **209** with hydrazine and triethyl orthoformate generated triazole **210** (Fig. 15). Rearrangement of **210** to the thermodynamically more stable triazole **211** was brought about by refluxing in ethylene glycol monomethyl ether. The final ring expansion of **211** with aqueous sodium hydroxide led to **205** as well as a minor amount of the isomer **212,** which might arise as illustrated in Fig. 15. Both **205** and **212** were methylated with methyl iodide and sodium methoxide to give **206** and **213,** respectively. Table 26 lists the compounds synthesized by this route (85).

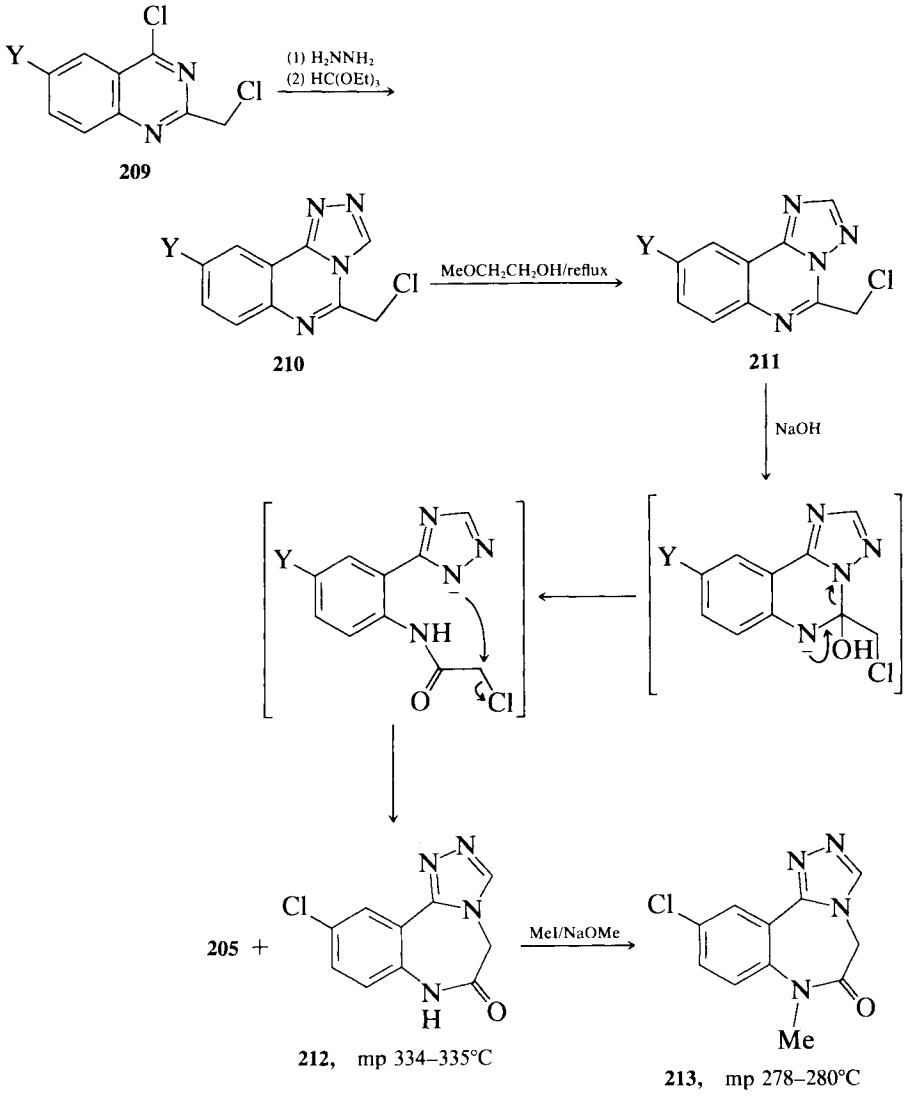
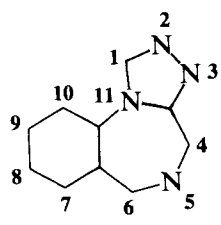
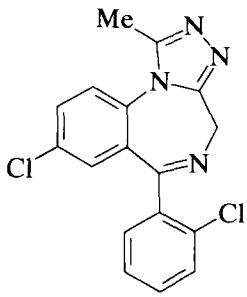



Figure 15

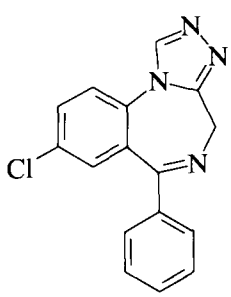
## 12. [1,2,4]Triazolo[4,3-*a*][1,4]benzodiazepines (see Section XV.8)



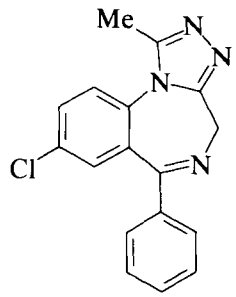
Since the discovery of their potent central nervous system activity, [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines have undergone extensive chemical investigation. Compounds of this general structure are patented as tranquilizers, muscle relaxants, anticonvulsants, sedatives, and hypnotics. One member, triazolam (**214**), was introduced in Belgium in 1978 as a hypnotic. In addition, estazolam (**215**) and alprazolam (**216**) are currently undergoing clinical studies.



**214**



**215**



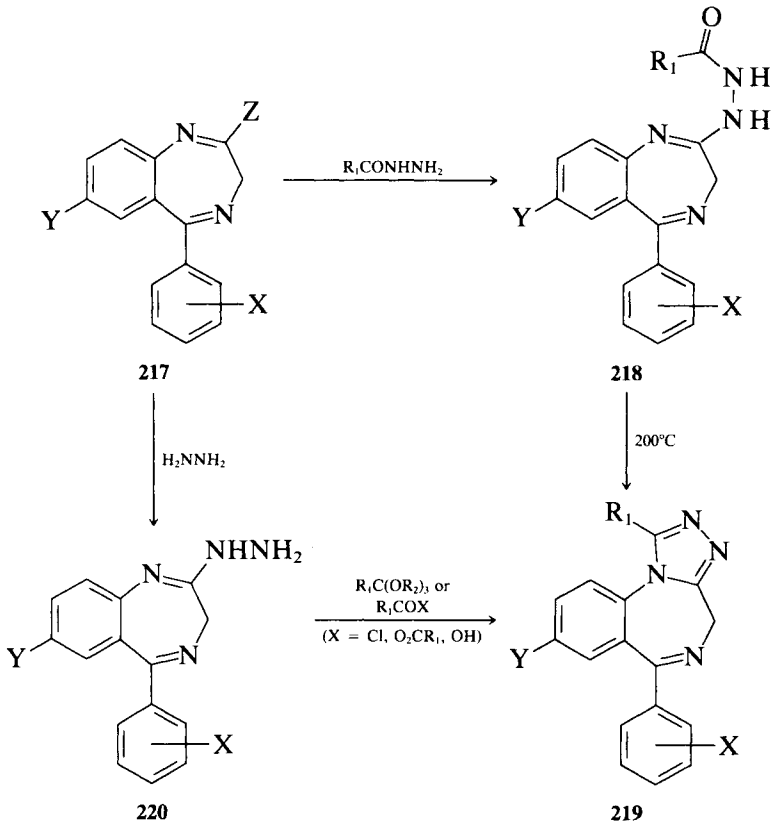
**216**

Several synthetic routes to this tricyclic skeleton have been developed. One method, probably the most general and versatile, uses the bicyclic benzodiazepine system as a foundation and builds the triazole ring onto it, as shown in Eq. 44. The benzodiazepines **217** are known compounds or may be prepared by well-established procedures (76,77). Substituent Z at the 2-position of **217** may be varied considerably, provided that it is a relatively good leaving group. Mercapto, alkylthio, amino, alkylamino, alkoxy, cyano, and *N*-nitroso alkylamino groups were used in the displacement reaction (88). The most commonly used Z group was mercapto, which exists in its tautomeric thione form. Although the starting materials (**217**) were generally prepared from the corresponding lactams, the 2-cyanobenzodiazepines were prepared from the reduced amines (**221**), as shown in Eq. 45.

A general sequence leading to 2-ethoxybenzodiazepines not involving the lactam intermediate was also developed from 2-aminobenzophenones (Eq. 46) (91). In a typical example, condensation of 2-amino-5-chlorobenzophenone with ethyl orthobromoacetate and treatment of the resulting imine with ammonia led to benzodiazepine **226.**

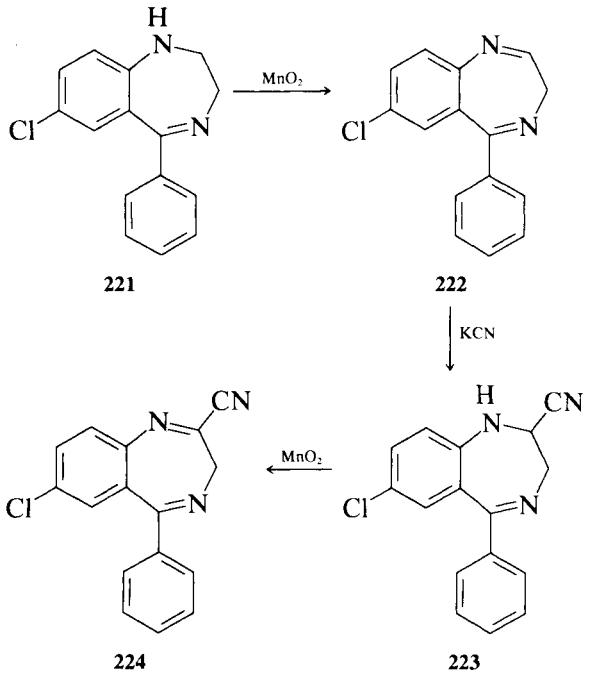
With the requisite bicyclic benzodiazepines **217** in hand, annelation of the triazole ring is straightforward (Eq. 44). Reaction of **217** with an acyl hydrazide produced the 2-acylhydrazino adduct **218,** which could be isolated and then cyclized or could be cyclized directly (typically by heating at 200°C for 15 min) to the desired triazolobenzodiazepine (**219**). As an alternative to the acyl hydrazine reagent, reaction of **217** with hydrazine led to the 2-hydrazinobenzodiazepine **220.** Treatment with orthoesters, acid halides, anhydrides, acids or other compounds of this oxidation state, or with acetal-

dehyde in the presence of air (92), completed the triazole ring formation. Intermediate hydrazine **220** was usually isolated, but was sometimes used *in situ*.




**217** **218** **220** **219** (44)

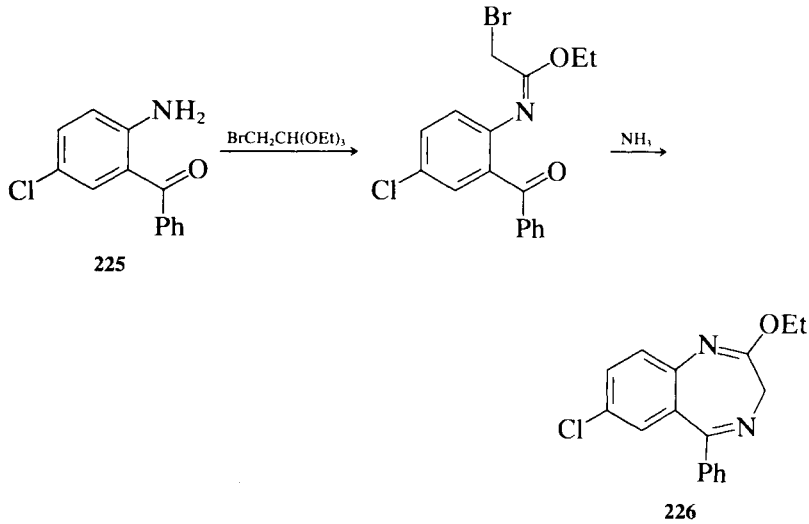
A wide range of 1-substitutions are available by this procedure. These include O, S, H, alkyl, aryl, ether, halide, amine, acetal, nitrile, and ester functionalities. Reaction of ethyl carbazate with **217** (X = H, Y = Cl, Z = SH) (Eq. 47) afforded the triazolobenzodiazepin-1-one **227** (68), which could also be prepared from hydrazine **220** (X = H, Y = Cl) by addition of methyl isocyanate (93,94). Thiones were prepared by condensation of **220** with thiophosgene (95). Similarly, thiophosgene was used in the synthesis of a 6-(2-pyridyl)-1-thione derivative (96). Examples of 1-oxo and 1-thioxo compounds prepared by this process are listed in Table 27. $N^4$-Oxides of **220** could also be used as substrates for this process, and these products are likewise included in Table 27 (83,86,88,92). 1-Oxo compounds were also obtained by hydrolysis of 1-bromo- and 1-chlorotriazoles (**228**) with aqueous phosphoric



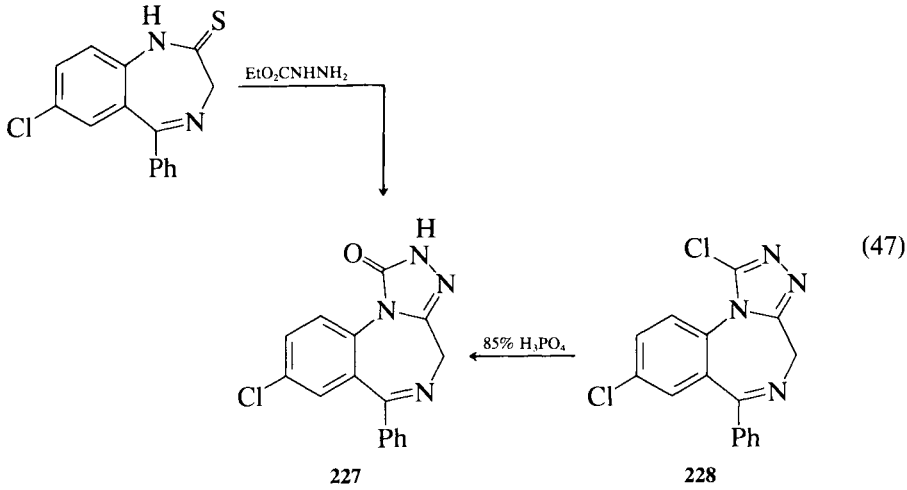

(45)

acid (Eq. 47) (98). Condensation of **220** with cyanogen bromide yielded a 1-amino derivative (95).

Formation of the system **219** ($R_1$ = H) was achieved by treatment of hydrazine **220** with ethyl orthoformate (91,101–107). Table 28 (Nos. 1–9)

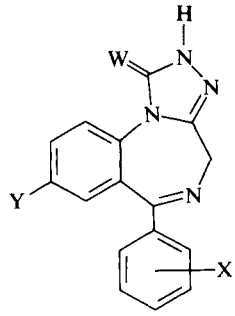



(46)



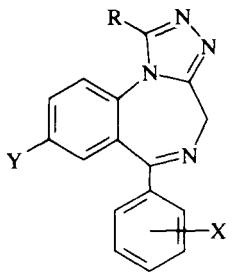

(47)

TABLE 27. 1-OXO- AND 1-THIOXO[1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES



| No. | X | Y | W | mp (°C) | Refs. |
|---|---|---|---|---|---|
| 1 | H | Cl | O | 255–256 | 68,93 |
| 2 | H | Cl | O | 255–266 | 98,99 |
| 3 | H | Cl | O | 252–253 | 93,94 |
| 4 | *p*-MeO | Cl | O | 199–200 | 93,94 |
| 5 | H | $NO_2$ | O | 239–240 | 93,94 |
| 6 | H | Cl | S | 237–238 | 93–95 |
| 7 | *o*-Cl | Cl | O | 204–205 | 97 |
| 8 | H | Cl | NH | 280 | 95 |
| | | | *$N^5$-Oxides* | | |
| 9 | H | Cl | O | 173–174 | 93,100 |
| 10 | H | Cl | S | 243–244 | 93 |
| 11 | *p*-Cl | Cl | O | 188–190 | 100 |
| 12 | H | $NO_2$ | O | 208–210 | 100 |
| 13 | H | $CF_3$ | O | 171–173 | 100 |

TABLE 28. [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES FROM BICYCLIC BENZODIAZEPINES

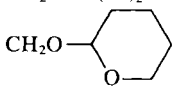


| No. | X | Y | R | Yield (%) | mp (°C) | Spectra | Refs. |
|---|---|---|---|---|---|---|---|
| 1 | H | H | H | 81 | 201–202 | | 102,107 |
| 2 | H | Cl | H | 43 | 228–229 | uv | 101,103,105,106 |
| 3 | H | Cl | H | 87 | 226–227 | | 102 |
| 4 | H | MeO | H | 69 | 209–210 | | 102,107 |
| 5 | H | $NO_2$ | H | 41 | 270–271 | | 91,102,107 |
| 6 | H | $CF_3$ | H | 58 | 258–260 | | 102 |
| 7 | H | Me | H | 75 | 177–178 | | 102,107 |
| 8 | *o*-Cl | Cl | H | 96 | 259–259.5 | | 102 |
| 9 | *p*-MeO | Cl | H | 67 | 216–217 | | 91,102,107 |
| 10 | H | H | Me | 61 | 230–231 | | 101,103,104,107 |
| 11 | H | H | Me | 86 | 230–231 | uv | 102 |
| 12 | H | Cl | Me | 69 | 228–228.5 | uv, X-ray | 89,91,92,101, 103,108,116 |
| 13 | H | Cl | Me | 92 | 225.5–226.5 | | 102 |
| 14 | H | $CF_3$ | Me | 54 | 135–137 | uv | 101,103 |
| 15 | H | $CF_3$ | Me | 39 | 112–113 | | 102,107 |
| 16 | H | $NO_2$ | Me | 26 | 231.5–232.5 | | 101–103 |

(*continued*)

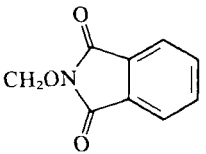
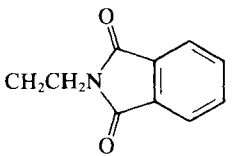
TABLE 28. *(Continued)*

| No. | X | Y | R | Yield (%) | mp (°C) | Spectra | Refs. |
|---|---|---|---|---|---|---|---|
| 17 | H | MeS | Me | 53 | 193–194 | | 101 |
| 18 | H | MeO | Me | 69 | 196–197 | | 102,107 |
| 19 | H | CN | Me | | 304–305 | | 104 |
| 20 | H | Me | Me | 76 | 211–212 | | 101–103 |
| 21 | *o*-Cl | Cl | Me | 43 | 223–225 | uv | 107,109 |
| 22 | *o*-Cl | Cl | Me | 95 | 223–224 | | 102,107,116 |
| 23 | *o*-F | Cl | Me | 70 | 203–204 | | 101,103,109 |
| 24 | *o*-Cl | $NO_2$ | Me | 71 | 229–231 | | 101,110 |
| 25 | *o*-F | Cl | Me | 70 | 278–279.5 | | 101,103 |
| 26 | *p*-MeO | Cl | Me | 76 | 268–269 | | 91,102,107 |
| 27 | *o*-F | $NO_2$ | Me | 70 | 278–279.5 | | 111 |
| 28 | *o*-Cl | H | Me | 73 | 211.5–213 | | 101,112 |
| 29 | H | Cl | Et | 37 | 231.5–232.5 | uv | 101,103,104,107 |
| 30 | H | Cl | Et | 94 | 229–230 | | 102 |
| 31 | H | Cl | *n*-Pr | 39 | 176–176.5 | uv | 101,103,104 |
| 32 | H | Cl | *n*-$C_6H_{13}$ | 87 | 75–78 | | 102,107 |
| 33 | *o*-Cl | Cl | Cyclopropyl | 68 | 185–186.5 | | 108,113 |
| 34 | H | Cl | Cyclopropyl | 68 | 186–187.5 | | 115 |
| 35 | *o*-Cl | Cl | Cyclopropyl | — | 197–198 | | 115 |
| 36 | H | Cl | $CH_2Ph$ | 69 | 192.5–193.5 | uv | 101,103,107 |
| 37 | H | Cl | $CH_2Ph$ | 78 | 190–192 | | 101 |
| 38 | H | Cl | Ph | 37 | 193.5–194.5 | | 101,103,107 |
| 39 | H | Cl | Ph | 89 | 193–194 | | 102 |
| 40 | H | Cl | 3-Pyridyl | 71 | 203–204 | | 114,115 |
| 41 | H | Cl | 2-Pyridyl | 65 | 189–190 | | 114,115 |
| 42 | H | Cl | 4-Pyridyl | 68 | 205.5–206.5 | | 114,115 |
| 43 | *o*-Cl | Cl | 4-Pyridyl | 71 | 264–265 | | 114,115 |
| 44 | *o*-Cl | H | 4-Pyridyl | 79 | 234–235 | | 114 |
| 45 | H | Cl | 2-Furyl | 84 | 125–126.5 | | 114 |
| 46 | H | Cl | 2-Thienyl | 38 | 173–174 | | 114 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 47 | *o*-Cl | Cl | 2-Thienyl | 73 | 261–263 | 114 |
| 48 | H | Cl | $CH_2CH_2OEt$ | | 128–132 | 117,118 |
| 49 | H | Cl | $CH_2CH_2OCH_2Ph$ | | 115–117 | 117,118 |
| 50 | H | Cl | $CH_2CH_2OCH_2C_6H_4OMe$-*p* | | 185–191 | 117 |
| 51 | H | H | $CH_2OEt$ | | 153–154 | 118 |
| 52 | H | H | $CH_2OCH_2Ph$ | | 167–168 | 117,118 |
| 53 | H | Cl | $CH_2OCH_2Ph$ | | 162–164 | 117,118 |
| 54 | H | Cl | $CH_2OMe$ | | 185–191 | 117,118 |
| 55 | H | Cl | $CH_2OEt$ | | 161–165 | 117,118 |
| 56 | *o*-Cl | Cl | $CH_2OCH_2Ph$ | | 200–203 | 117,119 |
| 57 | *o*-F | Cl | $CH_2OCH_2Ph$ | | 163.5–164.5 | 117 |
| 58 | H | Cl | $CH_2OCH_2C_6H_4OMe$-*p* | | 157–159 | 118,120 |
| 59 | *o*-Cl | Cl | $CH_2OCH_2C_6H_4OMe$-*p* | | 200–203 | 118,120 |
| 60 | *o*-F | Cl | $CH_2OCH_2C_6H_4OMe$-*p* | | 163.5–165 | 118,120 |
| 61 | H | Cl | $CH_2OCH(Ph)_2$ | | 202–203 | 118 |
| 62 | H | Cl |  | | 159–161 | 118 |
| 63 | H | Cl | $CH_2CH_2OH$ | | 227–231 | 118 |
| 64 | H | Cl | $CH(CH_3)CH_2OH$ | | 182–184 | 118 |
| 65 | H | Cl | $C(CH_3)_2OH$ | | 234–236 | 118 |
| 66 | H | Cl | $CH_2F$ | | 153–154 | 118 |
| 67 | H | Cl | $CH_2Cl$ | | 183–186.5 | 115,121 |
| 68 | H | Cl | $CH_2Br$ | | | 122 |
| 69 | H | Cl | $CH(CH_3)Cl$ | | 153.5–156.5 | 121 |
| 70 | H | Cl | $CHCl_2$ | | 196.5–198 | 115,121 |
| 71 | H | Cl | $CH_2NMe_2$ | | 165–166 | 117,120 |
| 72 | *o*-F | Cl | $CH_2NMe_2$ | | 143–144 | 117,120 |
| 73 | *o*-Cl | Cl | $CH_2NMe_2$ | | 198–200 | 117 |
| 74 | H | Cl | $CH_2NEt_2$ | | 126–128 | 117 |
| 75 | H | H | $CH(OMe)_2$ | | 166–172 | 117 |
| 76 | H | Cl | $CH(OMe)_2$ | | 166–172 | 117,119,123 |

*(continued)*

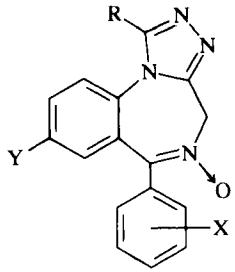
TABLE 28. (*Continued*)

| No. | X | Y | R | Yield (%) | mp (°C) | Spectra | Refs. |
|---|---|---|---|---|---|---|---|
| 77 | H | Cl | $CH(OEt)_2$ | | 133–135 | | 117,119,123,124 |
| 78 | *o*-Cl | Cl | $CH(OEt)_2$ | | 120–121.5 | | 117,119,124 |
| 79 | *o*-F | Cl | $CH(OEt)_2$ | | 120–121 | | 117,123,124 |
| 80 | *o*-Cl | H | $CH(OEt)_2$ | | 145–146 | | 123,124 |
| 81 | H | Cl | $CH_2CN$ | | 198–201 | | 115,125,126 |
| 82 | H | Cl | $CH_2Et$ | | 233–235 | | 101,103,118,128 |
| 83 | H | Cl | SH | | 240.5–241.5 | | 95 |
| 84 | H | Cl | $NH_2$ | | 280 | | 95 |
| 85 | H | Cl |  | | 256.5–257.5 | | 127 |
| 86 | H | Cl | $CH_2ONEt_2$ | | 136–139 | | 127 |
| 87 | H | Cl | $CH_2ONHEt$ | | 199–200.5 | | 127 |
| 88 | H | Cl | $CH_2ONMe_2$ | | 175 | | 127 |
| 89 | H | Cl |  | | 223.5–226 | | 131 |
| 90 | H | H | $CO_2Et$ | | 205–206 | | 128 |
| 91 | *o*-F | H | $CO_2Et$ | | 195–197 | | 128 |
| 92 | *o*-Cl | H | $CO_2Et$ | | 235–237 | | 128 |
| 93 | H | NHOH | Me | | 276–278 | | 129 |
| 94 | H | NO | Me | | 190–195 | | 129 |
| 95 | H |  | Me | | 160–165 | | 129 |

lists compounds that have been made via this route. Similarly, 1-alkyl (Nos. 10–35) and 1-aryl (Nos. 36–47) triazoles were prepared by reaction of **217** with the appropriate acyl hydrazides or by reaction of **220** with an orthoester, acid chloride, or anhydride (89,91,101–106). The 1-functionalized alkyl derivatives (Nos. 48–84) were obtained similarly (95,101,103,115,117–128,131). Not included in Table 28 are numerous other examples containing alkyl, cycloalkyl, and heteroaryl substituents at the 1-position, which were described only briefly in patents. A series of $N^5$-oxides were also prepared, as described above, from the *N*-oxides of **217** and **220.** These are summarized in Table 29 (88,92,102,105,116,122,130).

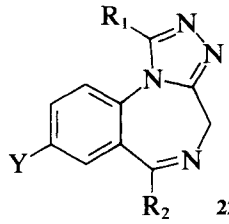
The substituent at the 6-position of **219** has not been limited to simple aryl groups in this method of synthesis. By starting with the appropriate bicyclic benzodiazepine, compounds with 6-(2-pyridyl) (88,132,133) and 6-methyl (132) substituents have likewise been prepared. Specific compounds are listed under structure **229** (Table 29a). Also prepared (but not tabulated

TABLE 29. $N^5$-OXIDES OF [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES




| No. | X | Y | R | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| 1 | H | Cl | H | 97 | 267–268 | 102,105,107,130 |
| 2 | H | Cl | Me | 94 | 272–274 | 92,102,107,130 |
| 3 | H | Cl | Et | 92 | 273–274 | 102,107,130 |
| 4 | *p*-MeO | Cl | H | 87 | 285–286 | 102,121 |
| 5 | *p*-MeO | Cl | Me | 89 | 286–287 | 102,130 |
| 6 | *o*-Cl | Cl | Me | 85 | 302–303 | 102,130 |
| 7 | H | $NO_2$ | H | 84 | 274–275 | 102,107 |
| 8 | H | $CF_3$ | Me | 64 | 141–143 | 102,107 |
| 9 | H | Cl | Me | | 272–275 | 88 |
| 10 | H | Me | Me | | 256–257 | 130 |
| 11 | *o*-F | Cl | Me | | 114–117 | 116 |
| 12 | H | Cl | $CH_2Br$ | | 249–251 | 122 |
| 13 | H | $CF_3$ | $CH_2Br$ | | 185–210 | 122 |
| 14 | *p*-Cl | Cl | $CH_2Br$ | | 264–269 | 122 |
| 15 | H | $NO_2$ | $CH_2Br$ | | 266–269 | 122 |
| 16 | H | Cl | $CH_2NMe_2$ | | 217–219 | 122 |
| 17 | *p*-Cl | Cl | $CH_2NMe_2$ | | 260–260.5 | 122 |
| 18 | H | $CF_3$ | $CH_2NMe_2$ | | 118–190 | 122 |
| 19 | H | $NO_2$ | $CH_2NMe_2$ | | 228–230 | 122 |

TABLE 29a. 6-SUBSTITUTED [1,2,4]TRIAZOLO [4,3-*a*][1,4]BENZODIAZEPINES

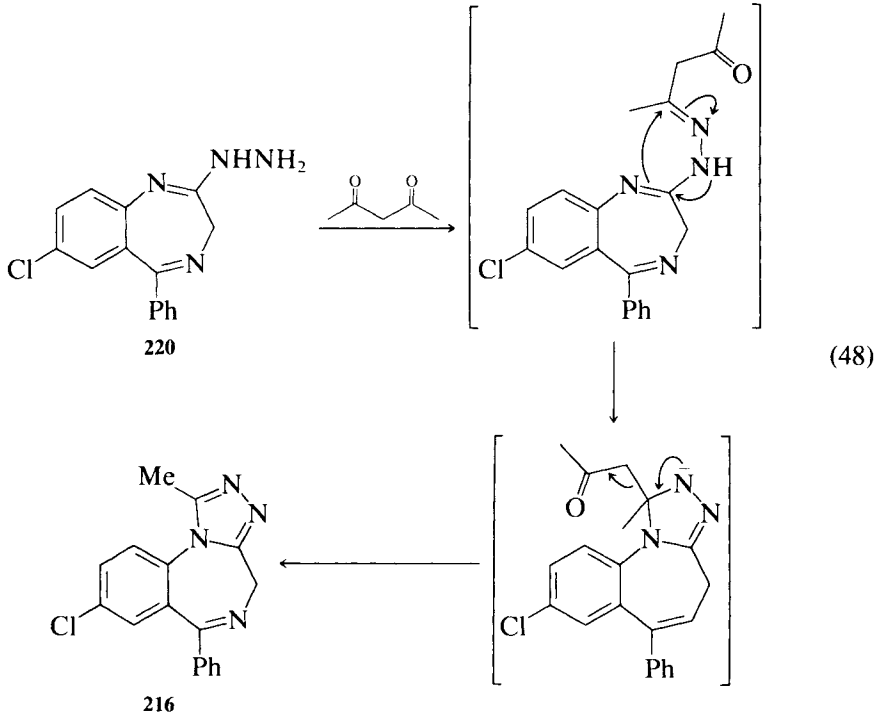


**229**

| Y | $R_1$ | $R_2$ | mp (°C) | Refs. |
|---|---|---|---|---|
| Br | Me | 2-Pyridyl | 248–250 | 88,132,144 |
| Cl | Me | Me | 219–219.5 | 132 |
| Br | Me | 2-Pyridyl ($N^5$-oxide) | 278–282 | 144 |

because of lack of supporting physical data) were the following 6-substitutions: cyclopentyl, cyclohexyl, and 2-pyrimidyl (113).

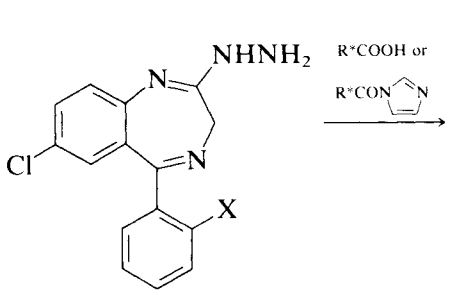
A modified synthesis of **216** from **220** employed pentane-2,4-dione to form the hydrazone, as shown in Eq. 48 (92). Subsequent thermolysis in refluxing



**220** **216** (48)

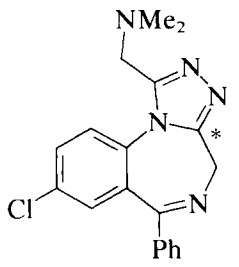
xylene led to **216,** probably by a stepwise mechanism involving cyclization and aromatization via the elimination of acetone.

The general method of triazole formation in Eq. 44 was also used in the synthesis of $^{14}$C-triazolobenzodiazepines. For example, reaction of **220** (X = H, Y = Cl) with $^{14}$C-formic acid or *N*-(1-$^{14}$C-acetyl)imidazole led to 1-$^{14}$C-**230** (Eq. 49) (134,135). Several additional labeled compounds, such as 3a-$^{14}$C-**231** and 3a-$^{14}$C-**232,** were prepared from 1-$^{14}$C-glycine (136).

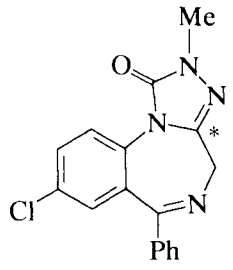



(49)

| | X | R | mp (°C) | Refs. |
|---|---|---|---|---|
| **230a** | H | H | 227–228 | 134 |
| **230b** | H | Me | 225–227 | 135 |
| **230c** | Cl | Me | 239–241 | 135 |




**231**




**232**

A rather different approach to the triazolobenzodiazepine skeleton requires the intermediacy of benzophenone derivatives. The most widely used process based on this concept is outlined in Fig. 16 for the preparation of 8-chloro-1-methyl-6-phenyl-4H-triazolo[4,3-*a*][1,4]benzodiazepine (**216**). Reaction of 2-amino-5-chlorobenzophenone (**225**) with triethyl orthoformate led to the ethoxyimide **233,** which on treatment with hydrazine resulted in displacement of ethoxide and hemiaminal formation to give **234.** Amidation of the primary amino function followed by acid-catalyzed cyclization generated the triazolobenzodiazepine **236.** Treatment with sodium iodide followed by ammonia led to the tricyclic compound **216.** Reaction of **236** with

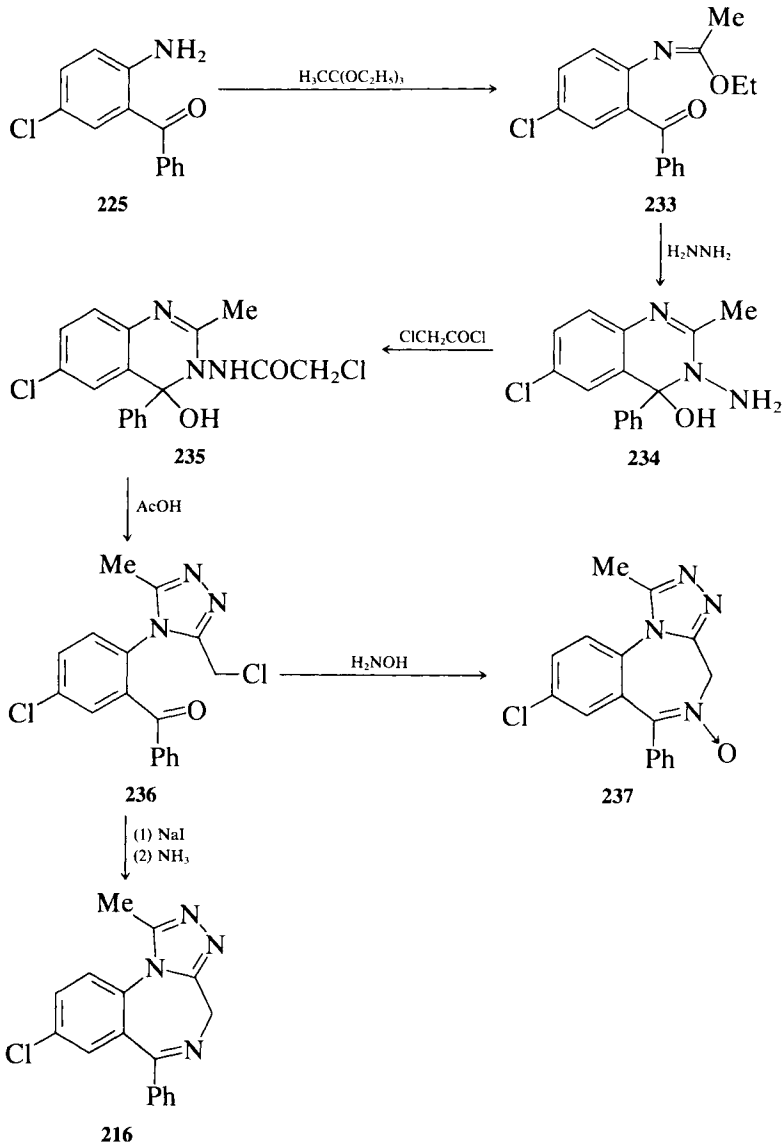
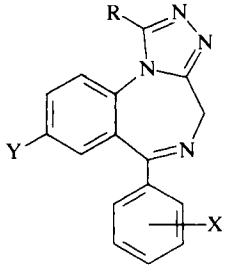



**Figure 16**

hydroxylamine led to the corresponding $N^5$-oxide **237** (137). Other tricyclic structures made by this method are listed in Table 30 (Nos. 1–11) (138–147), and the $N^5$-oxides are listed in Table 31 (137,139,148). The starting benzophenones and general methods for their preparation have been described (149).

A modification of this process that has been used to generate 1-aminomethyltriazolo[4,3-*a*][1,4]benzodiazepines is outlined in Fig. 17 (150,151).

TABLE 30. [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES FROM BENZOPHENONE DERIVATIVES

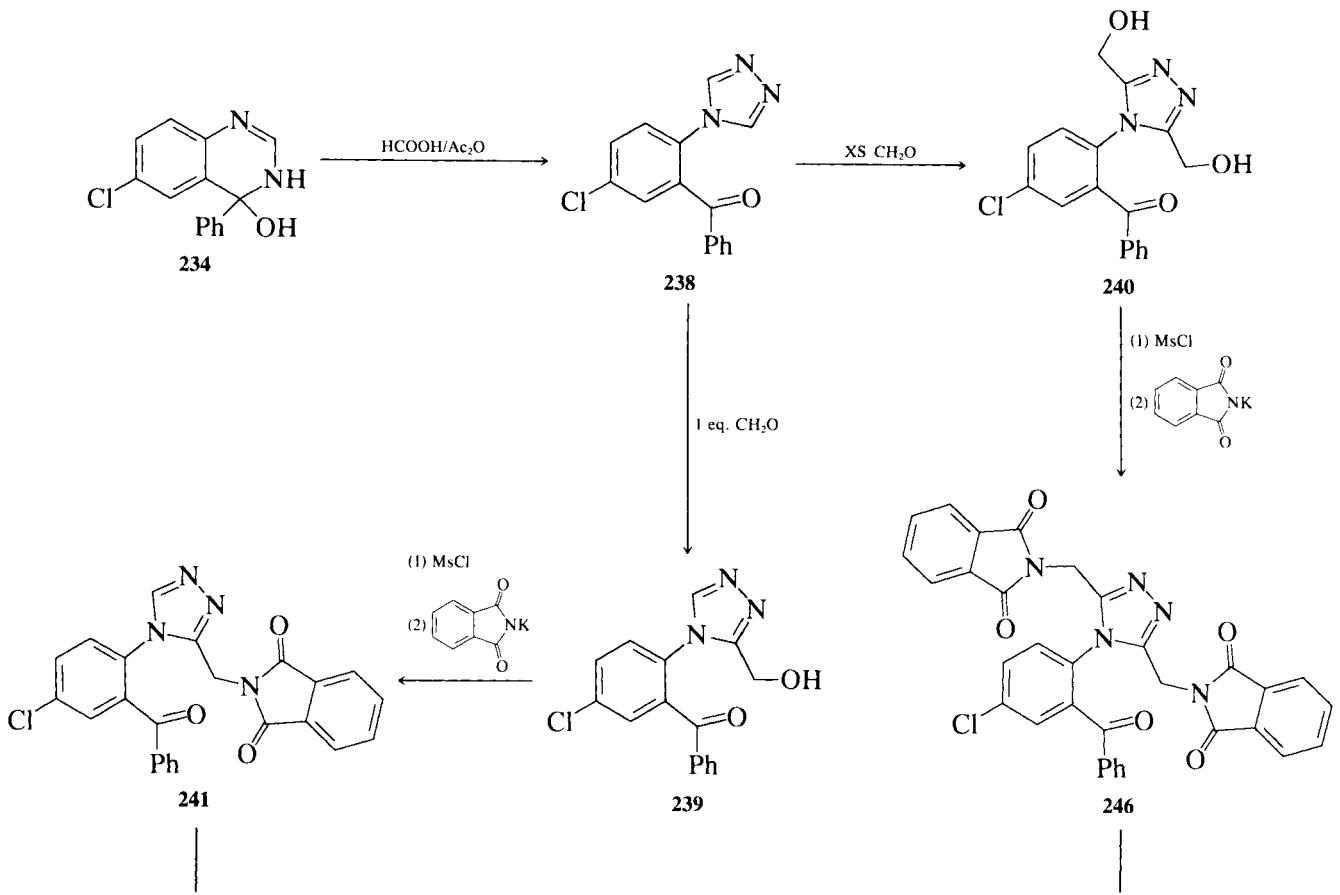


| No. | X | Y | R | mp (°C) | Refs. |
|---|---|---|---|---|---|
| 1 | H | H | H | 195–196 | 138 |
| 2 | H | Cl | H | 230–231 | 139,146 |
| 3 | H | $NO_2$ | H | 268–269 | 138 |
| 4 | H | $CF_3$ | H | 258–260 | 138 |
| 5 | *o*-Cl | Cl | H | 259 | 138 |
| 6 | *o*-F | Cl | H | 187.5–188.5 | 138 |
| 7 | *p*-MeO | Cl | H | 217–218 | 138 |
| 8 | H | $NO_2$ | Me | 230–231 | 138 |
| 9 | H | Me | Me | 211–211.5 | 138 |
| 10 | [a] | Br | Me | 253–254 | 143,144 |
| 11 | H | Cl | Me | 228–229.5 | 138–142,145 |
| 12 | H | Cl | $CH_2NH_2$ | 167.5–172.5 | 151 |
| 13 | H | Cl | $CH_2NHMe$ | 167.5–172.5 | 150 |
| 14 | H | Cl | $CH_2NMe_2$ | 171.5–174.5 | 150 |
| 15 | H | Cl | $CH_2OCH_2C_6H_5$ | 163–165 | 147 |
| 16 | H | Cl | $CH_2OMe$ | 185–191 | 147 |
| 17 | H | Cl | $CH_2OEt$ | 128–132 | 147 |
| 18 | H | Cl | $CH_2OH$ | 210–211 | 147 |
| 19 | *o*-F | Cl | $CH_2OMe$ | 105–106 | 147 |
| 20 | *o*-F | Cl | $CH_2OH$ | 195–197 | 147 |
| 21 | H | Cl | Br | 205–207 | 146 |

[a] 6-Phenyl replaced by 6-(2-pyridyl).

Starting with quinazoline **234,** prepared as shown in Fig. 16, treatment with formic acid–acetic anhydride resulted in triazole formation. The unsubstituted triazole **238** could then be condensed with paraformaldehyde. Reaction with one formaldehyde equivalent yielded the monosubstituted adduct **239,** whereas an excess led to the disubstituted product **240.** The next step, for both the mono- and bis(hydroxymethyl) compounds, was conversion of the alcohols to primary amines masked as phthalimides. This transformation could be accomplished stepwise by mesylate formation followed by displacement with potassium phthalimide, or directly by reaction of phthalimide, triphenylphosphine, and diethyl azodicarboxylate.

At this stage the monophthalimide **241** was condensed with additional paraformaldehyde to produce the hydroxymethyl triazole **242,** which was


HCOOH/Ac2O
XS CH2O
1 eq. CH2O
(1) MsCl
(2)
234
238
240
239
241
246

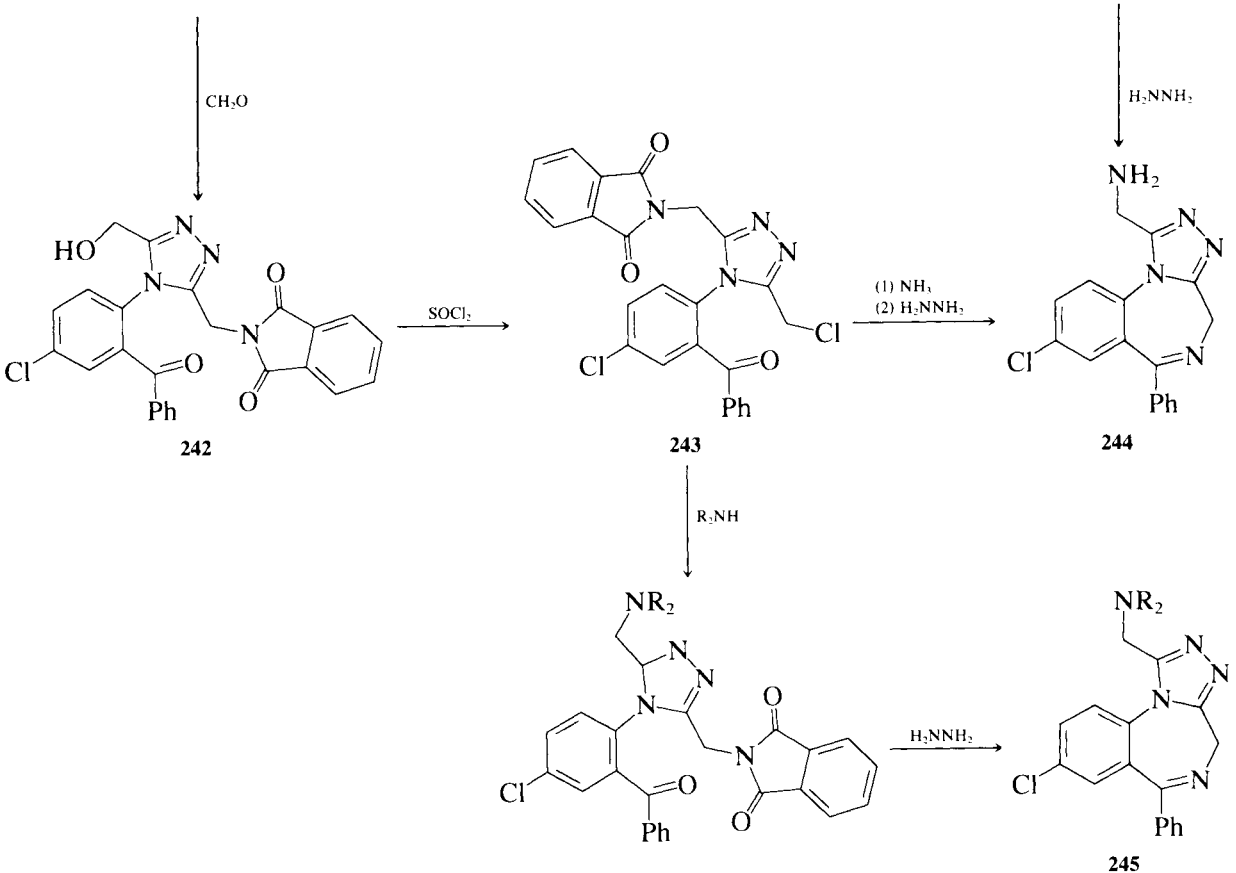
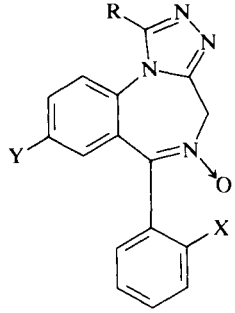

CH2O
HO
N
N
N
O
N
O
O
Cl
O
Ph
242
SOCl2
O
N
O
N
N
N
Cl
O
Cl
Ph
243
(1) NH3
(2) H2NNH2
H2NNH2
NH2
N
N
N
Cl
N
Ph
244
R2NH
NR2
N
N
N
O
N
O
Cl
O
Ph
H2NNH2
NR2
N
N
N
Cl
N
Ph
245

**Figure 17**

TABLE 31. $N^5$-OXIDES OF [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES



| X | Y | R | mp (°C) | Refs. |
|---|---|---|---|---|
| H | Cl | H | 268–270 | 137,139,148 |
| Cl | Cl | H | 273–277 | 137,148 |
| H | Cl | Me | 273–274 | 137,139,148 |
| H | Me | Me | 256–257 | 137,148 |
| Cl | H | Me | 260–262 | 148 |

converted to its chloride (**243**) with thionyl chloride. The chloride **243** was then transformed either to the 1-aminomethyl triazole **244** (by sequential treatment with ammonia and hydrazine) or to the 1-alkylaminomethyl derivative **245** (by addition of an alkyl amine followed by hydrazine, which removed the phthalimide group and allowed cyclization). The bis(phthalimide) **246** was also converted to 1-aminomethyltriazolo[4,3-*a*][1,4]benzodiazepine **244** by reaction with hydrazine. In this way Nos. 12–14 in Table 30 were prepared (150,151).

Another modification of the basic approach used in Fig. 16 for the synthesis of these tricyclic diazepines involved conversion of the starting 2-aminobenzophenone **225** to the 4-phenylquinoline **247,** as shown in Fig. 18 (151,152). For this process, annelation of the triazole to the quinoline was performed by conversion to the 2-chloro compound, displacement of chloride by hydrazine, and cyclization with ethyl orthoacetate (152). Oxidation of the triazoloquinoline **248** via ruthenium dioxide–catalyzed periodate cleavage resulted not only in the product of ring cleavage, aldehyde **249,** but also in the deformylated product **250.** The mixture of **249** and **250** was converted entirely to **250** by oxidation with alkaline silver nitrate. At this point triazole **250** was condensed with paraformaldehyde to give access to the pathway described in Fig. 17. This approach was utilized for the preparation of compound 11 in Table 30.

The by-product **249** was also elaborated to the tricyclic structure **216** by the alternate route shown in Fig. 18 (151,152). Oxime formation followed by platinum-catalyzed hydrogenation produced the dihydrodiazepine **252.** Dehydrogenation using diethyl azodicarboxylate generated the desired product **216.**

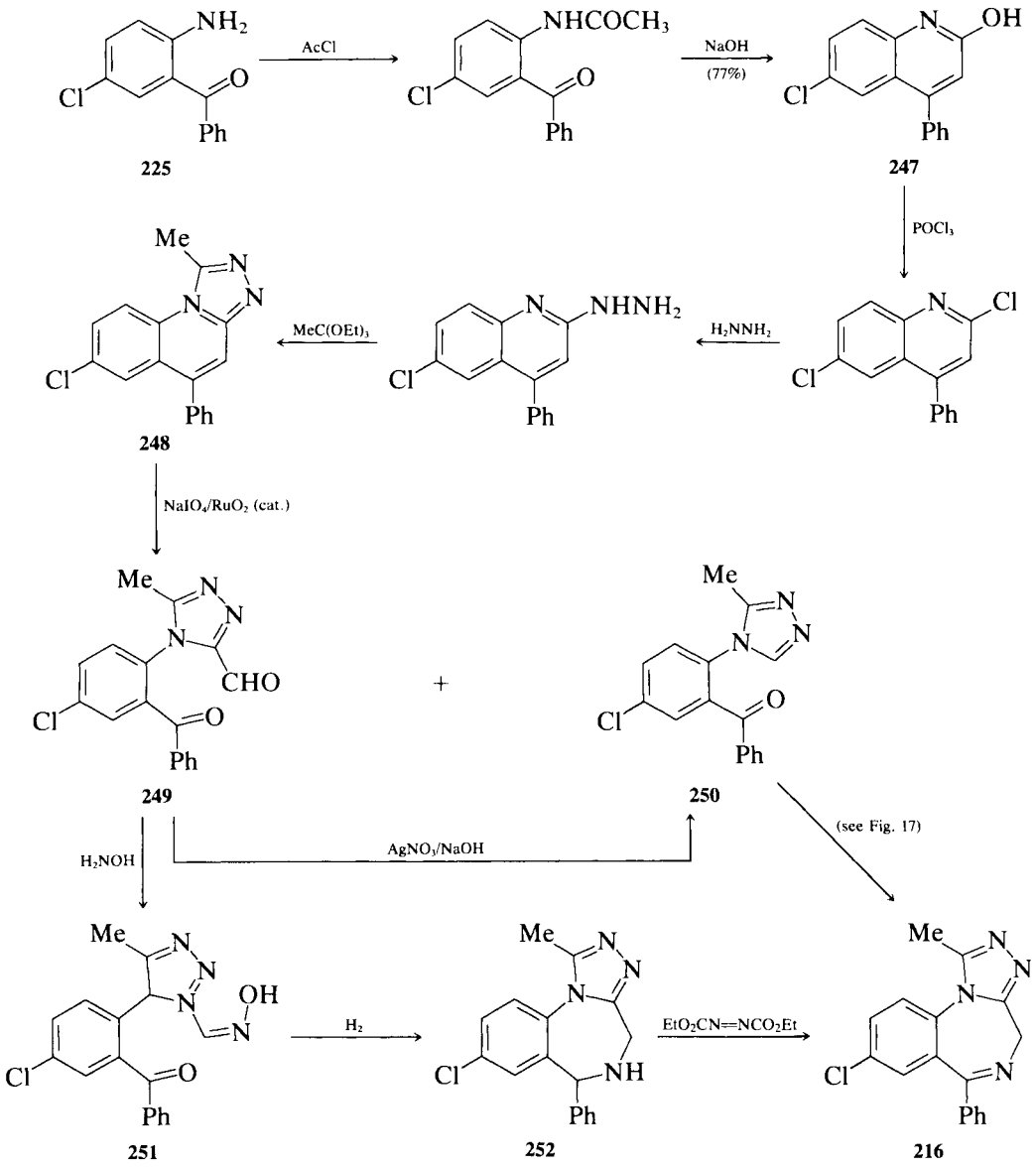
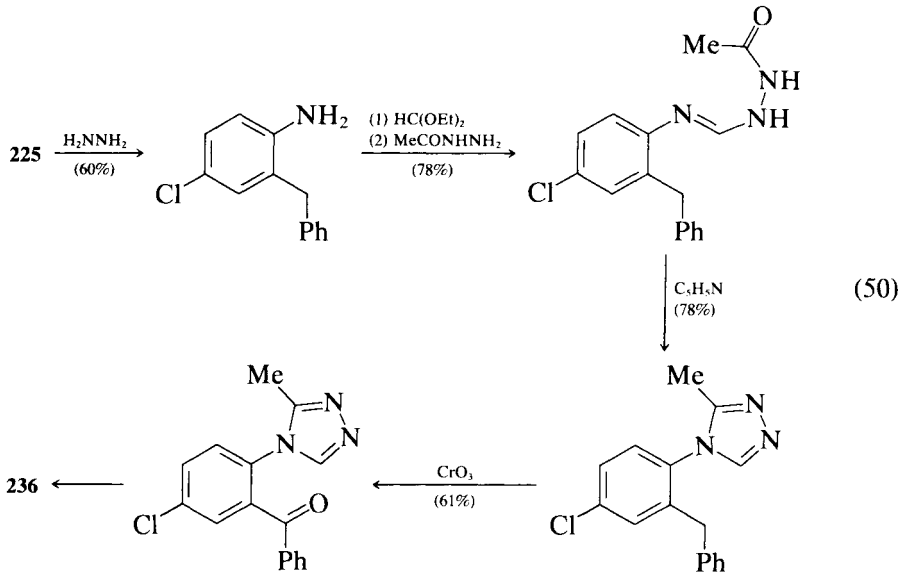



**Figure 18**

Another synthetic variation starting with 2-amino-5-chlorobenzophenone (**225**) but not involving quinazoline **234** is summarized in Eq. 50 (142). The method involves removal of the carbonyl group from **225** by the Wolff–Kishner method, triazole formation by the usual procedures, and regeneration of the carbonyl group by oxidation with chromic acid. The process appears to offer no synthetic advantages over the basic method of Fig. 16.

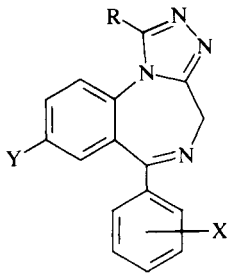


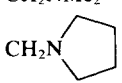

(50)

Given all the synthetic methods described above for the preparation of this ring system, whatever functionality can be built into these tricyclic compounds is amenable to further manipulation. Acid-catalyzed hydrolysis of the 1-alkyl ethers gave the corresponding alcohols (Table 32, Nos. 1–4) (118,120). One of these alcohols was esterified to an acetate (No. 5) (118), but these compounds have been used primarily as amine precursors. By conversion to a mesylate followed by displacement with various amines, the 1-aminomethyl compounds (Nos. 6–16) (120,153) were synthesized. Displacement using potassium phthalimide resulted in the phthalimidomethyl derivative (No. 17) (120). Amines were also prepared by displacement of the corresponding bromides (Table 32, Nos. 18–32, and Table 29, Nos. 16–19) (120,122). From the melting points of amines prepared by both methods, it appears that the latter process (via the bromide) yields a cleaner product. Treatment of primary aminomethyl derivatives with formaldehyde and formic acid afforded the dimethylaminomethyl compounds (Table 32, Nos. 33–35) (120,154). These products could also be obtained directly from the 1-unsubstituted triazoles by reaction with the preformed Mannich reagent (155). The unsubstituted aminomethyl derivative was attained from the phthalimide (No. 37) (156) and from the azide (No. 36) (157).

Direct substitution at $C_1$ was achieved by *N*-chlorosuccimimide and *N*-bromosuccinimide halogenation (Nos. 41 and 43) (158,159). These active halides were displaced with piperidine (No. 42), cyanide (No. 44), and methoxide (No. 45) (158). Treatment of the 1-mercapto derivative with sodium hydroxide and methyl iodide gave the 1-methylthio derivative (No. 46) (95). The 1-amino compound was diazotized and subjected to the action of fluo-

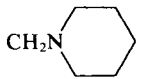
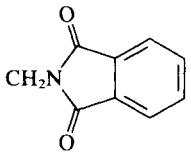
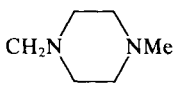
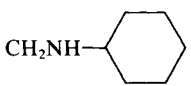
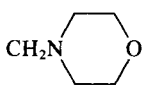
TABLE 32. 1-FUNCTIONALIZED [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES

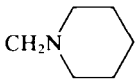
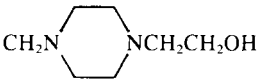
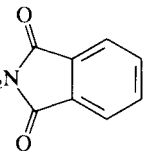



| No. | X | Y | R | $C_1$ Precursor | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| 1 | H | H | $CH_2OH$ | $CH_2OCH_2Ar$ | 205–206 | 118,120 |
| 2 | H | Cl | $CH_2OH$ | $CH_2OCH_2Ar$ | 210–211 | 118,120 |
| 3 | *o*-Cl | Cl | $CH_2OH$ | $CH_2OCH_2Ar$ | 235–237 | 118,120 |
| 4 | *o*-F | Cl | $CH_2OH$ | $CH_2OCH_2Ar$ | 195–197 | 118,120 |
| 5 | H | Cl | $CH_2OAc$ | $CH_2OH$ | 210–212 | 120 |
| 6 | H | Cl | $CH_2NH_2$ | $CH_2OH$ | 164–166 | 120 |
| 7 | H | Cl | $CH_2NHMe$ | $CH_2OH$ | 145–147 | 120 |
| 8 | H | Cl | $CH_2NHEt$ | $CH_2OH$ | 153–154 | 120 |
| 9 | H | Cl | $CH_2NMe_2$ | $CH_2OH$ | 165–166 | 120 |
| 10 | H | Cl | $CH_2NEt_2$ | $CH_2OH$ | 126–128 | 120 |
| 11 | *o*-F | Cl | $CH_2NMe_2$ | $CH_2OH$ | 143–144.5 | 120 |
| 12 | *o*-Cl | Cl | $CH_2NMe_2$ | $CH_2OH$ | 198–200 | 120 |
| 13 | H | Cl |  | $CH_2OH$ | 178–179 | 120 |

(*continued*)

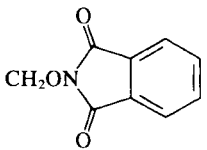
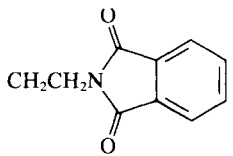
TABLE 32. *(Continued)*

| No. | X | Y | R | $C_1$ Precursor | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| 14 | H | Cl |  | $CH_2OH$ | 212–213 | 120 |
| 15 | H | H | $CH_2NMe_2$ | $CH_2OH$ | 180–180.5 | 120 |
| 16 | H | Cl | $CH_2NHCH_2CH_2OH$ | $CH_2OH$ | 165–167 | 120,153 |
| 17 | H | Cl |  | $CH_2OH$ | 242–244 | 120 |
| 18 | H | Cl | $CH_2NHEt$ | $CH_2Cl$ | 131.5–132.5 | 121 |
| 19 | H | Me | $CH_2NMe_2$ | $CH_2Br$ | 154–156 | 122 |
| 20 | H | H | $CH_2NMe_2$ | $CH_2Br$ | 181–182 | 122 |
| 21 | H | Cl | $CH_2NMe_2$ | $CH_2Br$ | 168–169.5 | 122 |
| 22 | H | Cl |  | $CH_2Br$ | 203–206 | 122 |
| 23 | H | Cl | $CH_2NHMe$ | $CH_2Br$ | 166–168 | 122 |
| 24 | H | Cl | $CH_2NEt_2$ | $CH_2Br$ | 130–132 | 122 |
| 25 | H | Cl | $CH_2NHCH_2CH_2OH$ | $CH_2Br$ | 162–164.5 | 122 |
| 26 | H | Cl | $CH_2N(CH_2CH_2OH)_2$ | $CH_2Br$ | 84–87 | 122 |
| 27 | H | Cl |  | $CH_2Br$ | 187–188 | 122 |
| 28 | H | Cl |  | $CH_2Br$ | 214–215 | 122 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 29 | H | Cl |  | $CH_2Br$ | 202–203 | 122 |
| 30 | H | Cl |  | $CH_2Br$ | 113–118 | 122 |
| 31 | *p*-MeO | Cl | $CH_2NMe_2$ | $CH_2Br$ | 224–225 | 122 |
| 32 | *o*-Cl | Cl | $CH_2NMe_2$ | $CH_2Br$ | 203–205 | 122 |
| 33 | H | Cl | $CH_2NMe_2$ | $CH_2NH_2$ | 165–166 | 154 |
| 34 | *o*-Cl | Cl | $CH_2NMe_2$ | $CH_2NH_2$ | 198–200 | 120,154 |
| 35 | *o*-F | Cl | $CH_2NMe_2$ | $CH_2NH_2$ | 143.5–144.5 | 120,154 |
| 36 | H | Cl | $CH_2NH_2$ | $CH_2N_3$ | 164–166 | 157 |
| 37 | H | Cl | $CH_2NH_2$ |  | 164–166 | 156 |
| 38 | H | Cl | $CH_2CN$ | $CH_2Cl$ | 199.5–200.5 | 121 |
| 39 | H | Cl | $CH_2CO_2Me$ | $CH_2CN$ | 202–203 | 125,126 |
| 40 | H | Cl | $CH_2CONMe_2$ | $CH_2CO_2Me$ | 204–205 | 126 |
| 41 | H | Cl | Cl | H | 198–199 | 158,159 |
| 42 | H | Cl |  | Cl | 184.5–185.5 | 158 |
| 43 | H | Cl | Br | H | 202–203.5 | 158 |
| 44 | H | Cl | CN | Br | 194–195 | 158 |
| 45 | H | Cl | OMe | Br | 163–164 | 158 |
| 46 | H | Cl | SMe | SH | 220–221 | 95 |
| 47 | H | Cl | F | $NH_2$ | | 95 |
| 48 | H | Cl | $NO_2$ | $NH_2$ | | 95 |

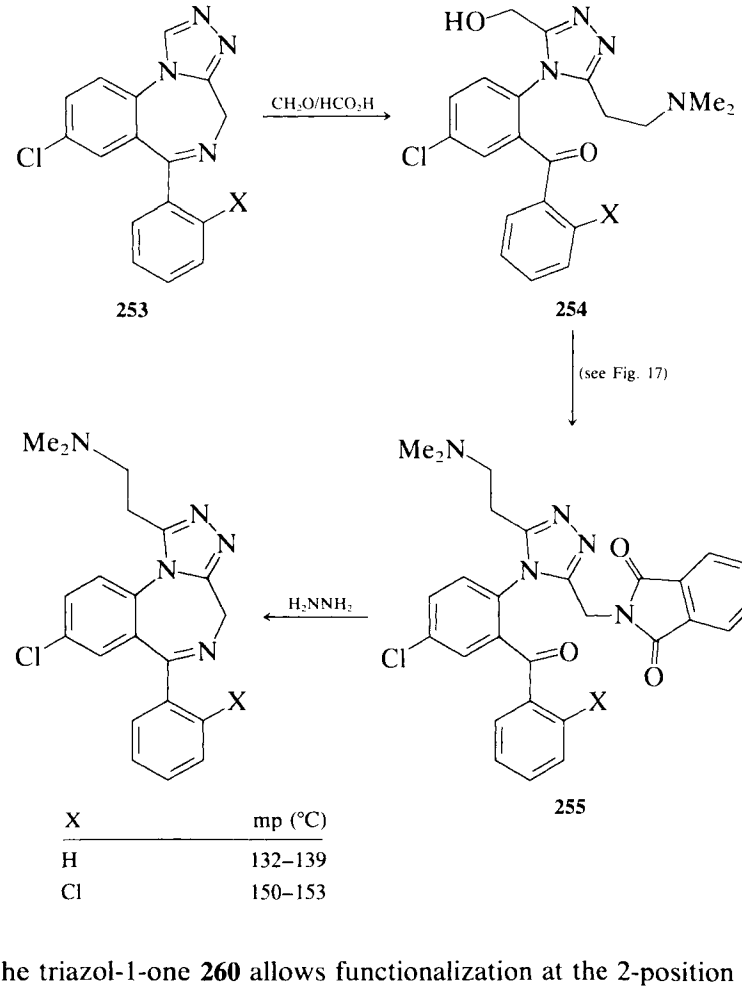
(*continued*)

TABLE 32. (*Continued*)

| No. | X | Y | R | $C_1$ Precursor | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| 49 | H | Cl | $CH_2ONH_2$ |  | 191–192 | 127 |
| 50 | H | Cl | $CH_2ON{=}CH_2$ | $CH_2ONH_2$ | 208.5–210 | 127 |
| 51 | H | Cl | $CH_2ON{=}CMe_2$ | $CH_2ONH_2$ | 168.5–170 | 127 |
| 52 | H | Cl | $CH_2NMe_2$ ($N^5$-oxide) | $CH_2NMe_2$ | 157.5–158.5 | 127 |
| 53 | H | Cl | $CH_2CH_2OH$ | $CH_3$ | 237.5–238 | 131 |
| 54 | H | Cl | $CH_2CH_2NH_2$ |  | 198–200 | 131 |
| 55 | H | Cl | $CH_2CH_2NMe_2$ | $CH_2CH_2NH_2$ | 132–139 | 131 |
| 56 | H | Cl | $CH_2OH$ | $CH_2Et$ | 210–211 | 128 |

roboric acid to obtain the 1-fluoro compound (No. 47) (95). In addition, the 1-amino compound was oxidized with peracid to the 1-nitro analog (No. 48) (95). Similar transformations were claimed for 8-bromo-6-(2-pyridyl)triazolo[4,3-*a*][1,4]benzodiazepine, but supporting physical or chemical data were not presented (96,160,161).

A novel method of synthesis of 1-(2-dimethylaminoethyl)triazoles involves benzodiazocine **253** as an intermediate (Eq. 51). *In situ* ring opening and reductive methylation of **253** afforded **254.** Transformation of **254** to the target compound **256** was carried out using previously described procedures (Fig. 17) (160).

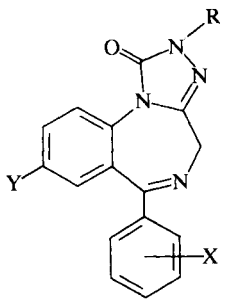


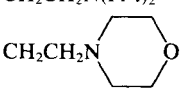

(51)

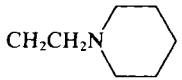
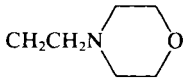
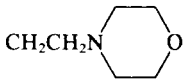
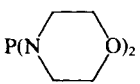
| | X | mp (°C) |
|---|---|---|
| **256a** | H | 132–139 |
| **256b** | Cl | 150–153 |

The triazol-1-one **260** allows functionalization at the 2-position by alkylation (Eq. 52). Typically, addition of sodium hydride generated the amido anion, and alkylation was effected with an alkyl halide. The alkyl and aminoalkyl derivatives prepared in this manner are shown in Table 33

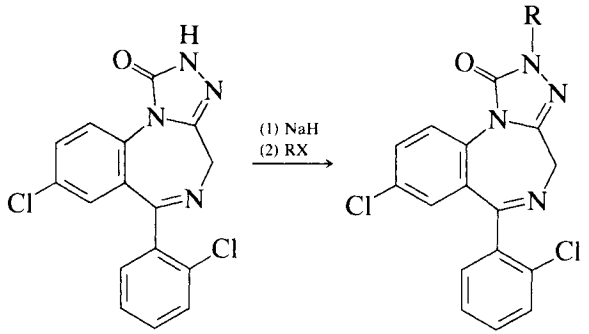
TABLE 33. 2-SUBSTITUTED[1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES




| X | Y | R | mp (°C) | Salt | Refs. |
|---|---|---|---|---|---|
| *o*-Cl | Cl | Me | 82–84 | | 93,97,148 |
| H | Cl | $CH_2CH_2NMe_2$ | 98.5–100.5 | | 161 |
| H | Cl | $CH_2CH_2NMe_2$ | 161–162.5 | Oxalate | 162 |
| H | Cl | $CH_2CH_2NEt_2$ | 254–258 | HBr | 161 |
| H | Cl | $CH_2CH_2NEt_2$ | 94–95 | | 162 |
| H | Cl | $CH_2CH_2CH_2NMe_2$ | 242–243 | HCl | 161 |
| H | Cl | $CH_2CH_2CH_2NMe_2$ | 171–173 | Oxalate | 162 |
| *o*-Cl | Cl | $CH_2CH_2NEt_2$ | 253.5–255 | HBr | 161 |
| H | Cl | $CH_2CH_2N(Pr\text{-}i)_2$ | 118.5–119.5 | | 162 |
| H | Cl |  | 163–164 | | 162 |

| | | | | | |
|---|---|---|---|---|---|
| H | Cl |  | 169.5–170.5 | | 162 |
| *p*-MeO | Cl | $CH_2CH_2NMe_2$ | 203–204 | Oxalate | 162 |
| H | H |  | 184–187 | 2HCl | 162 |
| H | Me |  | 192.5–194 | | 162 |
| *o*-MeO | Cl | Me | 220–231 | HCl | 163 |
| H | Cl | $CO_2Et$ | 148–149 | | 163 |
| H | Cl | $CO_2Et$ | 140–141 | Thione | 163 |
| H | Cl | $CH_2CH_2Ph$ | 125–127 | | 163 |
| H | $NO_2$ | $CO_2Et$ | 192–194 | | 163 |
| H | Cl | Et | 155–156 | | 163 |
| *o*-Cl | Cl | Et | 144–145 | | 163 |
| *o*-Cl | H | Me | 159.5–160 | | 163 |
| *o*-Cl | H | Et | 129.5–130.5 | | 163 |
| *o*-Cl | Cl | $(CH_2)_3NMe_2$ | 258–261 | HBr | 165 |
| H | Cl |  | 179–181 | | 164 |

(93,97,159,161–165). A series of similarly prepared $N^5$-oxides are listed in Table 34 (100,162,163).

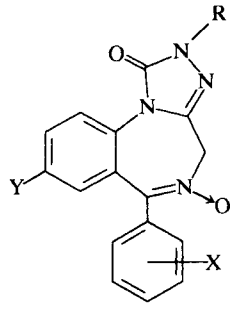



(52)

**260**

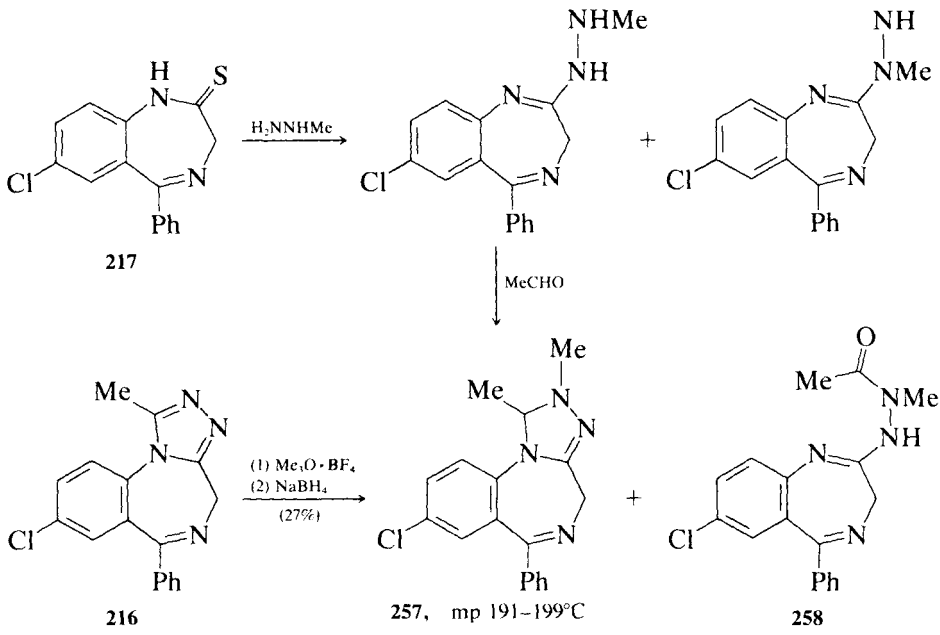
A less general and nonregioselective process for the construction of 2-alkyltriazole derivatives involves reaction of benzodiazepine **217** with alkylhydrazines (166,167). For example, addition of methyl hydrazine to **217** (Eq. 53) resulted in a mixture of 1- and 2-methylhydrazino derivitives. After

TABLE 34. *N*-OXIDES OF 2-SUBSTITUTED[1,2,4]TRIAZOLO[4,3-*a*]-[1,4]BENZODIAZEPINES




| X | Y | R | mp (°C) | Refs. |
|---|---|---|---|---|
| H | Cl | Me | 223–226 | 100,163 |
| H | Cl | Et | 250–253 | 100 |
| H | $NO_2$ | Me | 237–239 | 100,163 |
| *p*-Cl | Cl | Et | 204–205 | 100,163 |
| H | $CF_3$ | Et | 261–262 | 100,163 |
| *p*-Cl | Cl | $CH_2CH_2NEt_2$ | 92–94 ($\frac{2}{3}H_2O$) | 162 |
| *p*-Cl | Cl | $CH_2CH_2N$ O | 149–150 ($\frac{1}{2}H_2O$) | 162 |
| H | $NO_2$ | $CH_2CH_2NMe_2$ | 202–207 | 162 |
| H | $CF_3$ | $CH_2CH_2NMe_2$ | 169–170 | 162 |

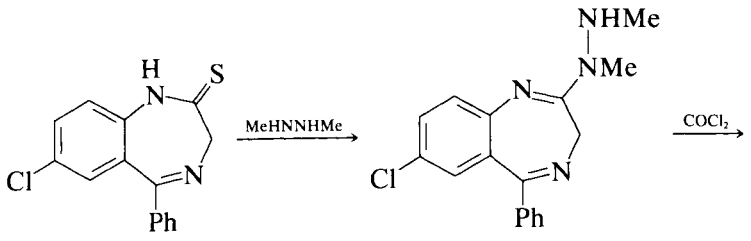
separation, aminal formation with acetaldehyde afforded the desired 1,2-dimethyl derivative **257** in 29% yield, along with the oxidized product **258.** Triazole **257** was also available by methylation of 8-chloro-1-methyltriazolo[4,3-*a*][1,4]benzodiazepine (**216**) with triethyloxonium fluoroborate followed by reduction of the 2-iminium salt with sodium borohydride (166).




(53)

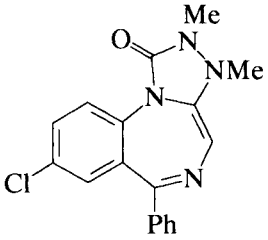
The 2- and 3-substituted members of this ring system were also obtained from both bicyclic and tricyclic precursors, as outlined in Eqs. 54 and 55 (168). Addition of *sym*-dimethylhydrazine to thione **217** followed by cyclization with phosgene gave the 2,3-dimethyl derivative **259.** Alkylation of **260** with an excess of thallous ethoxide and methyl iodide likewise afforded a 2,3-dimethyl derivative (**262a**). However, in this case the 2-methyl compound **261** was the major product. A small amount of the 1,4-dimethyl derivative **262b** was also formed.

Formation of *N*-oxides at the 5-position has been achieved not only by incorporation of the oxygen function prior to elaboration of the tricyclic system by the methods described above, but also by oxidation of the completed system with *m*-chloroperbenzoic acid. Direct thermal rearrangement of the intermediate oxazirine **263** led to the *N*-oxide **237** (Eq. 56). Oxazirine **263** could be isolated from the reaction mixture (169) or could be generated from the *N*-oxide by photolysis. The *N*-oxides prepared in this way are summarized in Table 35 (118,119,128,144,168). The isolated oxazirines are listed in Table 36 (119,169).

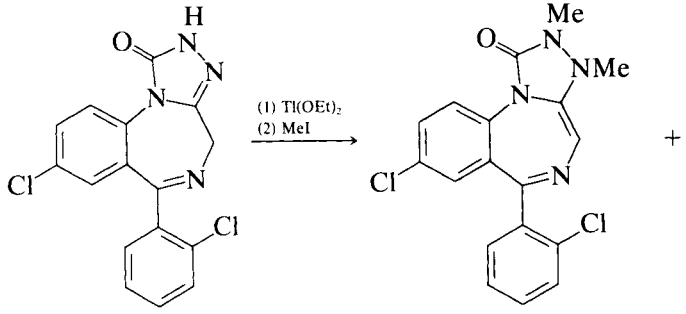



**217**

(54)

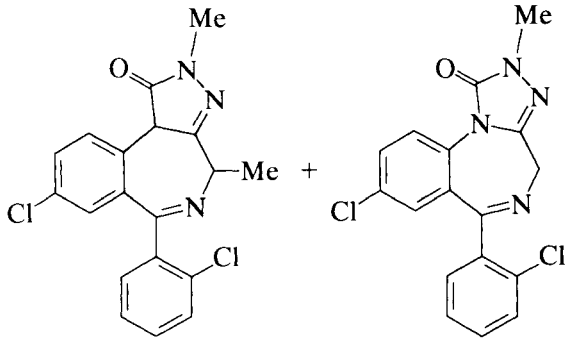



**259**, mp 175.5–176.5°C

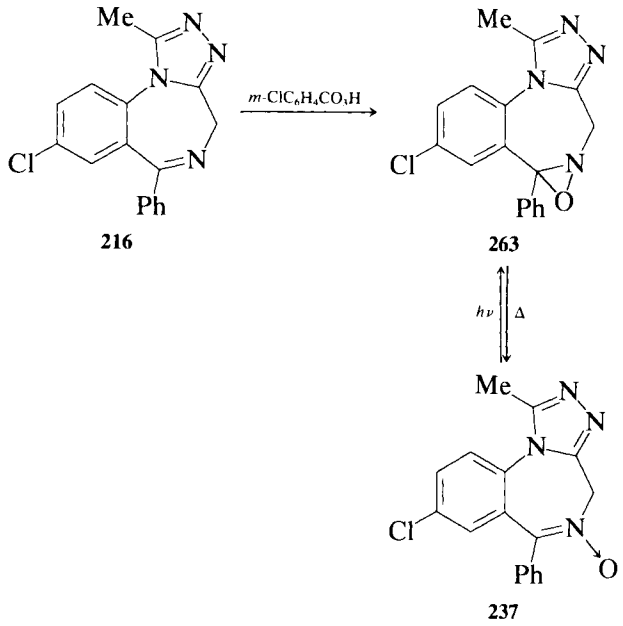



**260** **262a**, mp 208–210°C (6%)

(55)



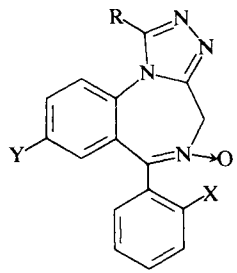

**262b**, mp 153–155°C (12%) **261**, mp 82–84°C (37%)




(56)

$N^5$-Oxides of this ring system could also be used to functionalize the 4-position via the Polonovski rearrangement, as shown in Fig. 19. Additional examples of these products are given in Table 37 (144,170,171). 4-Methoxy derivatives were prepared via the corresponding acetates or alcohols by

TABLE 35. $N^5$-OXIDES FROM [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES




| X | Y | R | mp (°C) | Refs. |
|---|---|---|---|---|
| H | Cl | Me | 267.5–268.5 | 119,144,159 |
| H | Cl | $CH_2OH$ | 267–269 | 118,119,128 |
| H | Cl | $CH(OEt)_2$ | 200–202 | 119 |
| Cl | Cl | $CH(OEt)_2$ | 221–222 | 119 |
| H | Cl | $CH_2OCH_2Ph$ | 189–193 | 118 |
| H | Cl | $CH_2OMe$ | 244–248 | 118 |

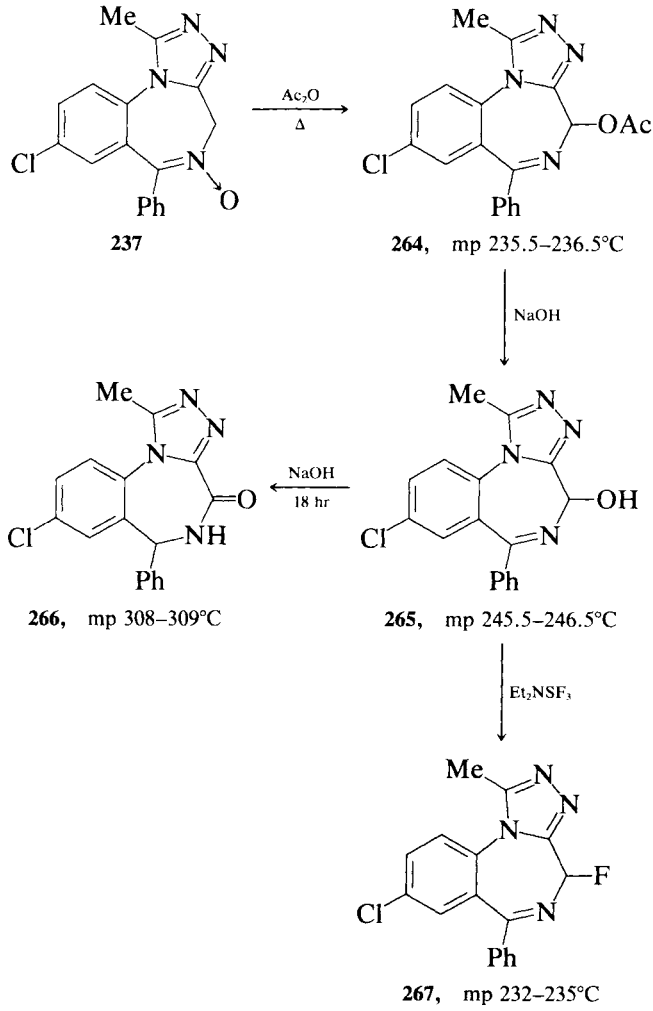



**Figure 19**

treatment with acidic methanol (170). The 4-fluoro derivative **267** was prepared by treatment of the hydroxy compound **265** with diethylaminosulfur trifluoride (171).

The 4-position is susceptible to direct alkylation, as outlined in Fig. 20. Treatment of **216** with sodium hydride and reaction of the resultant anion with diethyl carbonate gave the 4-carbethoxy derivative **268.** Repeated treatment with sodium hydride followed by methyl iodide led to the geminally substituted compound **269** (140). The anion of **268** was also condensed with *O*-(2,4-dinitrophenyl)hydroxylamine to produce the amino ester **271.** Ester hydrolysis with hot aqueous sodium hydroxide and concomitant decarbox-

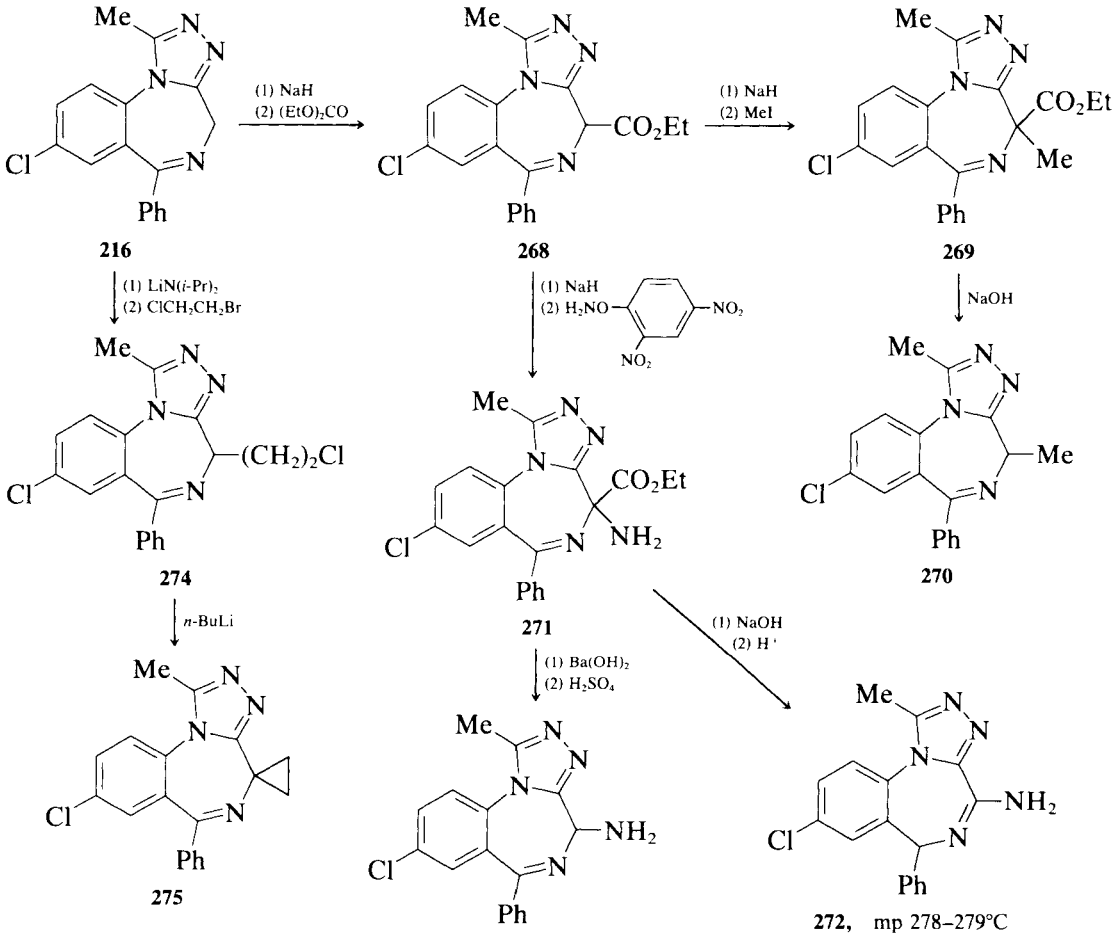
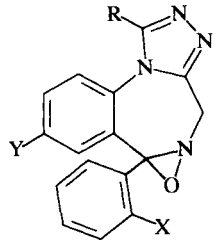

Me
N
N
N
Cl
N
Ph
(1) NaH
(2) (EtO)2CO
CO2Et
(1) NaH
(2) MeI
Me
216
268
269
(1) LiN(i-Pr)2
(2) ClCH2CH2Br
(CH2)2Cl
(1) NaH
(2) H2NO
NO2
NO2
NaOH
274
271
270
n-BuLi
NH2
(1) NaOH
(2) H+
(1) Ba(OH)2
(2) H2SO4
275
273, mp 208°C
272, mp 278–279°C

**Figure 20**

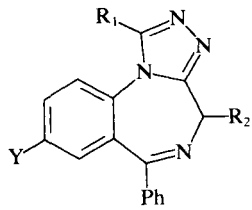
TABLE 36. OXAZIRINES FROM [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES



| X | Y | R | mp (°C) |
|---|---|---|---|
| H | Cl | $CH_2OH$ | 167–169 |
| H | Cl | $CH(OEt)_2$ | 136–137 |
| H | Cl | $CH(OMe)_2$ | 141–142 |
| H | Cl | Me | 227.5–228 |

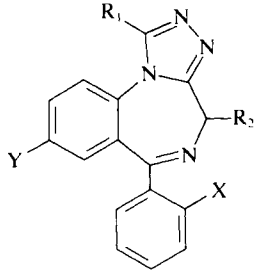
ylation gave the isomerized amino derivative **272.** Treatment of **271** with barium hydroxide at ambient temperature avoided this isomerization and gave amine **273** (98,172). A method of 4-spiroannelation involving alkylation with 2-chloroethyl bromide was also devised. The intermediate **274** was cyclized to spirocyclopropane **275** by intramolecular alkylation in the presence of butyllithium. Alkylations at $C_4$ are recorded in Table 38 (98,102,116,123,172,173).

TABLE 37. 4-SUBSTITUTED [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES



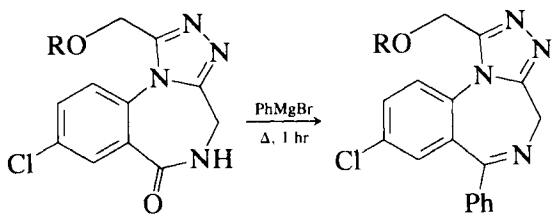
| Y | $R_1$ | $R_2$ | mp (°C) | Refs. |
|---|---|---|---|---|
| Cl | H | AcO | 232–233 | 144,170 |
| Cl | Me | AcO | 229–230 | 170 |
| Cl | Et | AcO | 254–255 | 170 |
| $NO_2$ | H | AcO | 253–254 | 170 |
| Cl | Me | OH | 241–242 | 144,170 |
| $NO_2$ | Me | OH | 236.5 | 170 |
| Cl | Me | MeO | 245.5 | 170 |
| Cl | H | MeO | 270–271 | 170 |
| Cl | Me | F | 232–235 | 171 |

TABLE 38. 4-SUBSTITUTED [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES



| X | Y | $R_1$ | $R_2$ | mp (°C) | Refs. |
|---|---|---|---|---|---|
| H | Cl | H | *i*-Pr | 140.5–141.5 | 102 |
| H | Cl | $CH(OEt)_2$ | Me | 151–153 | 123,124 |
| H | Cl | Me | $CO_2Et$ | 223–224 | 140 |
| H | Cl | Me | $CH_3$, $CO_2Et$ | 175.5–176.5 | 140 |
| H | Cl | Me | Me | 199–200.5 | 140 |
| Cl | Cl | Me | $CH_2CH_2Cl$ | 197–198 | 173 |
| Cl | Cl | Me | $—CH_2CH_2—$ | 199–202.5 | 173 |
| H | Cl | Me | $CH_2CH_2Cl$ | 205–209 | 173 |
| H | Cl | $CH_2NMe_2$ | $CH_2CH_2Cl$ | 160–162 | 173 |
| H | Cl | $CH_2NMe_2$ | $—CH_2CH_2—$ | 199–201 | 173 |
| Cl | Cl | $CH_2NMe_2$ | $CH_2CH_2Cl$ | 173–175 | 173 |
| Cl | Cl | $CH_2NMe_2$ | $—CH_2CH_2—$ | 273–275 | 173 |
| H | Cl | Me | $CO_2Et$, $NH_2$ | 177.5–178 | 98,172 |
| H | Cl | Me | $NH_2$ | 208 | 98,172 |
| F | Cl | Me | Me | 173–178 | 116 |

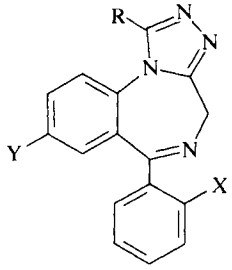
The 6-position has been substituted not only by incorporation of the appropriate group (usually aryl) at the start of the synthesis, but also by addition of an aryl Grignard reagent to a 6-amido derivative at the end of the synthetic sequence. Reaction of phenylmagnesium bromide with **276** (117,174) resulted in the desired addition–dehydration (Eq. 57). The compounds prepared in this manner are listed in Table 39 (117,175).




(57)

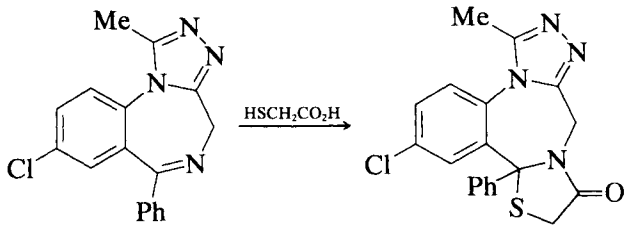
| | R | mp (°C) |
|---|---|---|
| **276a** | Me | 157–159 |
| **276b** | $CH_2Ph$ | 185–191 |

TABLE 39. [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES FROM 6-LACTAMS



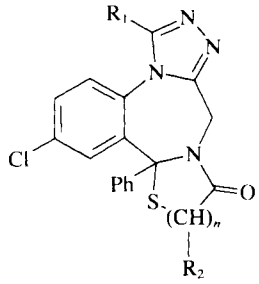
| X | Y | R | mp (°C) | Refs. |
|---|---|---|---|---|
| H | Cl | $CH_2OCH_2Ph$ | 162–164 | 117,175 |
| H | Cl | $CH_2NMe_2$ | 165–166 | 117,175 |
| F | Cl | $CH_2NMe_2$ | 143–144 | 117,175 |
| Cl | Cl | $CH_2NMe_2$ | 198–200 | 117,175 |
| H | Cl | $CH_2NEt_2$ | 126–128 | 117,175 |
| H | Cl | $CH_2OCH_2C_6H_4OMe$-*p* | 157–159 | 117,175 |
| H | Cl | $CH_2OEt$ | 161–165 | 117,175 |
| H | Cl | $CH_2CH_2OEt$ | 128–132 | 117,175 |
| H | Cl | $CH_2CH_2OCH_2Ph$ | 115–117 | 117,175 |
| H | H | $CH_2OCH_2Ph$ | 167–168 | 117,175 |
| H | Cl | $CH_2OMe$ | 185–191 | 175 |
| F | Cl | $CH_2OCH_2C_6H_4OMe$-*p* | 163.5–165 | 117,175 |
| Cl | Cl | $CH_2OCH_2C_6H_4OMe$-*p* | 200–203 | 117,175 |
| H | Cl | $CH(OEt)_2$ | 133–135 | 117,175 |
| F | Cl | $CH(OEt)_2$ | 120–121 | 117,175 |
| Cl | Cl | $CH(OEt)_2$ | 120–121.5 | 117,175 |
| H | Cl | $CH_2CH(OMe)_2$ | 166–172 | 117 |
| H | Cl | $CH_2OH$ | 210–211 | 117 |
| H | H | $CH_2OH$ | 205–206 | 117 |
| Cl | Cl | $CH_2OH$ | 235–237 | 117 |
| F | Cl | $CH_2OH$ | 195–197 | 117 |

Ring fusion onto the 5,6-imine bond of the tricyclic system has been carried out to produce tetracyclic diazepines (90,176). The use of mercaptoacetic acid led to **277** (Eq. 58). Use of other substrates and other mercapto acids led to the examples listed in Table 40 (90,176). Cycloaddition of the



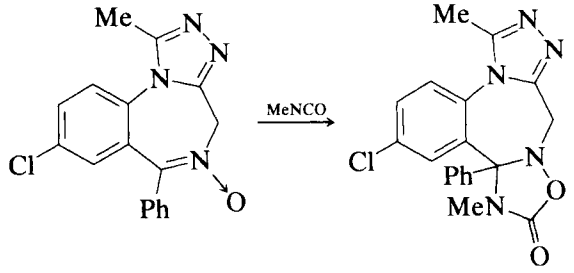
**216** **277** (58)

TABLE 40. TETRACYCLES FROM [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES



| $R_1$ | *n* | $R_2$ | Refs. |
|---|---|---|---|
| Me | 1 | H | 90,176 |
| Me | 2 | H | 176 |
| H | 1 | H | 176 |
| H | 1 | Me | 176 |
| Me | 1 | Me | 176 |

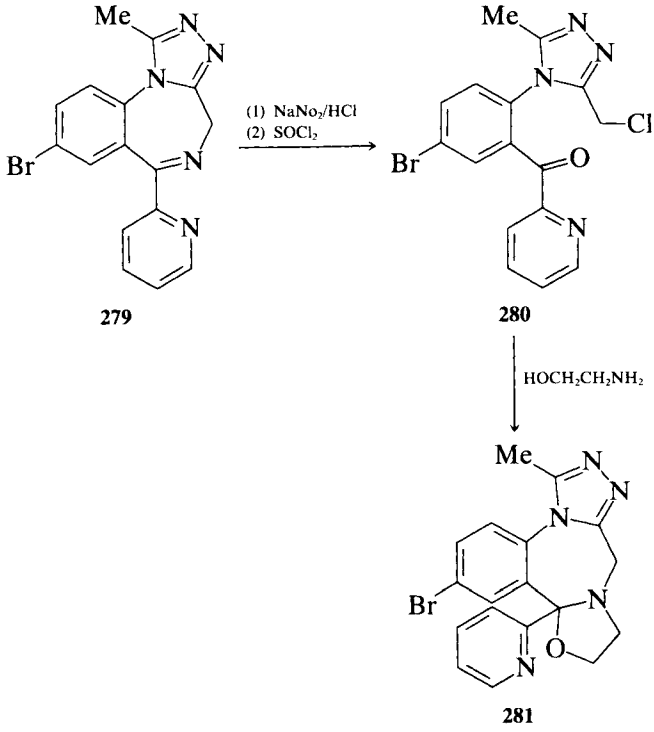
tricyclic $N^5$-oxides with isocyanates and thioisocyanates led to tetracyclic diazepines such as **278** (Eq. 59), with additional examples listed in Table 41 (177). Tetracyclic diazepines were also attained from tricyclic diazepines, such as **279,** by cleavage of the diazepine ring and subsequent cyclization. The sequence is outlined in Eq. 60. Compound **281** and related structures obtained by this route are listed in Table 42 (178).



(59)

**278**

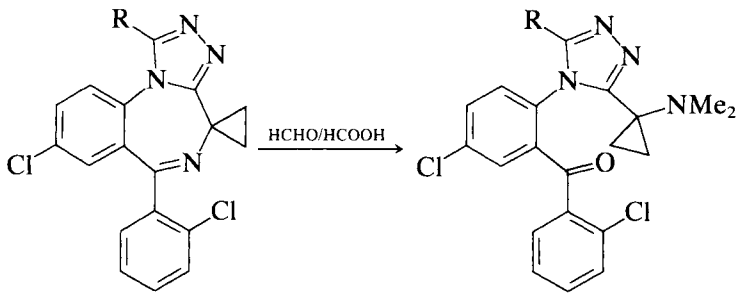
Several processes involving cleavage of the diazepine ring of the tricyclic system have been developed. Under Eschweiler–Clarke conditions (Eq. 61), the 5,6-imine bond was hydrolyzed and the free amine underwent reductive methylation to yield **282** (179). Other examples are listed in Table 43 (115,161,180,181). The diazepine ring was also cleaved to the secondary amine **283** by alkylation with trimethyloxonium fluoroborate followed by




(60)

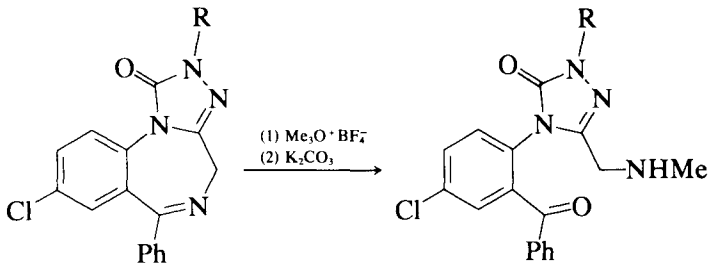
hydrolysis of the iminium salt with aqueous potassium carbonate (Eq. 62) (182,193).

An additional method of diazepine ring opening was developed using the Wolff–Kishner reaction, as summarized in Eq. 63 (184). Treatment of **214** with hydrazine presumably caused isomerization of the 5,6-bond to the 4,5-




(61)

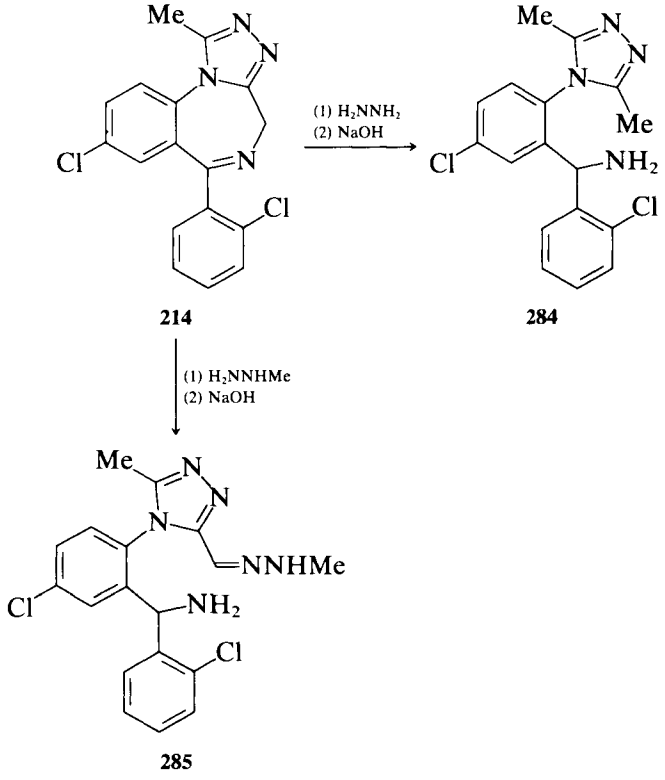
| | R | mp (°C) | Yield (%) |
|---|---|---|---|
| **282a** | Me | 150–158 | 63 |
| **282b** | $CH_2NMe_2$ | 168.5–170 | — |




(62)

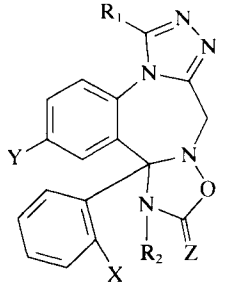
| | R | mp (°C) | Yield (%) |
|---|---|---|---|
| **283a** | H | 138–139 | 42 |
| **283b** | Me | 175–177 | 58 |

position, followed at once by hydrolysis of the imine and reduction of the exposed aldehyde to **284.** Use of methylhydrazine in place of hydrazine allowed the isolation of the intermediate hydrazone **285.** Compounds generated by this process are listed in Table 44 (184).




(63)

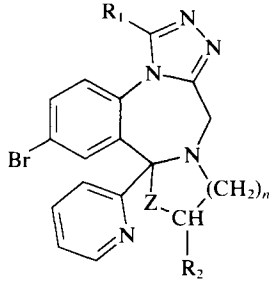
TABLE 41. TETRACYCLES FROM $N^5$-OXIDES OF [1,2,4]TRIAZOLO-[4,3-*a*][1,4]BENZODIAZEPINES[a]



| X | Y | $R_1$ | $R_2$ | Z |
|---|---|---|---|---|
| H | $NO_2$ | H | Me | O |
| H | Cl | Me | Me | O |
| H | Cl | H | $C_6H_4Cl$-*p* | O |
| Cl | Cl | H | Ph | O |
| H | Cl | Me | Me | S |

[a]Ref. 177.

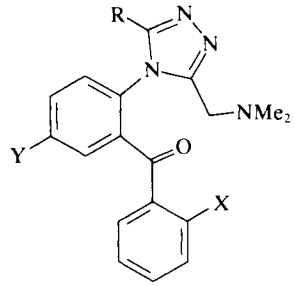
TABLE 42. TETRACYCLES BY CLEAVAGE–RECYCLIZATION OF [1,2,4]TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES[a]



| $R_1$ | *n* | $R_2$ | Z | mp (°C) |
|---|---|---|---|---|
| Me | 1 | H | O | 268–269 |
| H | 1 | Me | O | 247–249 |
| H | 1 | H | O | 265–267 |
| Et | 1 | H | O | 287–289 |
| Me | 2 | H | O | 238–239 |
| Me | 1 | Me | O | 233–235 |
| Me | 1 | H | NH | 245–246 |

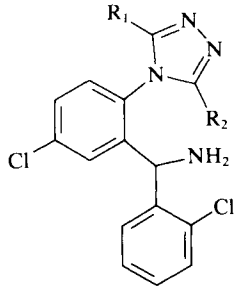
[a]Ref. 178.

TABLE 43. RING-OPENED PRODUCTS OF [1,2,4]TRIAZOLO-[4,3-*a*][1,4]BENZODIAZEPINES



| X | Y | R | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|
| H | Cl | $CH_2CH_2NMe_2$ | 47 | 85–88 | 161 |
| Cl | Cl | $CH_2OH$ | 25 | 154–162 | 161 |
| Cl | Cl | 4-Pyridyl | 48 | 171–173.5 | 115 |
| Cl | Cl | Cyclopropyl | 51 | 109–115 | 115 |
| H | Cl | 2-Furyl | 60 | 156–159 | 115 |
| Cl | Cl | $CH_2OH$ | | 138–141 | 181 |
| H | Cl | $CH_2NMe_2$ | | 150–152 | 181 |
| H | Cl | H | | 139–141 | 181 |

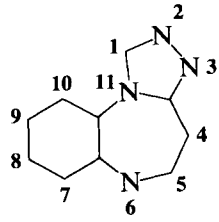
TABLE 44. HYDRAZINE CLEAVAGE PRODUCTS OF [1,2,4]TRIAZOLO-[4,3-*a*][1,4]BENZODIAZEPINES[a]



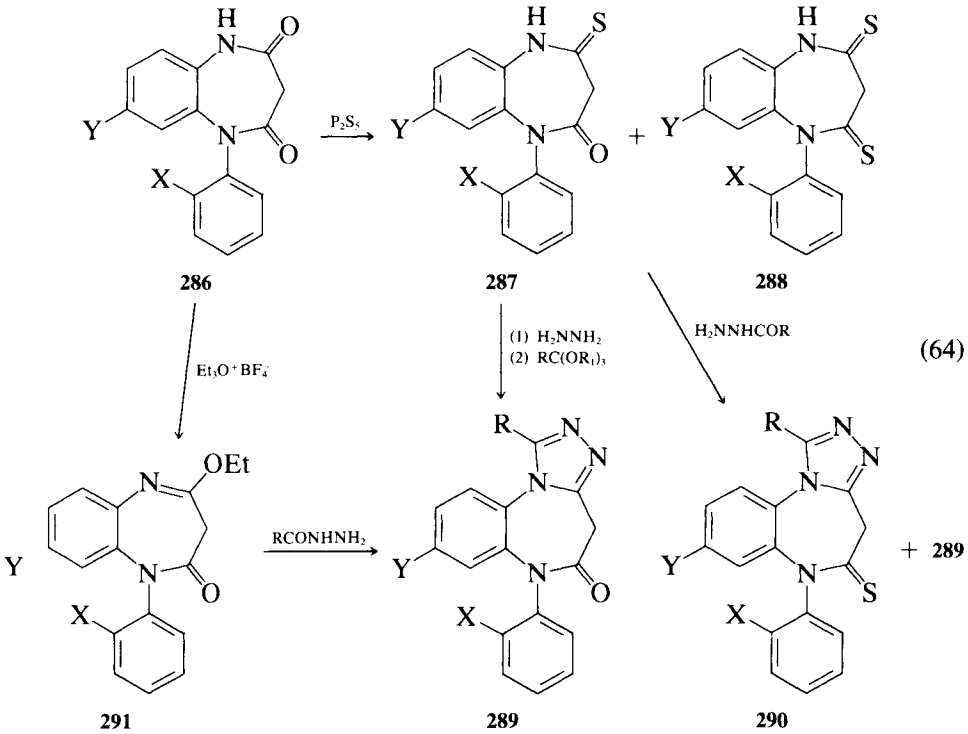
| $R_1$ | $R_2$ | mp (°C) |
|---|---|---|
| Me | Me | 192–193 |
| Me | CH=N—NHMe | 173–184 |
| Me | CH=N—$NMe_2$ | 217–219 |
| | | 197.5–198.5 |
| $CH_2NMe_2$ | Me | 148–150 |
| $CH_2OH$ | Me | 218–223 |
| | | 225–229 |

[a]Ref. 184.

## 13. [1,2,4]Triazolo[4,3-*a*][1,5]benzodiazepines (see Section XV.9)



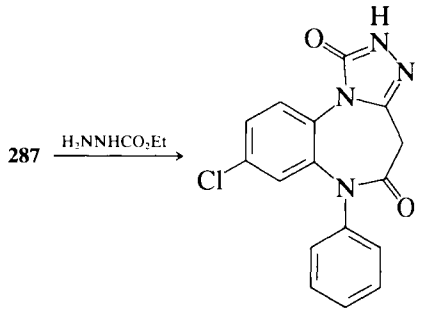

The primary mode of synthesis of the [1,2,4]triazolo[4,3-*a*][1,5]-benzodiazepine ring system begins with 1,5-benzodiazepinedione **286.** As outlined in Eq. 64, reaction of **286** with phosphorus pentasulfide led to a




(64)

mixture of thione **287** and dithione **288.** After chromatographic separation, thione **287** was converted to **289** by treatment with hydrazine and acid derivatives or directly with acyl hydrazides. Alternatively, the mixture of **287** and **288** could be converted to a mixture of triazoles **289** and **290,** which

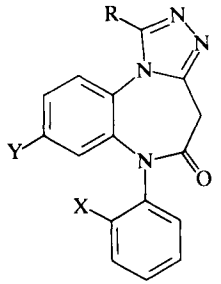
were then separated (185,186). Separation problems arising from nonspecific thione formation were avoided by initial conversion of **286** to the imino ether **291** with triethyloxonium fluoroborate, followed by reaction with acyl hydrazides, to give **289** as the sole product (187). When the acyl hydrazide was ethyl carbazate, thione **287** (Eq. 65) was converted to 1,5-dione **292** (188,189). The chemistry of this system parallels that of the corresponding [1,2,4]-triazolo[4,3-*a*][1,4]benzodiazepine system (190). Compounds prepared by these methods are listed in Table 45. These derivatives have anticonvulsant and tranquilizing properties.




(65)

**292**, mp 110–112°C

TABLE 45. 5-OXO[1,2,4]TRIAZOLO[4,3-*a*][1,5]BENZODIAZEPINES



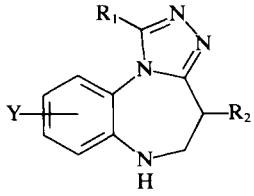

| R | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|
| Me | H | Cl | 302–305 | 185–188 |
| $CH_2Cl$ | H | Cl | 306–308 | 185,188 |
| $CH_2NMe_2$ | H | Cl | 235–236 | 185,188 |
| Me | H | $CF_3$ | 269–271 | 186,187 |
| Me | H | $NO_2$ | 302–305 | 187 |
| H | H | Br | 282–284 | 187 |
| Ph | H | $CF_3$ | 238–241 | 187 |

(*continued*

TABLE 45. (*Continued*)

| R | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|
| H | H | Cl | 284–286 | 187 |
| H | H | $NO_2$ | 310–313 | 187 |
| H | Cl | Cl | 280–283 | 187 |
| $CH_2OH$ | H | $NO_2$ | 175–180 | 187 |
| $CH_2OH$ | H | Cl | 278–280 | 187 |
| $CH_2OH$ | H | $CF_3$ | 240–242 | 187 |
| Et | H | Cl | 290–292 | 187 |
| H | Cl | $NO_2$ | 256–258 | 187 |
| H | $CF_3$ | Cl | 294–296 | 187 |
| H | F | Cl | 211–213 | 187 |
| Cyclohexyl | H | Cl | 260–262 | 187 |
| Isopropyl | H | Cl | 318–320 | 187 |
| H | $NO_2$ | $CF_3$ | 302–306 | 187 |
| *n*-Propyl | H | Cl | 318–320 | 187 |
| Me | $CF_3$ | Cl | 252–255 | 187 |
| *n*-Butyl | H | $NO_2$ | 233–235 | 187 |
| Me | Cl | Cl | 278–280 | 187 |
| H | $NO_2$ | Cl | 250–252 | 187 |
| Me | $NO_2$ | Cl | 287–290 | 187 |
| H | H | $CF_3$ | 261–263 | 187 |

TABLE 46. [1,2,4]TRIAZOLO[4,3-*a*][1,5]BENZODIAZEPINES[a]




| $R_1$ | $R_2$ | Y | Yield (%) | mp (°C) |
|---|---|---|---|---|
| *p*-$ClC_6H_4$ | Me | 9-Cl | 79 | 213–214 |
| *o*-$MeOC_6H_4$ | Me | 9-Cl | 79 | 226–227 |
| 2-Naphthyl | Me | 9-Cl | 73 | 205–206 |
| 2-Thienyl | Me | 9-Cl | 50 | 202 |
| 2-Furyl | Me | 9-Cl | 63 | 197–199 |
| $C_6H_5$ | H | H | 46 | 183–185 |
| $C_6H_5$ | Me | 9-MeO | 48 | 230–231 |
| *p*-$MeOC_6H_4$ | Me | 8-Cl | 59 | 203–204 |
| *p*-$MeOC_6H_4$ | Me | H | 37 | 232–234 |
| *p*-$ClC_6H_4$ | Me | 8-Cl | 69 | 240–242 |
| *p*-Tolyl | Me | 8-Cl | 76 | 244–246 |

[a]Ref. 191.

Another method used to obtain this ring system (Fig. 21) led to compounds with analgetic and anti-inflammatory effects (191). The key intermediate **293**, prepared from *o*-nitroaniline derivatives, was transformed into the product **294** by the usual methods. Other members of this series are listed in Table 46.

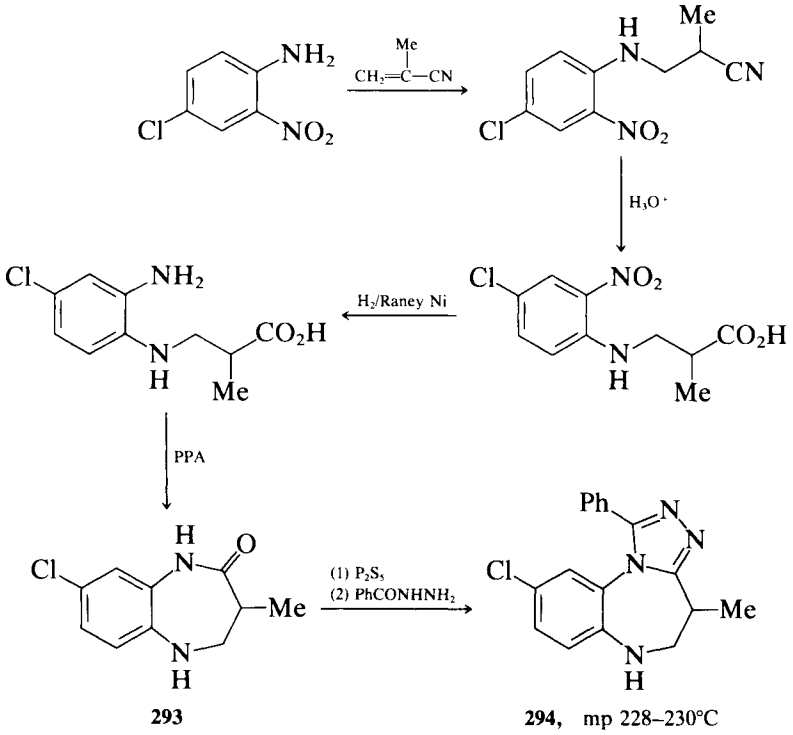
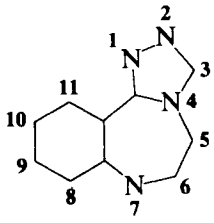
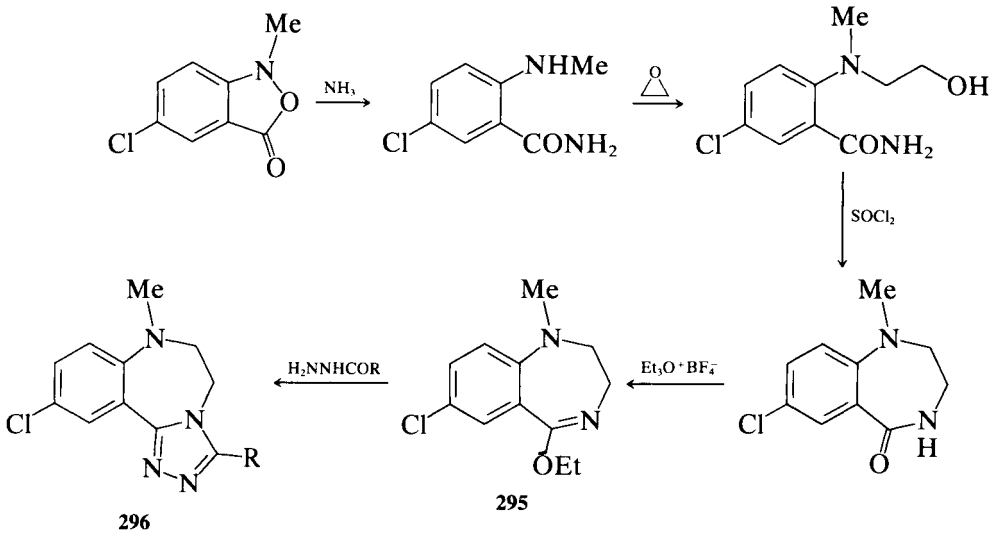



Figure 21

## 14. [1,2,4]Triazolo[4,3-*d*][1,4]benzodiazepines (see Section XV.10)

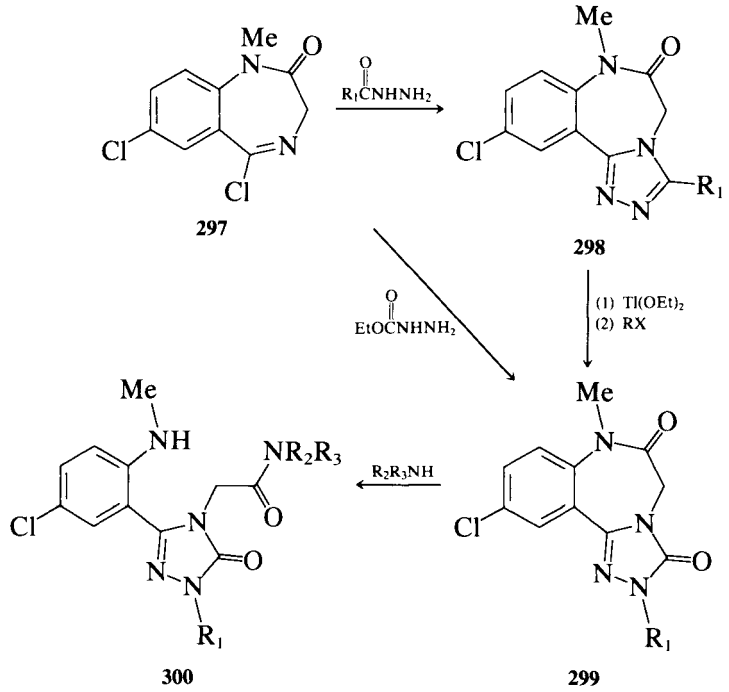



[1,2,4]Triazolo[4,3-*d*][1,4]benzodiazepines have anti-inflammatory, anticonvulsant, and anxiolytic properties. One method of preparation of the ring system (Eq. 66) began with the conversion of *N*-methyl-4-chloroisatoic an-




(66)

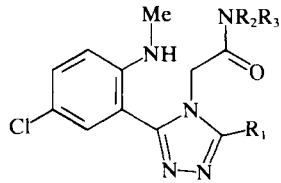
hydride to the key intermediate **295** (68,192). Reaction of benzodiazepine **295** with hydrazides then afforded the triazoles **296.** In a similar fashion, condensation of lactam **297** with acyl hydrazides (Eq. 67) gave the diazepinones **298** (193–197). By treatment with ethyl carbazate, **297** was trans-

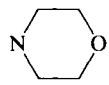
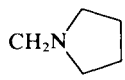



(67)

formed to the 3,6-dione derivative **299** (R = H), which could be alkylated at the 2-position (197,199). Finally, the diazepine ring of **299** could be opened by reaction with amines to form the amides **300**, examples of which are listed in Table 47. An alternative route to this ring system is exemplified by the reaction of quinazoline **301** with triethyl orthoformate, which yielded a triazole, as shown in Fig. 22. Subsequent ring expansion using aqueous sodium hydroxide afforded **302** (85,195). Compounds prepared by these methods are listed in Table 48.

TABLE 47. RING-OPENED [1,2,4]TRIAZOLO[4,3-*d*][1,4]BENZODIAZEPINES[a]

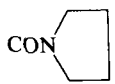
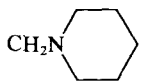
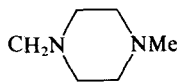


| $R_1$ | $NR_2R_3$ | mp (°C) | Salt |
|---|---|---|---|
| $CF_3$ |  | 161–162.5 | HCl |
| $CF_3$ |  | 152–153 | |
|  |  | 247–248.5 | HCl |

[a]Ref. 197.

The methiodide of **299** (R = $(CH_2)_2NMe_2$) was subjected to X-ray analysis (193), and some of the spectral properties of this class have been presented (85,193,194). In addition, the free energy of activation for ring inversion ($\Delta F^*$) has been determined by analysis of the temperature dependence of the chemical shift of the $C_5$ and $C_6$ methylene protons. The results indicate that replacement of the phenyl group in diazepam with fused triazole or triazolone results in a significant increase in the conformational mobility of the seven-membered ring, which is believed to be an important determinant of biological activity (193).

TABLE 48. [1,2,4]TRIAZOLO[4,3-*d*][1,4]BENZODIAZEPINES

| Intermediate | R | Yield (%) | mp (°C) | Salt | Refs. |
|---|---|---|---|---|---|
| **296** | Me | 62 | 185–186.5 | | 68,192 |
| **296** | Ph | | 207.5–208.5 | | 68 |
| **296** | OH | | 259–262 | | 68 |
| **298** | H | 84 | 273–275 | | 193,195,197 |
| **298** | Me | 74 | 229–230 | | 193 |
| **298** | Ph | 82 | 204–205.5 | | 193,195,197 |
| **298** | $CF_3$ | 70 | 186–187 | | 193,195,197 |
| **298** | $CO_2Et$ | 20 | 200–202 | | 193,194 |
| **298** | Me | | 278–280 | | 85 |
| **298** | $CONH_2$ | | 303–304 | | 194,195 |
| **298** |  | | 200.5–201 | | 194,195 |
| **298** | $CH_2CN$ | | 252–253.5 | | 195 |
| **298** | $CH_2Cl$ | | 193–194.5 | | 195,197 |
| **298** |  | | 238–240 | | 195 |
| **298** |  | | 228.5–230.5 | HCl | 195,197 |
| **298** | *o*-$ClC_6H_4$ | | 170–175 | | 196 |
| **299** | H | 85 | 268–269 | | 193,199 |
| **299** | Me | | 292–294 | | 193,198 |
| **299** | $CH_2CH_2NMe_2$ | 71 | 284–285.5 | HCl | 193,199 |
| **299** | $(CH_2)_3NMe_2$ | | 178–179 | | 199 |
| **299** | $(CH_2)_3OH$ | | 171–172 | | 199 |
| **299** | Ph | | 174–175 | | 198 |
| **299** | $CH_2Ph$ | | 120–122 | | 198 |

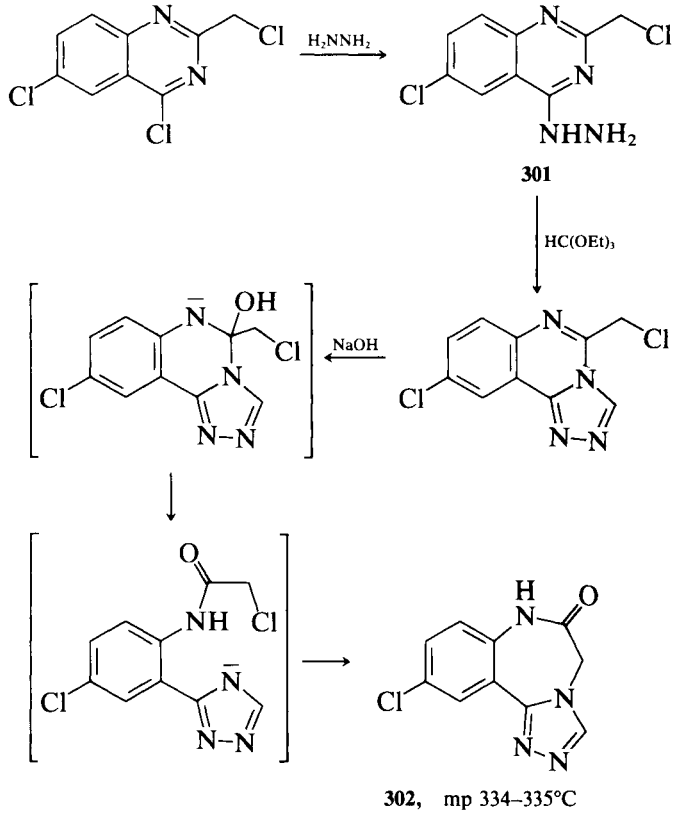
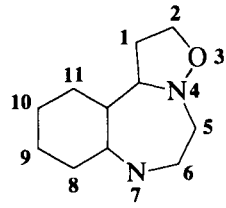
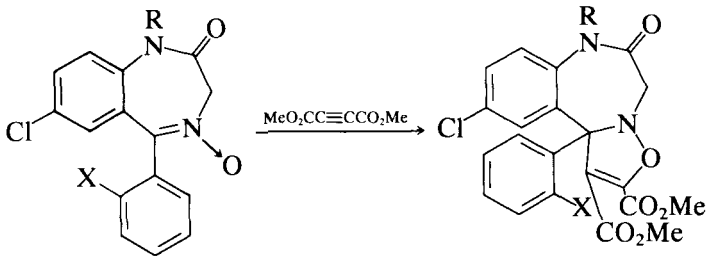



Figure 22

## 15. Isoxazolo[2,3-*d*][1,4]benzodiazepines (see Section XV.12)



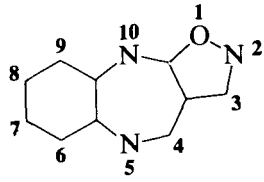
Isoxazolo[2,3-*d*][1,4]benzodiazepines are reported to have sedative, anticonvulsant, muscle relaxant, and hypnotic actions. Their synthesis was achieved by condensation of diazepine *N*-oxide **303** with dimethyl acetylenedicarboxylate (Eq. 68), which yielded the expected adduct **304** (200). Nmr studies showed that the energy barrier to stereochemical inversion for this ring system was comparable to that for diazepam (17.7 kcal/mole) (201).



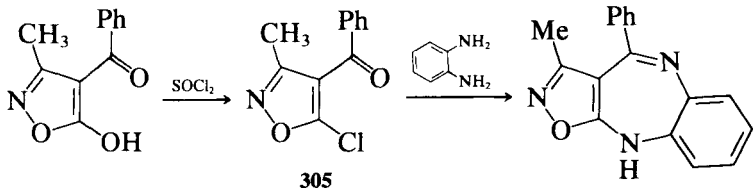

303 304 (68)

| | R | X | mp (°C) |
|---|---|---|---|
| **304a** | Me | H | 126–127 |
| **304b** | H | H | 118–119 |
| **304c** | Me | F | 144.5–145.5 |

## 16. Isoxazolo[5,4-*b*][1,5]benzodiazepines

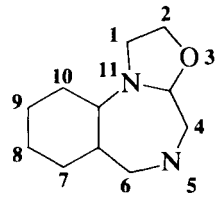



Among the reactions included in a study of the chemistry of 3-methyl-4-benzoyl-5-chloroisoxazole (**305**) was its reaction with *o*-phenylenediamine (Eq. 69), which gave the diazepine **306** in 98% yield (202). The starting material can be prepared from the corresponding 5-hydroxyisoxazole with thionyl chloride (203). Since compound **305** is essentially a β-chloro unsaturated ketone, its reaction with the diamine can be considered typical of the formation of simpler 1,5-benzodiazepines.

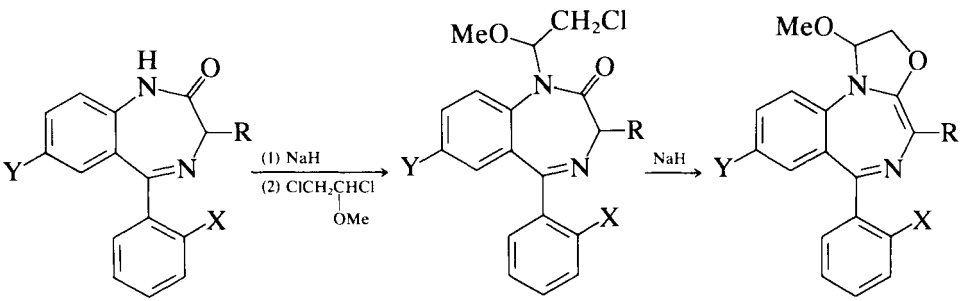



305 306, mp 182°C (69)

## 17. Oxazolo[3,2-*a*][1,4]benzodiazepines

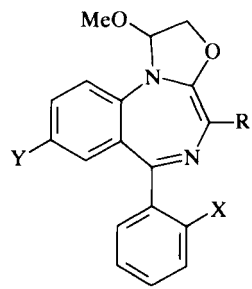


Diazepines of general structure **308**, which display tranquilizing and anticonvulsant activity, were prepared by alkylation of **307** with 1,2-dihaloethane derivatives followed by cyclization with base (204). The sequence is shown in Eq. 70, and the tricyclic diazepines synthesized in this way are listed in Table 49.



**307** **308** (70)

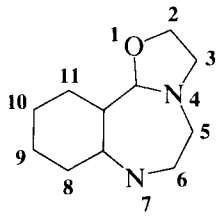
TABLE 49. OXAZOLO[3,2-*a*][1,4]BENZODIAZEPINES[a]



| X | Y | R | mp (°C) |
|---|---|---|---|
| H | Cl | H | 184–186 |
| H | Cl | $CO_2Et$ | 220–223 |
| F | I | H | 170–172 |

[a]Ref. 204.

## 18. Oxazolo[3,2-*d*][1,4]benzodiazepines (see Section XV.13)




A number of synthetic routes to the oxazolo[3,2-*d*][1,4]benzodiazepine ring system have been developed. One method (Fig. 23) employed aminobenzophenone derivative **309** as a starting material. Treatment of **309** with

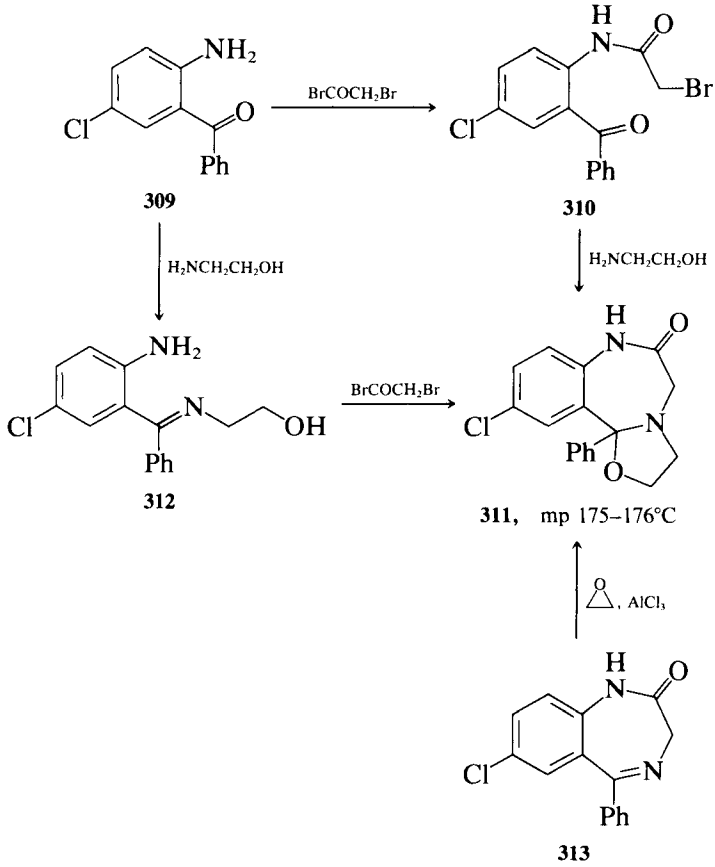


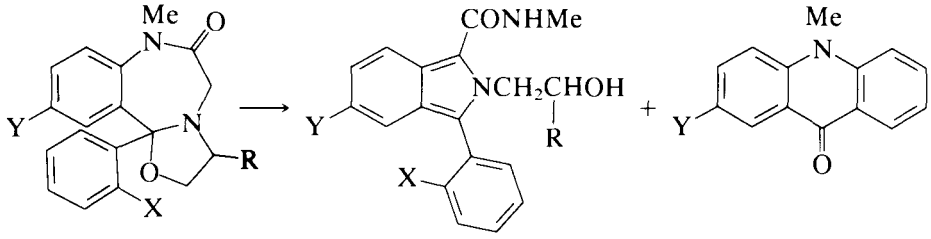

**Figure 23**

bromoacetyl bromide afforded bromoacetamide **310.** Condensation with ethanolamine completed the synthesis of **311.** Alternatively, the reactants were added in the reverse sequence to give the same product (**311**) via imine **312** (205,219). In a modification of the basic scheme, aziridine was substituted for ethanolamine in the transformation of **310** to **311** (220,221). Another approach to this tricyclic system began with the benzodiazepine **313.** Acid-catalyzed addition of ethylene oxide to **313** resulted in conversion to **311** (212,215,216,222,223). A closely related method replaced the epoxide with bromohydrins (224–226) and with ethylene carbonate (227). In a further functionalization of **311** the amide nitrogen was alkylated by treatment with base (sodium methoxide or sodium hydride) and subsequent addition of a reactive alkyl halide (205,211,212,215,216,222,228–230). Additional examples of this system are listed in Table 50. Several reduced derivatives prepared from **310** by treatment with lithium aluminum hydride are listed in Table 51.

Still another entry into this ring system was achieved via oxadiazolobenzodiazepine **314** (69). In the presence of an acidic catalyst, compound **314** rearranged to oxazolobenzodiazepine **315,** as shown in Fig. 24. Compound **315** was transformed to the lactam **316** by transoximation with formaldehyde. The oxime **315** could also be acylated to the corresponding chloroacetate **317.** These compounds are listed in Table 52.

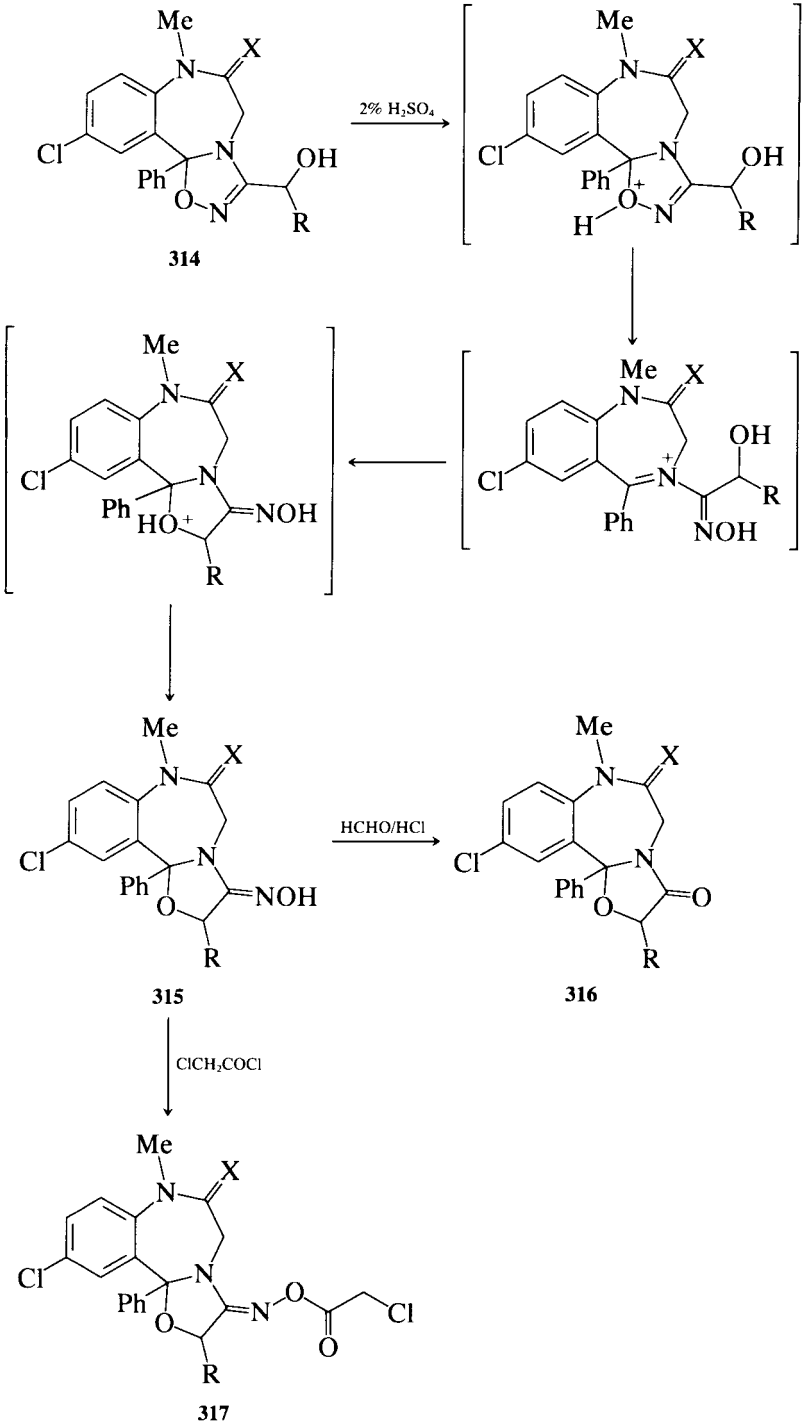
Several other reactions have been carried out with members of this ring system. Treatment of **311** with acid generated the iminium chloride **318** (Eq. 71). Additional examples of this fragmentation are listed in Table 53 (225).

An extensive rearrangement occurred under acylation conditions. Whereas compound **319a** was transformed to **320** (Fig. 25), compound **319b** underwent rearrangement to **321** and **322.** A possible mechanism for the formation of **321** and **322** is outlined in Fig. 26 (233).




**319b-d** **321** **322**

| X | Y | R | Yield (%) | mp (°C) | Yield (%) | mp (°C) |
|---|---|---|---|---|---|---|
| Cl | Cl | H | 7.5 | 186–189 | 4.5 | 176 |
| Cl | Br | H | 5.0 | 187–190 | 4.0 | 198–200 |
| Cl | Cl | Me | 2.5 | 182–183 | 5.0 | 176 |

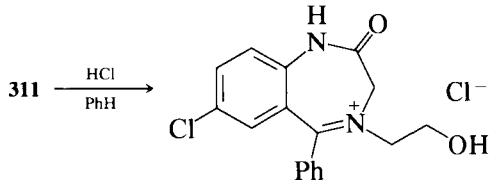



**314** **315** **316** **317**

**Figure 24**

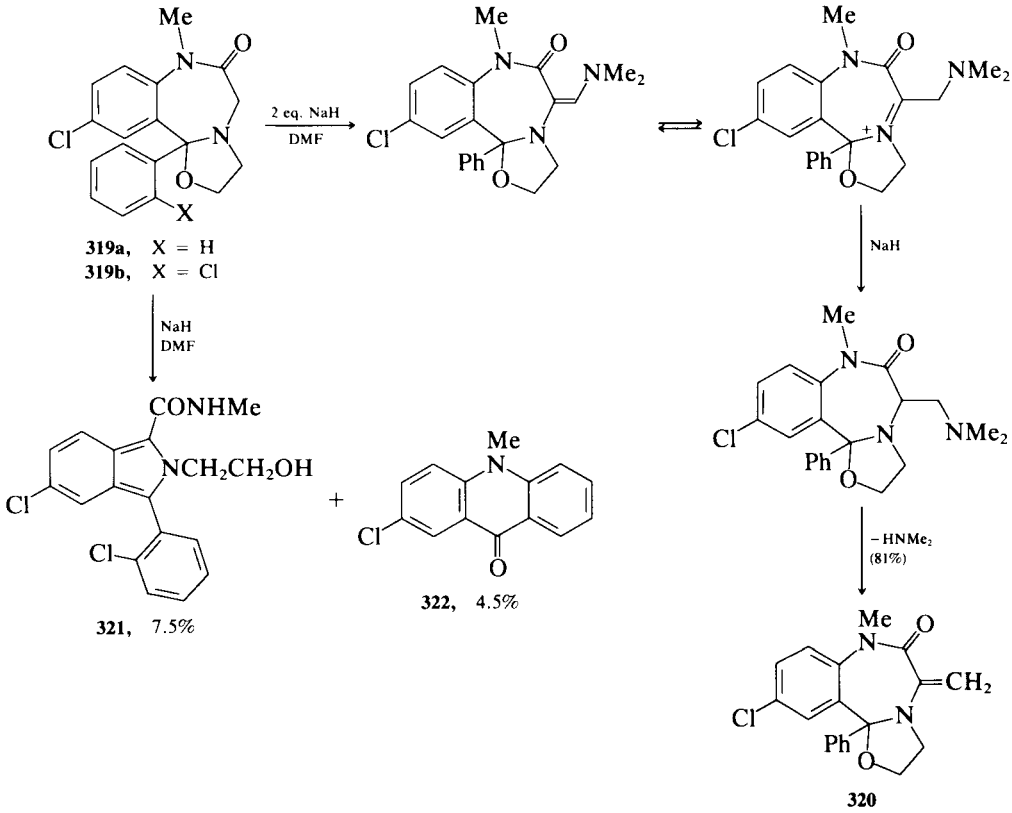
A similar ring contraction took place during the reaction of **319a** with sodium hydride and dimethylacetamide, which yielded **323** and **324** (234), as shown in Eq. 72.

Ring contraction to isoindoles **325, 326,** and **327** ensued on treatment of **319a** with acetic anhydride in pyridine (Eq. 73). The mechanism of these rearrangements is analogous to the sodium hydride/DMF reaction discussed above (235).




(71)

**318,** mp 243°C




**319a,** X = H
**319b,** X = Cl

**321,** 7.5%

**322,** 4.5%

**320**

**Figure 25**

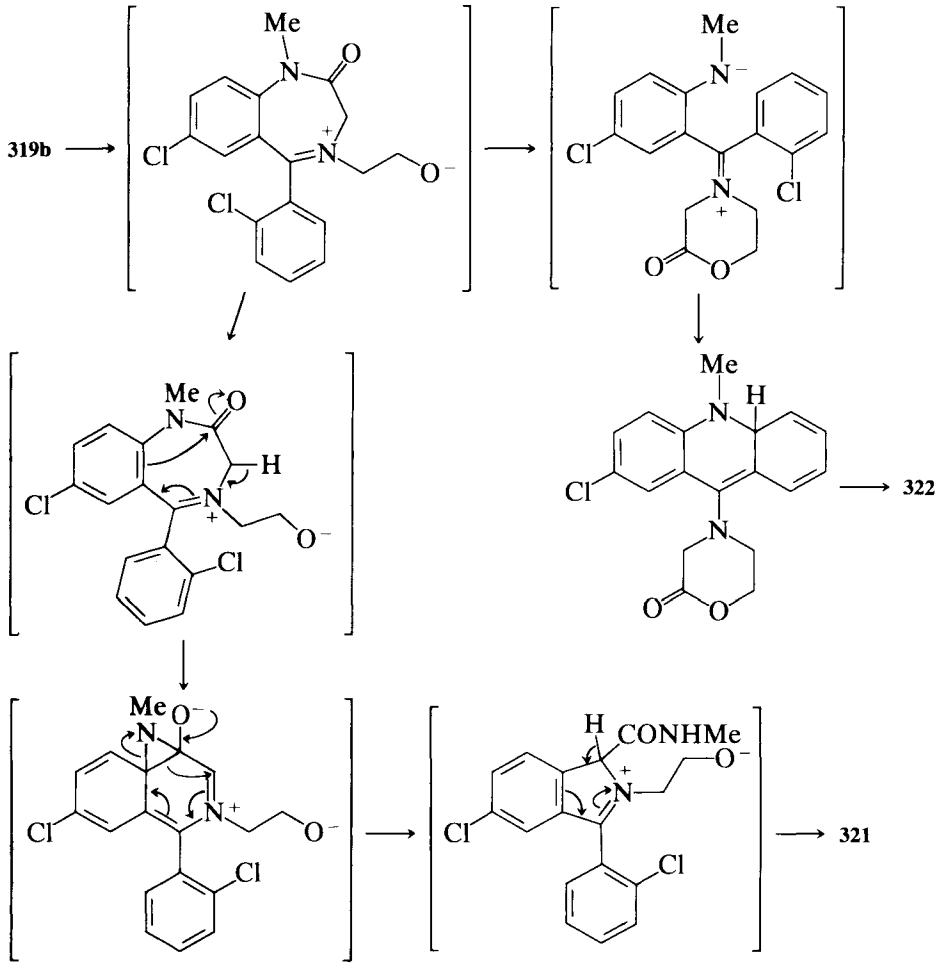
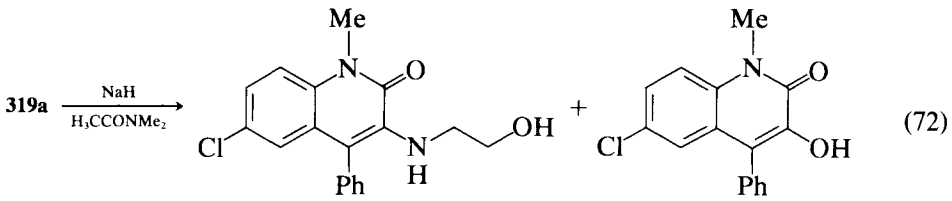


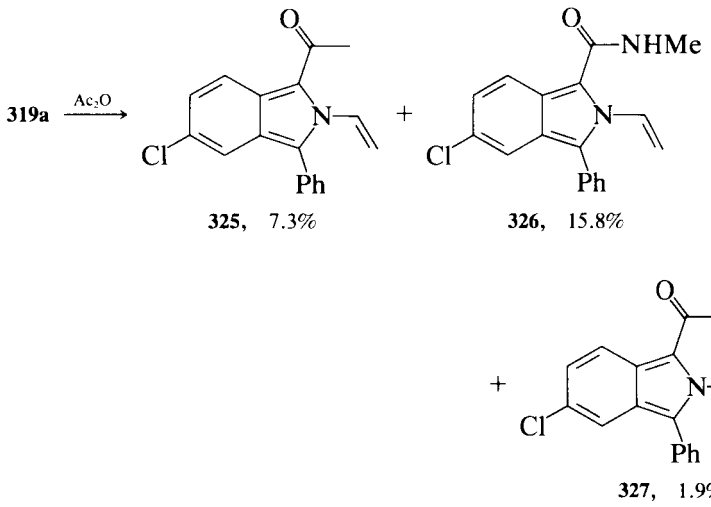

**Figure 26**

Work on the chemistry of this ring system has been stimulated primarily by the potent anxiolytic–sedative activity of some of its members. Three compounds of this class, cloxazepam (**328**), oxazolapam (**329**), and fluta-



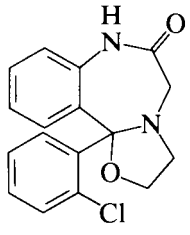

(72)

**323,** mp 167°C (10%) **324,** mp 248°C (10%)

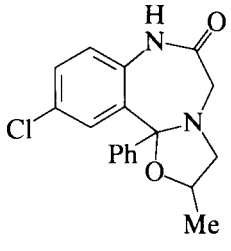



(73)

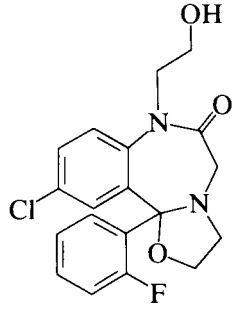
zolam (**330**) have been selected for clinical study (236). In addition, stereochemical nmr studies (219) and X-ray structural determinations (69,237) were carried out on **331** and **332.**



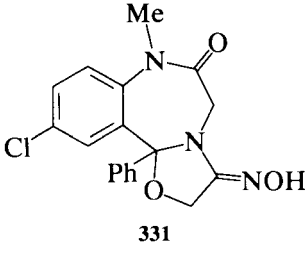

**328**



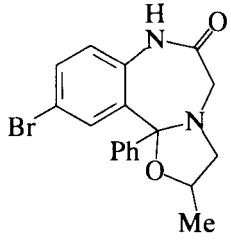

**329**




**330**

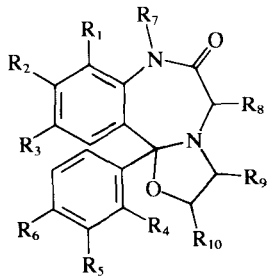



**331**




**332**

TABLE 50. OXAZOLO[3,2-*d*][1,4]BENZODIAZEPINES



| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $R_8$ | $R_9$ | $R_{10}$ | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | Cl | H | H | H | H | H | H | H | 64 | 175–176 | 205,206,212–215,218,220,221,224,231,232 |
| H | H | Br | H | H | H | H | H | H | H | 59 | 190–191.5 | 205,206,214,218,220,224 |
| H | H | $NO_2$ | H | H | H | H | H | H | H | 53 | 218–220 | 205,206,214,224,227 |
| H | H | H | H | H | H | H | H | H | Me | 58 | 174–176 | 205,206,214,218 |
| H | H | Cl | H | H | H | H | H | H | Me | 72 | 186–188 | 205,206,211,213,214,218–221,224,231,232 |
| H | H | Br | H | H | H | H | H | H | Me | 70 | 180–183 | 205,206,214,218 |
| H | H | $NO_2$ | H | H | H | H | H | H | Me | 52 | 209 | 205,206,214,218,221,224 |
| Me | H | Me | H | H | H | H | H | H | Me | 63 | 271–273 | 205,206,214,218,221,224 |
| H | Me | Me | H | H | H | H | H | H | Me | 66 | 172–174 | 205,206,214,218 |
| Cl | H | Cl | H | H | H | H | H | H | Me | 64 | 226–228 | 205,206,214,218,224 |
| H | Cl | Cl | H | H | H | H | H | H | Me | 65 | 196–197 | 205,206,214,218,221,224 |
| Me | H | Cl | H | H | H | H | H | H | Me | 58 | 254 | 205,206,214,218,220,221,224 |
| H | H | Cl | H | H | H | H | H | Me | H | 25 | 126–127 | 205,206,212,214,215,218 |
| H | H | Br | H | H | H | H | H | Me | H | 26 | 126–127 | 205,206,214,218 |
| H | H | $NO_2$ | H | H | H | H | H | Me | H | 23 | 182–183 | 205,206,214,218 |
| H | H | Cl | H | H | H | H | H | Et | H | 28 | 154–156 | 205,206,214,218 |
| H | H | H | Cl | H | H | H | H | H | H | 31 | 203–204 | 205,206,214,218 |
| H | H | H | Cl | H | H | H | H | H | Me | 58 | 195–196 | 205,206,214,218 |
| H | H | Cl | H | H | Cl | H | H | H | Me | 63 | 187.5–189 | 205,206,214,218 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | Cl | H | Cl | H | H | H | H | H | 67 | 165–167 | 205,206,214,218 |
| H | H | Cl | H | Cl | H | H | H | H | Me | 58 | 215 | 205,206,214,218 |
| H | H | Cl | Cl | H | H | H | H | H | H | 59 | 203–204 | 205,206,212–214,216–218,221,224,227,231,232 |
| H | H | Cl | Cl | H | H | H | H | H | Me | 65 | 192 | 205,206,213,214,221,224 |
| H | H | Cl | Cl | H | H | H | H | Me | H | 28 | 172–175 | 205,206,214,218 |
| H | H | Cl | F | H | H | H | H | H | H | 51 | 181–183 | 205,206,214,218,224,231,232 |
| H | H | Cl | F | H | H | H | H | H | Me | 56 | 199 | 205,206,214,221,224 |
| H | H | Cl | F | H | H | H | H | Me | H | 27 | 165–167 | 205,206,214,218 |
| H | H | Cl | Cl | H | Cl | H | H | H | Me | 68 | 201.5 | 205,206,214,218 |
| H | H | Cl | Me | H | H | H | H | H | Me | 63 | 205 | 205,206,214,218,221,224 |
| H | H | Cl | H | H | $NO_2$ | H | H | H | Me | 55 | 193–195 | 205,206,214,218,224 |
| H | H | Br | Cl | H | H | H | H | H | H | 61 | 207 | 205,206,214,218,221,224 |
| H | H | Br | Cl | H | H | H | H | H | Me | 64 | 197 | 205,206,214,218,224 |
| H | H | Br | Cl | H | H | H | H | Me | H | 23 | 182–184 | 205,206,214,218 |
| H | H | Cl | H | H | H | H | Me | H | H | 54 | 205–207 | 205,206,210,214,218 |
| H | H | Br | H | H | H | H | Me | H | H | 62 | 204–205 | 205,206,214,218,221,224 |
| Me | H | Me | H | H | H | H | Me | H | H | 61 | 219–221 | 205,206,214,218 |
| H | H | Cl | H | H | H | H | Me | H | Me | 59 | 216–217 | 205,206,214,218 |
| H | H | Cl | H | H | Cl | H | Me | H | H | 65 | 204.5–205.5 | 205,206,214,218 |
| H | H | Cl | Cl | H | H | H | Me | H | H | 70 | 222–224 | 205,206,214,218 |
| H | H | Cl | Cl | H | H | H | Me | H | Me | 62 | 220–223 | 205,206,214,218 |
| H | H | Br | Cl | H | H | H | Me | H | H | 59 | 216–217 | 205,206,214,218 |
| H | H | Cl | H | H | H | H | Et | H | H | 58 | 183–184 | 205,206,214,218,221,224 |
| H | H | Cl | H | H | H | H | $n$-$C_4H_9$ | H | H | 51 | 173–175 | 205,206,214,218 |
| H | H | Cl | H | H | H | Me | H | H | H | 78 | 181–183 | 205,206,212–215,218,219,224,227,231,232 |
| H | H | Cl | H | H | H | Et | H | H | H | 75 | 118–120 | 205,206,214,218,220,224 |
| H | H | Cl | H | H | H | $CH_2CH_2Cl$ | H | H | H | 66 | 128–131 | 205,206,214,218 |
| H | H | Cl | H | H | H | $CH_2C_6H_4Cl$-$o$ | H | H | H | 53 | 144–146 | 205,206,214,218 |
| H | H | Br | H | H | H | Me | H | H | H | 76 | 184–185.5 | 205,206,214,218 |
| H | H | Br | H | H | H | Et | H | H | H | 75 | 136–138 | 205,206,214,218,221,224 |
| H | H | $NO_2$ | H | H | H | Me | H | H | H | 62 | 191–192 | 205,206,213,214,218 |

(*continued*)

TABLE 50. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $R_8$ | $R_9$ | $R_{10}$ | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | $NO_2$ | H | H | H | Et | H | H | H | 48 | 112–114 | 205,206,214,218 |
| Me | H | Me | H | H | H | Et | H | H | H | 72 | 141–143 | 205,206,213,214,218 |
| H | H | Cl | H | H | H | Me | H | H | Me | 70 | 134–135 | 205,206,209,214,218,231,232 |
| H | H | Cl | H | H | H | Et | H | H | Me | 69 | 157–168 | 205,206,214,218 |
| H | H | Cl | H | H | H | $CH_2CH{=}CH_2$ | H | H | Me | 54 | 113–115 | 205,206,214,218 |
| H | H | Cl | H | H | H | *n*-$C_4H_9$ | H | H | Me | 58 | 121–122 | 205,206,214,218 |
| H | H | Cl | H | H | H | $CH_2C_6H_5$ | H | H | Me | 51 | 154–157 | 205,206,214,218 |
| H | H | Cl | H | H | H | $CH_2C_6H_4Cl$-*p* | H | H | Me | 53 | 162–163.5 | 205,206,214,218 |
| H | H | Cl | H | H | H | $CH_2C_6H_4Cl$-*o* | H | H | Me | 55 | 172–174 | 205,206,214,218 |
| H | H | Cl | H | H | H | $CH_2C_6H_4NO_2$-*p* | H | H | Me | 36 | 211 | 205,206,214,218 |
| H | H | Cl | H | H | H | $CH_2COC_6H_5$ | H | H | Me | 41 | 175–176 | 205,206,214,218 |
| H | H | Br | H | H | H | Me | H | H | Me | 71 | 149–150 | 205,206,214,218 |
| H | H | $NO_2$ | H | H | H | Me | H | H | Me | 45 | 170–173 | 205,206,214,218,221,224 |
| Me | H | Me | H | H | H | Me | H | H | Me | 69 | 136–138 | 205,206,214,218 |
| Me | H | Cl | H | H | H | Me | H | H | Me | 73 | 163–164 | 205,206,214,218 |
| H | H | Cl | H | H | H | Me | H | Me | H | 72 | 142–145 | 205,206,214,218 |
| H | H | Cl | Cl | H | H | Me | H | H | H | 68 | 154–155 | 205,206,214,218 |
| H | H | Cl | Cl | H | H | Et | H | H | H | 72 | 153–156 | 205,206,214,218 |
| H | H | Cl | Cl | H | H | Me | H | Me | H | 75 | 177.5–179 | 205,206,214,218 |
| H | H | Br | Cl | H | H | Me | H | H | H | 75 | 170–172 | 205,206,214,218 |
| H | H | Br | Cl | H | H | Et | H | H | H | 73 | 157–160 | 205,206,214,218 |
| H | H | Cl | H | H | Cl | Me | H | H | Me | 75 | 164–166 | 205,206,214,218 |
| H | H | Cl | Cl | H | H | Me | H | H | Me | 68 | 173–175 | 205,206,214,218 |
| H | H | Br | Cl | H | H | Me | H | H | Me | 65 | 188–189 | 205,206,214,218 |
| H | H | Cl | H | H | H | Et | Me | H | H | 72 | 184–186 | 205,206,214,218 |
| H | H | Cl | Cl | H | H | Me | Me | H | H | 78 | 186–187 | 205,206,214,218 |
| H | H | Cl | H | H | H | Me | Me | H | Me | 73 | 162–165 | 205,206,214,218 |
| H | H | Cl | H | H | H | Me | Et | H | Me | 64 | 155–158 | 205,206,214,218 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | Br | H | H | H | Me | Me | H | Me | 59 | 159–161 | 205,206,214,218 |
| H | H | Cl | Cl | H | H | Me | Me | H | Me | 79 | 199–201 | 205,206,214,218 |
| H | H | Cl | H | H | H | H | OH | H | Me | | 218–223 | 207 |
| H | H | Me | H | H | H | H | Me | H | H | | 219–221 | 209 |
| H | H | Br | H | H | H | H | Me | H | H | | 198–201 | 209 |
| H | H | $NO_2$ | H | H | H | H | Me | H | H | | 220–224.5 | 210 |
| H | H | Cl | H | H | H | H | H | H | $CH_2OH$ | | 162–165 | 211 |
| H | H | Cl | H | H | H | Me | H | H | $CH_2OMe$ | | 131–133 | 211 |
| H | H | Cl | H | H | H | Me | H | H | $CH_2OH$ | | 193–196 | 211 |
| H | H | Cl | H | H | H | $CH_2CH_2OH$ | H | H | H | | 134–137 | 212,215,231,232 |
| H | H | Cl | F | H | H | H | H | H | H | | 183–184 | 212,215 |
| H | H | Cl | F | H | H | $CH_2CH_2OH$ | H | H | H | | 147–150 | 212,215,231,232 |
| H | H | H | H | H | H | Me | H | H | Me | | 140–145 | 212 |
| H | H | Cl | Cl | H | H | $CH_2OMe$ | H | H | H | | 144–146 | 212,216,231,232 |
| H | H | I | F | H | H | H | H | H | H | | 193–196 | 212,231,232 |
| H | H | I | F | H | H | $CH_2CH_2OH$ | H | H | H | | 160–165 | 212,231,232 |
| H | H | $NO_2$ | Cl | H | H | H | H | H | H | | 201–203 | 212,231,232 |
| H | H | $NO_2$ | Cl | H | H | $CH_2CH_2OH$ | H | H | H | | 185–190 | 212,231,232 |
| H | H | Cl | F | H | H | $CH_2CH_2OAc$ | H | H | H | | 120–123 | 212,231,232 |
| H | H | Cl | $NO_2$ | H | H | H | H | H | Me | | 193–195 | 213,221 |
| H | H | Cl | H | H | H | Me | H | H | $CH_2Cl$ | | 140–142 | 215,231,232 |
| H | H | Cl | H | H | H |  | H | H | H | | 131–135 | 216 |
| H | H | $NO_2$ | Cl | H | H | $CH_2OMe$ | H | H | H | | 139–141 | 222,233 |
| H | H | NHOH | Cl | H | H | $CH_2OMe$ | H | H | H | | 160–162 | 129,222 |
| H | H | Cl | F | H | H | H | H | H | H | | 129–134 | 229 |
| H | H | Cl | H | H | H | $(CH_2)_3NMe_2$ | H | H | Me | | 164–169 | 230 |
| H | H | Cl | H | H | H | $(CH_2)_2NMe_2$ | H | H | Me | | 174–179 | 230 |
| H | H | $NO_2$ | H | H | H | $(CH_2)_2NMe_2$ | H | H | Me | | 208–215 | 230 |

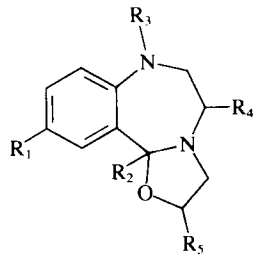
(*continued*)

TABLE 50. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $R_8$ | $R_9$ | $R_{10}$ | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | Cl | Cl | H | H | $(CH_2)_3NMe_2$ | H | H | Me | | 134–136 | 230 |
| H | H | Cl | F | H | H | $(CH_2)_3NMe_2$ | H | H | Me | | 130–131 | 230 |
| H | H | Cl | F | H | H | Me | H | H | H | | 156–158 | 224 |
| Me | H | Me | H | H | H | H | Me | H | H | | 218–221 | 224 |
| H | H | Cl | H | H | H | Me | $=CH_2$ | H | H | | 210–212 | 228 |
| H | H | Br | H | H | H | Me | $=CH_2$ | H | H | | 206–210 | 228 |
| H | H | Cl | Cl | H | H | Me | $=CH_2$ | H | H | | 168–172 | 228 |
| H | H | Cl | H | H | H | Me | $=CH_2$ | H | Me | | 122–126 | 228 |
| H | H | Cl | H | H | H | Me | $=CH_2$ | Me | H | | 180–182 | 228 |
| H | H | Cl | H | H | H | Me | $=CHCH_3$ | H | H | | 226–227 | 228 |
| H | H | Cl | [a] | H | H | Me | $=CH_2$ | H | H | | 214–218 | 228 |
| H | H | Cl | [a] | H | H | $(CH_2)_3NMe_2$ | H | H | H | | 118–121 | 230 |
| H | H | Cl | Cl | H | H | $(CH_2)_2NMe_2$ | H | Me | H | | 167–169 | 230 |
| H | H | Br | Cl | H | H | $(CH_2)_2NMe_2$ | H | Me | H | | 147 | 230 |

[a] 2-Pyridyl derivatives.

TABLE 51. REDUCED OXAZOLO[3,2-*d*][1,4]BENZODIAZEPINES



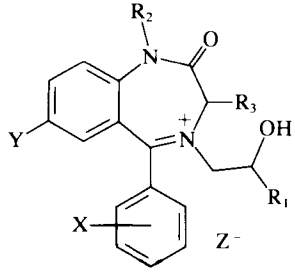
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| Cl | Ph | H | $CO_2Et$ | H | 205–207 | 212 |
| Cl | Ph | Me | H | H | 107–108 | 212,231,232 |
| Cl | Ph | H | H | Me | 181–184 | 212 |
| Cl | 2-Thienyl | H | H | Me | 154–156 | 217 |
| Cl | 2-Pyridyl | H | H | H | 202–204 | 217 |
| Cl | 2-Pyridyl | H | H | Me | 201–202 | 217 |
| Br | 2-Thienyl | H | H | Me | 186.5–187.5 | 217 |
| Br | 2-Thienyl | H | H | H | 195–196 | 217 |
| Cl | 2-Thienyl | H | H | H | 178–179 | 217 |

TABLE 52. OXAZOLO[3,2-*d*][1,4]BENZODIAZEPINES FROM OXADIAZOLOBENZODIAZEPINES[a]

| Compound | X | R | Yield (%) | mp (°C) |
|---|---|---|---|---|
| **315** | $H_2$ | H | 58 | 175–178 |
| **315** | O | H | 68 | 211–214 |
| **315** | $H_2$ | Me | 56 | 180–188 |
| **316** | $H_2$ | Me | 59 | 203–205 |
| **316** | $H_2$ | Ph | 31 | 125–140 |
| **316** | $H_2$ | H | 79 | 148–150 |
| **316** | O | H | 85 | 168–170 |
| **317** | $H_2$ | H | 71 | 118–120 |
| **317** | O | H | 80 | 192–196 |

[a]Ref. 69.

TABLE 53. RING-OPENED OXAZOLO[3,2-*d*][1,4]BENZODIAZEPINES[a]



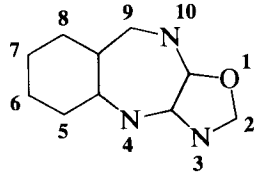
*(continued)*

TABLE 53. *(Continued)*

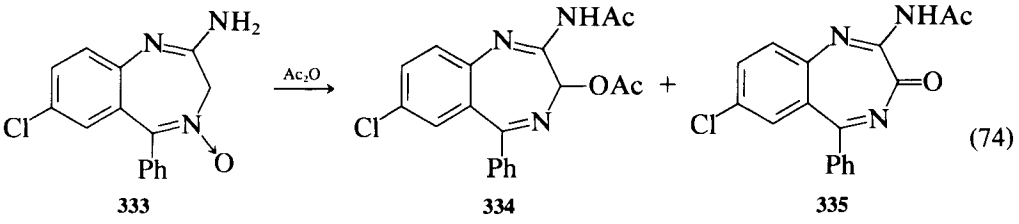
| X | Y | $R_1$ | $R_2$ | $R_3$ | mp (°C) | Z |
|---|---|---|---|---|---|---|
| H | Br | H | H | H | 160 | Cl |
| *o*-Cl | Cl | H | H | H | 170 | Cl |
| *p*-$NO_2$ | Cl | Me | H | H | 170 | Cl |
| H | Cl | Me | H | Me | 169 | Cl |
| *o*-Cl | Br | H | H | H | 150 | Cl |
| H | Cl | Me | H | H | 130 | OTs |
| H | 7,9-$Me_2$ | Me | H | Me | 200 | Br |
| H | Cl | Me | Et | H | 150 | Cl |
| *o*-Me | Cl | Me | H | H | 170 | Cl |
| H | $NO_2$ | H | H | H | 224–230 | Cl |
| *o*-Me | Cl | Me | H | H | 200 | Cl |
| H | Cl | Me | H | H | 160 | Cl |
| H | H | Me | $CH_2C_6H_4Cl$-*p* | H | 140 | Cl |

[a]Ref. 225.

## 19. Oxazolo[4,5-*b*][1,4]benzodiazepines (see Section XV.14)



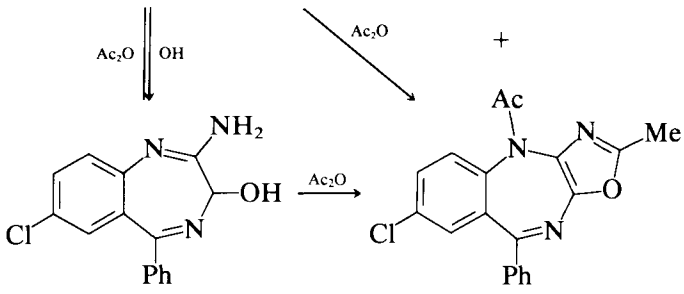
Reaction of amine oxide **333** with acetic anhydride (238) gave the three rearranged products **334, 335,** and **336.** The expected product **334** was predominant. Hydrolysis of **334** yielded **337,** which was converted back to **334** in warm acetic anhydride and to **336** in refluxing acetic anhydride. The formation of the tricyclic product **336** is assumed to proceed via acetylation of the tautomer of **334** followed by elimination of acetic acid, as shown in Eq. 74.



(74)

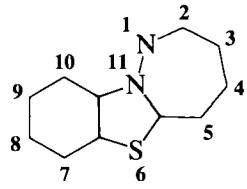
**333** **334** **335**

*(see next page)*

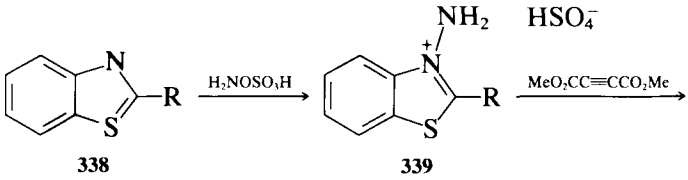



337 336, mp 183–185°C (74 *cont'd*)

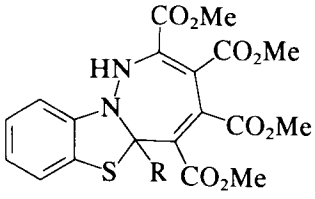
## 20. [1,2]Diazepino[7,1-*b*]benzothiazoles




*N*-Amination of benzothiazole **338** (R = H, Me, Ph) with hydroxylamine-*O*-sulfonic acid gave the corresponding *N*-aminobenzothiazolium salts **339.** Reaction of the 1,3-dipole **339** with dimethyl acetylenedicarboxylate (Eq. 75) afforded 23–41% yields of the 1:2 adduct **340** instead of the anticipated 1:1 adduct. No physical or spectral data were given to support the structures assigned to these products (239).

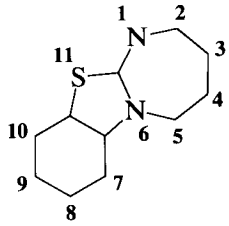



338 339

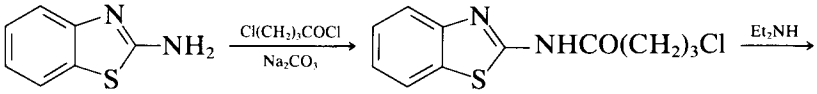



340 (75)

## 21. [1,3]Diazepino[2,1-*b*]benzothiazoles (see Section XV.15)

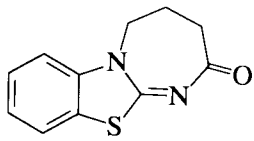


Reaction of 2-aminobenzothiazole with 4-chlorobutyryl chloride in the presence of sodium carbonate led to the corresponding amide **341** (Eq. 76) in 80% yield. Treatment of **341** with diethylamine or piperidine led to the cyclized product **342** instead of simple alkylation. The structure of **342** was confirmed by elemental analysis and spectral data. The nmr spectrum contained signals at δ 2.0–2.8 (4H, *m*), δ 4.21 (2H, *t*), and δ 7.2–7.9 (4H, *m*), which are consistent with the tricyclic formulation (240).



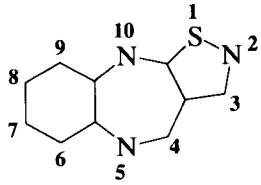
**341**

(76)



**342**, mp 177–178°C

## 22. Isothiazolo[5,4-*b*][1,5]benzodiazepines



Using the method of Goerdeler (241) for the preparation of the isothiazole ring, condensation of *t*-butyl β-aminocrotonate and *o*-nitrophenyl isothio-

cyanate at 90°C for 30 min led to thioamide **343** (Fig. 27). Oxidation of **343** with bromine followed by hydrolysis in trifluoroacetic acid yielded the isothiazole **344.** Reduction of the nitro group of **344** followed by lactam formation with ethyl chloroformate afforded the *N*-carbethoxy derivative **345.** The final product (**346**) was obtained by alkaline hydrolysis; its structure was verified by nmr, ir (1680 $cm^{-1}$), and mass spectral analysis (242).

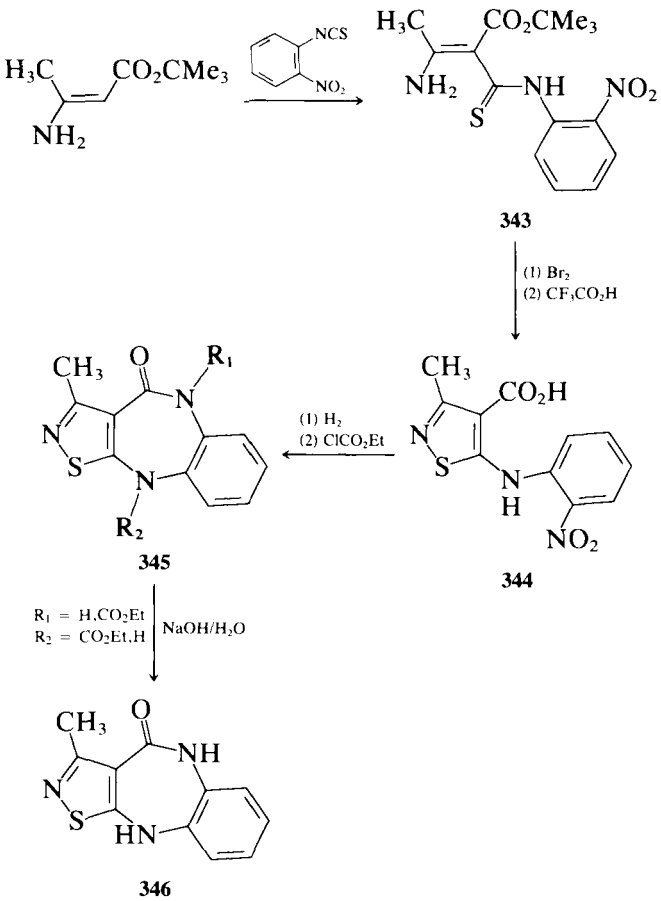
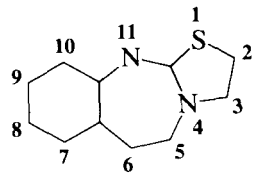
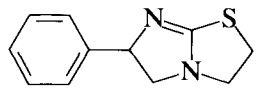



Figure 27

## 23. Thiazolo[2,3-*b*][1,3]benzodiazepines



Thiazolo[2,3-*b*][1,3]benzodiazepines were synthesized as analogs of the anthelmintic tetramisole (**347**). The key building block (**348**) was prepared from 4-methylcinnoline by Raney nickel hydrogenation followed by treatment with carbon disulfide. Members of the tricyclic system were constructed by condensation of **348** with a series of α-halogenated carbonyl compounds (Fig. 28). The reagents and yields of these transformations are listed in Table 54. Structural assignments were based on the analogous chemistry of monocyclic thiazoles and on nmr spectral evidence (243).

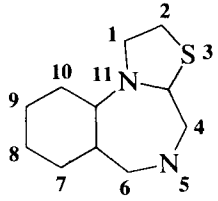


**347**

TABLE 54. REACTIONS OF 1,3,4,5-TETRAHYDRO-5-METHYL-2H-[2,3-*b*][1,3]-BENZODIAZEPINE-2-THIONE (**348**)

| Product | Reagent | Yield (%) | mp (°C) |
|---|---|---|---|
| **349** | $ClCH_2CO_2Et$ | 81 | 115–116 |
| **350** | $n$-$C_4H_9CHBrCO_2Et$ | 35 | 163–166 |
| **351** | $CH_3COCHClCO_2Et$ | 64 | 142–144 |
| **352** | 2-Chlorocyclopentanone | 30 | 131–133 |
| **353** | 2-Chlorocyclohexanone | 77 | 158–159 |
| **354** | $BrCH_2COC_6H_4OMe$-$o$ | 48 | 241–243 |
| **355** | $BrCH_2COPh$ | 26 | 137–140 |
| **356** | MeI | 68 | 225–226 |
| **357** | Raney nickel | 10 | 269–272 |

## 24. Thiazolo[3,2-*a*][1,4]benzodiazepines




Thiazolo[3,2-*a*][1,4]benzodiazepines are claimed to have anticonvulsant, muscle relaxant, and sedative properties. Two synthetic routes to this system are outlined in Eq. 77 and Fig. 29. The first one starts with imine **358,** which is available by manganese dioxide oxidation of the corresponding amine. Condensation of **358** with mercaptoacetic acid (Eq. 77) afforded a mixture of **359** and **360** in a 3:5 ratio (90). A specific route to the desired monothiazole **359** was achieved by first converting imine **358** to epithiobenzodiazepine **361,** which was then condensed with mercaptoacetic acid (244).

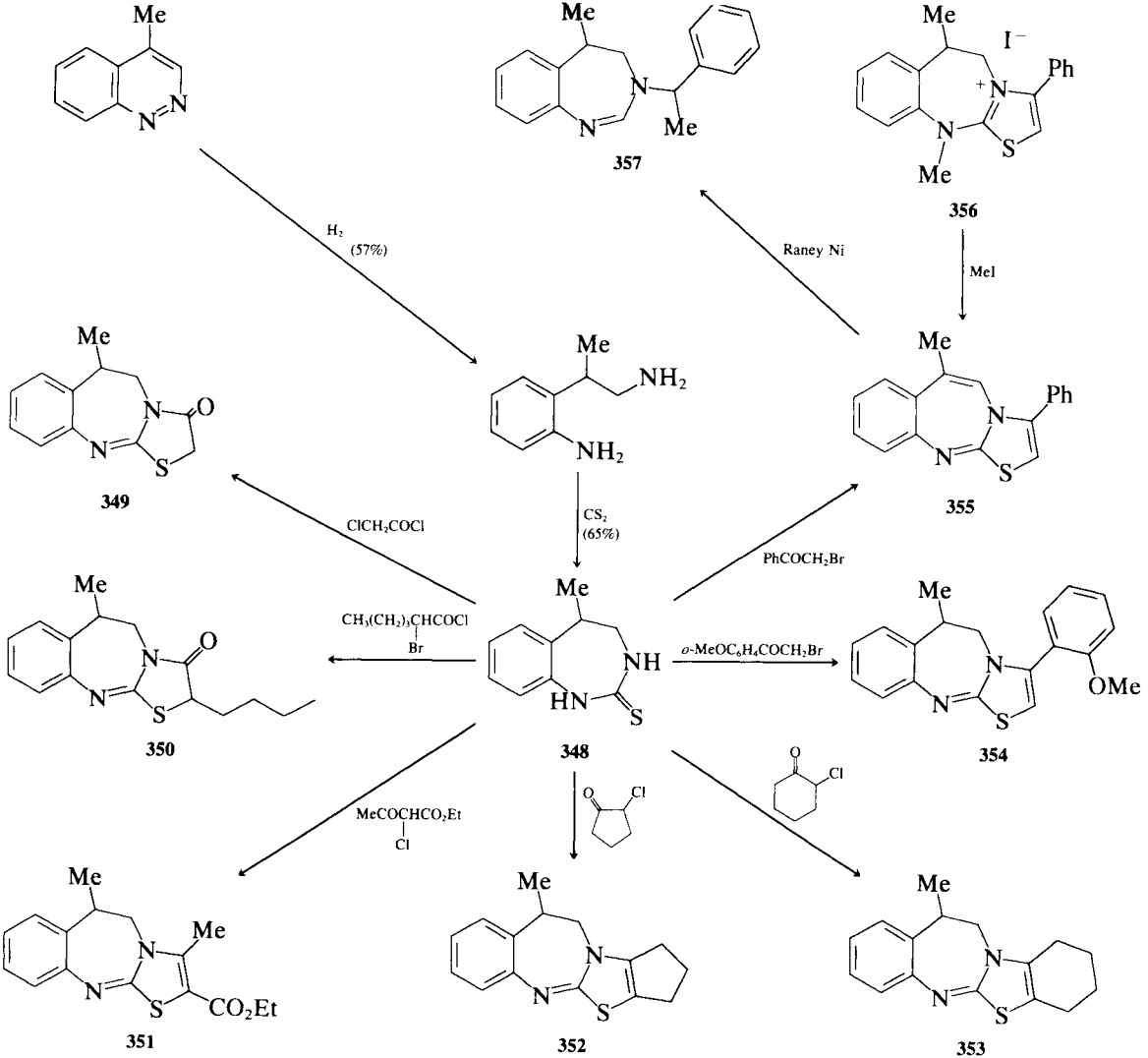
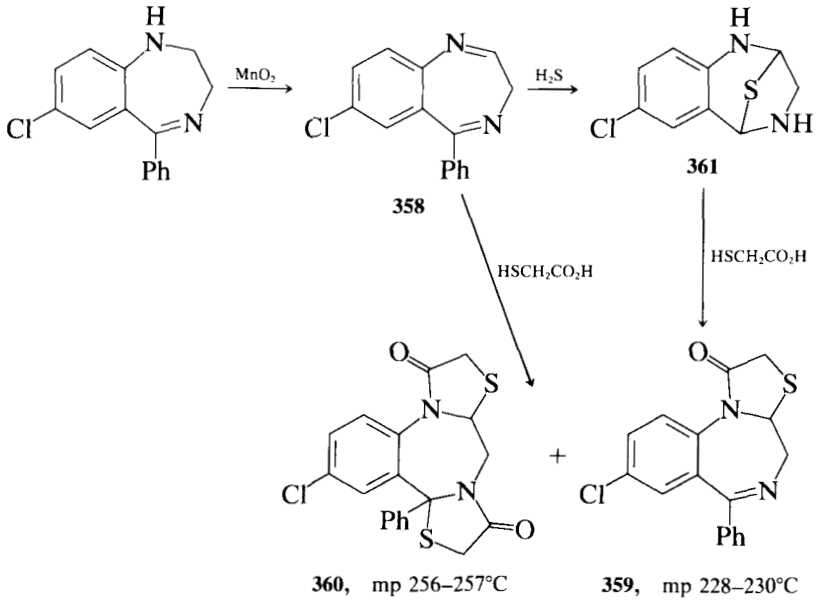

Me
N=N
H2
(57%)
Me
NH2
NH2
CS2
(65%)
Me
NH
HN
S
Me
N
N
Me
357
Raney Ni
Me
I−
Ph
+N
N
S
Me
356
MeI
Me
Ph
N
S
355
PhCOCH2Br
Me
N
O
N
S
349
ClCH2COCl
Me
N
O
N
S
350
CH3(CH2)3CHCOCl
Br
o-MeOC6H4COCH2Br
Me
N
S
OMe
354
MeCOCHCO2Et
Cl
Me
Me
N
N
S
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O
Cl
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N
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352
O
Cl
Me
N
N
S
353

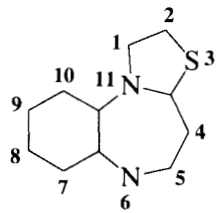
Figure 28



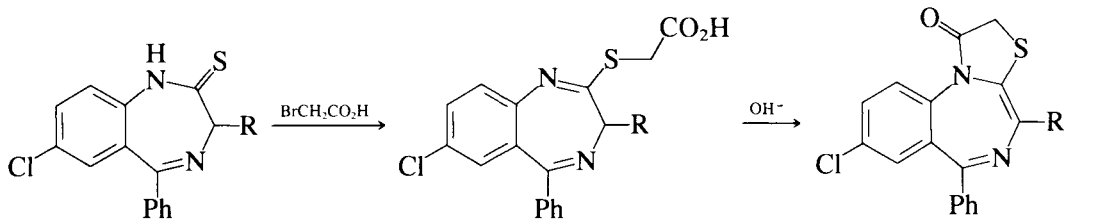

(77)

A second approach to this ring system began with thione **362.** *S*-Alkylation of **362** with bromoacetic acid led to **363,** which was cyclized in base to the thiazoline **364** (Fig. 29). Alkylation of the $\alpha$-methylene carbon in **364** could be carried out. For example, treatment of **364a** with lithium diisopropyl amide followed by methyl iodide produced the mono- and dimethyl derivatives **365** and **366** (245). Similar methodology provided access to the fused thiazolidones **367** (204,246). Alkylation of thione **362** with 1,2-dihaloethane derivatives resulted in initial *S*-alkylation followed *in situ* by *N*-alkylation.

## 25. Thiazolo[3,2-*a*][1,5]benzodiazepines



Thiazolo[3,2-*a*][1,5]benzodiazepines were prepared by annelation of the thiazole moiety onto benzodiazepine-2-thione substrates. Thus reaction of thione **368** with bromoacetaldehyde diethyl acetal afforded **369** in 12% yield (Eq. 78) (186). Similarly, condensation of thione **370** (Eq. 79) with ethyl chloroacetate or ethyl 2-chloropropionate led to **371** and **372,** respectively (247,248). Finally, treatment of thione **373** with bromoacetone produced

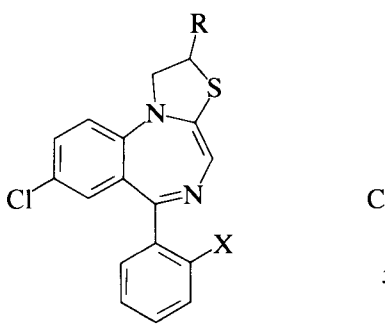



**362** **363**

| | R | mp (°C) |
|---|---|---|
| **364a** | H | 182–183 |
| **364b** | Me | 136.5–141.5 |

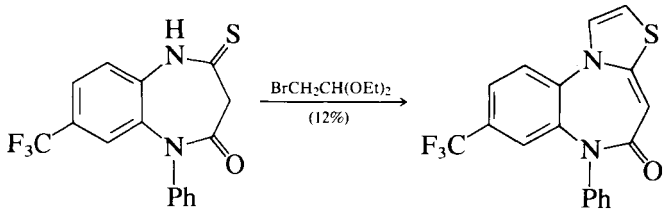
**366,** mp 193.5–195.5 **365,** mp 107–110°C

**365/366** = 1.33

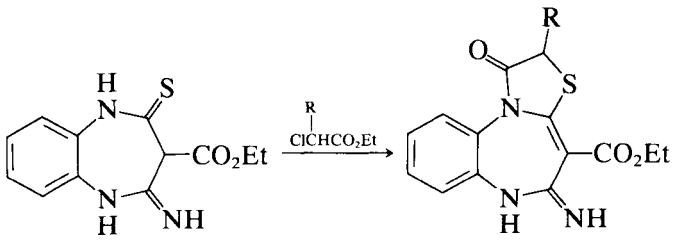



| | X | R | mp (°C) |
|---|---|---|---|
| **367a** | H | OMe | 200–203 |
| **367b** | F | OMe | 100–104 |
| **367c** | F | H | 145–148 |

**Figure 29**

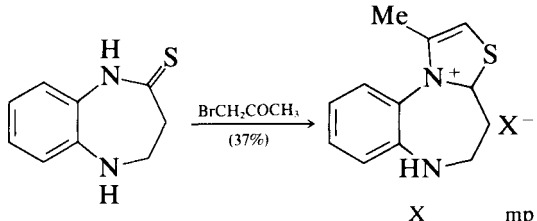



**368** **369**, mp 155.5–156.5°C (78)




**370** (79)

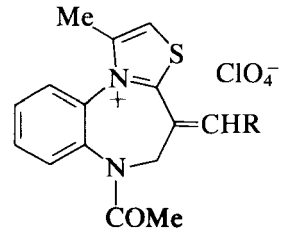
| | R | Yield (%) | mp (°C) |
|---|---|---|---|
| **371** | H | 74 | 220 |
| **372** | Me | 94 | 222–224 |




**373**

| | X | mp (°C) |
|---|---|---|
| **374** | Br | 217 |
| **375** | $ClO_4$ | 201 |

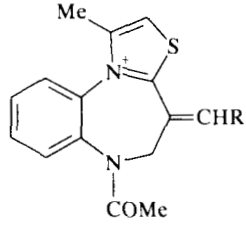
(80)

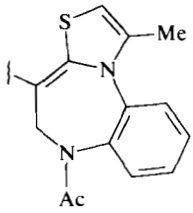
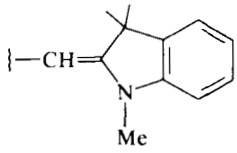
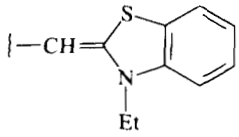
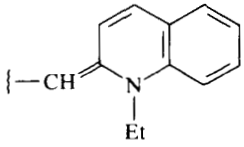



**376**

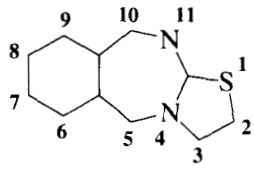
benzodiazepinium bromide **374** (Eq. 80), which was converted into the perchlorate **375** by exchange. Salt **375** was then converted to a series of cyanine dyes (**376**), which are listed in Table 55 (249).

TABLE 55. CYANINE DYES **376**

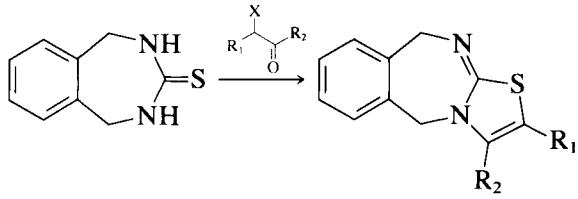


| R | Yield (%) | mp (°C) |
|---|---|---|
|  | | |
|  | 57 | 238 |
|  | 46 | 193 |
|  | 22 | 240 |

## 26. Thiazolo[3,2-*b*][2,4]benzodiazepines



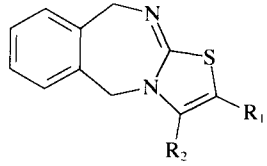
Thiazolo[3,2-*b*][2,4]benzodiazepines were formed by treatment of 2,4-benzodiazepine **377** with aryl α-haloketones (Eq. 81). The 3-arylthiazolo-benzodiazepines (**378**) listed in Table 56 were prepared by this procedure. These compounds are inhibitors of ADP-induced platelet aggregation (250). Other tricyclic derivatives were synthesized by condensation of **377** with a variety of α-halocarbonyl compounds, as summarized in Fig. 30. Table 57 lists the reagents and yields for these transformations (251).



(81)

**377** **378**

TABLE 56. 3-ARYLTHIAZOLO[3,2-*b*][2,4]BENZODIAZEPINES



| $R_1$ | $R_2$ | Yield (%) | mp (°C) |
|---|---|---|---|
| H | 4-Bromophenyl | 74 | 257–260 |
| H | 4-Chlorophenyl | 68 | 250–251 |
| H | 4-Nitrophenyl | 63 | 282–285 |
| H | 2-Hydroxyphenyl | 60 | 273 |
| H | 3,4-Dihydroxyphenyl | 29 | 258–259 |
| H | Phenyl | 90 | 256–257 |
| H | 2-Methoxyphenyl | 55 | 243 |
| H | 3-Methoxyphenyl | 71 | 252–254 |
| H | 4-Methoxyphenyl | 78 | 244 |
| H | 4-Acetamidophenyl | 68 | 262–263 |
| H | 2,5-Dimethoxyphenyl | 63 | 248 |
| H | 2,4-Dimethylphenyl | 76 | 259–260 |
| H | 4-(3-Dimethylaminopropyl)phenyl | 80 | 263–264 |
| H | 4-Phenylphenyl | 53 | 217–220 |
| H | 2-(1-Morpholino)ethoxyphenyl | 55 | 265 |
| H | 3-(2,5-Dichloro)thienyl | 55 | 249–252 |
| H | 2-(5-Bromo)thienyl | 38 | 253–255 |
| H | 2-(5-Chloro)thienyl | 48 | 248–249 |
| H | 2-Thienyl | 52 | 232–233 |
| H | 2-(5-Methyl)thienyl | 49 | 223–226 |
| H | 2-Furyl | 39 | 207–209 |
| H | 2-Naphthyl | 67 | 230–232 |
| Me | Phenyl | 61 | 229–230 |

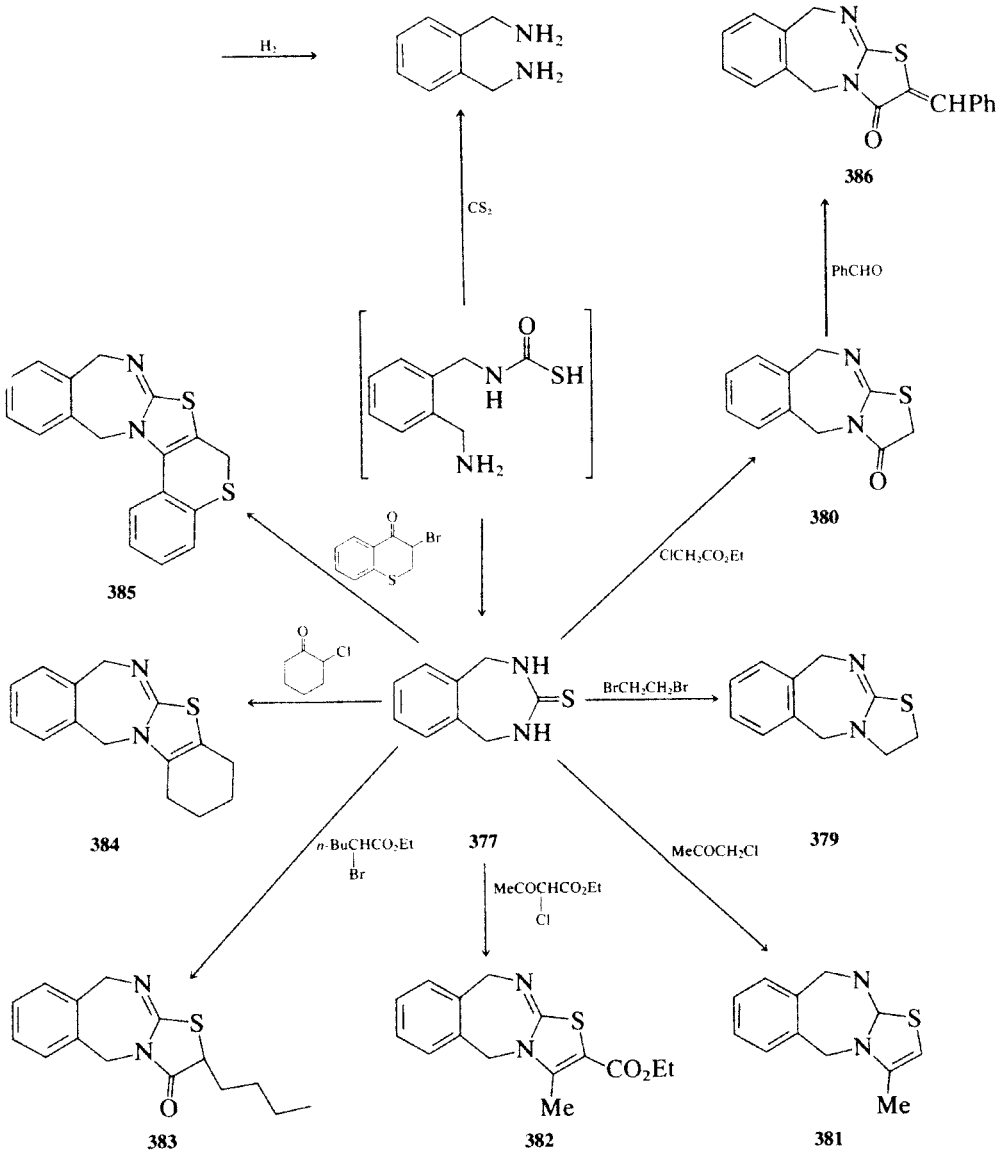
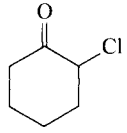
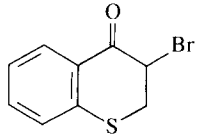
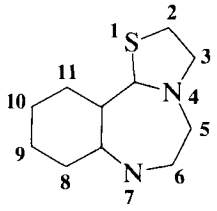

H2
NH2
NH2
CS2
N
S
CHPh
O
386
PhCHO
O
N
H
SH
NH2
N
S
N
O
380
N
S
N
S
385
O
Br
S
ClCH2CO2Et
O
Cl
NH
S
NH
BrCH2CH2Br
N
S
N
384
n-BuCHCO2Et
Br
377
MeCOCH2Cl
379
MeCOCHCO2Et
Cl
N
S
N
O
383
N
S
N
CO2Et
Me
382
N
S
N
Me
381

**Figure 30**

TABLE 57. ADDITIONAL THIAZOLO[3,2-*b*][2,4]BENZODIAZEPINES

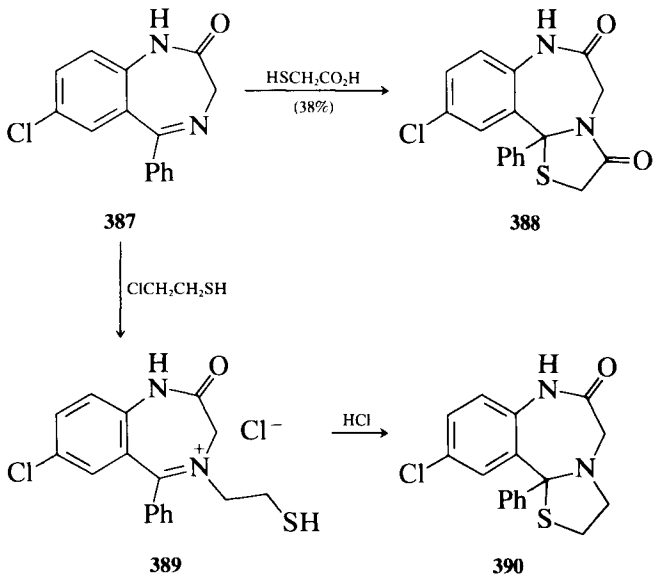
| Product | Reagent | Yield (%) | mp (°C) |
|---|---|---|---|
| **379** | $BrCH_2CH_2Br$ | 52 | 151–153 |
| **380** | $ClCH_2CO_2Et$ | 68 | 277 |
| **381** | $CH_3COCH_2Cl$ | 41 | 250–252 |
| **382** | $CH_3COCHClCO_2Et$ | 57 | 152–154 |
| **383** | *n*-$C_4H_9CHBrCO_2Et$ | 16 | 89–91 |
| **384** |  | 38 | 267–270 |
| **385** |  | 16 | 138–140 |
| **386** | PhCHO | 43 | 179–183 |

## 27. Thiazolo[3,2-*d*][1,4]benzodiazepines



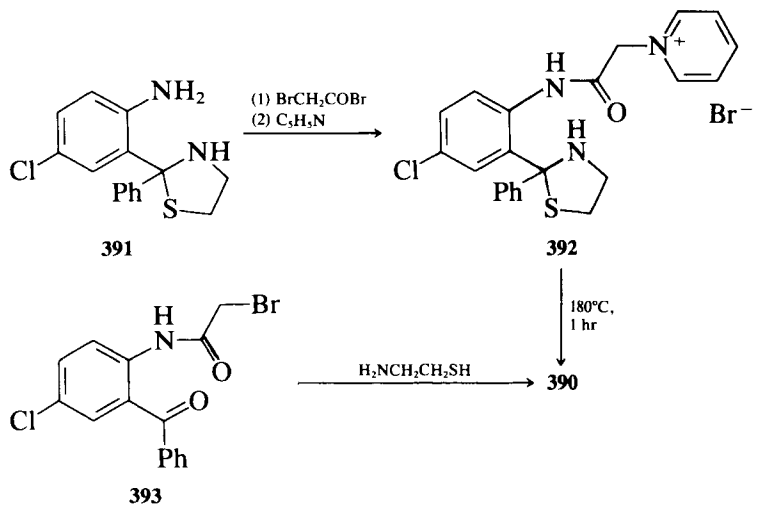

Several synthetic pathways were devised for thiazolo[3,2-*d*]-[1,4]benzodiazepines. Condensation of benzodiazepine **387** (Eq. 82) with mercaptoacetic acid afforded the tricyclic product **388** (90,252). The corresponding thiazolidine derivative **390** was obtained by treatment of **387** with 2-chloroethyl mercaptan, to give the salt **389,** followed by cyclization with dry hydrogen chloride.

A different approach to this ring system employed the thiazolidine **391** as a key intermediate (Eq. 83). Diazepine ring formation was achieved by amidation with bromoacetyl bromide followed by quaternization with pyridine to give **392.** Compound **392** was cyclized to **390** by heating at 180°C for 1 hr (218). A related route, in which the triazole and diazepine rings were gen-



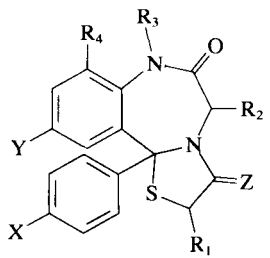

(82)

erated in the same reaction, made use of the bromoacetamide derivative **393.** Condensation with 2-mercaptoethylamine yielded **390** in a single step (205–210). Examples of compounds prepared by these methods are listed in Table 58.



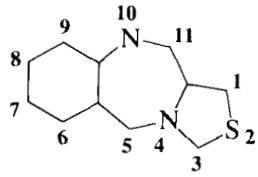

(83)

TABLE 58. THIAZOLO[3,2*d*][1,4]BENZODIAZEPINES




| $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Y | Z | mp (°C) | Refs. |
|---|---|---|---|---|---|---|---|---|
| H | Me | H | H | H | Cl | $H_2$ | 137–138 | 205,225,226 |
| H | H | Me | H | H | Cl | $H_2$ | 218–219 | 206 |
| H | Me | H | Me | H | Cl | $H_2$ | 253–256 | 206 |
| H | OH | H | H | H | Cl | $H_2$ | 270 | 207–210 |
| H | H | H | H | H | Cl | $H_2$ | 241–243 | 225,226,252 |
| Me | H | H | H | H | Cl | O | 213–214 | 226,252 |
| Me | H | H | H | H | $NO_2$ | O | 248–251 | 252 |
| Me | H | Me | H | H | Cl | O | 185–186 | 252 |
| H | H | H | H | H | $NO_2$ | O | 263–264 | 252 |
| H | H | H | H | H | Me | O | 206–207 | 252 |
| H | H | H | H | H | H | O | 196–198 | 252 |
| H | H | H | H | MeO | Cl | O | 195–197 | 252 |

## 28. Thiazolo[4,3-*c*][1,4]benzodiazepines




Thiazolo[4,3-*c*][1,4]benzodiazepines were studied for anti-inflammatory, analgetic antagonist, and psychomotor depressant activity. The synthesis is illustrated in Fig. 31. Condensation of *o*-nitrobenzoyl chloride with methyl 4-thiazolidinecarboxylate followed by reduction of the nitro group with iron in acetic acid led to the tricyclic dione **394.** Lithium aluminium hydride reduction of **394** gave **395.** *N*-Acylation with propionyl chloride afforded the thiazolidine **396,** which was converted to the sulfoxide **397** or sulfone **398** using one or two equivalents of hydrogen peroxide (253–255).

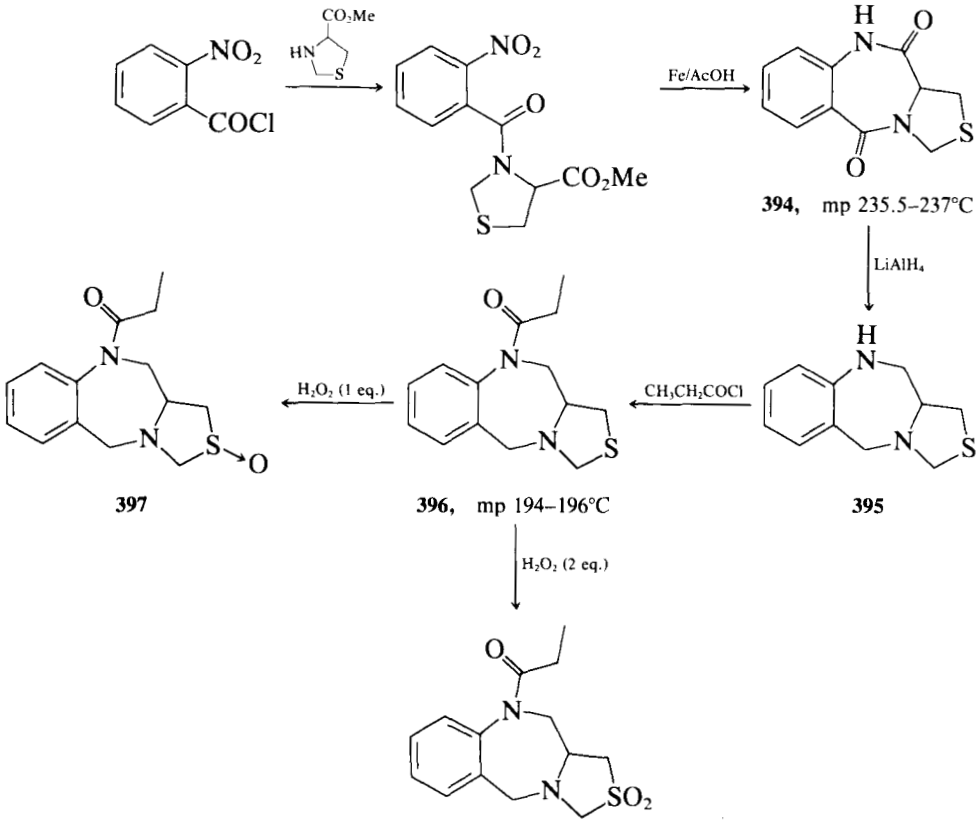
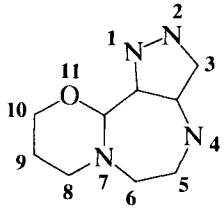
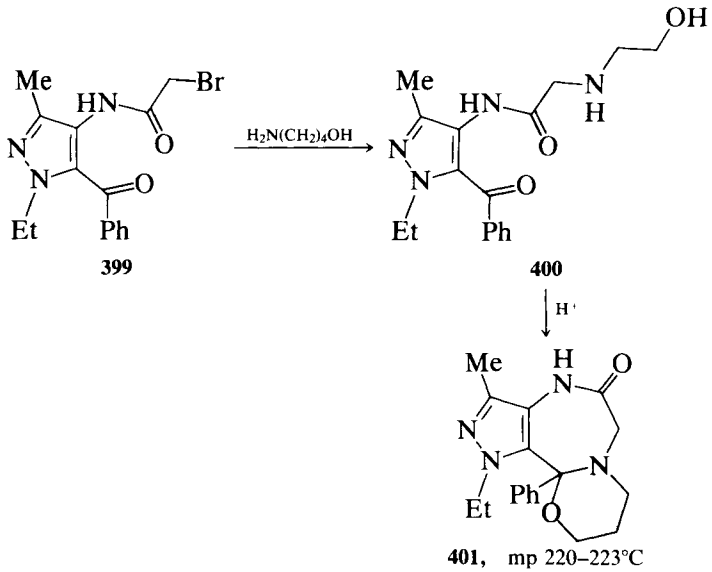



**Figure 31**

### 29. [1,3]Oxazino[3,2-*d*]pyrazolo[3,4-*f*][1,4]diazepines

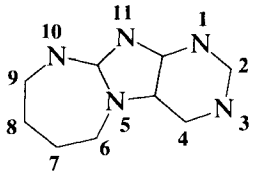


The only example of the [1,3]oxazino[3,2-*d*]pyrazolo[3,4-*f*][1,4]diazepine ring system is found in a patent dealing primarily with the corresponding oxazolopyrazolodiazepine system, which had anticonvulsant properties. Compound **401** was prepared by addition of 3-amino-1-propanol to pyrazole **399** followed by acid-catalyzed cyclization (Eq. 84) (48).



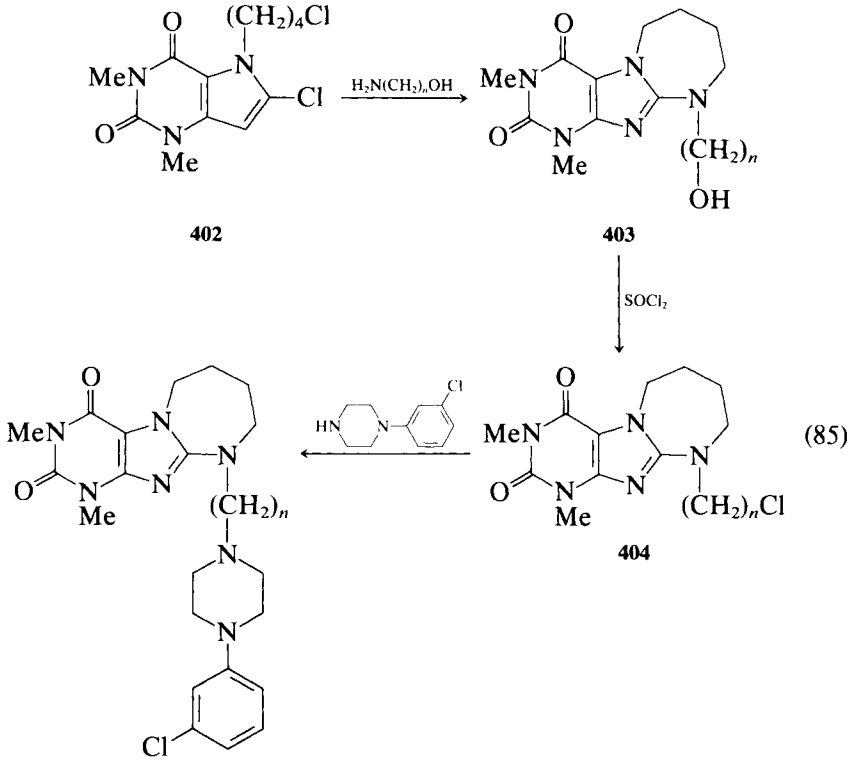
**399** **400** **401**, mp 220–223°C (84)

### 30. [1,3]Diazepino[2,1-*f*]purines (see Section XV.16)



[1,3]Diazepino[2,1-*f*]purines, some of which are claimed to have antidepressant and anti-inflammatory properties, were prepared as outlined in Eq.

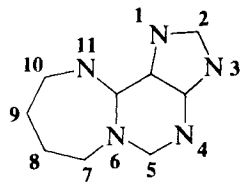
85. The dichloropurine **402** was cyclized to the tricyclic diazepine **403** on treatment with ethanolamine or 3-amino-1-propanol. Treatment of **403** with thionyl chloride afforded chloro compound **404,** which was then used to alkylate N-(3-chlorophenyl)piperazine to generate the final product **405.** In addition to this ring system, the corresponding imidazopurines and pyrimidinopurines were prepared (256).



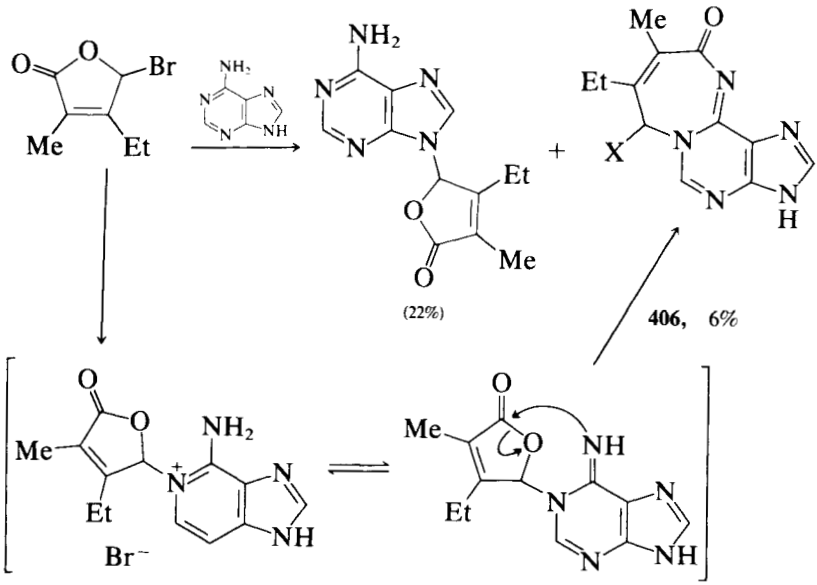
(85)

| | *n* | mp (°C) | λ, nm (ε × $10^4$) |
|---|---|---|---|
| **405a** | 2 | 171 | 254 (1.48), 300 (3.00) |
| **405b** | 3 | 116 | 254 (1.70), 300 (2.12) |

## 31. [1,3]Diazepino[2,1-*i*]purines



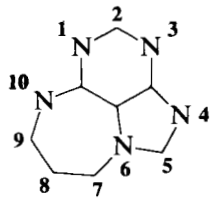
In a study of the condensation of 5-bromo-2(5H)-furanones with adenine, an unexpected product was observed and identified as **406a.** The formation of **406a** was maximal (40% yield) when the reaction was carried out in refluxing pyridine. A possible mechanism is shown in Eq. 86. The structure of **406a** was supported by chemical transformation to chloride **406b** and its conversion to the alkoxy derivatives **406c** and **406d.** The structure of the ring system was confirmed by nmr, ir, uv, and mass spectral data (257).



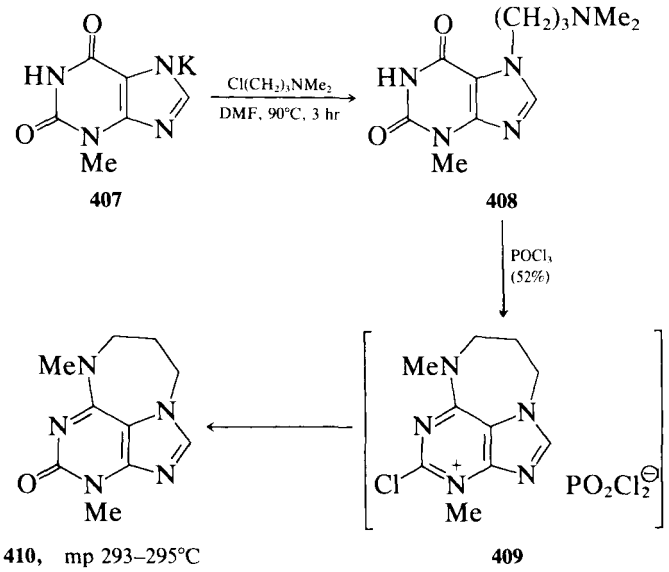

(86)

| | X | Yield (%) | mp (°C) |
|---|---|---|---|
| **406a** | OH | 40 | 236–241 |
| **406b** | Cl | 88 | 204–210 |
| **406c** | OMe | 63 | 127–146 |
| **406d** | OEt | 43 | 145–150 |

## 32. [1,4]Diazepino[1,2,3-*gh*]purines

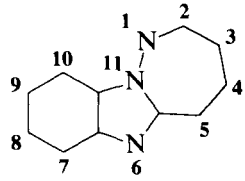


Entry into the [1,4]diazepino[1,2,3-*gh*]purine ring system was achieved as shown in Eq. 87. The potassium salt of the 3-methylxanthine **407** was alkylated with 3-dimethylaminopropyl chloride in dimethylformamide to give **408.** Cyclization of **408** in refluxing phosphoryl chloride led to **410,** probably via the intermediate **409.** The structure of the tricyclic product was supported by ir, uv, and nmr data. The compound had no bronchospasmolytic or coronary dilating activity (258).

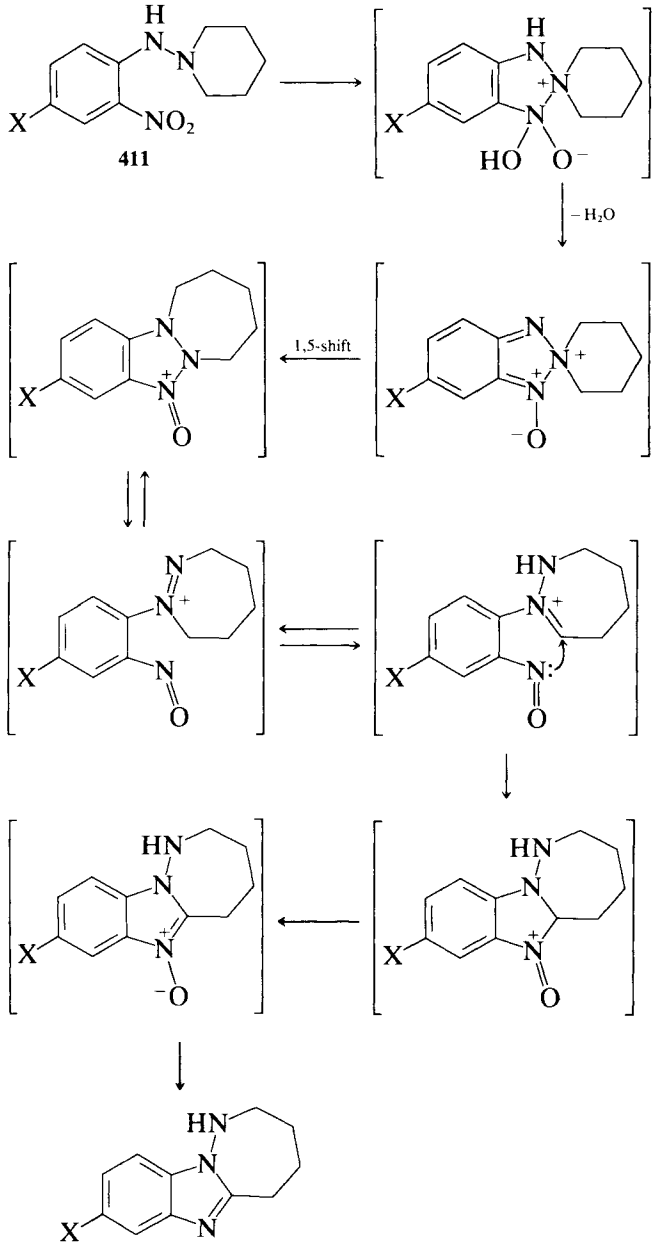



**407** **408** **409** **410,** mp 293–295°C (87)

## 33. [1,3]Diazepino[1,7-*a*]benzimidazoles (see Section XV.17)



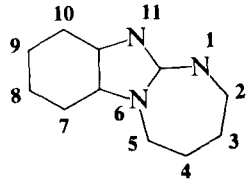
Acid-catalyzed cyclization of *o*-nitrophenylhydrazines resulted in the formation of the *N*-aminobenzimidazoles **412** (Fig. 32). Use of hydrochloric acid led to comcomitant ring chlorination. Use of hydrobromic, trifluoroacetic, or polyphosphoric acid avoided this substitution. A possible mechanism for the reaction, involving a 1,5-sigmatropic shift, is outlined in Fig. 32 (259).



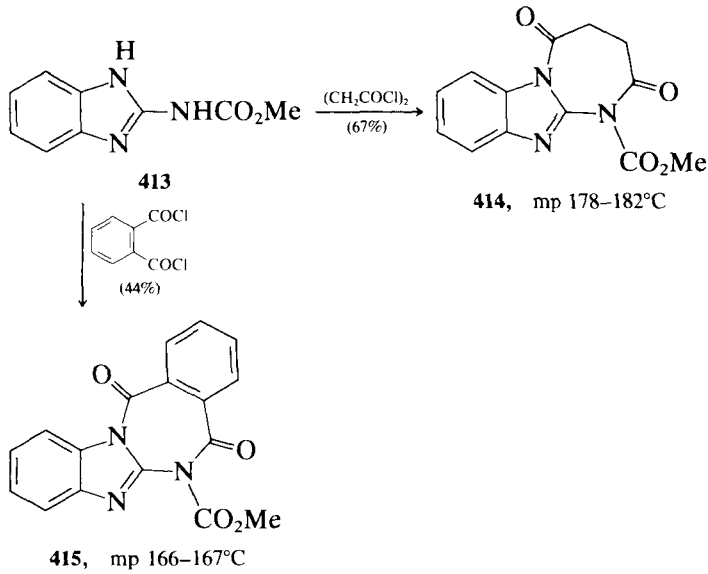

| | X | Yield (%) |
|---|---|---|
| **412a** | Cl | 63 |
| **412b** | $NO_2$ | 50 |

**Figure 32**

## 34. [1,3]Diazepino[1,2-*a*]benzimidazoles



[1,3]Diazepino[1,2-*a*]benzimidazoles were found to have fungicidal or fungistatic properties. Their synthesis was achieved by treatment of methyl 2-benzimidazolecarbamate (**413**) with succinoyl chloride (Eq. 88) or phthaloyl chloride in the presence of sodium bicarbonate to afford the dilactams **414** and **415**, respectively (260).



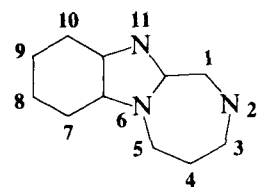
**413**

**414**, mp 178–182°C

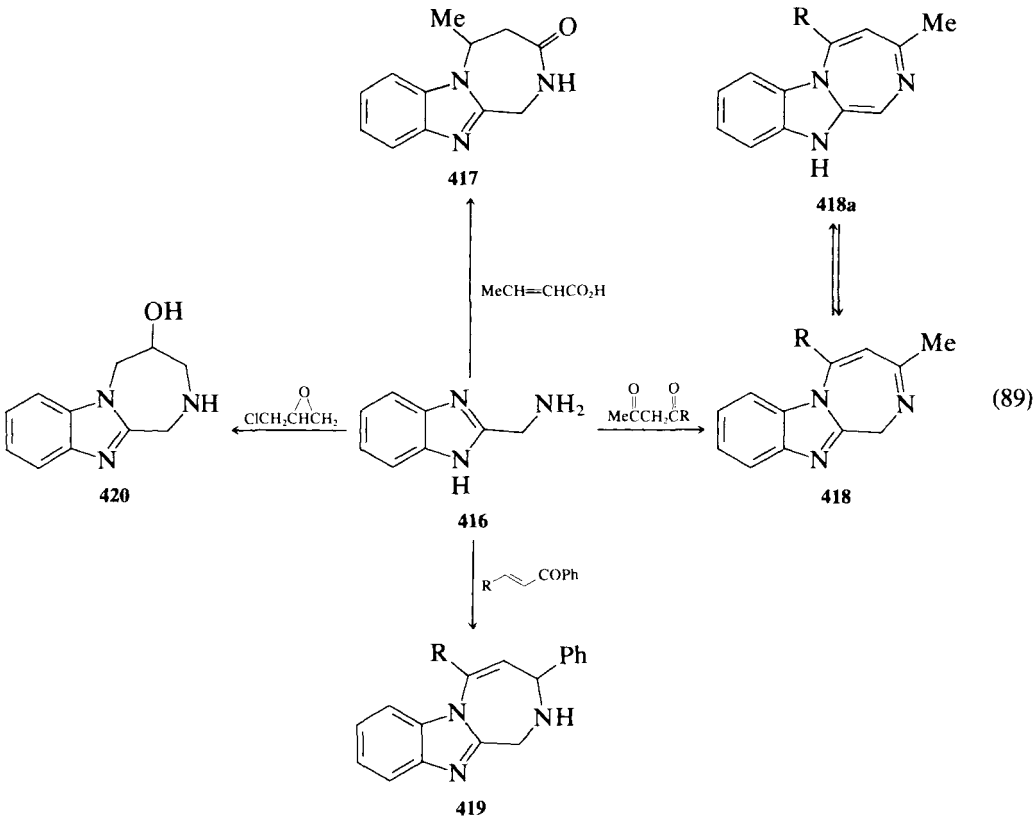
**415**, mp 166–167°C

(88)

## 35. [1,4]Diazepino[1,2-*a*]benzimidazoles (see Section XV.18)



A fundamental building block for the [1,4]diazepino[1,2-*a*]benzimidazole ring system is 2-aminomethylbenzimidazole (**416**), whose condensation with various three-carbon units afforded the tricyclic diazepines shown in Eq. 89 and Table 59 (261,262). Thus reaction with crotonic acid led to derivative **417.** Condensation with β-diketones generated a mixture of **418** and its isomer **418a.** Treatment with enones produced the diazepine system **419.** Addition of epichlorohydrin resulted in compound **420.**




(89)

The same approach was used with 2-(4-thiazolyl)benzimidazole **421,** as shown in Fig. 33. Addition of 1,3-dibromopropane to **421** (R = H) led to the thiazolium salt **422,** which was converted to **423** on treatment with base followed by methyl iodide, or to a mixture of **424** and **425** on reaction with base followed by Raney nickel dethiation. The major product (**425**) was transformed further to **426** by acidic hydrolysis. Similarly, compound **421** (R = Me), on alkylation with 1,3-dibromopropane, was converted to the dibromide **427,** which yielded the stable thione **428** on treatment with base. These products are listed in Table 60 (263).

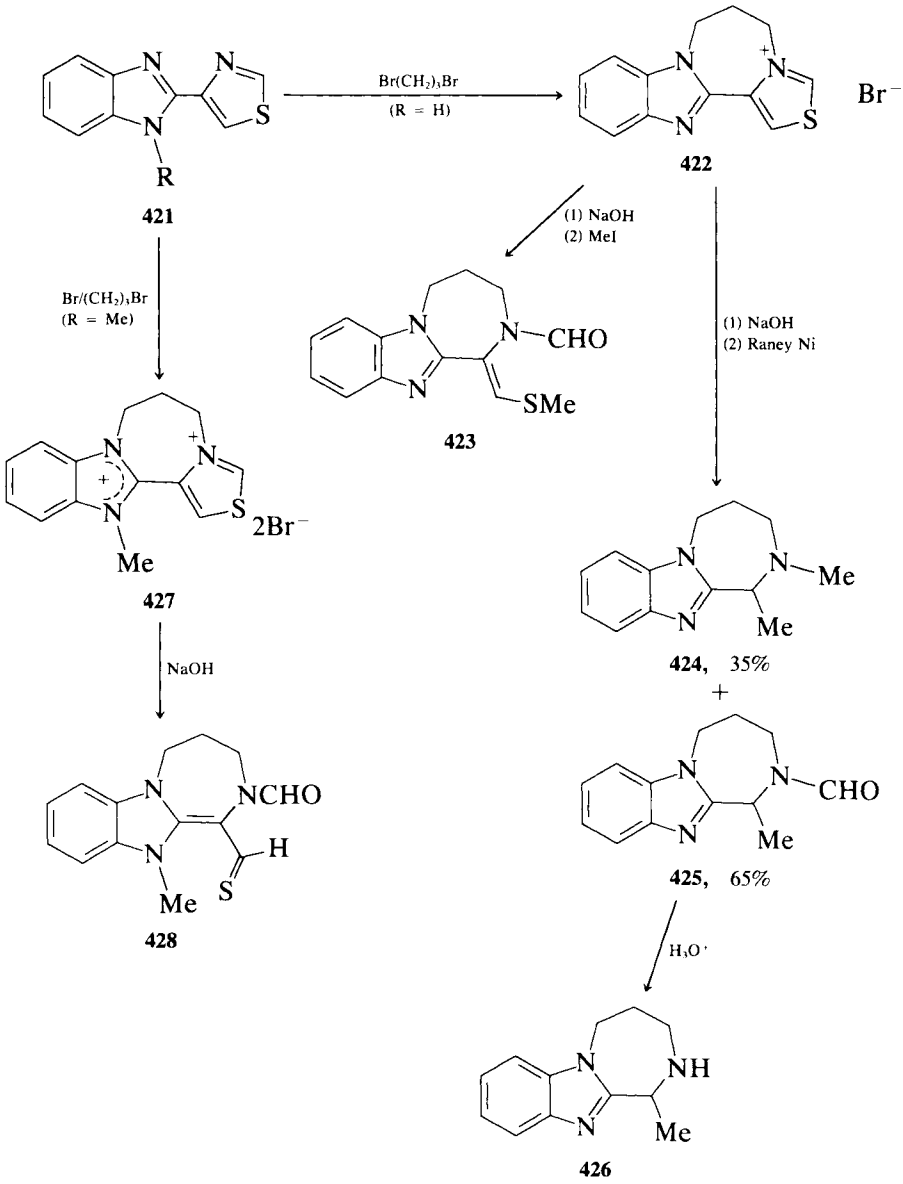

Br(CH2)3Br
(R = H)
Br⁻
422
421
(1) NaOH
(2) MeI
Br/(CH2)3Br
(R = Me)
423
CHO
SMe
(1) NaOH
(2) Raney Ni
427
2Br⁻
Me
NaOH
424, 35%
+
425, 65%
NCHO
H
S
428
H3O⁺
426
NH

**Figure 33**

TABLE 59. [1,4]DIAZEPINO[1,2-*a*]BENZIMIDAZOLES FROM **416**

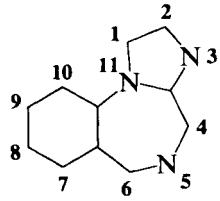
| Compound | R | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|
| **418** | Me | 81 | 220 | 261 |
| **418** | Ph | | 176 ($2H_2O$) | 261 |
| **419** | Ph | 64 | 243 | 261 |
| **419** | 2-Thienyl | 58 | 256 | 261 |
| **420** | | 76 | 251–253 (2HCl) | 262 |

TABLE 60. [1,4]DIAZEPINO[1,2-*a*]BENZIMIDAZOLES FROM **421**[a]

| Compound | Yield (%) | mp (°C) | Spectra |
|---|---|---|---|
| **422** | 45 | 282 | nmr |
| **423** | 92 | 150–151 | nmr, ms |
| **424** | 35 | 146 | nmr, ms |
| **425** | 65 | 127–128 | nmr, ms |
| **426** | 81 | 152 | nmr, ms |
| **427** | 98 | 278 | nmr |
| **428** | 91 | 259–260 | ms |

[a]Ref. 263.

## 36. Imidazo[1,2-*a*][1,4]benzodiazepines (see Section XV.20)

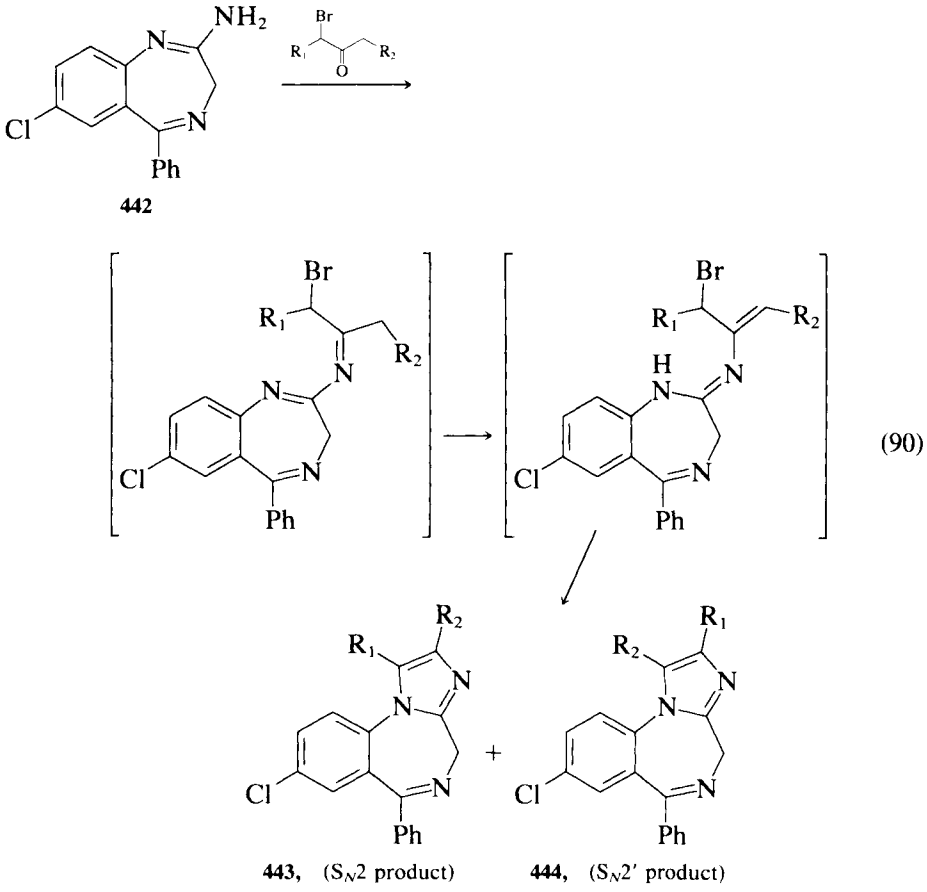



The imidazo[1,2-*a*][1,4]benzodiazepine class of central nervous system depressants was prepared by annelation of the imidazole ring to an appropriate benzodiazepine substrate (Fig. 34). In one method, reaction of thione **429** (or its methylthio derivative) with propargylamine afforded amidine **430.** Mercuric sulfate–catalyzed hydration and cyclization led to the tricyclic imidazole **431.** Alternatively, reaction of **430** with mercuric acetate in a mixture of acetic and formic acid led to **432,** which was decarbonylated to **433** with tris(triphenylphosphine)rhodium chloride (264–270).

A somewhat different synthetic approach, likewise using thione **429,** began by condensation with amino acetals or ketals. From aminoacetaldehyde dimethyl acetal, the unsubstituted imidazole **433** was obtained via **434.** Re-

action of **429** with the ethylene ketal of 3-phthalimidoacetonylamine afforded the imidazole **436,** which could then be cleaved to **437** by hydrazinolysis. Reductive methylation of **437** generated **438.** As an alternative to the phthalimido reagent, the corresponding azido and bromo compounds could be employed to obtain compounds **437** and **438** (269,271).

A third synthetic variation provided access to 2-substituted derivatives. Condensation of 2-aminobenzodiazepine **442** with α-bromoketone derivatives (Eq. 90) generated the tricyclic products **443** and **444.** The compounds

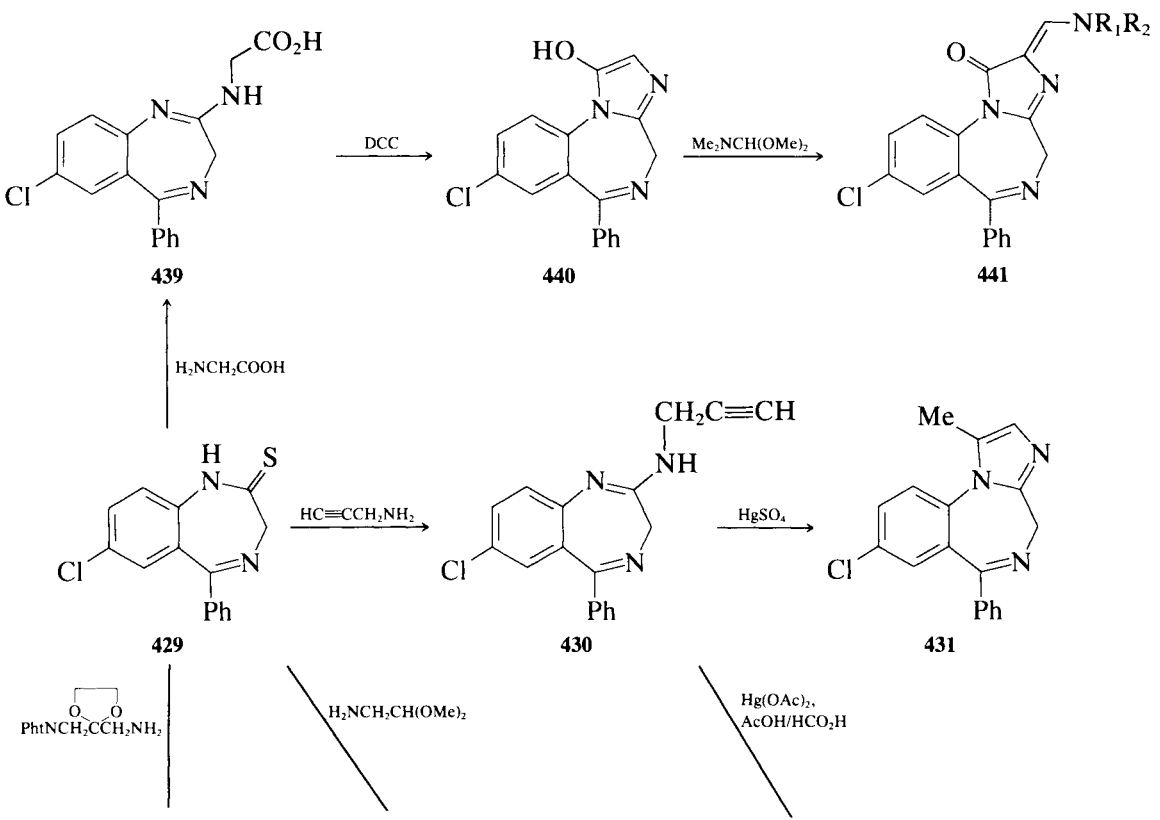


**442**

**443,** ($S_N2$ product) **444,** ($S_N2'$ product)

(90)

were identified by comparison with identical products prepared by alternate routes and by analysis of the nmr spectra of isomeric products. The major product from **442** can be predicted by attack ($S_N2$ or $S_N2'$) at the least hindered site of the allylic bromide intermediate (272). Compounds prepared by these three methods are listed in Table 61 (264–280).


CO2H
NH
N
N
Cl
Ph
439
DCC
HO
N
N
Cl
Ph
440
Me2NCH(OMe)2
NR1R2
O
N
N
Cl
Ph
441
H2NCH2COOH
H
N
S
N
Cl
Ph
429
HC≡CCH2NH2
CH2C≡CH
NH
N
N
Cl
Ph
430
HgSO4
Me
N
N
Cl
Ph
431
O
O
PhtNCH2CCH2NH2
H2NCH2CH(OMe)2
Hg(OAc)2,
AcOH/HCO2H

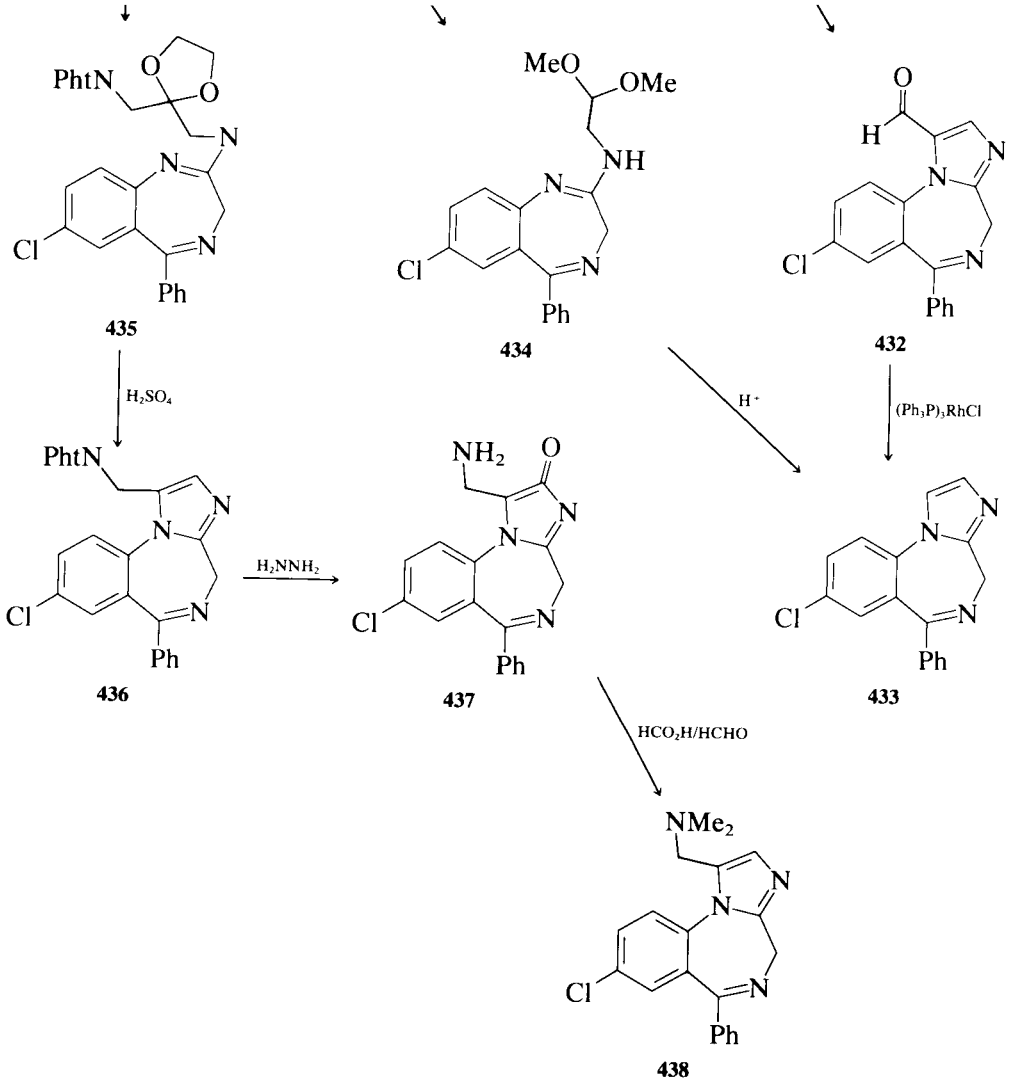
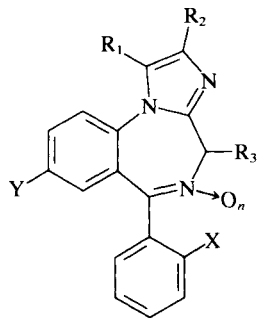
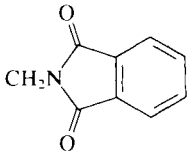

PhtN
O
O
N
N
Cl
N
Ph
435
H2SO4
PhtN
N
N
Cl
N
Ph
436
H2NNH2
NH2
O
N
N
Cl
N
Ph
437
HCO2H/HCHO
NMe2
N
N
Cl
N
Ph
438
MeO
OMe
NH
N
Cl
N
Ph
434
H+
O
H
N
N
Cl
N
Ph
432
(Ph3P)3RhCl
N
N
Cl
N
Ph
433

Figure 34

TABLE 61. IMIDAZO[1,2-*a*][1,4]BENZODIAZEPINES

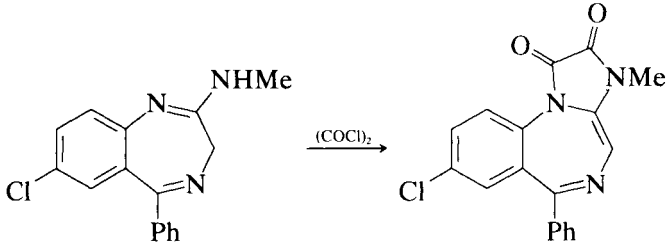



| $R_1$ | $R_2$ | *n* | $R_3$ | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|---|---|---|
| Me | H | 0 | H | H | Cl | 192–193 | 264–268 |
| Me | H | 0 | H | Cl | Cl | 148–149 | 264,265,268 |
| H | H | 0 | H | Cl | Cl | 179–180 | 264,265,268, 273,275,277 |
| Me | Br | 0 | H | H | Cl | 194 | 266,267 |
| Me | H | 1 | H | H | Cl | 224–226 | 266,267 |
| H | H | 0 | H | H | Cl | 146–148 | 266–268,273, 275,277 |
| H | H | 1 | H | H | Cl | 264 | 266,267 |
| Me | H | 0 | AcO | H | Cl | 238 | 267 |
| Me | H | 0 | OH | H | Cl | 220–221 | 267,278 |
| H | H | 0 | AcO | H | Cl | 226 | 267,278 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| H | H | 0 | OH | H | Cl | 292–294 | 267,278 |
| OH | H | 1 | H | H | Cl | 257 | 267,280 |
|  | H | 0 | H | H | Cl | 240–242 | 269,271 |
| " | H | 0 | H | Cl | Cl | 218–220 | 269,271 |
| $CH_2NH_2$ | H | 0 | H | H | Cl | 275–280 | 269,271 |
| $CH_2NH_2$ | H | 0 | H | Cl | Cl | Oil | 271 |
| $CH_2NMe_2$ | Me | 0 | H | H | Cl | 194–197 (HBr) | 269,271,279 |
| $CH_2NMe_2$ | H | 0 | H | Cl | Cl | 168–171 | 269,271,279 |
| $CH_2NMe_2$ | H | 0 | H | H | Cl | 181–182 | 269,271,279 |
| H | H | 0 | H | Cl | H | 148.5–150 | 267,277 |
| H | Me | 0 | H | Cl | Cl | 169.5–170.5 | 273,276,277 |
| $CH_2OH$ | H | 0 | H | Cl | Cl | 193–195 | 274 |
| $CH_2OH$ | H | 0 | H | H | Cl | 210–213 | 274,276 |
| H | Me | 0 | H | H | Cl | 174–176 | 272 |
| H | Et | 0 | H | H | Cl | 147–149 | 272 |
| H | $n$-$C_3H_7$ | 0 | H | H | Cl | 158–159 | 272 |
| H | $i$-$C_3H_7$ | 0 | H | H | Cl | 138–140 | 272 |
| H | $CH_2Ph$ | 0 | H | H | Cl | 143–145 | 272 |
| Me | Me | 0 | H | H | Cl | 152–153 | 272 |
| Et | Me | 0 | H | H | Cl | 136–137 | 272 |
| H | H | 0 | H | Cl | $NO_2$ | 242–243 | 270 |

An approach to imidazolone products was achieved by addition of glycine to thione **429.** The product (**439**) was cyclized in the presence of *N,N'*-dicyclohexylcarbodiimide to **440,** which on treatment with dimethylformamide dimethylacetal generated the imidazolone **441** ($R_1 = R_2 = Me$). A variety of other substituted aminomethylene derivatives was obtained from the *N,N*-dimethyl compound by amine interchange. These products are listed in Table 62 (281).

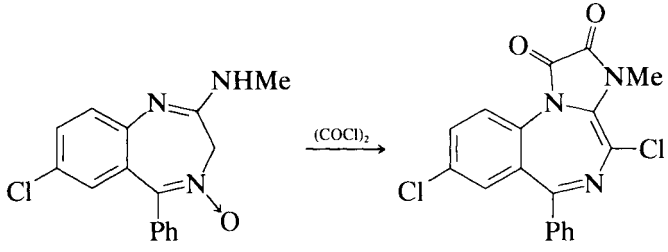
An imidazolidin-2,3-dione derivative (**446**) was obtained by treatment of **445** with oxalyl chloride (Eq. 91). Similar reaction of the $N^4$-oxide derivative




(91)

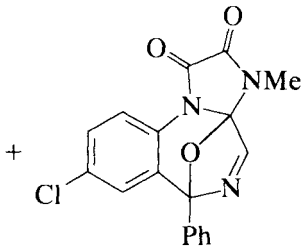
**445** **446,** mp 203–204.5°C

of **445** under these conditions did not lead to the simple tricyclic imidazole, but instead gave products **447** and **448** (Eq. 92). Under the same conditions,



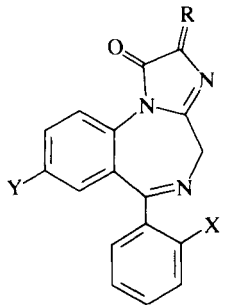

**447,** mp 258–262°C (79%)

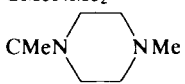
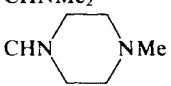
(92)




**448,** mp 238–242°C (8%)

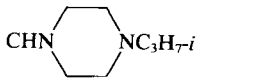
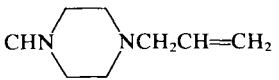
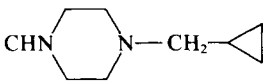
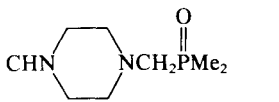
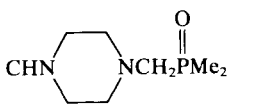
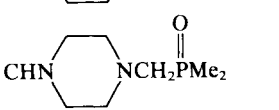
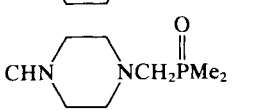
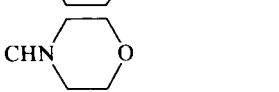
TABLE 62. IMIDAZO[1,2-*a*][1,4]BENZODIAZEPIN-1-ONES

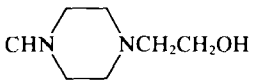
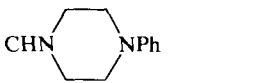
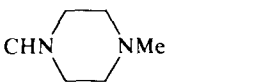
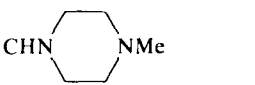
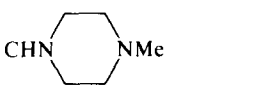
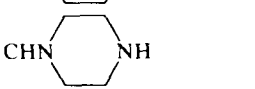
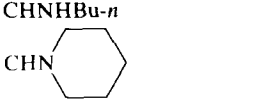
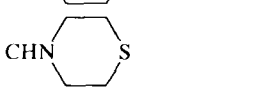
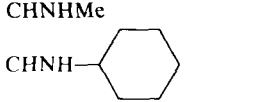


| R | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|
| $H_2$ | H | Cl | Oil | 281 |
| $H_2$ | H | $NO_2$ | 154–155 | 281 |
| $H_2$ | Cl | Cl | 136–139 | 281 |
| $H_2$ | Cl | $NO_2$ | 158–161 | 281 |
| $CHNMe_2$ | H | Cl | 264–265 | 281 |
| $CMeNMe_2$ | H | Cl | 251–252 | 281 |
|  | H | Cl | 193–195 | 281 |
| $CHNMe_2$ | H | $NO_2$ | 227–228 | 281 |
| $CHNMe_2$ | Cl | Cl | 288–290 | 281 |
| $CHNMe_2$ | Cl | $NO_2$ | 253–255 | 281 |
| $CHNMe_2$ | F | Cl | 257–260 | 281 |
| $CHNMe_2$ | F | $NO_2$ | 228–231 | 281 |
|  | H | Cl | 255–256 | 281 |

(*continued*)

TABLE 62. (*Continued*)

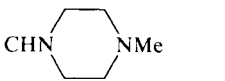
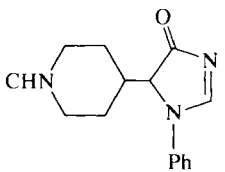
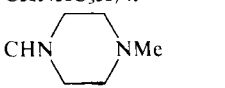
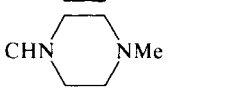
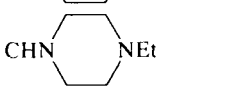
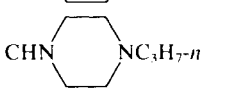
| R | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|
| $CHNH_2$ | H | Cl | 265–267 | 281 |
|  | H | Cl | 146–148 | 281 |
|  | H | Cl | 187–188 | 281 |
|  | H | Cl | 202–204 | 281 |
|  | H | Cl | 261–262 | 281 |
|  | C | Cl | 231–234 | 281 |
|  | H | H | 245–247 | 281 |
|  | Cl | $NO_2$ | 245–248 | 281 |
|  | H | Cl | 223 | 281 |

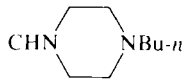
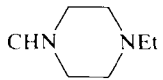
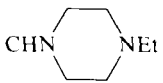
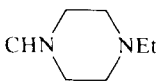
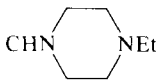
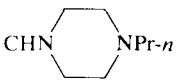
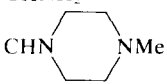
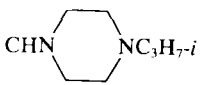
| | | | | |
|---|---|---|---|---|
|  | H | Cl | 178 | 281 |
|  | H | Cl | 207 | 281 |
|  | Cl | Cl | 248 | 281 |
|  | Cl | Cl | 155–160 | 281 |
|  | H | $NO_2$ | 284 | 281 |
|  | H | Cl | 233 | 281 |
| CHNHBu-*n* | H | Cl | 166 | 281 |
|  | H | Cl | 249 | 281 |
|  | H | Cl | 256 | 281 |
| $CHNHCH_2CH_2NEt_2$ | H | Cl | 113 | 281 |
| $CHNHCH_2CH_2NMe_2$ | H | Cl | 152 | 281 |
| CHNHMe | H | Cl | 233 | 281 |
|  | H | Cl | 143 | 281 |



(*continued*)

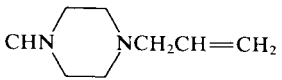
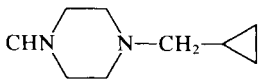
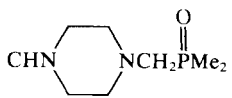
TABLE 62. (*Continued*)

| R | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|
|  | F | Cl | 249 | 281 |
|  | H | Cl | 290 | 281 |
| CHNHPh | H | Cl | 249 | 281 |
| $CHNHCMe_3$ | H | Cl | 230 | 281 |
| $CHNHCH_2CH_2OH$ | H | Cl | 223 | 281 |
| $CHNHC_3H_7$-*n* | H | Cl | 153 | 281 |
|  | Cl | $NO_2$ | 214 | 281 |
|  | F | $NO_2$ | 303 | 281 |
|  | H | Cl | 183 | 281 |
|  | H | Cl | 148 | 281 |

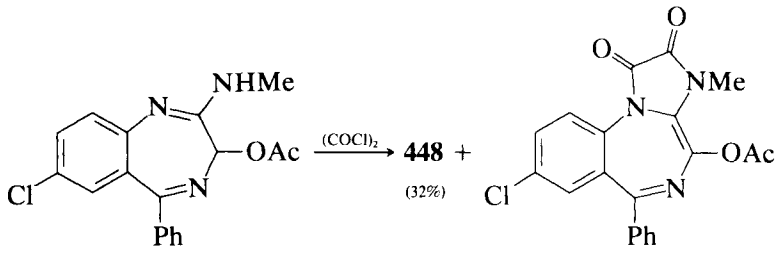
| | | | | |
|---|---|---|---|---|
|  | H | Cl | 187 | 281 |
|  | Cl | Cl | 243 | 281 |
|  | F | Cl | 235 | 281 |
|  | Cl | $NO_2$ | 265 | 281 |
|  | F | $NO_2$ | 262 | 281 |
| CHNHEt | H | Cl | 234 | 281 |
|  | Cl | Cl | 248 | 281 |
| CHNHEt | Cl | Cl | 235 | 281 |
| CHNHPr-*n* | Cl | Cl | 228 | 281 |
| $CHNH_2$ | H | Cl | 266 | 281 |
|  | H | Cl | 193 | 281 |
|  | H | Cl | 147 | 281 |

(*continued*)

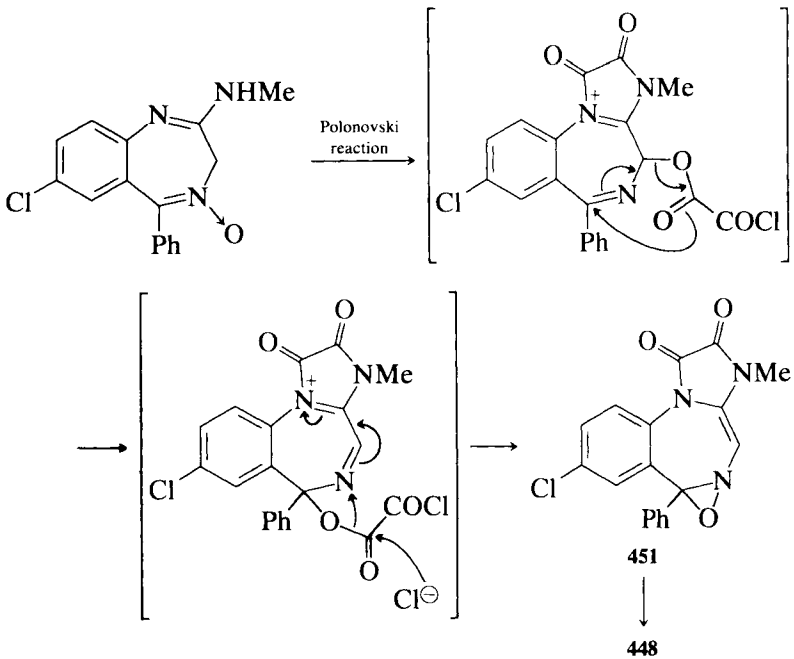
TABLE 62. *(Continued)*

| R | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|
|  | H | Cl | 188 | 281 |
|  | H | Cl | 202 | 281 |
|  | H | Cl | 261 | 281 |
| O | Cl | Cl | 169 | 282 |
| O | H | Cl | 185 | 282 |

the acetoxy derivative **449** afforded **448** and the acetate **450** (Eq. 93). The $N^5$-oxide of **448** was also obtained from **446** by reaction with *m*-chloroperbenzoic acid. Thus structure **451** is implicated as an intermediate, and a possible mechanism for the formation of **448** from the $N^4$-oxide of **445** is presented in Eq. 94 (282,283).

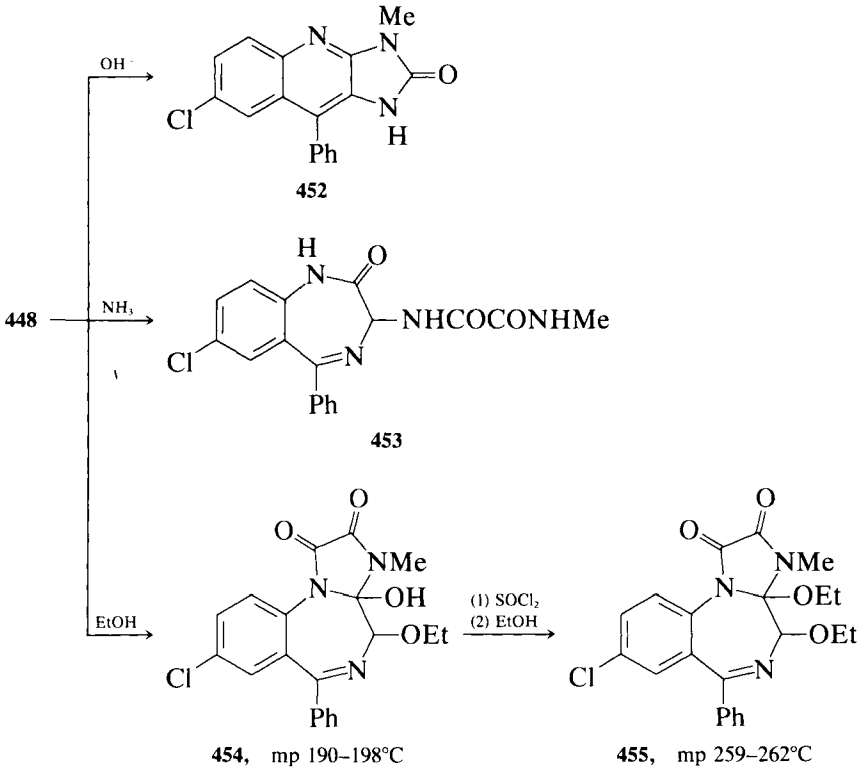



(93)

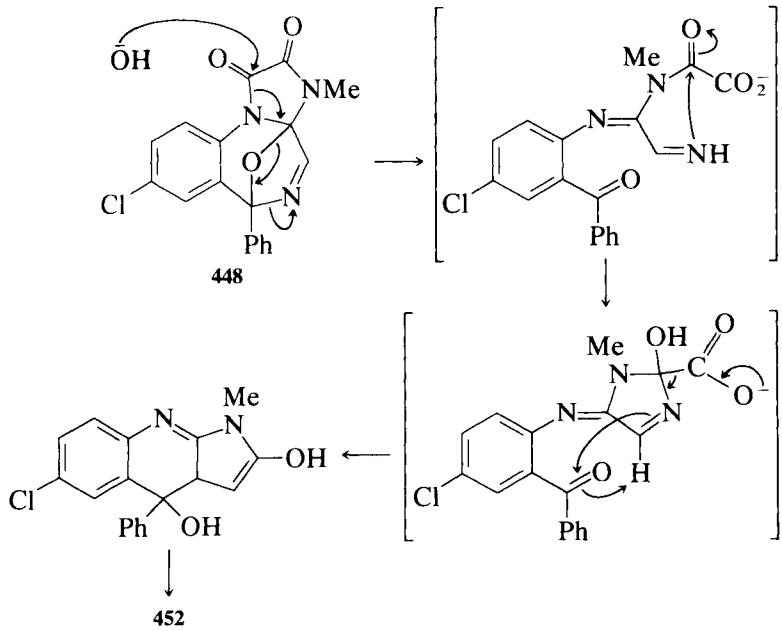



(94)

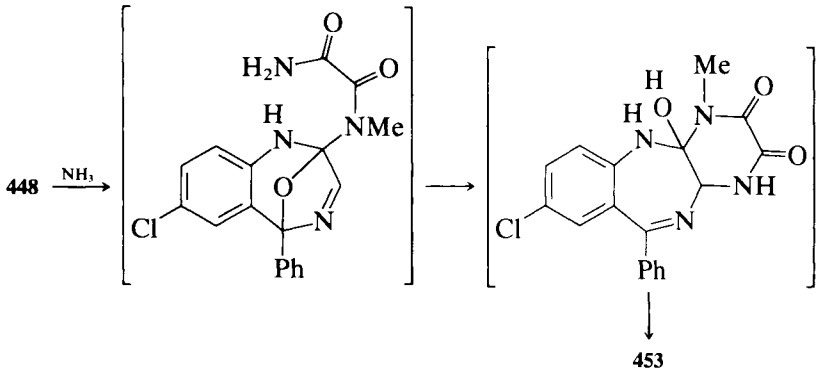
Some reactions of **448** are summarized in Eq. 95. An unusual rearrangement, occurring on treatment with sodium hydroxide, gave the quinoline derivative **452,** perhaps by the route outlined in Eq. 96. When **448** was allowed to react with ammonia, diamide **453** was the sole product. A possible mechanism for the formation of **453** is suggested in Eq. 97. Finally, in refluxing ethanol, **448** was converted to the hydroxy ether **454,** probably by addition of ethanol to the imine double bond of **448** followed by opening of


OH⁻
NH₃
EtOH
448
452
453
454, mp 190–198°C
(1) SOCl₂
(2) EtOH
455, mp 259–262°C

(95)


448
452

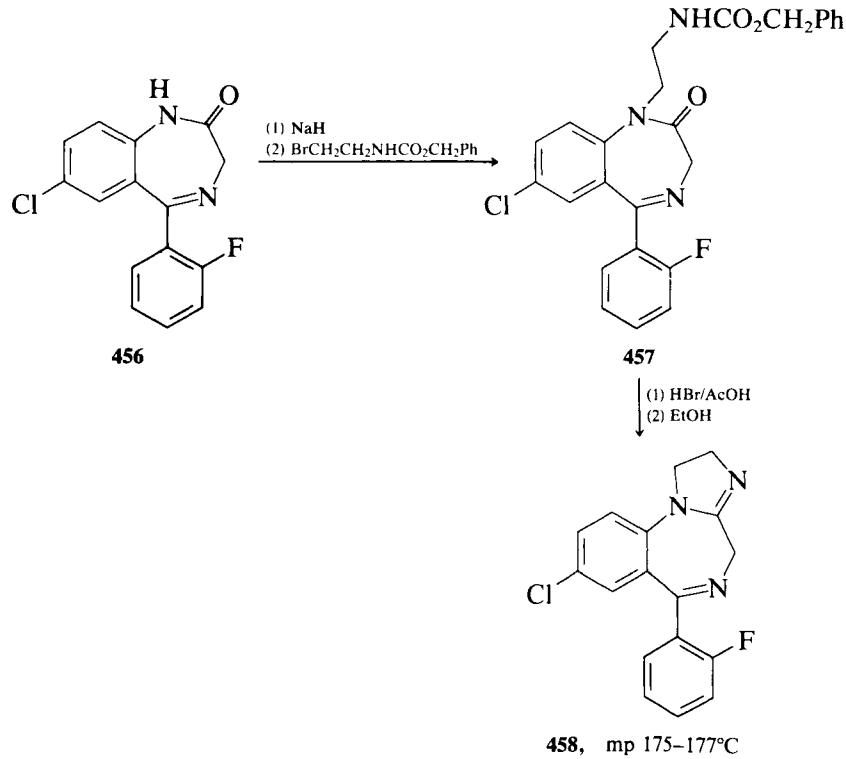
(96)




(97)

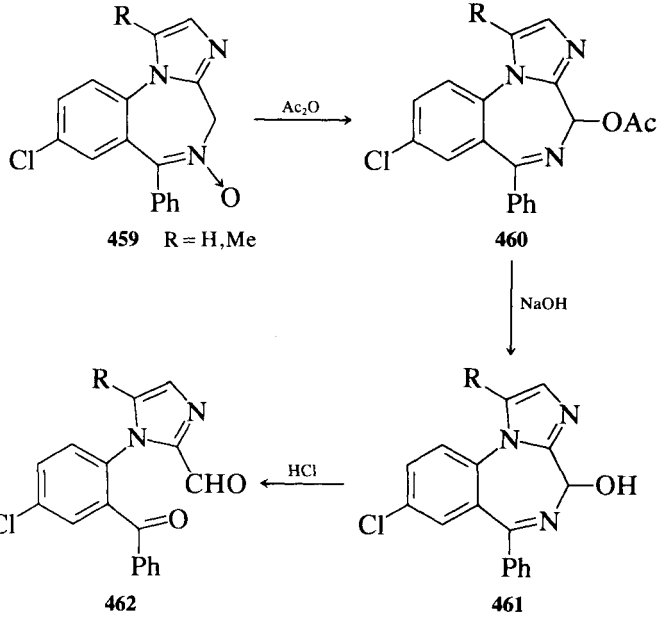
the ether bridge. Compound **454** could be further transformed to **455** by sequential treatment with thionyl chloride and ethanol (282).

Dihydroimidazoles were obtained by treatment of benzodiazepine **456** with sodium hydride followed by alkylation with a protected bromoethylamine to give the intermediate **457** (Eq. 98). Unmasking of the amine with acid followed by cyclization in refluxing ethanol completed the synthesis of **458** (284,285).



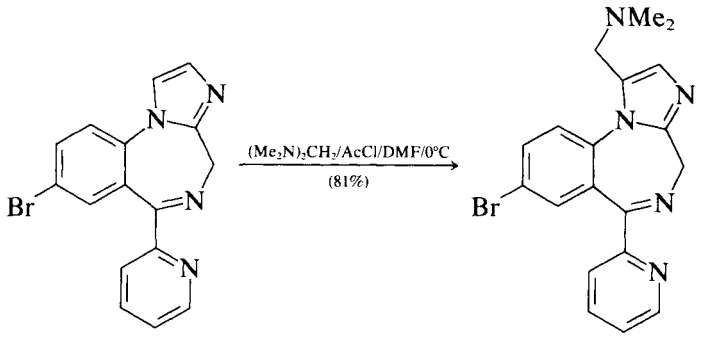

(98)

Turning to reactions carried out on this ring system, imidazole **459** underwent the expected Polonovski rearrangement in the presence of acetic anhydride to yield the acetate **460.** As outlined in Eq. 99, acetate **460** could be hydrolyzed with aqueous sodium hydroxide to give **461,** whose diazepine ring could be opened with hydrochloric acid to afford aldehyde **462** (278).



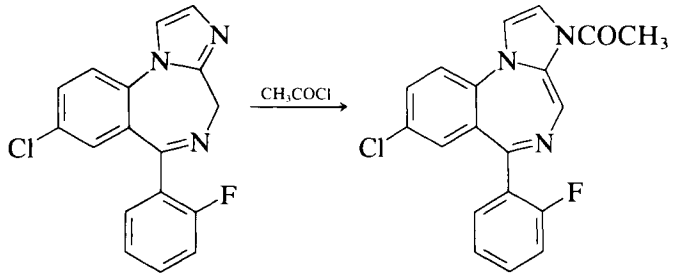

(99)

Other chemical transformations of this ring system (Eqs. 100–105) include Mannich reaction on **463** to yield **464** (279,286), acetylation of **465** to give **466** (287), and reaction of **431** with bromine to generate the 2-bromoimidazole **467.** Cleavage of the diazepine occurred during the acetylation of **431** in acid to yield **468** and during the Wolff–Kishner reduction of **433** to **469.** Similarly,

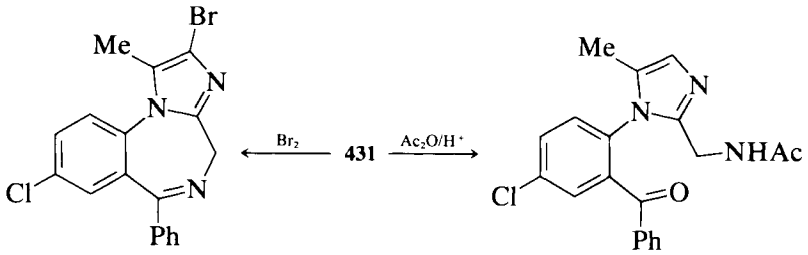



(100)

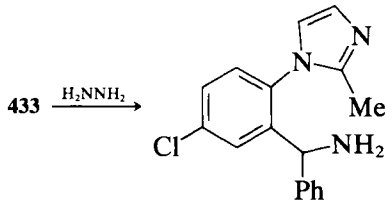
**471** was obtained from **470** (184). Finally, ring opening accompanied by reductive methylation under Eschweiler–Clarke conditions yielded **472** (288). Ring-opened products are listed in Table 63.



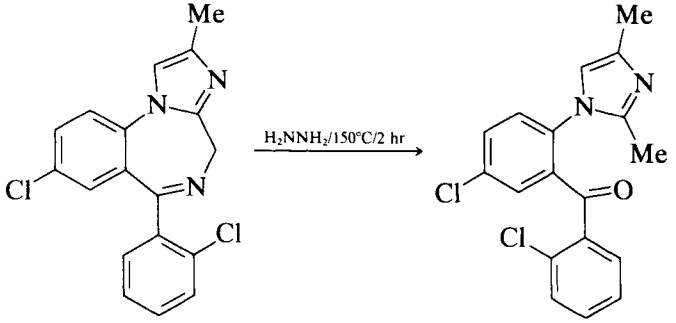

**465** **466**, mp 166–169°C (101)



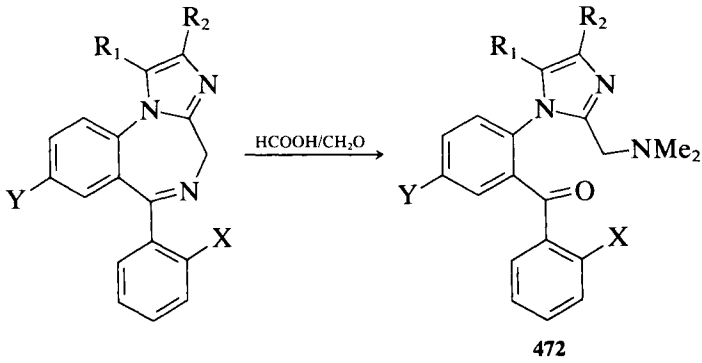

**467** **468** (102)




**469** (103)

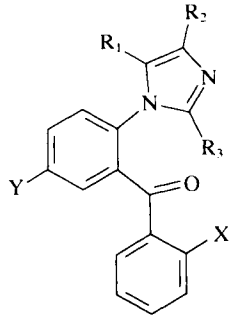



**470** **471** (104)



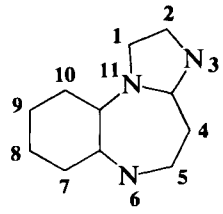

472 (105)

TABLE 63. RING-OPENED IMIDAZO[1,2-*a*][1,4]BENZODIAZEPINES




| $R_1$ | $R_2$ | $R_3$ | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| H | H | $CH_2NMe_2$ | Cl | Cl | 105–108 | 273,288 |
| Me | H | $CH_2NMe_2$ | H | Cl | Oil | 273,288 |
| Me | $CH_2OH$ | $CH_2NMe_2$ | H | Cl | 154–155 | 273 |
| $CH_2OH$ | Me | $CH_2NMe_2$ | Cl | Cl | 77–81 | 273 |
| Me | H | CHO | H | Cl | 132 | 278 |

## 37. Imidazo[1,2-*a*][1,5]benzodiazepines (see Section XV.21)




Imidazo[1,2-*a*][1,5]benzodiazepines were prepared from benzodiazepine derivative **473** by three routes. Treatment of **473** with propargylamine in the

presence of *p*-toluenesulfonic acid (Fig. 35) led to the imidazoles **475** (method A). Reaction of **473** with 2-bromoketones in the presence of diisopropylethylamine likewise afforded **475** (method B). Finally, condensation of **473** with $\alpha$-amino acetal derivatives followed by cyclization of the intermediate amidine with formic acid provided another route to **475** (method C) (289).

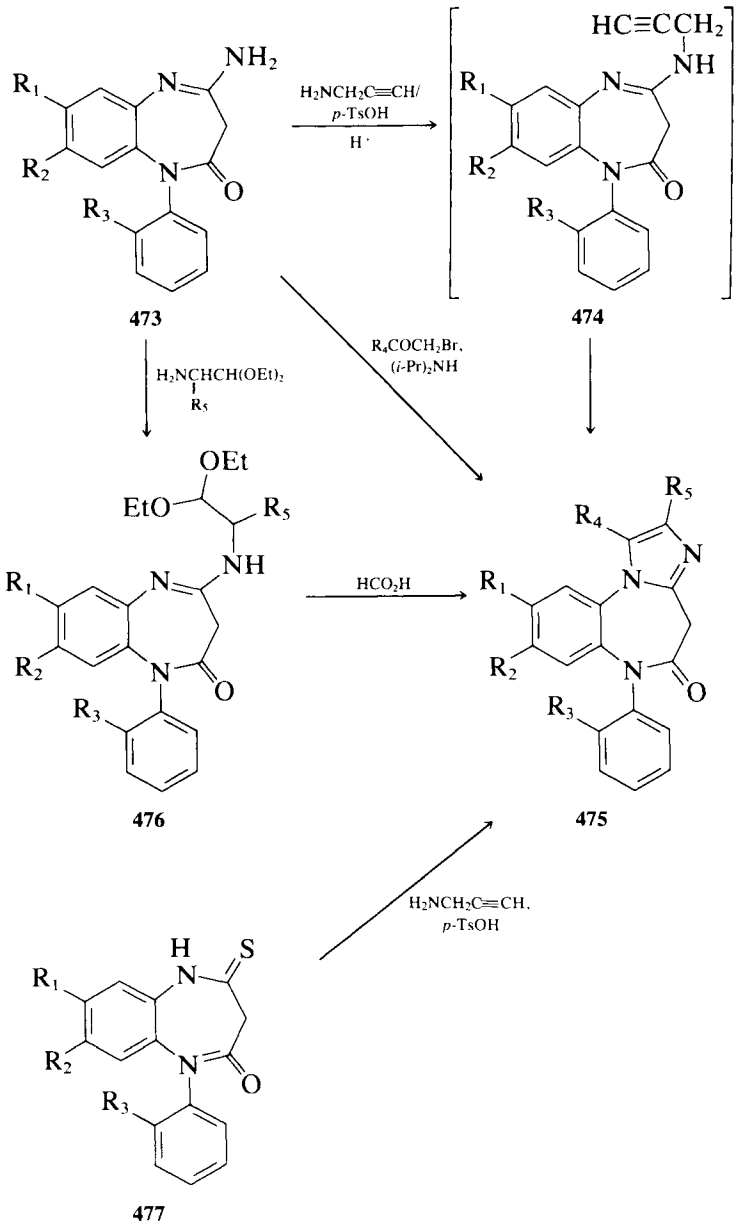
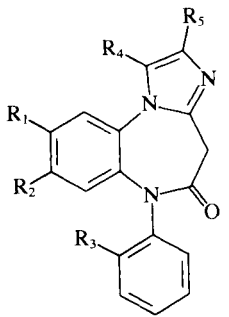



Figure 35

TABLE 64. IMIDAZO[1,2-*a*][1,5]BENZODIAZEPINES

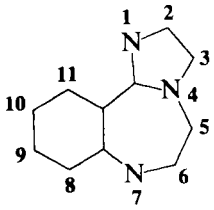



| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Method[a] | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|---|---|
| H | H | H | H | H | C | 84 | 108 | 186 |
| H | H | H | Me | H | A | 94 | 206–207 | 186 |
| H | Cl | H | Me | H | A | 33 | 204–205 | 186 |
| H | Cl | F | Me | H | A | 36 | 186.5–188 | 186 |
| $CF_3$ | H | H | Me | H | A | 35 | 182–183 | 186 |
| H | H | H | H | Me | B | 18 | 195–195.5 | 186 |
| H | Cl | H | H | Me | C | 67 | 199.5–200.5 | 186 |
| | | | | | B | 14 | | |
| H | Cl | H | H | Et | B | 21 | 173–174 | 186 |
| H | Cl | H | H | $n$-$C_3H_7$ | B | 25 | 185–187 | 186 |
| H | Cl | F | H | Et | B | 10 | 180.5–182 | 186 |
| H | $CF_3$ | H | Me | H | A | 40 | 110.5–112.5 | 289 |

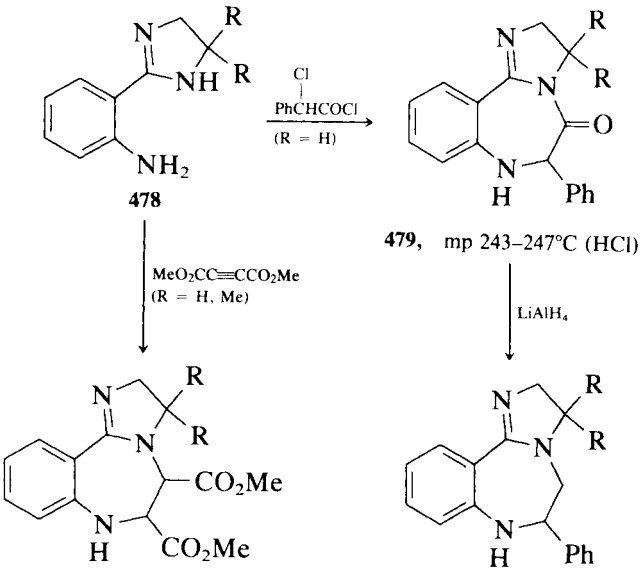
[a]A: **473** + $H_2NCH_2C{\equiv}CH$; B: **473** + $R_4COCH_2Br$; C: **473** + $H_2NCHR_5CH(OEt)_2$

It was also found that thione **477** could be used in place of **473** in the reaction with propargylamine (186). The location of the substituents in products obtained via method B was suggested by analogy to previous work on the corresponding imidazo[1,2-*a*][1,4]benzodiazepine system and was confirmed in one case by the synthesis of the same product by methods B and C. The compounds prepared by these methods are summarized in Table 64. All products were characterized by ir, nmr, and mass spectral data.

## 38. Imidazo[1,2-*d*][1,4]benzodiazepines (see Section XV.23)



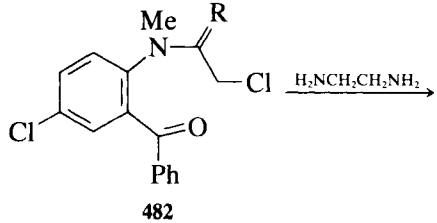

Two routes to the imidazo[1,2-*d*][1,4]benzodiazepine ring system have been developed. One process, which begins with the preformed imidazoline **478,** is outlined in Eq. 106 (290). Condensation of **478** with α-chlorophenyl-




(106)

| | R | mp (°C) |
|---|---|---|
| **481a** | Me | 103–105 |
| **481b** | H | 188–190 |

acetyl chloride resulted in acylation of the imidazole and concomitant closure of the diazepine ring. Compound **479** could be reduced to **480** with lithium aluminum hydride. Other members of this family, prepared by the same approach, are listed in Table 65. The starting imidazole **478** was also condensed with dimethyl acetylenedicarboxylate, which led to a double Michael reaction and formation of diazepine **481** (291). Another route to this ring system begins with the 2-aminobenzophenone derivative **482,** which on reaction with ethylenediamine affords **483** directly (Eq. 107) (215,231,232). Compounds **479** and **480** are claimed to be CNS depressants, and **481** is claimed to possess antiarrhythmic activity.

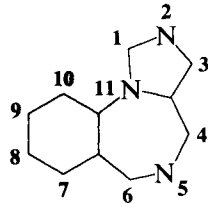



**482**

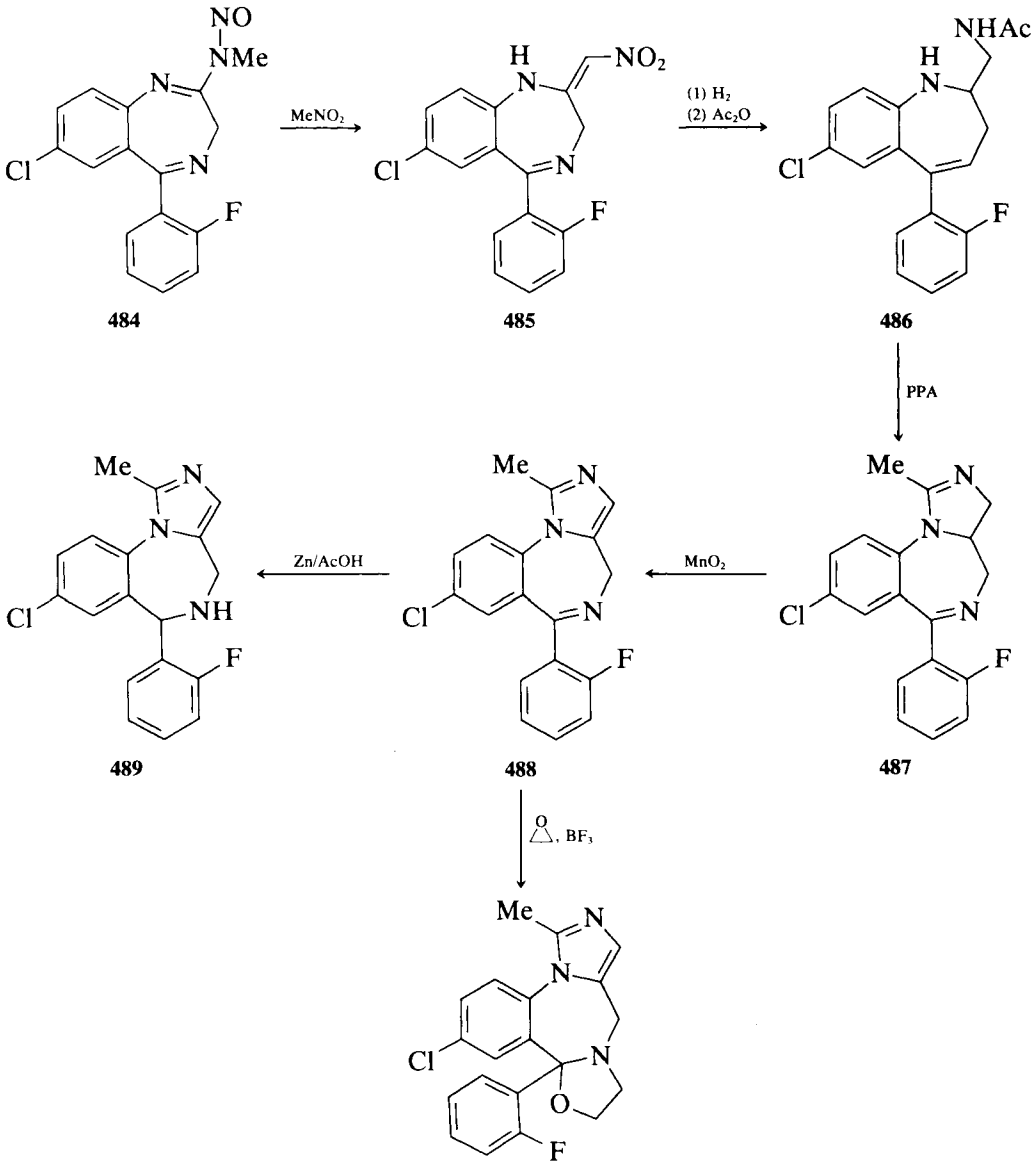
(107)

| | R | mp (°C) |
|---|---|---|
| **483a** | O | 164–167 |
| **483b** | $H_2$ | 100–102 |

## 39. Imidazo[1,5-*a*][1,4]benzodiazepines (see Section XV.24)




Several pathways to the imidazo[1,5-*a*][1,4]benzodiazepine ring system have been developed. Entry into the 1-substituted series was attained as shown in Fig. 36. Displacement of the *N*-nitrosamino group of **484** with nitromethane led to **485,** which, after reduction and acylation, was cyclized with polyphosphoric acid to the 3,4-dihydro product **487.** Manganese dioxide oxidation of **487** afforded the imidazole **488.** Additional examples of these products were prepared similarly (55,276). Treatment of **488** with zinc in acetic acid provided the corresponding 5,6-dihydro derivatives **489.** Reaction of **488** with *m*-chloroperbenzoic acid generated the $N^2$- and/or $N^5$-oxides,



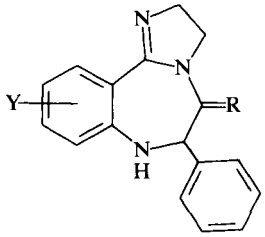

**484** **485** **486**

**487** **488** **489**

**490,** mp 178–180°C

**Figure 36**

TABLE 65. IMIDAZO[1,2-*d*][1,4]BENZODIAZEPINES[a]



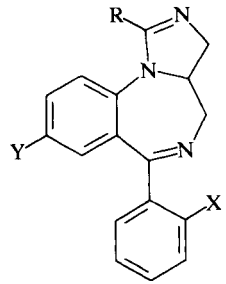
| R | Y | mp (°C) |
|---|---|---|
| O | H | 230 (HCl) |
| O | 9-Cl | 324–326 (HCl) |
| $H_2$ | 9-Cl | 220–223 |
| O | 10-Cl | 196–198 |
| $H_2$ | 10-Cl | 308–310 (HCl) |

[a]Ref. 290.

each of which could be subjected to the Polonovski rearrangement to give the usual acetoxy and hydroxy derivatives. Treatment of **488** with ethylene oxide in the presence of boron trifluoride afforded the tetracyclic derivative **490** (55). Analogs of compounds **487–489** and *N*-oxides of **488** are listed in Tables 66–69, respectively.

A route to 3-substituted members of this ring system was developed from benzodiazepine **491.** Condensation with diethyl acetamidomalonate (Eq. 108)

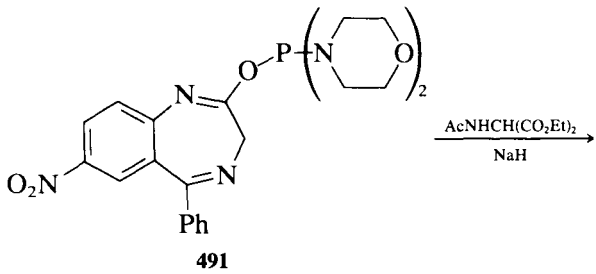
TABLE 66. DIHYDROIMIDAZO[1,5-*a*][1,4]BENZODIAZEPINES[a]



| R | X | Y | mp (°C) |
|---|---|---|---|
| Et | F | Cl | 131–133 |
| Me | H | Cl | 116–118 |
| Me | F | Cl | 142–144 |

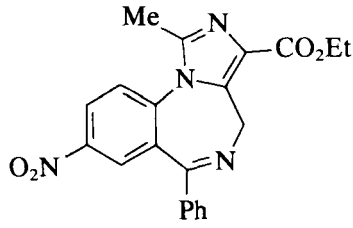
[a]Ref. 55.

afforded the 3-carbethoxy derivative **492.** Further reactions of the ester moiety yielded a variety of functional groups at the 3-position. Specific compounds prepared by this approach are listed in Table 67. Several of the corresponding 6-(2-pyridyl) compounds (**493**) were also prepared (55).

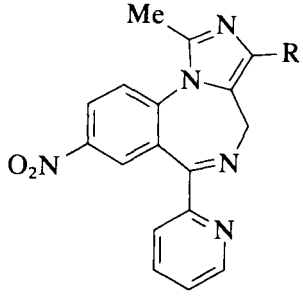



**491**

(108)



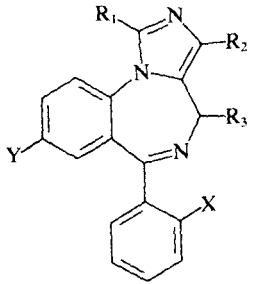

**492**

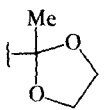


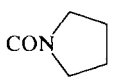

| | R | mp (°C) |
|---|---|---|
| **493a** | $CO_2Et$ | 243–244 |
| **493b** | $CO_2H$ | 245–250 |
| **493c** | H | 189–190 |

Imidazoline-2,4-dione derivatives of this ring system have also been prepared (Eq. 109). Reaction of cyanobenzodiazepine **494** with methyl isocyanate produced **495,** which underwent cyclization with methanolic ammonium hydroxide in air to give the benzodiazepine hydantoins **496** and **497.** Compound **496** was not converted to **497** under these reaction conditions, indicating that oxidation probably preceded ring closure (90).

TABLE 67. IMIDAZO[1,5-*a*][1,4]BENZODIAZEPINES



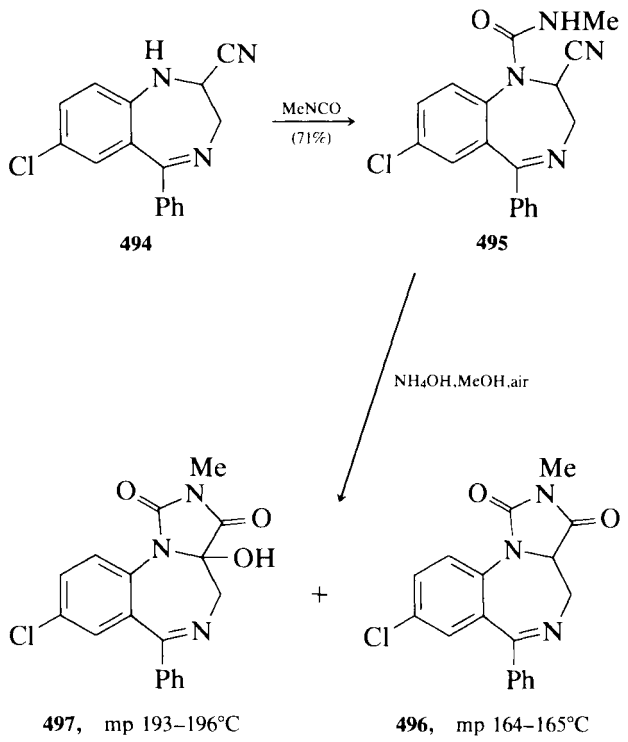

| $R_1$ | $R_2$ | $R_3$ | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| Et | H | H | F | Cl | 143–145 | 55 |
| Me | H | H | F | Cl | 152–154 | 55 |
| Me | H | H | Cl | Cl | 142–144 | 55 |
| Me | H | H | H | Cl | 187–188 | 55 |
| Me | H | AcO | H | Cl | 200–201 | 55 |
| Me | H | OH | H | Cl | 173–174 | 55 |
| Me | Me | H | F | Cl | 178–180 | 55 |
| Me | H | H | H |  | 179–182 | 55 |
| Me | H | H | H | $COCH_3$ | 225–230 | 55 |
| Me | H | H | H | $CHOHCH_3$ | 223–225 | 55 |
| Me | H | H | F | Et | 152–154 | 55 |
| Me | $CO_2Me$ | H | F | Cl | 162–164 | 55 |
| Me | $CO_2Et$ | H | F | Cl | 195–198 | 55 |
| Me | COOH | H | F | Cl | 271–274 | 55 |
| Me | $CONH_2$ | H | F | Cl | 300–305 | 55 |
| Me | $CONHNH_2$ | H | F | Cl | 235–237 | 55 |
| Me | $CONMe_2$ | H | F | Cl | 177–179 | 55 |
| Me | $CONEt_2$ | H | F | Cl | 183–185 | 55 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Me | $CONHCH_2CH_2NMe_2$ | H | F | Cl | 210–213 | 55 |
| H | $CO_2Me$ | H | F | Cl | 178–181 | 55 |
| H | COOH | H | F | Cl | 245–247 | 55 |
| Me | $CO_2Me$ | H | H | Cl | 254–256 | 55 |
| Me | COOH | H | H | Cl | 270–273 | 55 |
| Me | $CH_2OH$ | H | H | Cl | 252–255 | 55 |
| Me | CHO | H | H | Cl | 218–220 | 55 |
| Me | $CONH_2$ | H | H | Cl | 335–340 | 55 |
| Me | CONHMe | H | H | Cl | 260–263 | 55 |
| Me | $CH_2OH$ | H | F | Cl | 233–235 | 55 |
| H | H | H | F | Cl | 150–151 (4H) | 55 |
| H | H | H | F | Cl | 195–196 (6H) | 55 |
| Me | $CO_2Me$ | $(CH_3)_2$ | H | Cl | 220–222 | 55 |
| H | $CO_2Me$ | Me | F | Cl | 190–191 | 55 |
| Me | $CH_2NH_2$ | H | H | Cl | 217–219 | 55 |
| Me | H | H | F | NHAc | 217–223 | 55 |
| Me | H | H | F | $NHCH_3$ | 255–259 | 55 |
| Me | $CH{=}NNMe_2$ | H | Cl | Cl | 238–242 | 55 |
| Me | $CH_2OMe$ | H | H | Cl | 163–165 | 55 |
| Me | CH=NOMe | H | H | Cl | 193–195 | 55 |
| Me |  | H | F | Cl | 220–221 | 55 |
| Me | $CONHNMe_2$ | H | F | Cl | 238–240 | 55 |
| Me | $NHCO_2Me$ | H | F | Cl | 272–275 | 55 |
| Me | $NHCOCH_2Ph$ | H | F | Cl | 253–255 | 55 |
| Me | H | AcO | F | Cl | 201–202 | 55 |
| Me | H | OH | F | Cl | 185–186 | 55 |
| $CH_2OAc$ | H | H | F | Cl | 151–152 | 55 |
| Me | Br | H | F | Cl | 203–205 | 55 |
| Me | $CO_2Et$ | H | F | CN | 272–274 | 55 |
| Me | H | H | F | CN | 198–203 | 55 |
| Ph | $CO_2Me$ | H | F | Cl | 208–209 | 55 |
| Ph | COOH | H | F | Cl | 267–269 | 55 |
| Ph | $CONEt_2$ | H | F | Cl | 221–223 | 55 |
| Ph | $CONH_2$ | H | F | Cl | 260–262 | 55 |

(*continued*)

TABLE 67. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| Ph | COOH | H | F | Cl | 267–269 (3H) | 55 |
| Me | $CO_2Me$ | H | Cl | Cl | 228–230 | 55 |
| Me | $CONH_2$ | H | Cl | Cl | 318–320 | 55 |
| Me | COOH | H | Cl | Cl | 265–267 | 55 |
| Me | $CO_2Et$ | H | Cl | Cl | 214–215 | 55 |
| Me | $CH_2OH$ | H | Cl | Cl | 217–218 | 55 |
| Me | $CH_2Cl$ | H | Cl | Cl | 200–210 | 55 |
| Me | $CH_2NMe_2$ | H | Cl | Cl | 136–138 | 55 |
| Me | $CH_2CN$ | H | Cl | Cl | 215–217 | 55 |
| Ph | H | H | F | Cl | 241–243 | 55 |
| Me | H | H | F | H | 164–168 | 55 |
| Me | H | H | *o*-F, *m*-$NO_2$ | H | 199–203 | 55 |
| Me | $CO_2Me$ | H | F | $NO_2$ | 231–233 | 55 |
| Me | COOH | H | Cl | $NO_2$ | 274–276 | 55 |
| Me | $CO_2Et$ | H | Cl | $NO_2$ | 233–234 | 55 |
| Me | $CONH_2$ | H | Cl | $NO_2$ | 300 | 55 |
| Me | $CO_2Et$ | H | H | $NO_2$ | 240–241 | 55 |
| Me | COOH | H | H | $NO_2$ | 240–243 | 55 |
| Me | H | H | H | $NO_2$ | 168–170 | 55 |
| Me | CN | H | H | Cl | 228–229 | 55 |
| Me | CHO | H | H | Cl | 237–239 | 55 |
| Me | CH=NOH | H | H | Cl | 272–275 | 55 |
| Me | $NHCOCH_3$ | H | F | Cl | 175–178 | 55 |
| Me | H | $CO_2Me$ | F | F | 203–205 | 55 |
| Cl | $CHOHCH_3$ | H | Cl | Cl | 197–199 | 55 |
| Cl | $COCH_3$ | H | Cl | Cl | 234–236 | 55 |
| $CH_2Ph$ | $CO_2Me$ | H | Cl | Cl | 160–162 | 55 |
| $CH_2Ph$ | COOH | H | Cl | Cl | 305–310 | 55 |
| $CH_2Ph$ | $CONH_2$ | H | Cl | Cl | 266–268 | 55 |
| $CH_2NMe_2$ | H | H | H | Cl | 213–215 | 276 |
| $CH_2NMe_2$ | H | H | Cl | Cl | 185–186.5 | 276 |

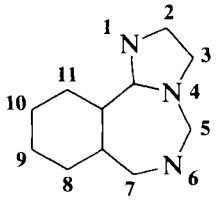



494 495

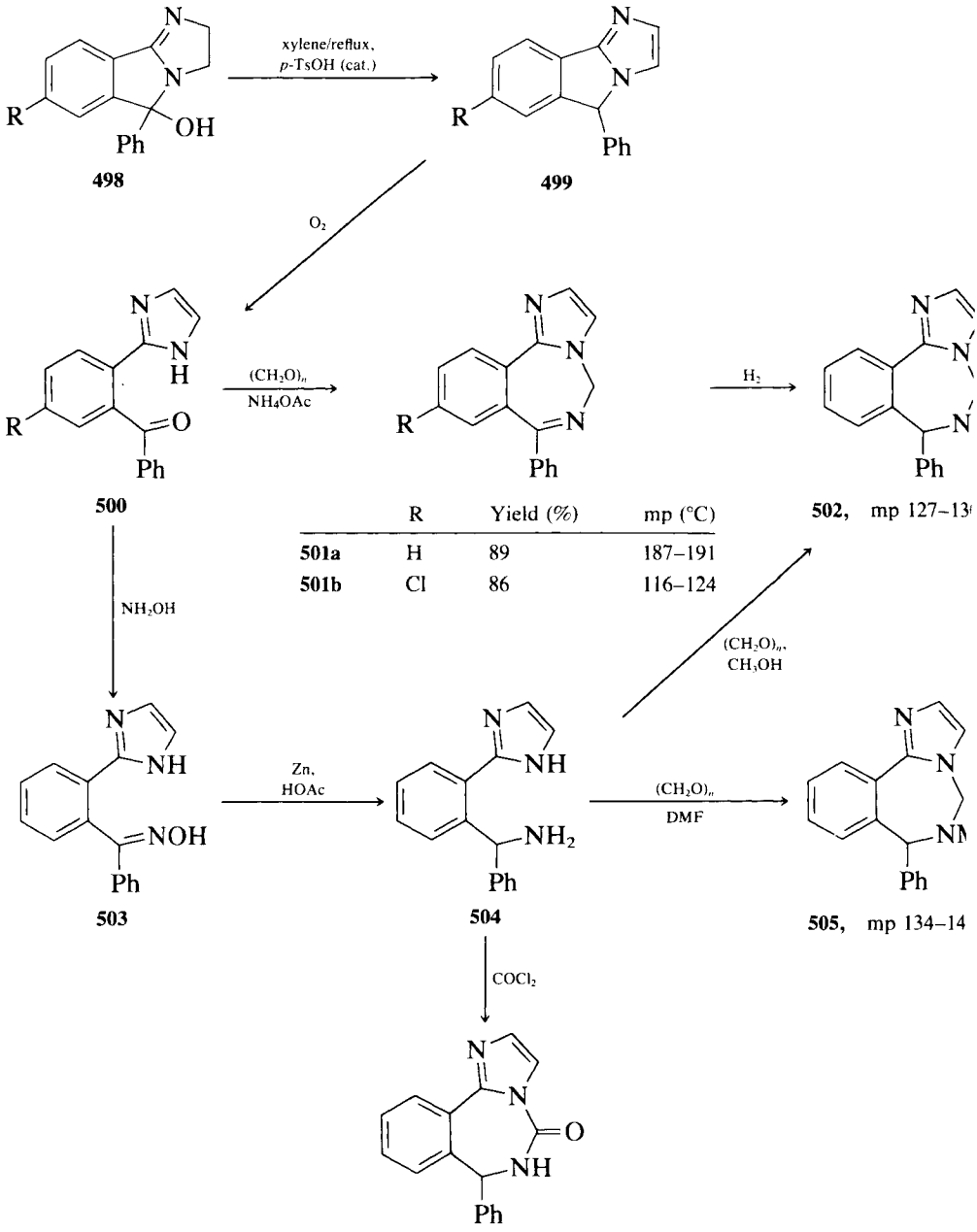
497, mp 193–196°C 496, mp 164–165°C

(109)

## 40. Imidazo[2,1-*a*][2,4]benzodiazepines




Benzophenone **500,** prepared from **498** as shown in Fig. 37, was treated with paraformaldehyde in the presence of ammonium acetate to yield the tricyclic derivative **501.** In another route, intermediate **500** was converted to benzhydrylamine **504** and then cyclized to products **502, 505,** and **506** by reaction with paraformaldehyde in methanol, paraformaldehyde in DMF, and phosgene, respectively. Diazepine **502** was also obtained directly from **501** (R = H) by hydrogenation (292).




**498** **499** **500**

| | R | Yield (%) | mp (°C) |
|---|---|---|---|
| **501a** | H | 89 | 187–191 |
| **501b** | Cl | 86 | 116–124 |

**502,** mp 127–13

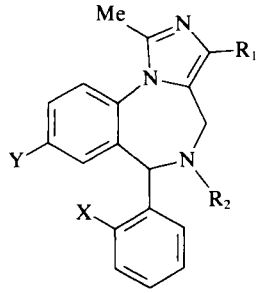
**503** **504**

**505,** mp 134–14

**506,** mp 225–229°C

**Figure 37**

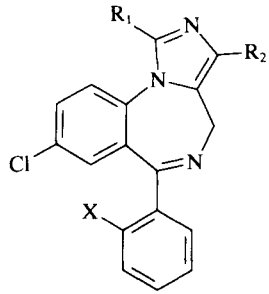
TABLE 68. 5,6-DIHYDROIMIDAZO[1,5-*a*][1,4]BENZODIAZEPINES[a]



| $R_1$ | $R_2$ | X | Y | mp (°C) |
|---|---|---|---|---|
| H | H | F | Cl | 200–203 |
| H | H | H | $CHOHCH_3$ | 143–145 |
| $CO_2Me$ | H | H | Cl | 234–236 |
| $CONHNH_2$ | H | H | Cl | 228–230 |
| NHCOMe | NO | H | Cl | 255–258 |
| NHCOMe | H | H | Cl | 280–290 |
| H | Ts | F | Cl | 252–253 |
| H | NO | F | Cl | 238–240 |
| H | OH | F | Cl | 251–252 |
| H | Me | F | Cl | 158–159 |
| H | $CH_2CH{=}CH_2$ | F | Cl | 153–154 |
| H | $COCH_3$ | F | Cl | 186–187 |

[a]Ref. 55.

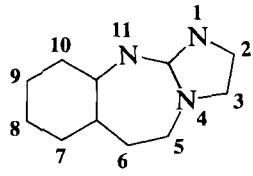
TABLE 69. *N*-OXIDES OF IMIDAZO[1,5-*a*][1,4]BENZODIAZEPINES[a]



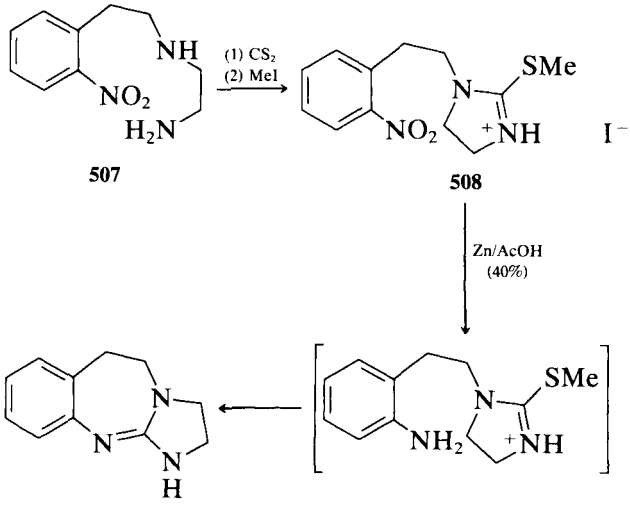
| *N*-Oxide | $R_1$ | $R_2$ | X | mp (°C) |
|---|---|---|---|---|
| 5 | Me | H | H | 260–261 |
| 5 | Me | H | F | 245–246 |
| 2 | Me | H | F | 179–181 |
| 2,5 | Me | H | F | 225–230 |
| 5 | $CH_2OAc$ | H | F | 203–205 |
| 5 | Me | $CO_2Et$ | Cl | 247–249 |

[a]Ref. 55.

## 41. Imidazo[2,1-*b*][1,3]benzodiazepines (see Section XV.27)



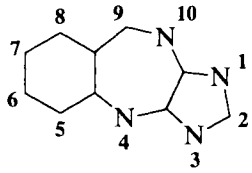

Since the corresponding imidazoquinazoline showed hypotensive activity, imidazo[2,1-*b*][1,3]benzodiazepines were prepared, as outlined in Eq. 110.



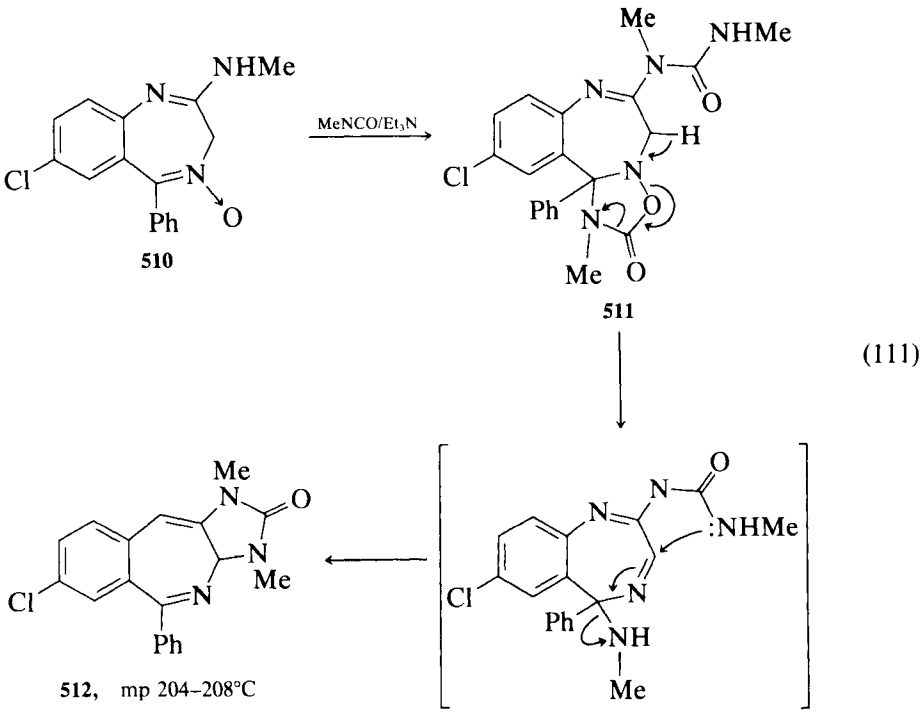

507 508 509, mp 200–202°C (110)

The diamine **507** was obtained by reaction of an excess of ethylenediamine with *o*-nitrophenethyl bromide, which was prepared from *o*-nitrophenylacetic acid. Reaction of **507** with carbon disulfide followed by methyl iodide gave the imidazoline **508.** Reduction of the nitro group of **508** with zinc in acetic acid unmasked the aniline and produced **509** by cyclization. Although the guanidine moiety in **509** is potentially tautomeric, the other isomer was excluded on the basis of nmr analysis. In particular, a four-proton singlet at $\delta$ 3.52, corresponding to the $C_2$ and $C_3$ protons of **509,** indicates the absence of an anisotropic effect of the imino bond on the $C_2$ protons. In addition, the structure was supported by uv and mass spectral data (293).

## 42. Imidazo[4,5-*b*][1,4]benzodiazepines

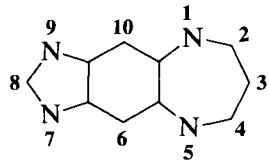



Treatment of chlordiazepoxide (**510**) with excess methyl isocyanate gave **511** in 85% yield. On standing for two years in a sealed bottle, this material was converted to **512.** The latter compound could be formed more rapidly by reaction of **510** with methyl isocyanate and triethylamine. A possible mechanism for this conversion is postulated in Eq. 111. An alternative process (via an initial Polonovski rearrangement) was excluded by synthesis of the required intermediate and subjecting it to the reaction conditions, which did not produce **512.** Structural assignments were supported by ir, uv, nmr, and mass spectral evidence (71).

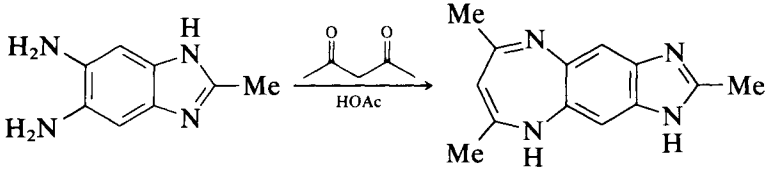



(111)

## 43. Imidazo[4,5-*h*][1,5]benzodiazepines

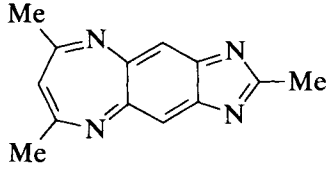


In an attempted synthesis of the nonbenzenoid heterocycle **513,** 5,6-diamino-2-methylbenzimidazole was condensed with acetylacetone in glacial acetic acid (Eq. 112). The resulting dihydrodiazepinobenzimidazole **514** (purple acetate salt, mp >300°C) had a satisfactory elemental analysis. Treatment of the silver salt of **514** with bromine gave a fluorescent, scarlet solution (green in alkali). Attempted isolation of the possible product **513** led to decomposition (294).



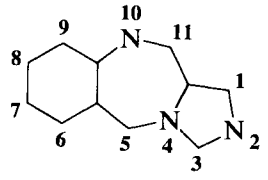
**514**

(112)

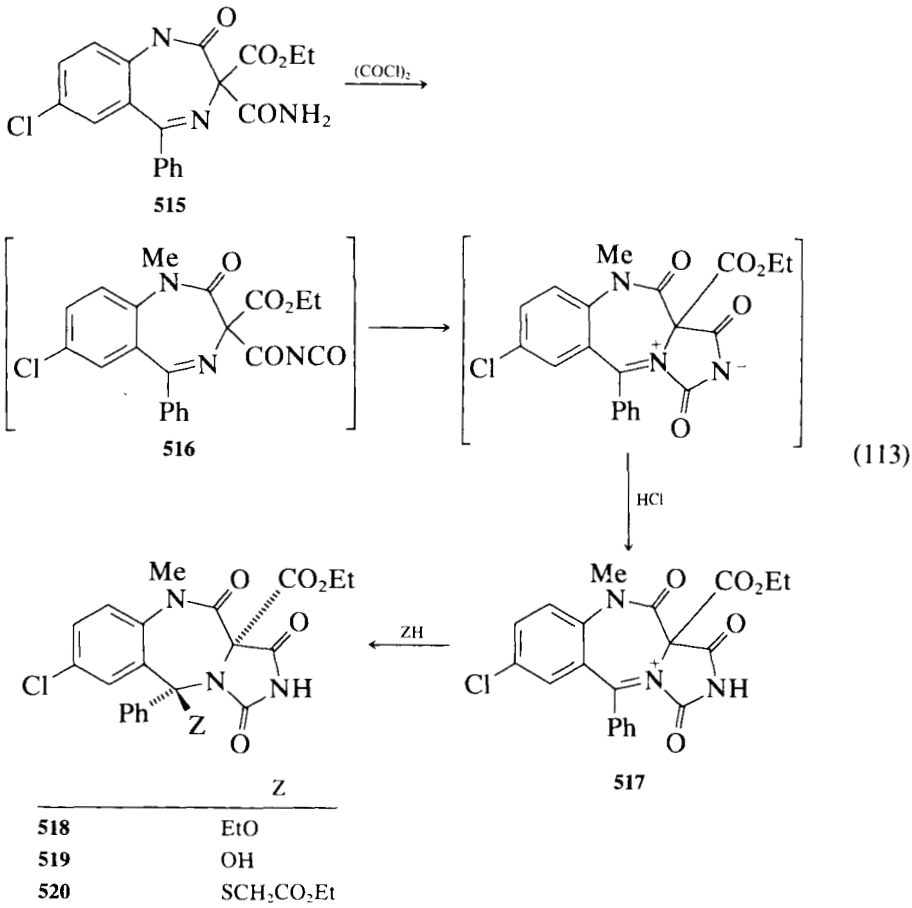


**513**

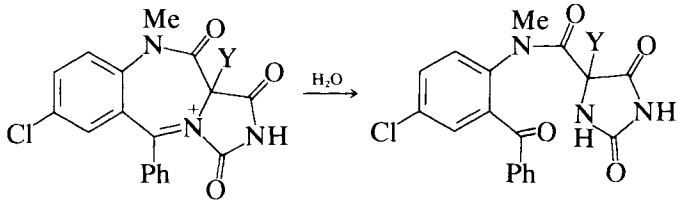
## 44. Imidazo[5,1-*c*][1,4]benzodiazepines



Jaunin and Arnold (295) found that treatment of 3-carbamoylbenzodiazepines with oxalyl chloride followed by reaction with a nucleophile resulted in the stereospecific formation of tricyclic compounds, as outlined in Eq. 113. Compound **515** was converted to the acyl isocyanate **516,** which underwent ring closure to the tricyclic iminium salt **517.** Addition of ethanol, water, and ethyl mercaptoacetate to **517** led to the products **518, 519,** and **520,** respectively. Compounds **521** and **522** (Table 70) were prepared analogously. Hydroxy adducts (Z = OH) were not formed on addition of water to the intermediate iminium salts; instead, the hydrolytic ring cleavage products **523** and **524** were obtained (Eq. 114). The tricyclic structures were confirmed by ir, uv, and nmr spectral evidence. In particular, the conjugated imine absorbance band was absent in the uv spectrum, and two bands for the cyclopentylimide carbonyl system were present in the ir spectrum at 1760 and 1800 $cm^{-1}$.



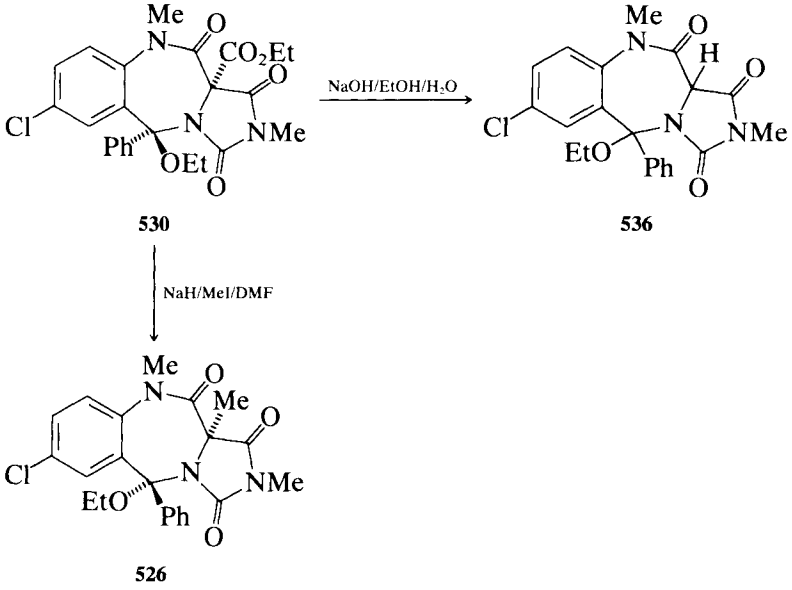

(113)




(114)

**523**, Y = MeO
**524**, Y = Me

Compound **522** and its 2-methyl and 2-ethyl derivatives (**528** and **529**, Table 70) underwent isomerization at the 5-position on treatment with *p*-toluenesulfonic acid in ethanol to give **525**, **526**, and **527**, respectively. Compounds **530** through **535** were prepared by $N^2$-alkylation using sodium hydride or potassium carbonate in DMF. On treatment with sodium hydride as the base, followed by addition of methyl iodide, **530** was converted to **526**, with inversion of the relative configurations at the 5 and 11a positions. Compound **536** was obtained as a 1:1 mixture of isomers on addition of aqueous sodium hydroxide to **530** by hydrolysis and decarboxylation (Eq. 115).



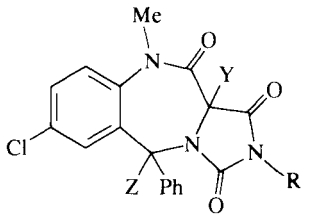

**530** **536**

(115)

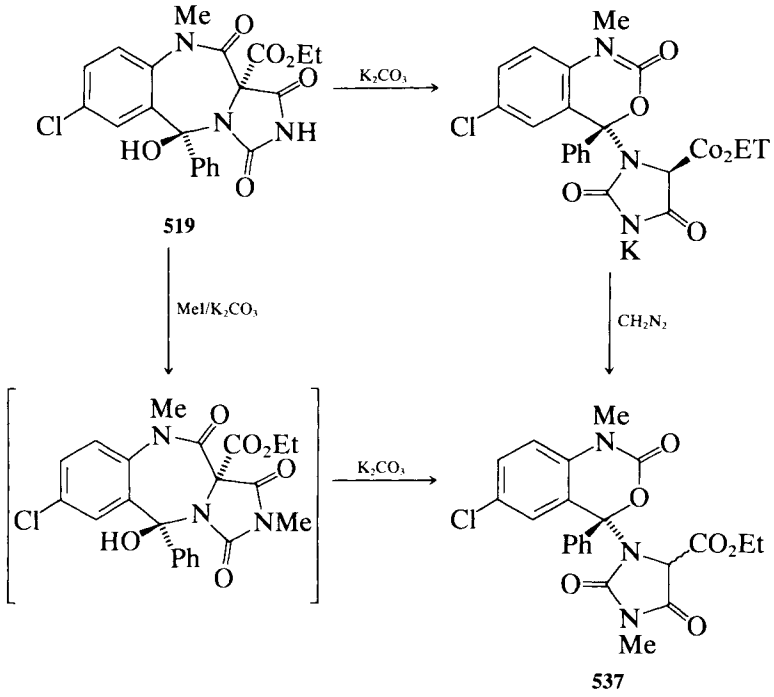
**526**

Tricyclic compound **519** was found to be unstable to both potassium carbonate followed by diazomethane and to potassium carbonate–methyl iodide, in each case generating the same cleavage product (**537**) as outlined in Eq. 116.

TABLE 70. IMIDAZO[5,1-*c*][1,4]BENZODIAZEPINES




| Compound | Y | Z | R | YZ Stereochemistry | Yield (%) | mp (°C) | Spectra |
|---|---|---|---|---|---|---|---|
| **518** | $CO_2Et$ | EtO | H | *Trans* | 65 | 211–215 | ir |
| **519** | $CO_2Et$ | OH | H | *Trans* | 67 | 170–175 | ir |
| **520** | $CO_2Et$ | $SCH_2CO_2Et$ | H | *Trans* | 54 | 223–226 | ir |
| **521** | MeO | MeO | H | *Trans* | 64 | 245–250 | ir |
| **522** | Me | EtO | H | *Trans* | 68 | 230–234 | ir |
| **525** | Me | EtO | H | *Cis* | 12 | 270–273 | ir |
| **526** | Me | EtO | Me | *Cis* | 73 | 260–262 | |
| **527** | Me | EtO | Et | *Cis* | 71 | 242–244 | |
| **528** | Me | EtO | Me | *Trans* | 80 | 206–208 | |
| **529** | Me | EtO | Et | *Trans* | 68 | 177–179 | |
| **530** | $CO_2Et$ | EtO | Me | *Trans* | 90 | 228–231 | |
| **531** | MeO | MeO | Me | *Trans* | 79 | 280–285 | |
| **532** | $CO_2Et$ | EtO | $CH_2CO_2Et$ | *Trans* | 68 | 228–231 | |
| **533** | $CO_2Et$ | EtO | $CH_2CH_2NEt_2$ | *Trans* | 68 | 164–166 | |
| **534** | MeO | MeO | $CH_2CH{=}CH_2$ | *Trans* | 71 | 260–263 | |
| **535** | MeO | MeO | $CH_2CH_2NEt_2$ | *Trans* | 31 | 163–165 | |
| **536** | H | EtO | Me | | 55 | 215–220 | ir |




(116)

Comparative analysis of the nmr spectra of this tricyclic series allowed the relative stereochemistry at carbons 5 and 11a to be assigned. The diazepine ring was determined to have the pseudochair conformation by comparison of the chemical shift of the proton on carbon 11a with the starting bicyclic benzodiazepines, which were a mixture of two conformers. Deshielding effects of the phenyl group at the 5-position could be observed at carbon 6 for the *cis* series and at carbon 10 for the *trans* series. The nmr data are summarized in Table 71 (295).

## 45. Imidazo[1,5,4-*ef*][1,5]benzodiazepines (see Section XV.28)

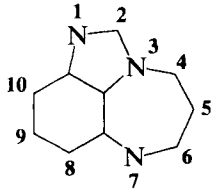
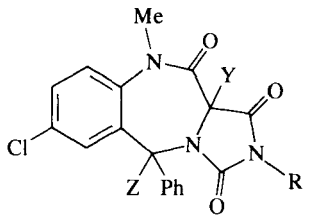


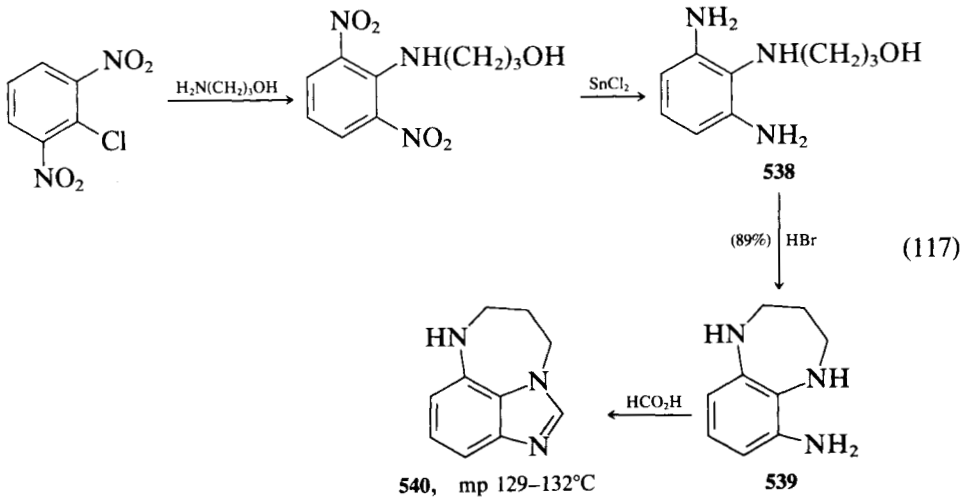
TABLE 71. NMR DATA FOR IMIDAZO[5,1-*c*][1,4]BENZODIAZEPINES[a]




| Compound | Y | Z | R | YZ Sterochemistry | $H_6$ | $N^{10}$—Me | $N^2$—H ($N^2$—Me) |
|---|---|---|---|---|---|---|---|
| **518** | $CO_2Et$ | EtO | H | *Trans* | 5.97 | 3.40 | 11.8 |
| **519** | $CO_2Et$ | OH | H | *Trans* | 6.05 | 3.38 | 11.65 |
| **520** | $CO_2Et$ | $SCH_2CO_2Et$ | H | *Trans* | 5.93 | 3.44 | 11.9 |
| **521** | MeO | MeO | H | *Trans* | 6.00 | 3.32 | 11.7 |
| **522** | Me | EtO | H | *Trans* | 6.00 | 3.40 | 11.3 |
| **525** | Me | EtO | H | *Cis* | 7.75 | 2.88 | 11.3 |
| **528** | Me | EtO | Me | *Trans* | 6.27 | 3.47 | (3.04) |
| **526** | Me | EtO | Me | *Cis* | 7.89 | 2.95 | (3.12) |
| **529** | Me | EtO | Et | *Trans* | 6.25 | 3.46 | |
| **527** | Me | EtO | Et | *Cis* | 7.87 | 2.95 | |
| **530** | $CO_2Et$ | EtO | Me | *Trans* | 6.24 | 3.48 | (3.04) |
| **531** | MeO | MeO | Me | *Trans* | 6.23 | 3.44 | (3.07) |
| ***536a*** | H | EtO | Me | *Trans* | 6.27 | 3.44 | (3.04) |
| **536b** | H | EtO | Me | *Cis* | 8.00 | 2.84 | (3.13) |

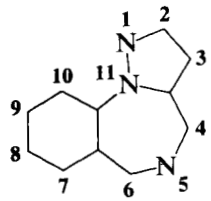
[a]Numbers in the last three columns are $\delta$ values in ppm relative to tetramethylsilane.

The symmetric triamine **538,** prepared as outlined in Eq. 117, underwent cyclization to benzodiazepine **539** in refluxing hydrobromic acid. Imidazole formation in refluxing formic acid resulted in a 59% yield of the tricyclic compound **540** (296).




(117)

## 46. Pyrazolo[1,5-*a*][1,4]benzodiazepines (see Section XV.30)




In a study of the nucleophilic displacement of fluorine in 2-fluoro-5-nitrobenzophenone (**541**) by various heterocyclic compounds to obtain intermediates of potential synthetic utility in the preparation of novel [1,4]benzodiazepines, pyrazoles **542** and **559** afforded the adducts **543** (66% yield) and **560** (82% yield), respectively (Figs. 38, 39). Without the nitro group, the reaction failed. The nitro compound **543** was transformed into the corresponding chloro derivative by reduction with stannous chloride followed by a Sandmeyer reaction. Condensation with hydroxylamine gave **544.** Reduction of **544** with zinc in acetic acid led to the diazepine **545** (55% yield) and the quinoline **546** (26% yield). Reduction of **545** with borane–dimethylsulfide gave **547,** whereas reduction with diborane generated a mix-

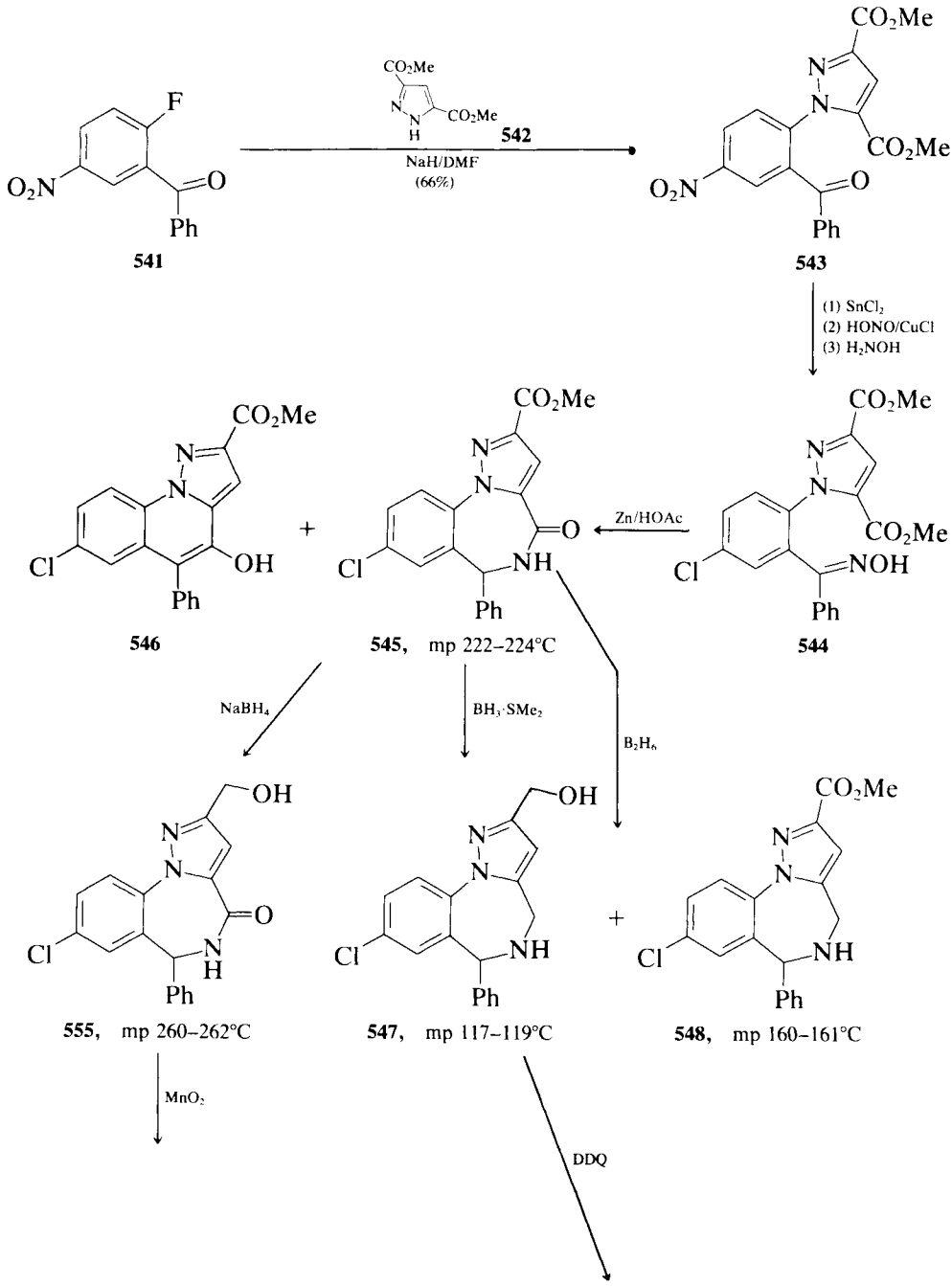
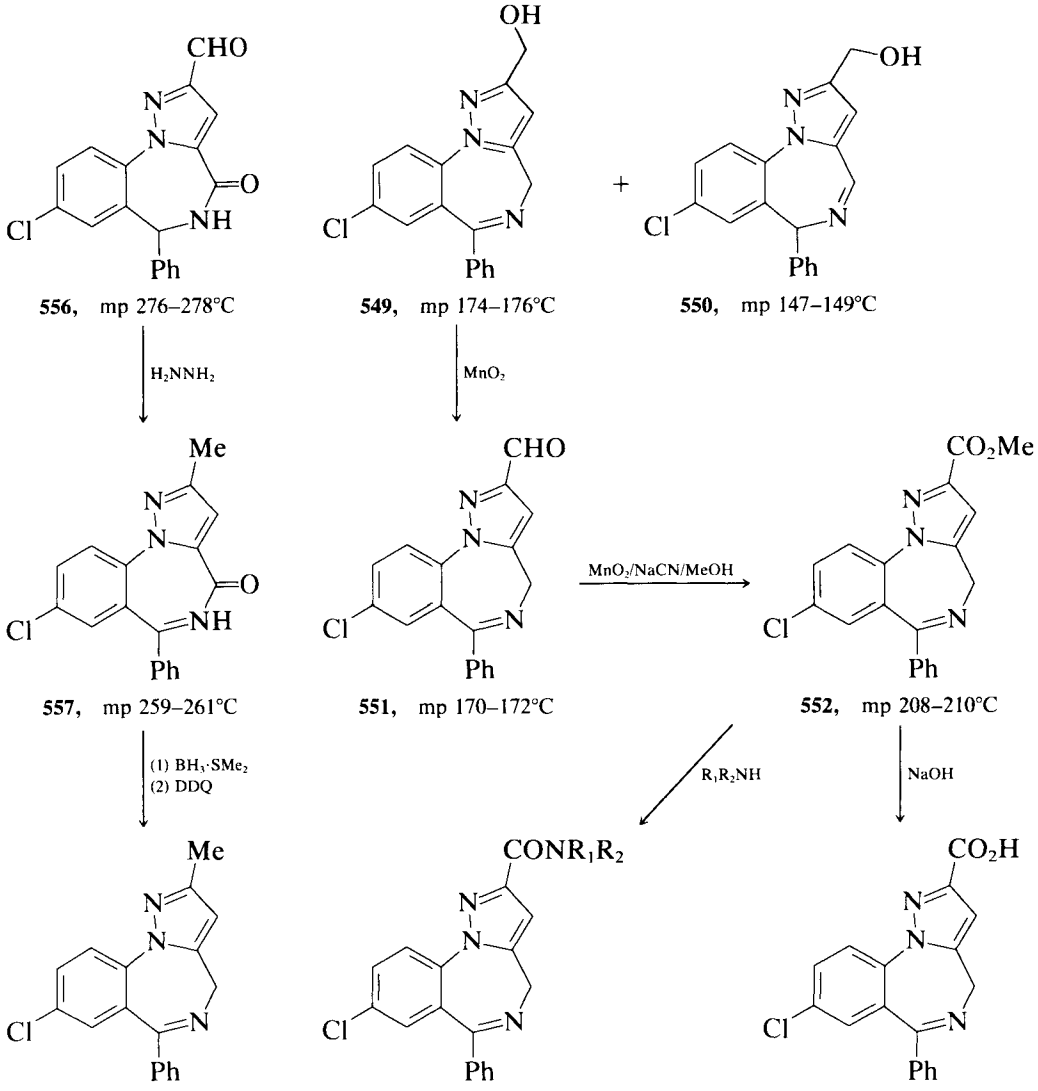



**Figure 38** (*cont'd on next page*)




| | $NR_1R_2$ | mp (°C) |
|---|---|---|
| **554a** | $NH_2$ | 216–218 |
| **554b** | NHMe | 170–172 |
| **554c** | $NMe_2$ | 176–178 |

**Figure 38 (*continued*)**

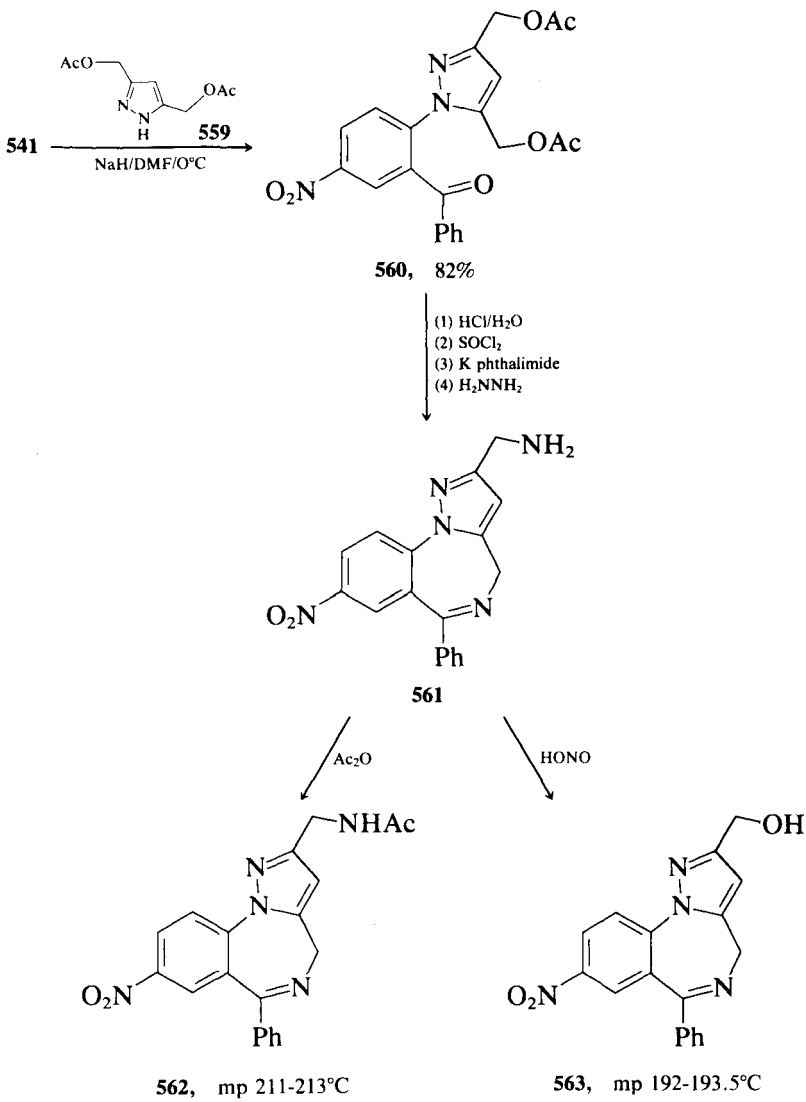
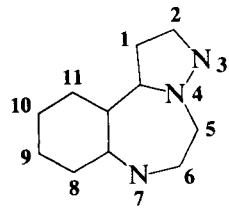



**Figure 39**

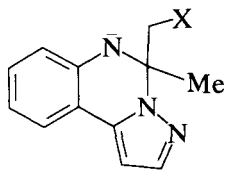
ture of **547** and partially reduced **548.** Oxidation of **547** with DDQ afforded imine **549** in 62% yield as well as a minor amount of its isomer **550** (10% yield). Conversion of **549** to aldehyde **551** was carried out with manganese dioxide. Reaction of **551** with manganese dioxide and sodium cyanide in methanol generated the methyl ester **552,** which was converted to the acid **553** and the amides **544a–c** by standard procedures. Intermediate **545** was also transformed into the 2-methyl derivative **558** by the sequence shown in

Fig. 38. Transformation of adduct **560** to the 2-aminomethyldiazepine **561** was carried out as shown in Fig. 39. The latter product was converted to the acetamide **562** with acetic anhydride and to the hydroxymethyl compound **563** with nitrous acid (297).

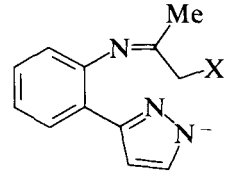
## 47. Pyrazolo[1,5-*d*][1,4]benzodiazepines




The pyrazolo[1,5-*d*][1,4]benzodiazepine system was studied to determine which anion, **A** or **B**, precedes ring expansion to form the benzodiazepine system. The key intermediates, pyrazolo[1,3-*c*]quinazolines **564** and **565**, were prepared from 6-chloro-4-hydroxy-2-methylquinoline and hydrazine followed by condensation with the appropriate chloro ketone. Further trans-




**A**




**B**

formations of these compounds are outlined in Fig. 40. Reaction of **564** with potassium *tert*-butoxide afforded aziridine **566**, which on reduction with lithium aluminum hydride gave the ring-opened structure **567**. Reaction of **566** with methanolic sodium borohydride led to the methoxy derivative **568**, which could also be obtained directly from **564** with sodium methoxide in methanol. Acid hydrolysis of **568** opened the diazepine ring to give **569**. Similarly, reaction of the dichloromethyl derivative **565** with methanolic sodium methoxide led to the dimethoxy diazepine **570**. Reduction of **570** with lithium aluminum hydride produced **568**, thus confirming the presence of a seven-membered ring. These structures were supported by nmr spectral evidence. The transformations of **564** and **565** indicate that the nitrogen in position 1 is alkylated by the chloromethyl or dichloromethyl group, supporting the intermediacy of **A** rather than **B** (298).

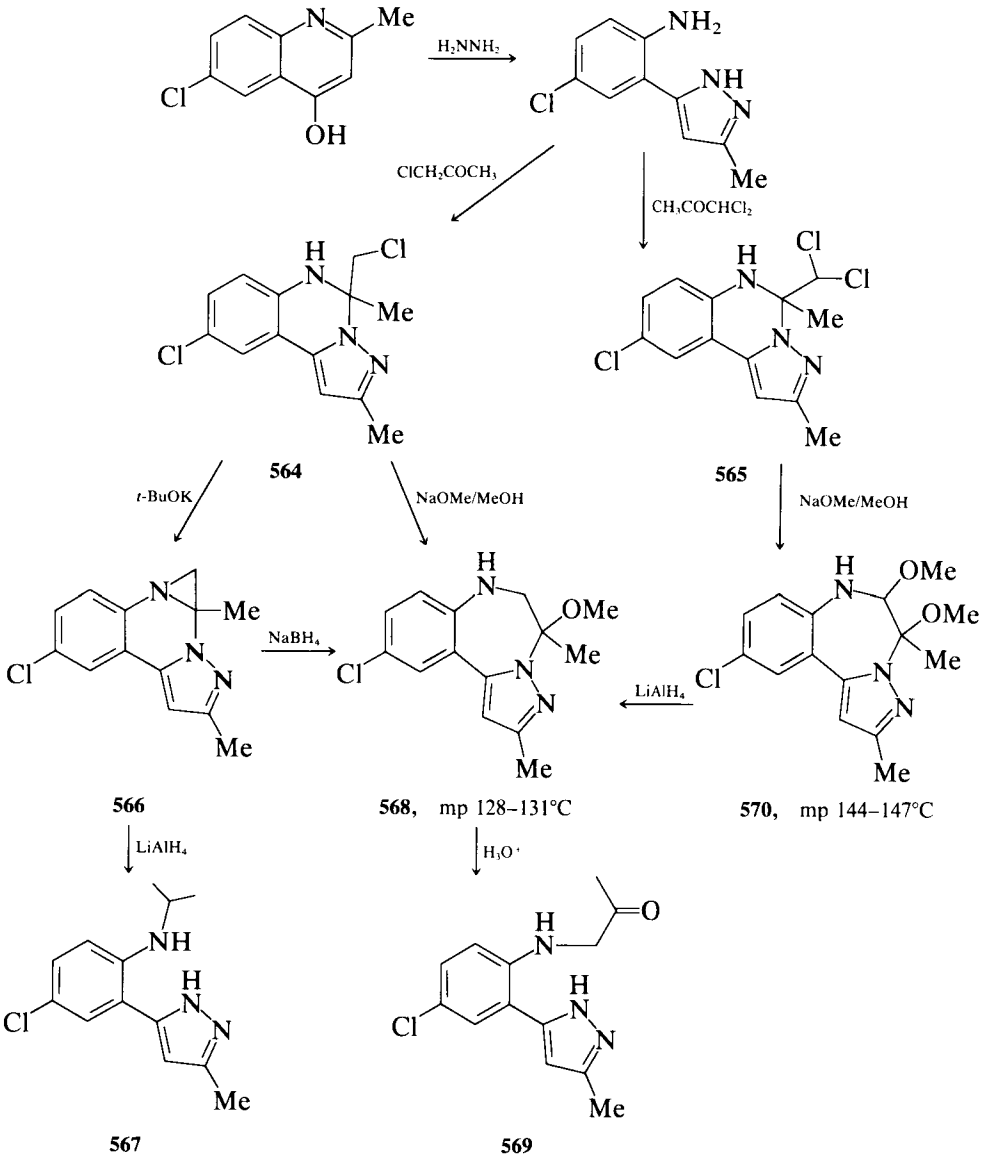
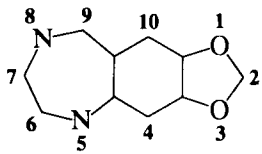
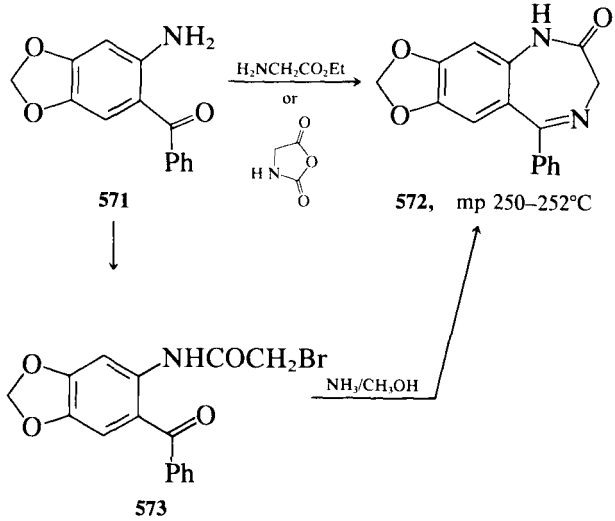



Figure 40

## 48. [1,3]Dioxolo[4,5-*h*][1,4]benzodiazepines

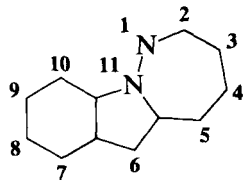


A [1,3]dioxolo[4,5-*h*][1,4]benzodiazepine derivative was prepared by several methods starting with aminobenzophenone **571.** Direct transformation of **571** to **572** was attained using glycine ethyl ester in refluxing pyridine or glycine *N*-carboxyanhydride in ethereal hydrochloric acid (Eq. 118). Alternatively, **571** could be converted to **573** with bromoacetyl bromide. Subsequent reaction with methanolic ammonia afforded the ring-closed product **572.** Compound **572** was also prepared from the corresponding aminoacetamide in hot dimethylformamide and from the phthalimidoacetamide in ethanolic hydrazine (299).

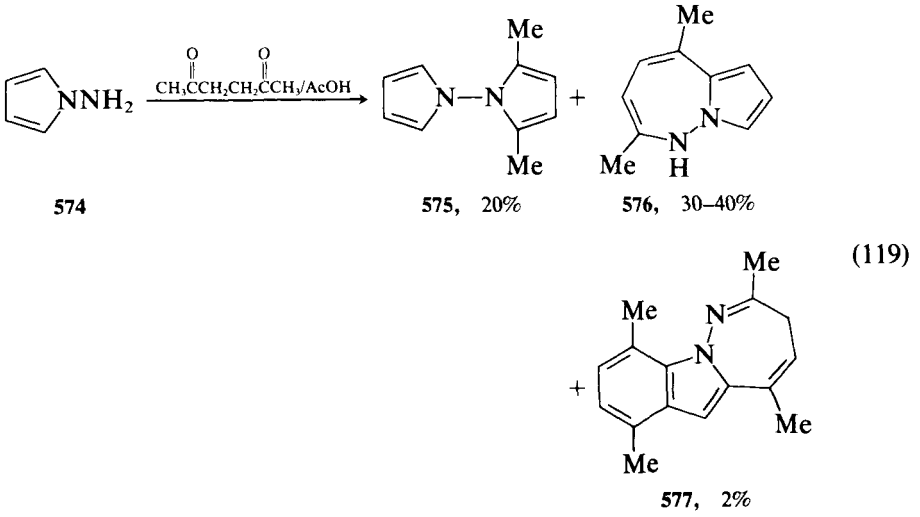



(118)

## 49. [1,2]Diazepino[1,7-*a*]indoles

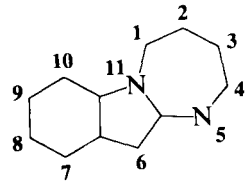



During a study of the chemistry of 1-aminopyrroles the reaction of **574** with hexane-2,5-dione in acetic acid was found to give the bipyrrole **575** and the diazaazulene **576,** along with the diazepinoindole **577** as a minor product (Eq. 119). 1-Aminopyrrole **574** was prepared from *N*-aminophthalimide (300) by reaction with 2,5-diethoxytetrahydrofuran followed by hydrazinolysis. The structure of the tricyclic diazepinoindole **577** was supported by nmr and uv spectral data (301).




(119)

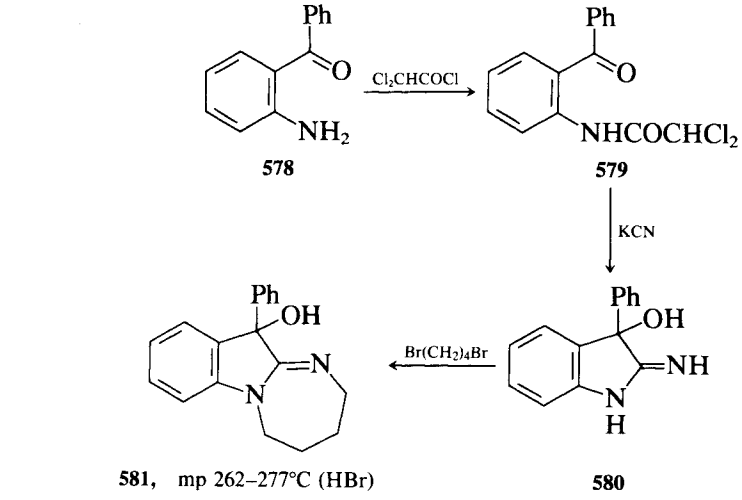
## 50. [1,3]Diazepino[1,2-*a*]indoles (see Section XV.32)



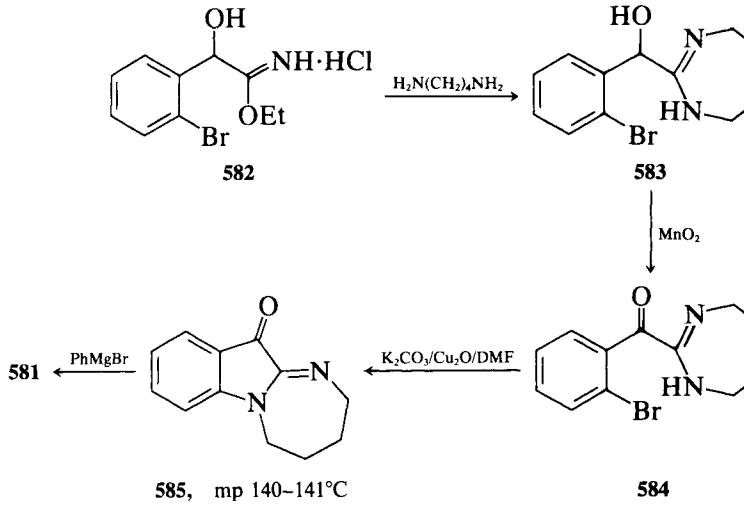

Several routes to the [1,3]diazepino[1,2-*a*]indole ring system have appeared. One method (Eq. 120) begins with dichloroacetylation of 2-benzoylaniline **578** to give **579.** Further reaction with potassium cyanide in aqueous ethanol affords the indole **580,** and formation of diazepine **581** can be effected by reaction of **580** with 1,4-dibromobutane in isopropanol (302).

An alternative approach to **581** (Eq. 121) begins with *o*-bromomandelimidate **582,** which on reaction with 1,4-diaminobutane followed by manganese dioxide leads to **584.** Cyclization of **584** in the presence of cuprous oxide yields the diazepine **585,** which on addition of aryl Grignard reagents is converted to **581** (303). Variously substituted analogs of **581** are listed in Table 72. These compounds were reported to have antidepressant activity.

Another route that produces compounds with CNS depressant activity involves treatment of **586** with potassium cyanide in refluxing 95% ethanol and subsequent ring closure of the cyanohydrin intermediate **587** to the diazepine **588** (Eq. 122). Other examples obtained by this approach are included in Table 72 (304).




(120)




(121)

TABLE 72. [1,3]DIAZEPINO[1,2-*a*]INDOLES

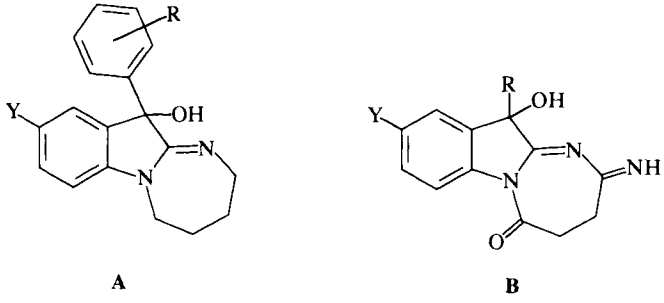
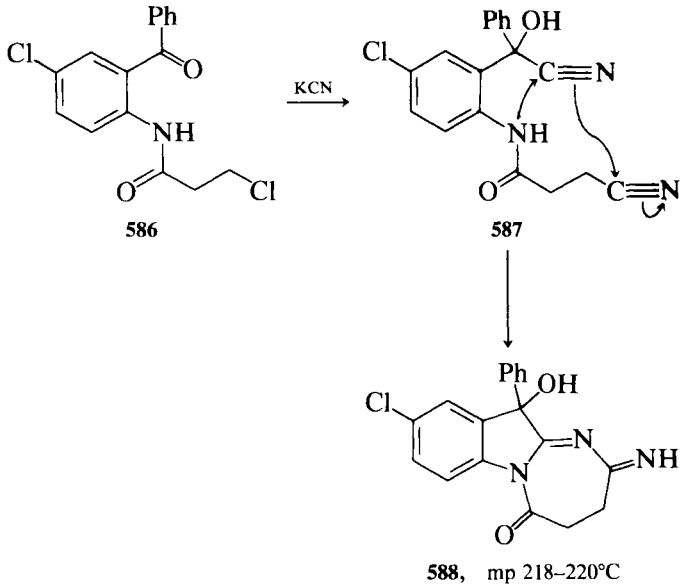


TABLE 72. (*Continued*)

| Structure | Y | R | mp (°C) | Salt | Refs. |
|---|---|---|---|---|---|
| **A** | H | *m*-Cl | 270–275 | HBr | 302,303 |
| **A** | Cl | *o*-Cl | 295–300 | HBr | 302,303 |
| **A** | Cl | H | 298–300 | HBr | 302,303 |
| **B** | H | Me | 218–220 | | 304 |
| **B** | Cl | *o*-$ClC_6H_4$ | 258–260 | | 304 |

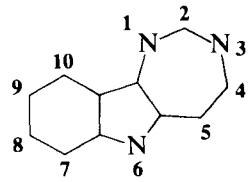



**586** **587**

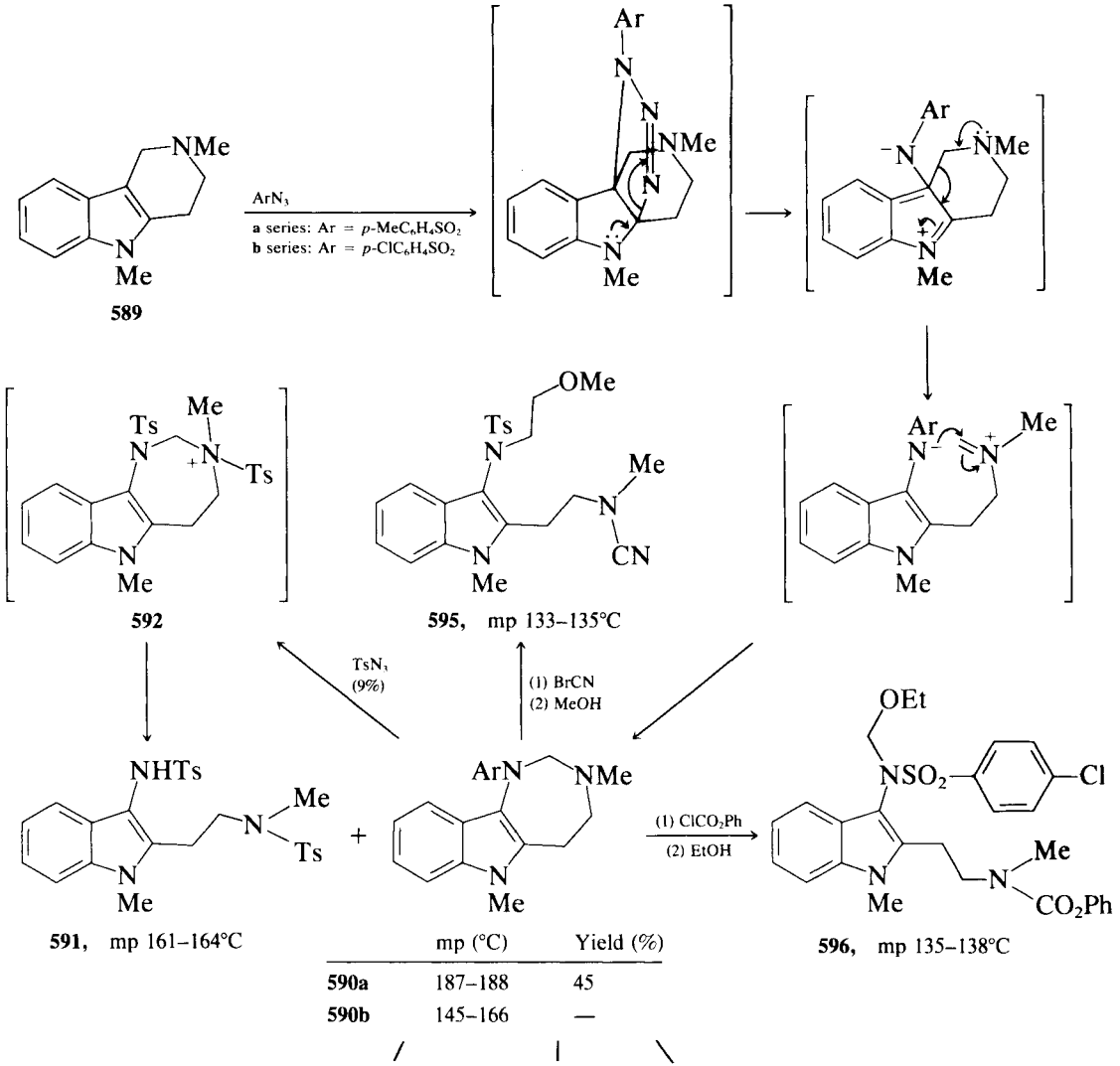
**588**, mp 218–220°C

(122)

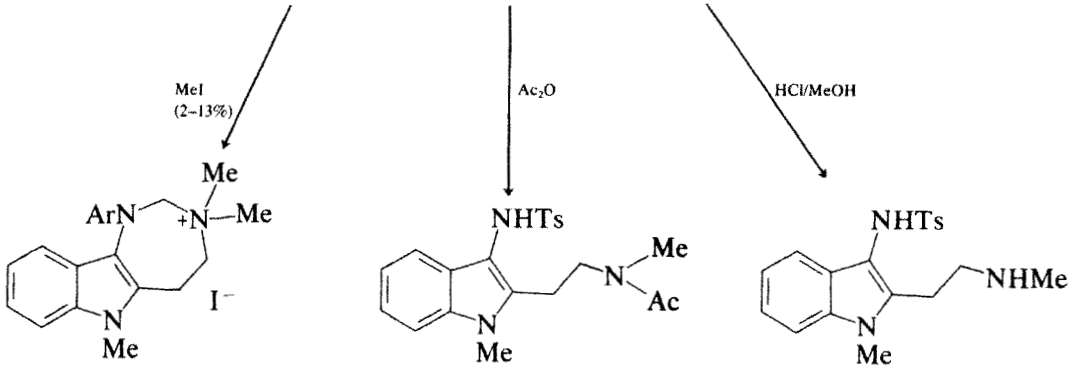
## 51. [1,3]Diazepino[5,4-*b*]indoles




The [1,3]diazepino[5,4-*b*]indole ring system was the outcome of an examination of the reactions of 1,2,3,4-tetrahydro-2,5-dimethyl-5H-pyrido[4,3-*b*]indole (**589**) with azides. Compound **589** reacted with *p*-toluenesulfonyl azide and *p*-chlorobenzenesulfonyl azide to give the diazepines **590a** and **590b**, respectively (Fig. 41). Careful analysis of the spectral data supported



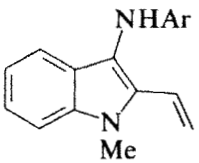

| | mp (°C) | Yield (%) |
|---|---|---|
| **590a** | 187–188 | 45 |
| **590b** | 145–166 | — |




**597a**, mp 212–214°C
**597b**, mp 212–214°C

**593**, mp 195–197°C

**594**, mp 247–249°C (HCl)

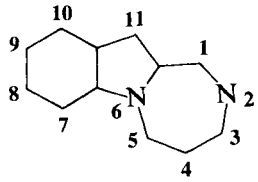



| | mp (°C) | Yield (%) |
|---|---|---|
| **598a** | 160–163 | — |
| **598b** | 146–147 | 50 |

**Figure 41**

structure **590** for the product and eliminated several alternative possibilities. Further evidence for the structure of **590** was obtained by an investigation of the chemistry of the system. From the mother liquors of the preparation of **590a,** a minor product (**591**) was isolated. Product **591** was also formed on prolonged reaction of **590a** with *p*-toluenesulfonyl azide, suggesting that the quaternary salt **592** was an intermediate. This possibility was supported by reaction of **590a** with acetic anhydride to give **593** and by hydrolysis of **590a** in methanolic hydrochloric acid to yield **594.** Von Braun reaction (with cyanogen bromide) of **590a** afforded cyanoamine **595.** Cleavage of the amino group of **590b** with phenyl chloroformate led to the analogous carbamate **596.** Finally, Hofmann degradation of **590a** and **590b** (quaternization with methyl iodide followed by elimination with potassium carbonate) generated the 2-vinylindoles **598a** and **598b.** A probable mechanism for the formation of **590** is outlined in Fig. 41. Addition of the sulfonyl azide to the indole followed by loss of nitrogen, ring opening, and reclosing would lead to the observed product **590** (305).

## 52. [1,4]Diazepino[1,2-*a*]indoles (see Section XV.33)




Several methods for the synthesis of the [1,4]diazepino[1,2-*a*]indole ring system were developed; they have in common the annelation of the diazepine ring onto an indole. One approach began by cyanoethylation of 2-carbethoxyindole to yield **599.** Transformation of **599** to the diazepinoindole **602** was effected either via the aminopropylindole **600,** obtained by diborane reduction, or via the acetamidopropylindole **601,** obtained by catalytic reduction (Fig. 42). The pivotal diazepine **602** was converted by alkylation to **603,** by acylation to **604,** and by reduction to **605.** Hexahydrodiazepine **605** could be further transformed to the urea derivative **606** by reaction with phosgene followed by an amine. Compounds made by these methods are listed in Table 73 (306–311). These compounds have blood pressure lowering activity. Compounds of structure **605** also show antidepressant effects (312).

In a different approach (Eq. 123), the diazepine system **608** was prepared from **607** by cyclization with phosphoryl chloride. The tetrahydrodiazepine **608** was reduced with lithium aluminum hydride to **609** and was also ace-

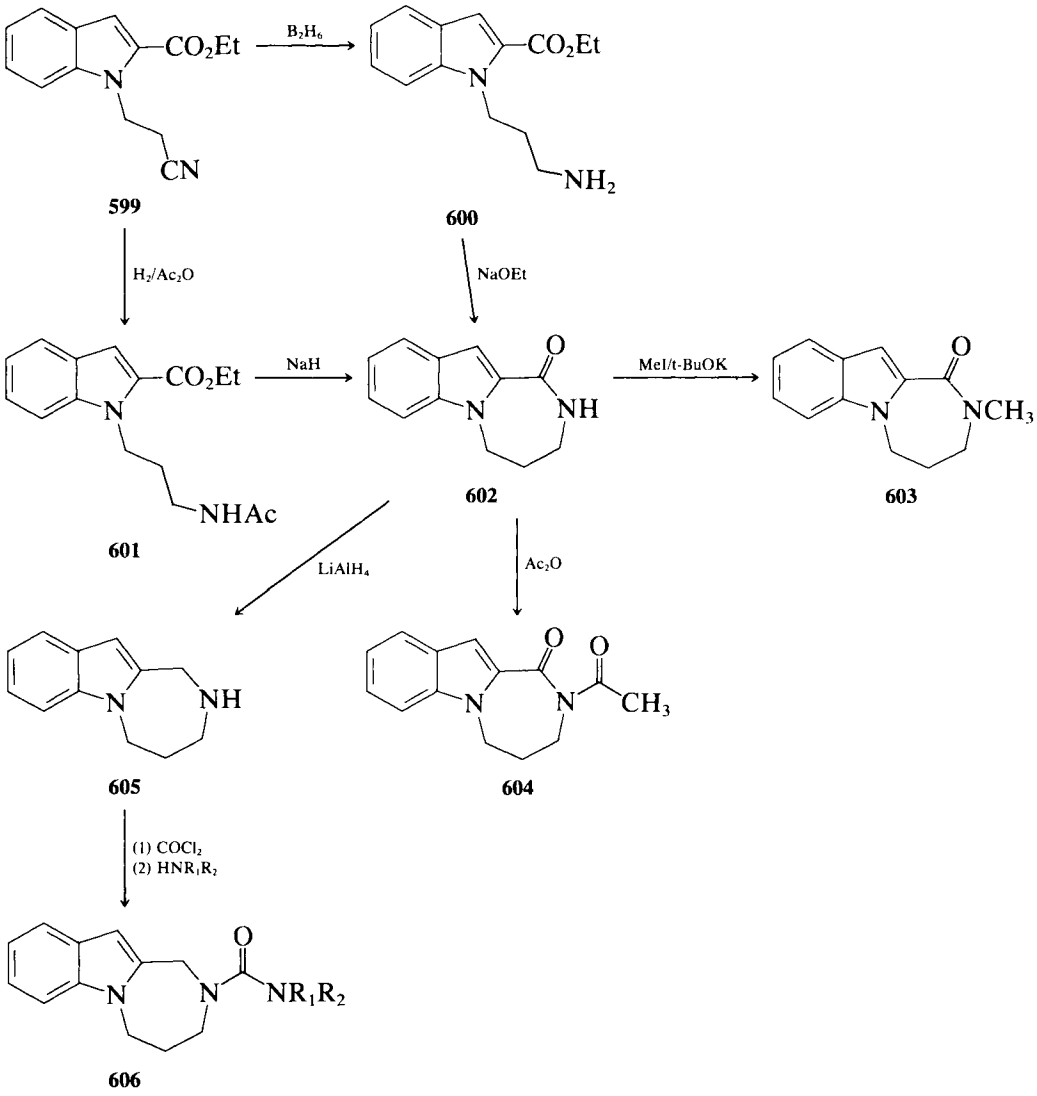
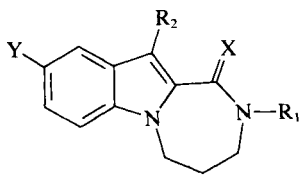



**Figure 42**

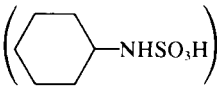
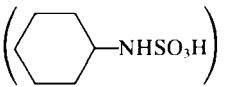
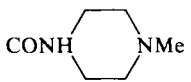
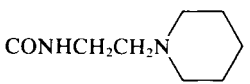
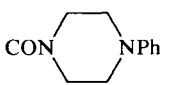
tylated to give **610.** Compounds generated in this manner are listed in Table 74 (313).

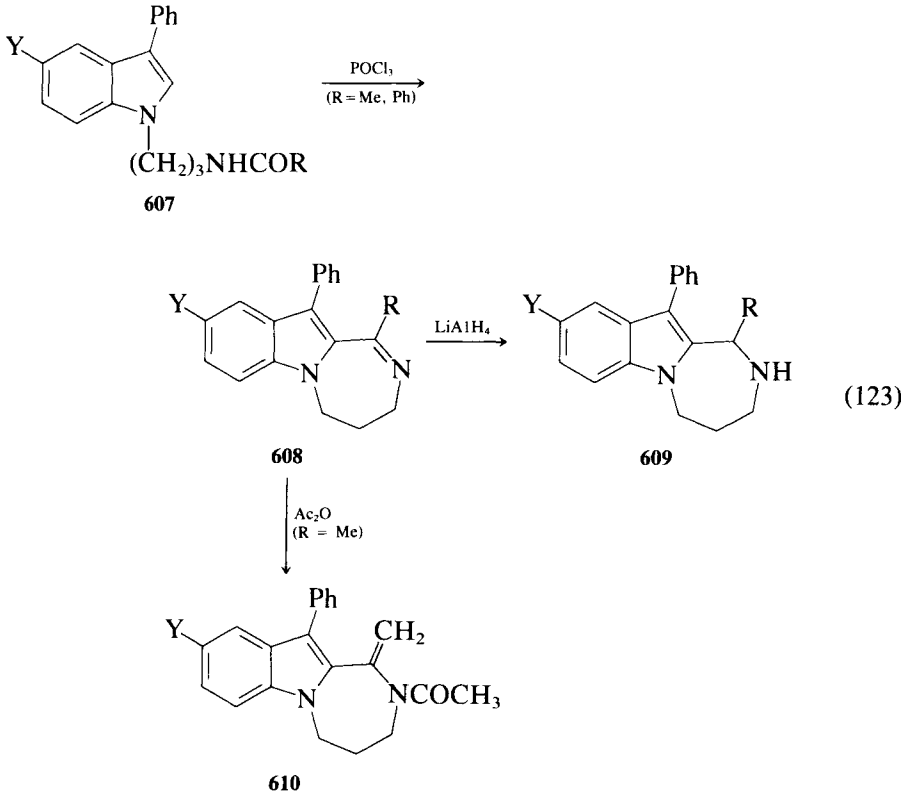
In a related route (Fig. 43), Mannich condensation of indole **611** with acetaldehyde or benzaldehyde gave indoles **612a** and **612b,** respectively. Bischler–Napieralski cyclization of **613** afforded the diazepine **614** as well as a minor amount of **615.** Both **614** and **615** were reduced to the same tetracyclic diazepine (**616**) (314).

TABLE 73. [1,4]DIAZEPINO[1,2-*a*]INDOLES FROM **599**




| X | Y | $R_1$ | $R_2$ | mp (°C) | Refs. |
|---|---|---|---|---|---|
| O | H | H | H | 181–183 | 306–308 |
| $H_2$ | H | Me | H | 98–100 | 306–308 |
| $H_2$ | Cl | H | H | 88–90 | 306–308 |
| $H_2$ | MeO | H | H | 110–112 | 306–308 |
| $H_2$ | Cl | H | Me | 269–271 (HCl) | 306–308 |
| $H_2$ | H | H | H | 75–77 | 306–308 |
| O | H | Me | H | 145–147 | 306–308 |
| O | Cl | Me | H | 154–155.5 | 306–308 |
| O | H | H | Me | 221–222 | 306–308 |
| O | H | $COCH_3$ | Me | 160–162 | 306–308 |
| $H_2$ | H | H | Me | 92–94 | 306–308 |
| O | MeO | H | H | 174–176 | 306–308 |

| | | | | | |
|---|---|---|---|---|---|
| O | MeO | $(CH_2)_3NMe_2$ | H | 132–134  | 306–308 |
| $H_2$ | MeO | $(CH_2)_3NMe_2$ | H | 132–134  | 306–308 |
| O | Cl | H | H | 222–223 | 306–308 |
| O | Cl | $COCH_3$ | H | 135–136.5 | 306–308 |
| O | Cl | $COC_3H_7$-*n* | H | 114–115 | 306–308 |
| O | Cl | H | Me | 188–189.5 | 306–308 |
| O | Cl | $COCH_3$ | Me | 120–122 | 306–308 |
| O | Cl | $CH_2C_6H_4Me$-*p* | H | 147–149 | 306–308 |
| O | Cl | Et | H | 183–185 | 306–308 |
| O | Cl | $(CH_2)_2NMe_2$ | H | 236–237 (HCl) | 306–308 |
| $H_2$ | H |  | H | 212–214 | 309–311 |
| $H_2$ | H |  | H | 140.5–142 | 309–311 |
| $H_2$ | H |  | H | 178–181 | 309–311 |




(123)

TABLE 74. [1,4]DIAZEPINO[1,2-*a*]INDOLES FROM **607**[a]

| Compound | Y | R | Yield (%) | mp (°C) |
|---|---|---|---|---|
| **608** | H | Ph | 72 | 202–204 |
| **608** | Cl | Ph | 80 | 211–213 |
| **608** | H | Me | 72 | 149–150 |
| **608** | Cl | Me | 77 | 164–165 |
| **609** | H | Ph | 70 | 154–155 |
| **609** | Cl | Ph | 64 | 193–194 |
| **609** | H | Me | 79 | 135–136 |
| **609** | Cl | Me | 77 | 138–140 |
| **610** | H | | 71 | 136–137 |
| **610** | Cl | | 79 | 185–186 |

[a]Ref. 313.

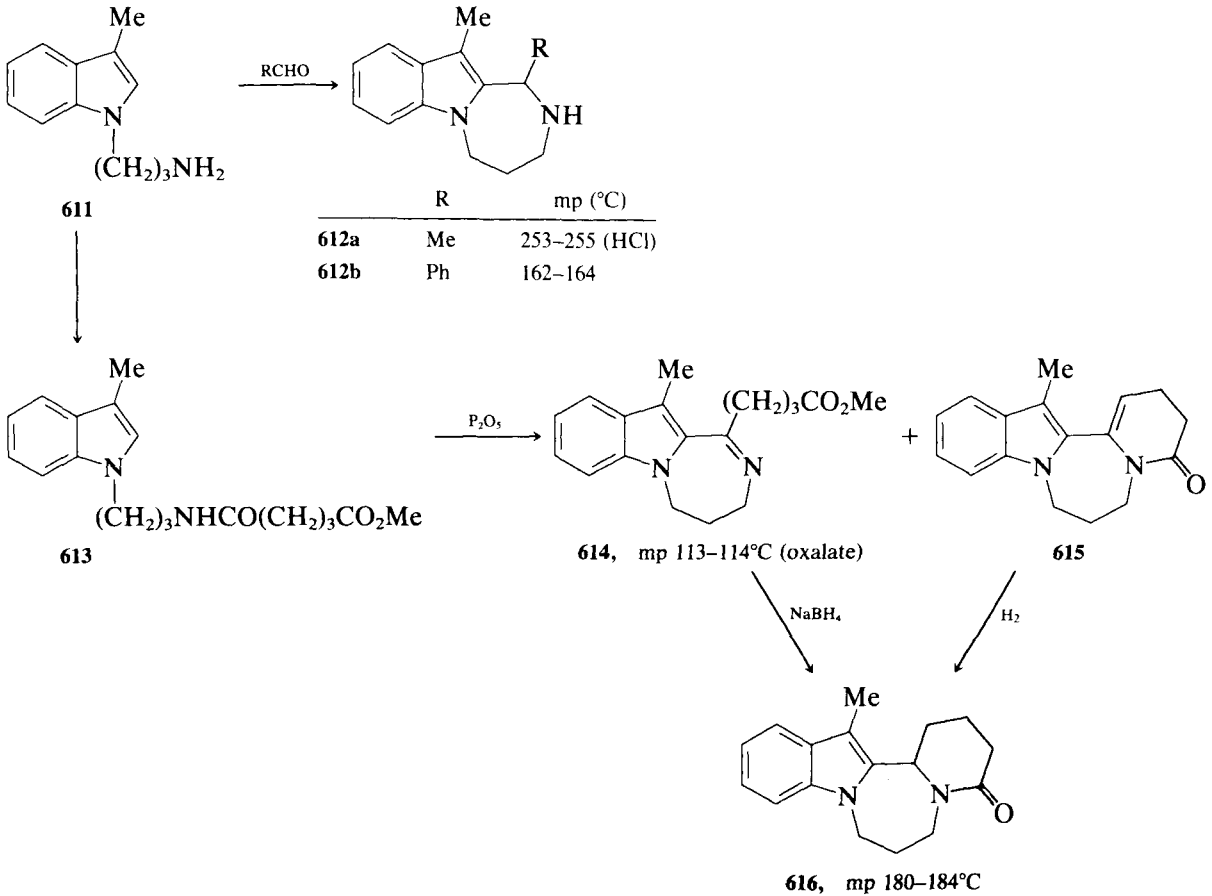
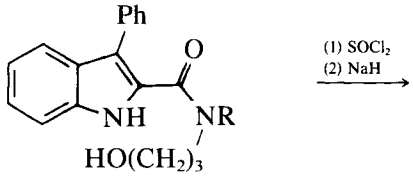
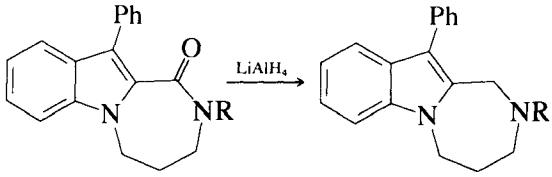

Me
RCHO
R
NH
(CH2)3NH2
611
612a Me 253–255 (HCl)
612b Ph 162–164
(CH2)3NHCO(CH2)3CO2Me
613
P2O5
(CH2)3CO2Me
614, mp 113–114°C (oxalate)
615
NaBH4
H2
616, mp 180–184°C

Figure 43

Closure of the diazepine ring was also achieved in the reverse direction (Eq. 124). Reaction of hydroxyamide **617** with thionyl chloride and then with sodium hydride resulted in cyclization to **618.** As before, the diazepinoindole **618** could be transformed into **619** by reduction. The products of this sequence are summarized in Table 75 (Nos. 1–6) (315).



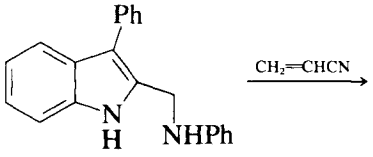

**617**



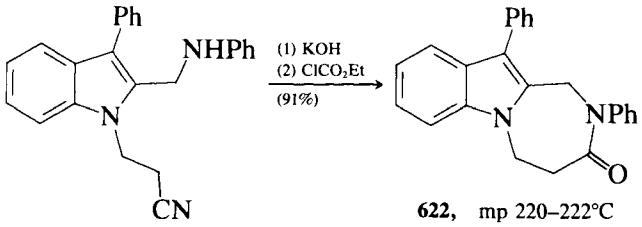

(124)

**618** **619**

A route in which formation of the 2,3-diazepine bond was the last step began with indole **620** (Eq. 125). Cyanoethylation led to **621,** which was converted to diazepine **622** by hydrolysis of the nitrile group and treatment of the resultant acid with ethyl chloroformate (315).




**620**




(125)

**621** **622,** mp 220–222°C

TABLE 75. [1,4]DIAZEPINO[1,2-*a*]INDOLES FROM **617**

| No. | Compound | Y | R | Yield (%) | mp (°C) | Salt | Refs. |
|---|---|---|---|---|---|---|---|
| 1 | **618** | H | H | 19 | 264–266 | | 315 |
| 2 | **618** | H | $CH_2Ph$ | 78 | 186–187 | | 315 |
| 3 | **618** | H | Ph | 74 | 267–269 | | 315 |
| 4 | **619** | H | H | 69 | 97–98 | | 315 |
| 5 | **619** | H | $CH_2Ph$ | 81 | 136–138 | | 315 |
| 6 | **619** | H | Ph | 75 | 133–135 | | 315 |
| 7 | **631** | H | | | 234 | HCl | 316 |
| 8 | **631** | 9-F | | | 202 | HCl | 316 |
| 9 | **631** | 8-Cl | | | 226 | HCl | 316 |
| 10 | **631** | 9-Cl | | | 158 | HCl | 316 |
| 11 | **631** | 10-Cl | | | 258 | HCl | 316 |
| 12 | **631** | 9-Me | | | 223 | HCl | 316 |
| 13 | **631** | 9-MeO | | | 240 | HCl | 316 |
| 14 | **632** | H | Me | | 237 | HCl | 316 |
| 15 | **632** | H | *n*-Hexyl | | 214 | HBr | 316 |
| 16 | **632** | H | Allyl | | 211 | HCl | 316 |
| 17 | **632** | H | $(CH_2)_3NMe_2$ | | 261 | 2HBr | 316 |
| 18 | **632** | H | $(CH_2)_3NEt_2$ | | 212 | 2HBr | 316 |
| 19 | **632** | 8-Cl | $(CH_2)_3NMe_2$ | | 209 | 2HBr | 316 |
| 20 | **633** | H | *i*-Pr | | 187 | HCl | 316 |
| 21 | **633** | H | $CH_2NMe_2$ | | 230 | 2HBr | 316 |
| 22 | **634** | 8-Cl | | | 167 | HCl | 316 |
| 23 | **634** | 10-Cl | | | 182 | HCl | 316 |
| 24 | **634** | H | | | 165 | HCl | 316 |
| 25 | **637** | 9-F | | | 188 | | 316 |
| 26 | **637** | 8-Cl | | | 174 | | 316 |
| 27 | **637** | 9-Cl | | | 180 | | 316 |
| 28 | **637** | 9-Me | | | 154 | | 316 |
| 29 | **637** | H | | | 159 | | 316 |
| 30 | **638** | H | $(CH_2)_3NMe_2$ | | 197 | 2HBr | 316 |
| 31 | **638** | Me | Me | | 241 | HBr | 316 |
| 32 | **638** | Allyl | Allyl | | 170 | | 316 |
| 33 | **638** | $CH_2Ph$ | $CH_2Ph$ | | 210 | HBr | 316 |
| 34 | **632** | 9-Cl | Me | | 237 | | 316 |
| 35 | **632** | 8-Cl | Et | | 195 | HCl | 316 |
| 36 | **632** | 9-Me | Et | | 226 | HCl | 316 |

Another route beginning with cyanoethylation of an indole led to **624** (Fig. 44). Raney nickel reduction of **624** produced the acetamide **625,** which under acidic conditions underwent cyclization to the diazepine **626.** Catalytic reduction of **626** afforded the hexahydrodiazepine **627.** Alternatively, **627** could be obtained from **628** by reaction with 1,3-dibromopropane (to yield **629**) followed by hydrolysis of the N-tosyl bond with acid (315).

The analogous diazepinoindoline system was obtained by cyclization of **630** in the presence of potassium carbonate (Eq. 126). Compound **631** was aklylated to give **632,** acylated to five **633,** and condensed with methyl vinyl ketone to five **634.** The corresponding 1-oxo compounds could be prepared from cyanoethylindole **635** (Eq. 127). Reduction of the nitrile to **636,** followed by cyclization, gave the diazepine **637,** and further reduction of **637** afforded **631.** Aklylation of **637** led to **638,** which could be reduced to **632** with lithium aluminum hydride. Indolines prepared by this approach are listed in Table 75 (Nos. 7–36). These compounds are CNS depressants (316).

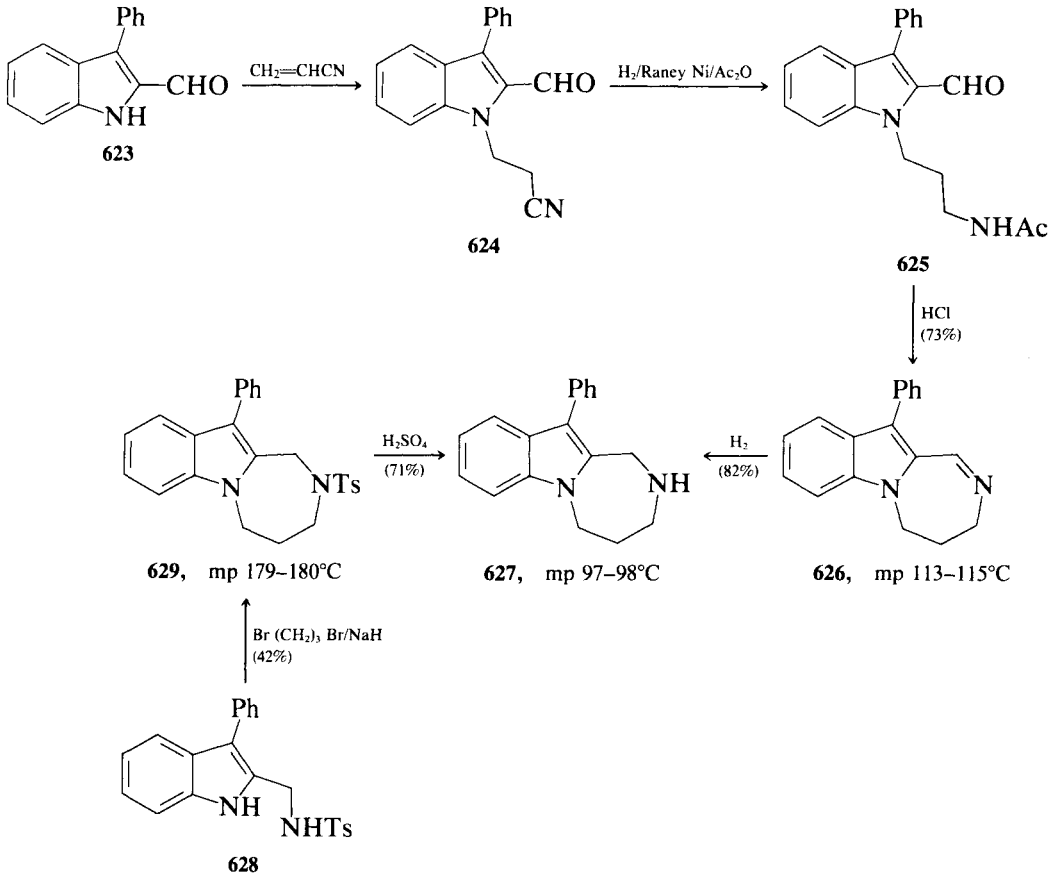
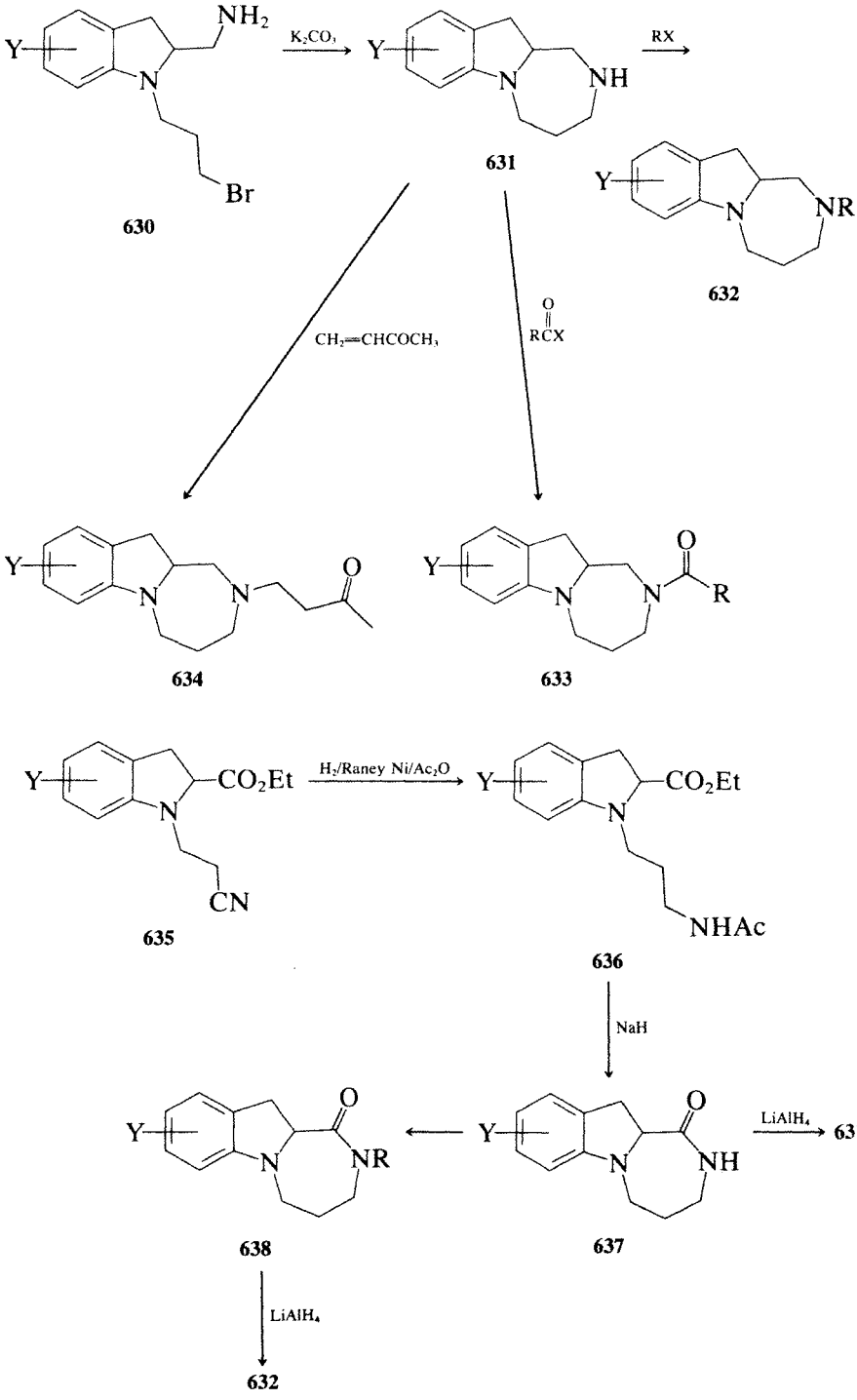


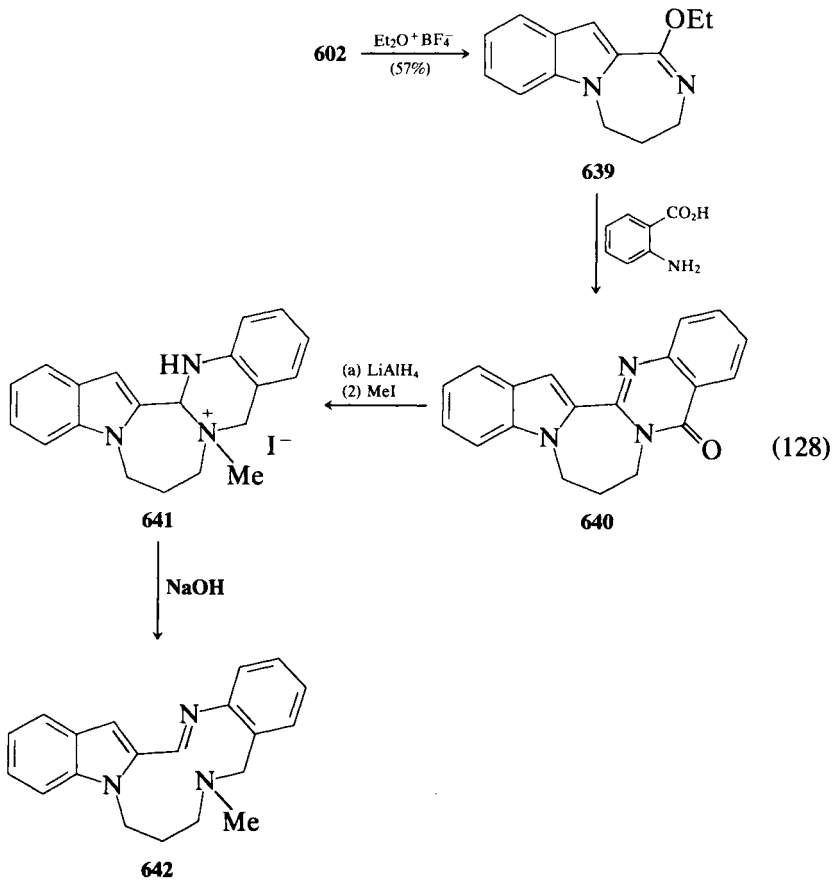

**Figure 44**


NH2
K2CO3
RX
Y
N
NH
NR
Br
630
631
632
CH2=CHCOCH3
O
RCX
634
633
R
CO2Et
H2/Raney Ni/Ac2O
CN
NHAc
635
636
NaH
637
638
LiAlH4
631
632

(126)

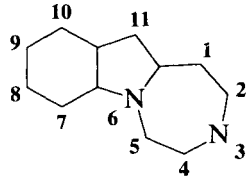
(127)

Diazepinoindole **602** was used as a starting material for a ring-expansion procedure (Eq. 128). Imino ether **639** was condensed with anthranilic acid to give the pentacyclic quinazolinone **640**. Reduction of **640** with lithium aluminum hydride followed by alkylation with methyl iodide yielded the quaternary salt **641**. Treatment of **641** with sodium hydroxide resulted in fragmentation to give the ring-expanded product **642** (317).

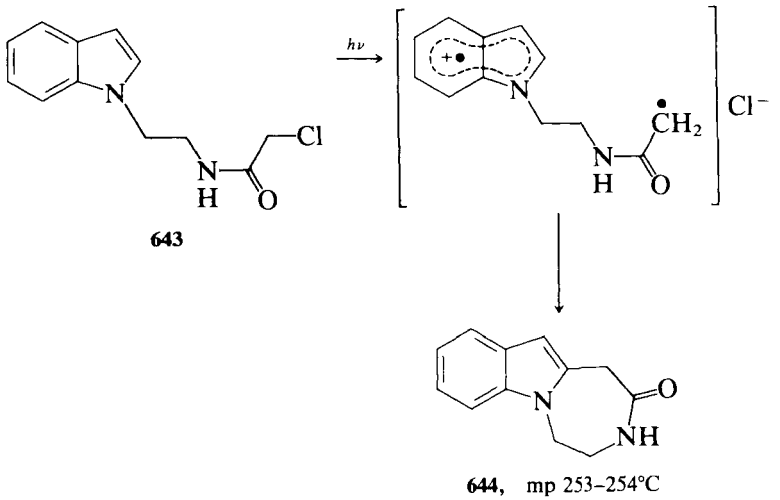



(128)

## 53. [1,4]Diazepino[1,7-*a*]indoles (see Section XV.34)

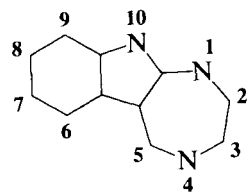


A study of the photocyclization of the *N*-chloroacetyl derivatives of the seven isomeric indolylethylamines was carried out to measure the radical reactivity for each position from the quantum yields. The results were found to correlate with MO calculations. The photocatalyzed cyclization of indole **643** to the diazepinoindole **644** illustrates this reaction (Eq. 129) and constitutes the sole example of the [1,4]diazepino[1,7-*a*]indole ring system (318).



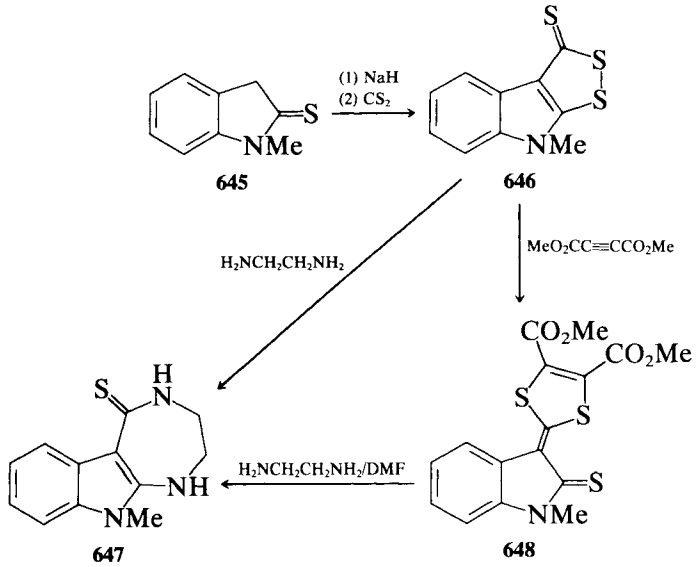
**643** **644**, mp 253–254°C (129)

## 54. [1,4]Diazepino[5,6-*b*]indoles



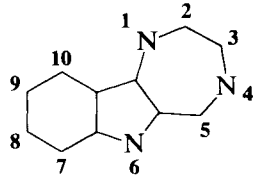
The only synthesis of the [1,4]diazepino[5,6-*b*]indole ring system was achieved during a study of the chemistry of 1,2-dithiolo[3,4-*b*]indole-3-thione derivatives. Starting with 1-methylthioxindole (**645**), the key intermediate **646** was prepared by reaction with sodium hydride and carbon disulfide (Eq. 130). Reaction of **646** with ethylenediamine afforded the diazepine **647** in 30% yield. Alternatively, reaction of **646** with dimethyl acetylenedicarboxylate led to **648** in 90% yield. Addition of ethylenediamine to **648** generated the diazepine **647** via retro-1,3-dipolar cycloaddition. Compound **647** (mp 245–246°C) showed infrared (3115, 3340 $cm^{-1}$) and ultraviolet [$\lambda_{max}$(EtOH),

nm (log $\epsilon$): 263 (4.67), 287 (4.41), 340 (4.34)] properties that were consistent with its assigned structure (319).



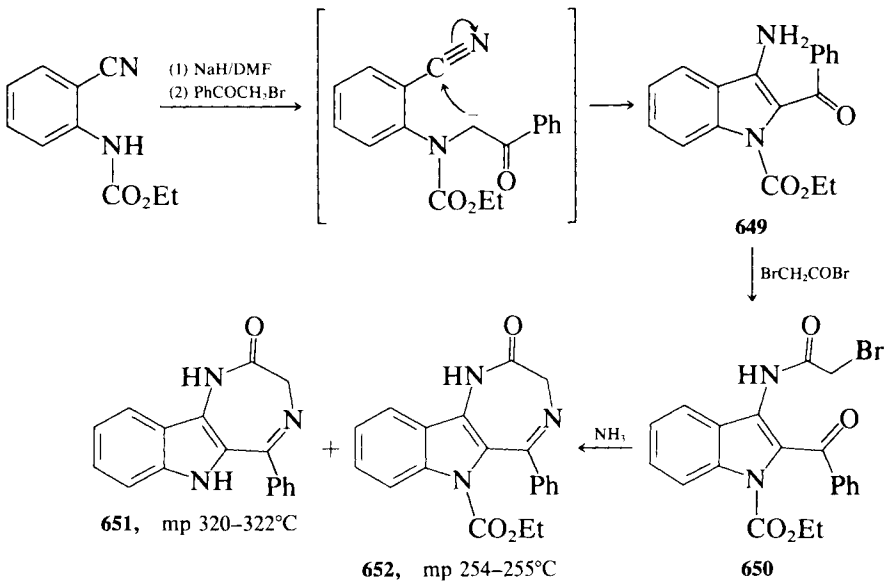

(130)

## 55. [1,4]Diazepino[6,5-*b*]indoles



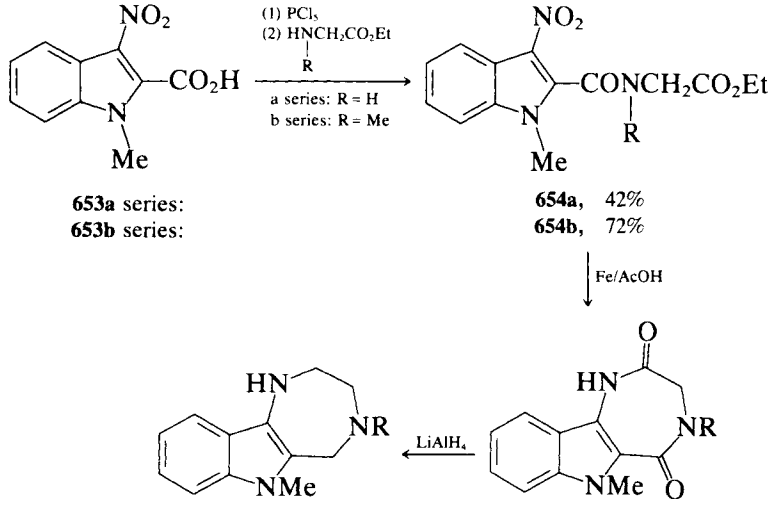
As an extension of benzodiazepine chemistry, the corresponding [1,4]diazepino[6,5-*b*]indole system was prepared. The key intermediate, indole **649,** was obtained from *N*-carbethoxyanthranilonitrile by reaction with sodium hydride and phenacyl bromide in DMF. Bromoacetylation of **649** followed by cyclization with ammonia afforded diazepine **651** as well as a minor amount of **652** (Eq. 131).

The corresponding 2,5-dione system was prepared from the 3-nitroindole-2-carboxylic acid ester **653.** The starting material (**653**) was synthesized in two steps from indole-2-carboxylic acid by treatment with nitric acid followed by *N*-alkylation with dimethyl sulfate. Condensation of **653** with glycine ethyl ester or sarcosine ethyl ester yielded the indole-2-carboxamides **654a** and **654b,** respectively (Eq. 132). Treatment of **654** with iron and acetic




(131)

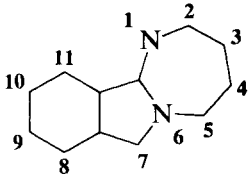
acid effected nitro group reduction and cyclization to the diones **655a** and **655b.** Lithium aluminum hydride reduction of **655** afforded the hexahydrodiazepines **656a** and **656b.** Spectral data were presented in support of the structures of these and related compounds in the series (320).




(132)

| | Yield (%) | mp (°C) | | Yield (%) | mp (°C) |
|---|---|---|---|---|---|
| **656a** | 45 | 160–200 (2HCl) | **655a** | 79 | 284–286 |
| **656b** | 81 | 165–170 (2HCl) | **655b** | 81 | 215–216 |

## 56. [1,3]Diazepino[2,1-*a*]isoindoles (see Section XV.35)




Several derivatives of [1,3]diazepino[2,1-*a*]isoindoles have been reported to have anti-inflammatory, anticonvulsant, or appetite-depressant effects. The first synthesis of this ring system (Fig. 45) was effected by condensation of 1,4-diaminobutane with an 2-acylbenzoic acid (**657**) (321). The product

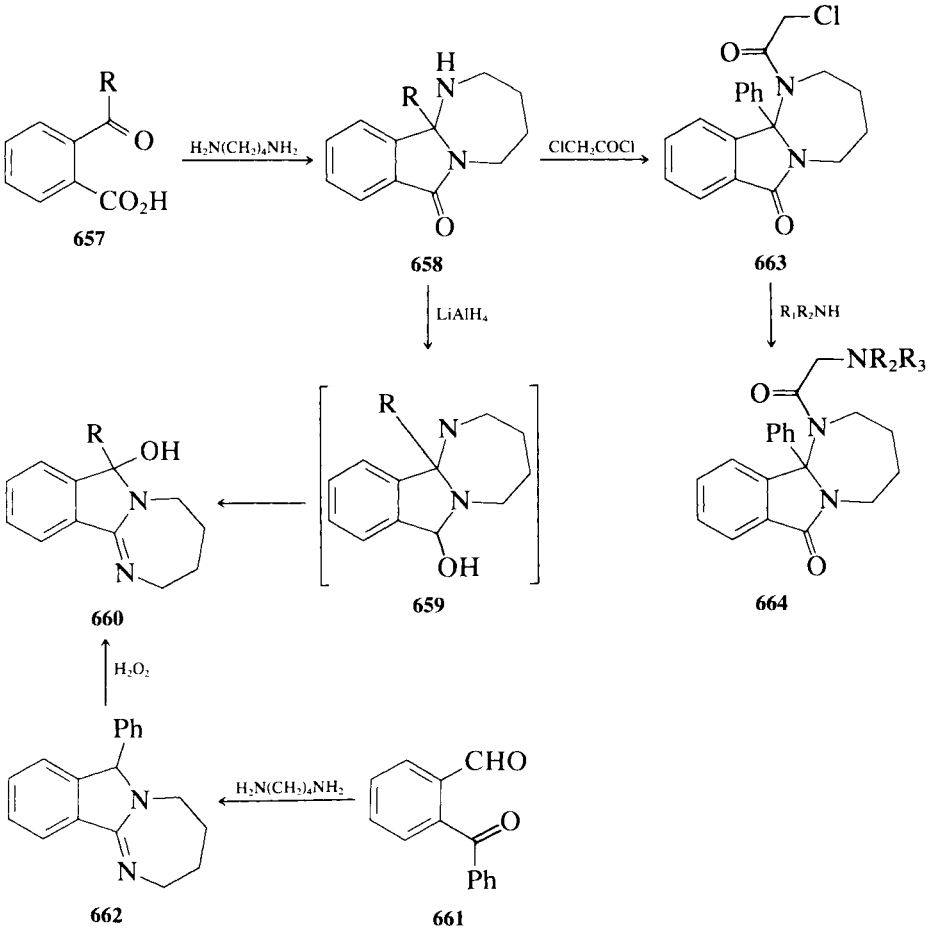
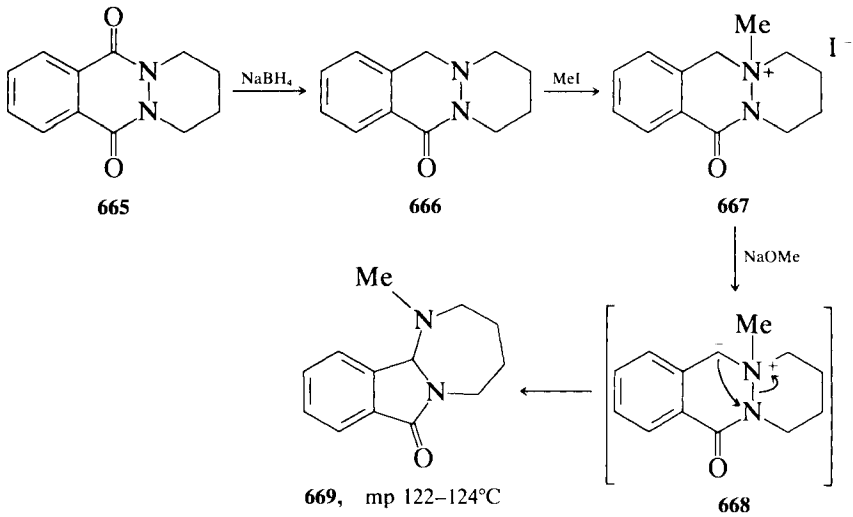



**Figure 45**

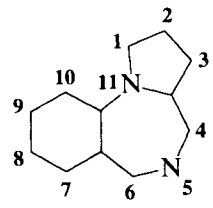
(**658**) could be transformed into another member of the same ring system by reduction to **659** followed by *in situ* oxidation and rearrangement to **660** (321–329). The same product was also obtained from 2-benzoylbenzaldehyde (**661**) by reaction with 1,4-diaminobutane to give diazepine **662,** followed immediately by oxidation to **660** with hydrogen peroxide or air (327,329–333). The diazepine **658** could be *N*-chloroacetylated to **663** and then converted to the amines **664** (334). Specific compounds made by this approach are listed in Table 76 (321–335).

An alternative synthesis of this ring system was achieved via a Stevens rearrangement. The starting material, pyrazolo[1,2-*b*]phthalazine-5,10-dione (**665**), was reduced to **665** with sodium borohydride. Quaternization with methyl iodide led to the ammonium salt **667.** Treatment with sodium methoxide afforded the diazepine **669** via the ylide **668,** as shown in Eq. 133 (336).



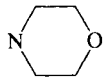

**665** **666** **667** **669,** mp 122–124°C **668** (133)

## 57. Pyrrolo[1,2-*a*][1,4]benzodiazepines (see Section XV.37)

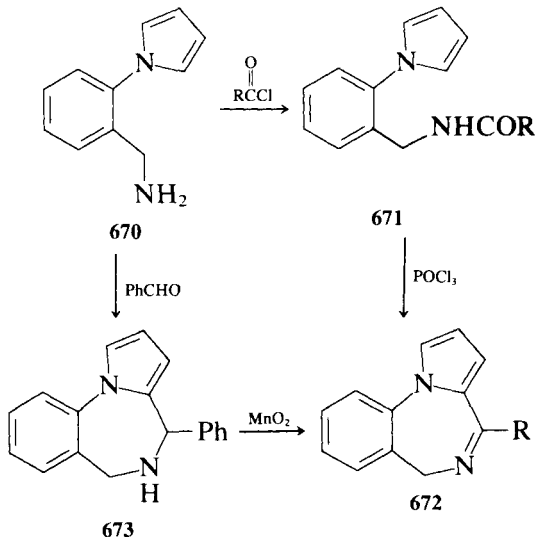



Pyrrolo[1,2-*a*][1,4]benzodiazepines were prepared both as novel heterocyclic systems and for their possible anxiolytic properties. A method for the synthesis of the parent member of this ring system began with amine **670.**

TABLE 76. [1,3]DIAZEPINO[2,1-*a*]ISOINDOLES

| Structure | R ($NR_2$) | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|
| **658** | Ph | 75 | 180–182 | 321,322,326–328 |
| **658** | *p*-$ClC_6H_4$ | 65 | 134–135 | 321,327 |
| **658** | Me | | 136.5 | 321 |
| **658** | 3,4-$Cl_2C_6H_3$ | 28 | 193–195 | 327 |
| **660** | Ph | 29 | 224–226 | 327,329,330,333 |
| **660** | *p*-$ClC_6H_4$ | 29 | 241–243 | 327,329 |
| **660** | 3,4-$Cl_2C_6H_3$ | 35 | 246–247 | 327 |
| **663** | | | 203–207 | 324 |
| **664** | $NMe_2$ | | 205–207 | 324 |
| **664** |  | | 210–213 | 324 |
| **664** |  | | 211–213 | 324 |
| **664** | $NEt_2$ | | 135–141 | 324 |
| **664** | NMeEt | | 160–165 | 324 |
| **664** | $NEtCH_2Ph$ | | 136–138 | 324 |

Formation of the amide **671** was achieved by acylation with an acid chloride (or with chloral and triethylamine in the case of the *N*-formyl derivative). Treatment of **671** with phosphoryl chloride afforded the cyclized product **672.** A higher-yield synthesis of one member of the series was attained via condensation of **670** with benzaldehyde to give **673,** followed by manganese dioxide oxidation to give **672** (R = Ph). Compounds made by this process (Eq. 134) are listed in Table 77 (337–339).




(134)

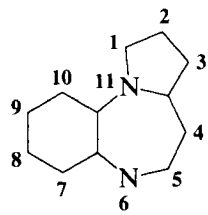
TABLE 77. PYRROLO[1,2-*a*][1,4]BENZODIAZEPINES

| Compound | R | mp (°C) | Spectra | Refs. |
|---|---|---|---|---|
| **672** | H | 190–195 (HCl) | uv, ir, nmr, ms | 337,339 |
| **672** | Me | 60–61 | | 338,339 |
| **672** | Ph | 112–113 | | 338 |
| **673** | | 110–111 | | 338 |
| **676** | | Oil | ir, nmr | 339 |
| **677** | Me | 75–77 | ir | 339 |
| **677** | $CHCl_2$ | 147–148 | ir | 339 |
| **667** | $CH_2Cl$ | 141–143 | ir | 339 |
| **677** | $NMe_2$ | 102–104 | ir | 339 |
| **679** | | 205–207 | ir | 339 |
| **683** | | 142.5–143.5 | ir, nmr | 340 |
| **687** | | 191–193 | nmr | 341 |
| **688** | | 125–126 | nmr | 341 |
| **689** | | 145–146 | nmr | 341 |

Another route to these compounds is outlined in Fig. 46. Reaction of **670** with phthalic anhydride led to **674.** Friedel–Crafts acylation of **674** generated **675,** which on treatment with hydrazine yielded the tricyclic product **672.** Reduction of **672** afforded the dihydro derivative **676,** which was acylated to the amides **677.** The 4-oxo derivative **679** was also prepared from **670** via carbamate **678** (339). The products of these transformations are listed in Table 77.

A related pathway using phthalimide intermediates led to 6-phenyl derivatives, as outlined in Fig. 47. Benzophenone derivative **680** was transformed to pyrrole **682** by condensation with **681.** Hydrazinolysis of **682** led to **683** (340). From oxime **684** pyrrole **685** was prepared and then subjected to a Mannich reaction followed by quaternization with methyl iodide to yield **686.** Cyclization was achieved by heating **686** in DMF. The *N*-oxide **687** thus obtained was deoxygenated with phosphorus trichloride to give **688,** which was reduced to the dihydro product **689** (341). These compounds are listed in Table 77.

## 58. Pyrrolo[1,2-*a*][1,5]benzodiazepines (see Section XV.38)




Access to this novel azulenoid ring system was gained via compound **690,** which was prepared from *o*-phenylenediamine and acetylacetone or ben-

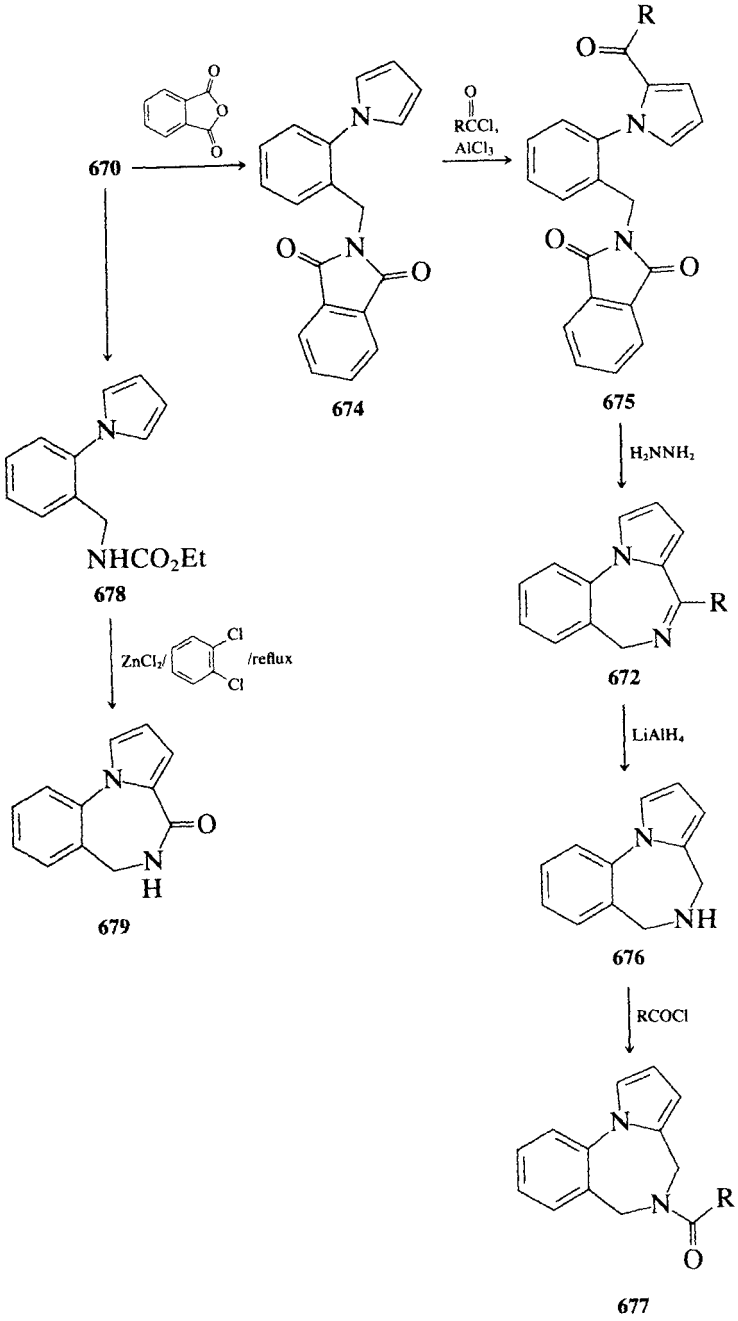

670
674
675
678
679
672
676
677
RCOCl, AlCl3
H2NNH2
LiAlH4
RCOCl
ZnCl2/
/reflux

**Figure 46**

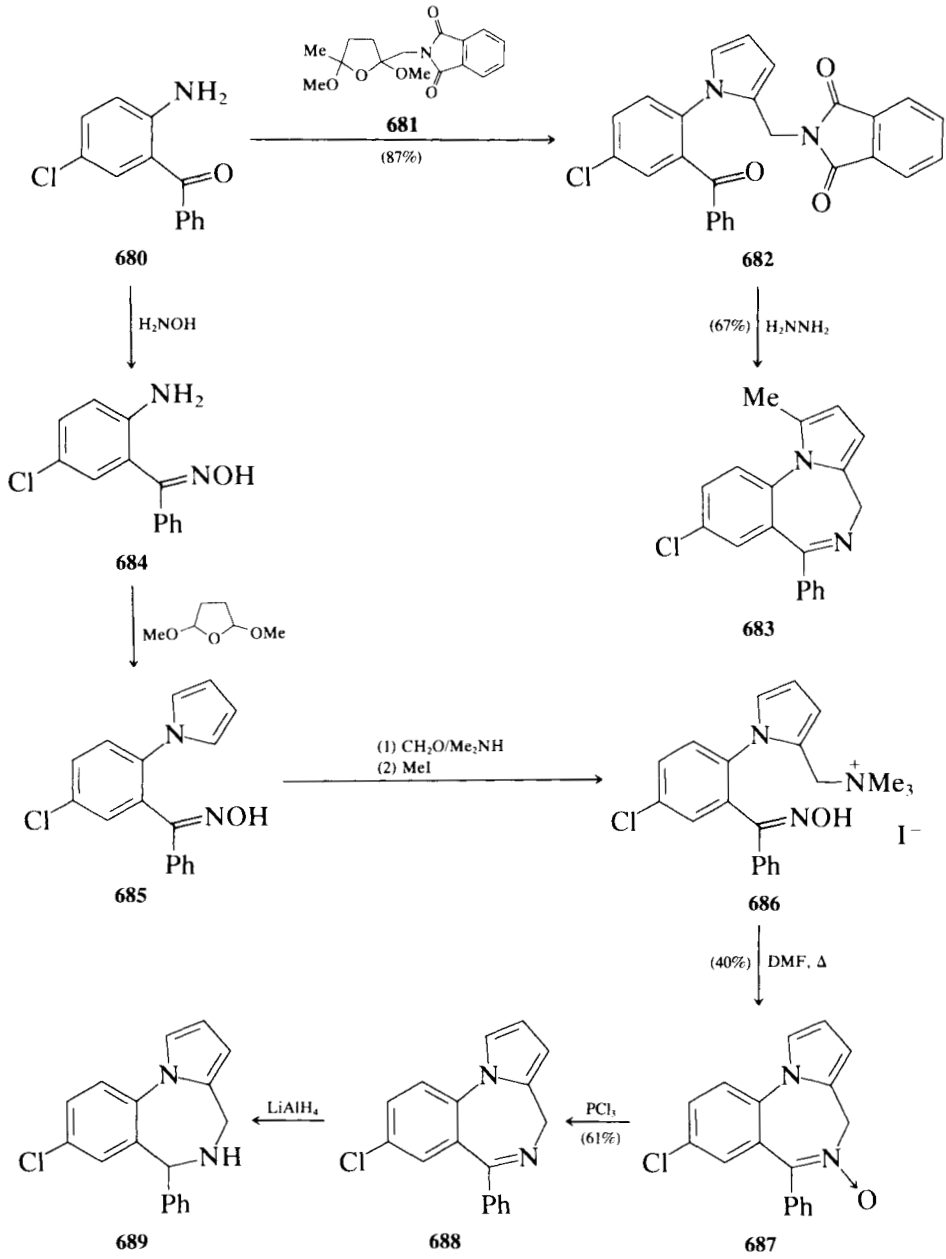
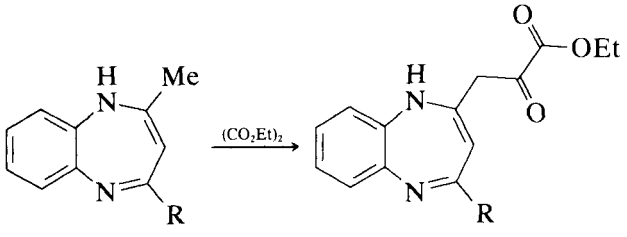

NH2
Cl
O
Ph
680
Me
MeO
OMe
681
(87%)
N
O
682
H2NOH
NOH
684
(67%)
H2NNH2
Me
683
MeO
OMe
(1) CH2O/Me2NH
(2) MeI
NMe3
I−
685
686
(40%)
DMF, Δ
LiAlH4
NH
689
PCl5
(61%)
688
687

**Figure 47**

zoylacetone. Claisen condensation of benzodiazepine **690** with ethyl oxalate (Eq. 135) resulted in reaction at the methyl group to give **692** via the intermediate condensation product **691** (342).



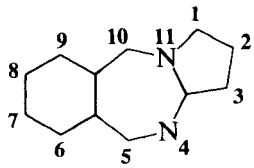

(135)

**690a**, R = Me
**690b**, R = Ph

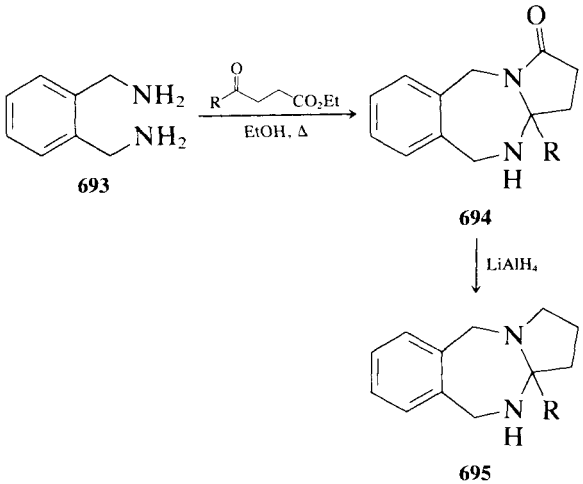
**691**

**692**

## 59. Pyrrolo[1,2-*b*][2,4]benzodiazepines




Condensation of *o*-phenylenebismethylamine (**693**) with 4-keto esters (Eq. 136) afforded the pyrrolobenzodiazepine-1-ones **694** in 25–85% yield. Lithium aluminum hydride reduction effected the conversion of **694** to the corresponding hexahydro derivatives **695**. The results are summarized in Table 78 (343).

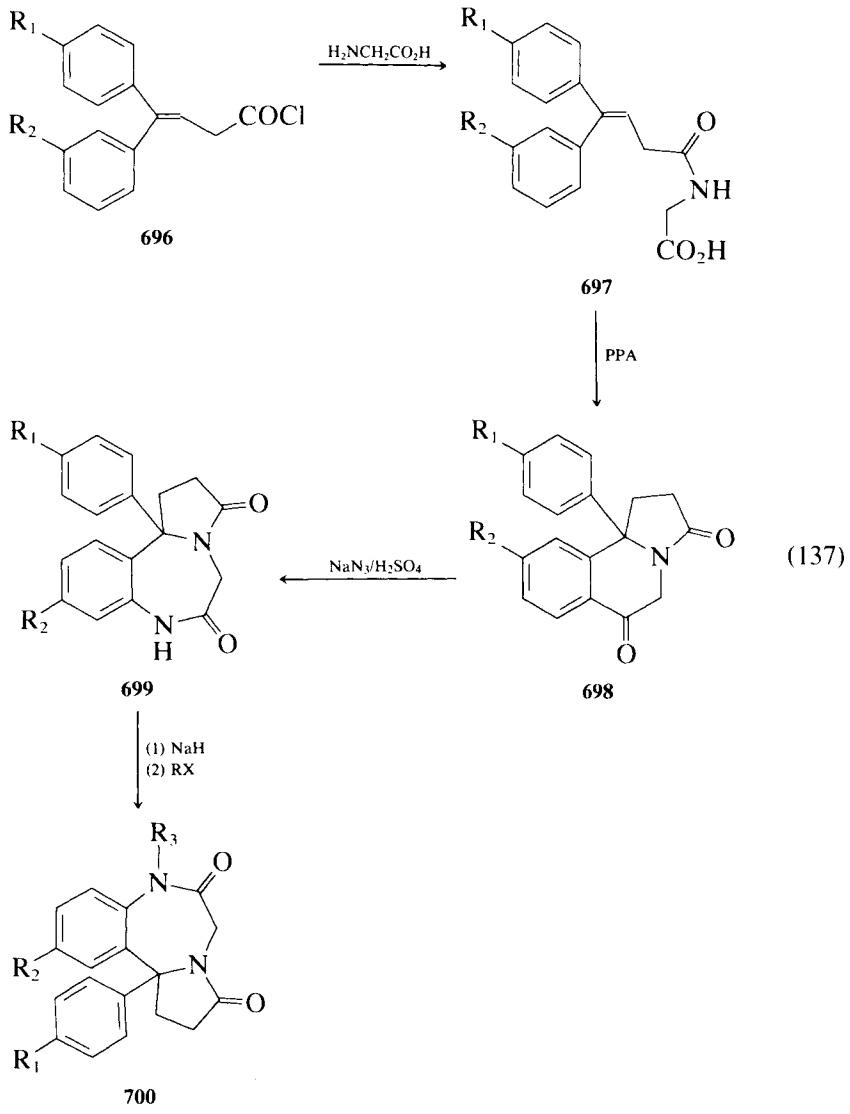



**693**

**694**

(136)

**695**



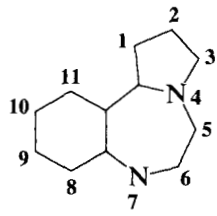

(137)

TABLE 78. PYRROLO[1,2-*b*][2,4]BENZODIAZEPINES[a]

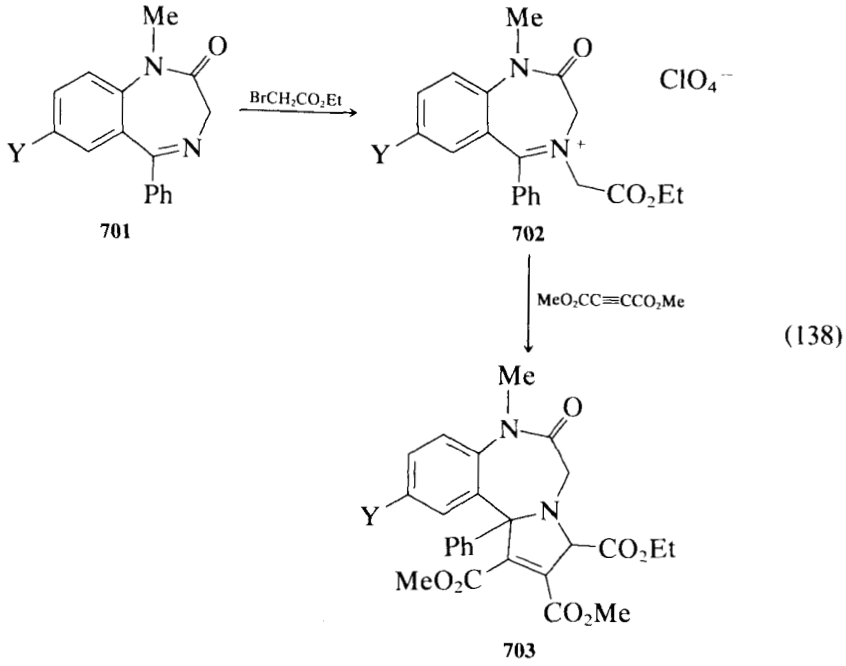
| Structure | R | Yield (%) | mp (°C) | Salt | Spectra |
|---|---|---|---|---|---|
| **694** | H | 54 | 173–175 | | ir, nmr |
| **694** | Me | 85 | 171–172 | | ir, nmr |
| **694** | Et | 25 | 125–126 | | ir, nmr |
| **695** | H | 58 | 58.5–60 | | ir, nmr |
| **695** | Me | 65 | 266–267 | 2HCl | ir, nmr |
| **695** | Et | 46 | 248–251 | 2HCl | ir |

[a]See Ref. 343.

## 60. Pyrrolo[1,2-*d*][1,4]benzodiazepines (see Section XV.39)

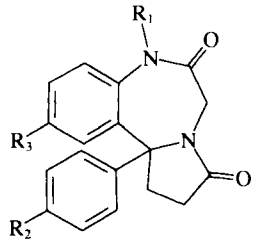



Pyrrolo[1,2-*d*][1,4]benzodiazepines, which are CNS agents, were prepared by two different methods. One approach (Eq. 137) began with the addition of glycine to the 4,4-diphenyl-4-butenoyl chloride **696** to afford the amide **697.** Friedel–Crafts cyclization in polyphosphoric acid (to **698**) followed by Schmidt reaction with sodium azide in sulfuric acid led to the benzodiazepine **699.** Alkylation of amide **699** to give the product **700** was achieved with sodium hydride. These products are listed in Table 79 (344). Another method of preparation of this tricyclic system involved 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate to diazepinium salt **702** (Eq. 138), which yielded the adduct **703.** Compounds prepared in this manner are listed in Table 80 (345).




(138)

TABLE 79. PYRROLO[1,2-*d*][1,4]BENZODIAZEPINES FROM **696**



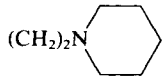
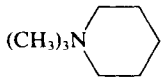
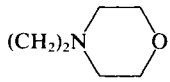
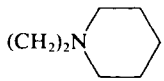
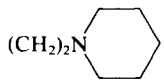
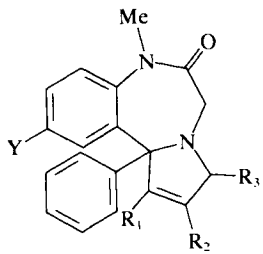
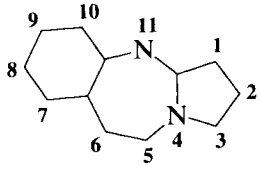
| $R_1$ | $R_2$ | $R_3$ | mp (°C) |
|---|---|---|---|
| Me | H | H | 217–219.5 |
| $(CH_2)_3NMe_2$ | H | H | 154–157 |
| $(CH_2)_2NMe_2$ | H | H | 144–146.5 |
| Me | Cl | H | 214–216 |
| $(CH_2)_3NMe_2$ | Cl | H | 210–212 |
| $(CH_2)_2NMe_2$ | Cl | H | 185–186 |
| Me | H | Cl | 213–214.5 |
| $(CH_2)_2NMe_2$ | H | Cl | 213.5–214.5 |
| $(CH_2)_3NMe_2$ | H | Cl | 217–219 |
|  | H | Cl | 256–258 |
|  | H | Cl | 189–191 |
|  | H | Cl | 255–258 |
|  | $NO_2$ | H | 217–220 |
|  | $NO_2$ | $NO_2$ | 210–212 |

TABLE 80. PYRROLO[1,2-*d*][1,4]BENZODIAZEPINES FROM **702**



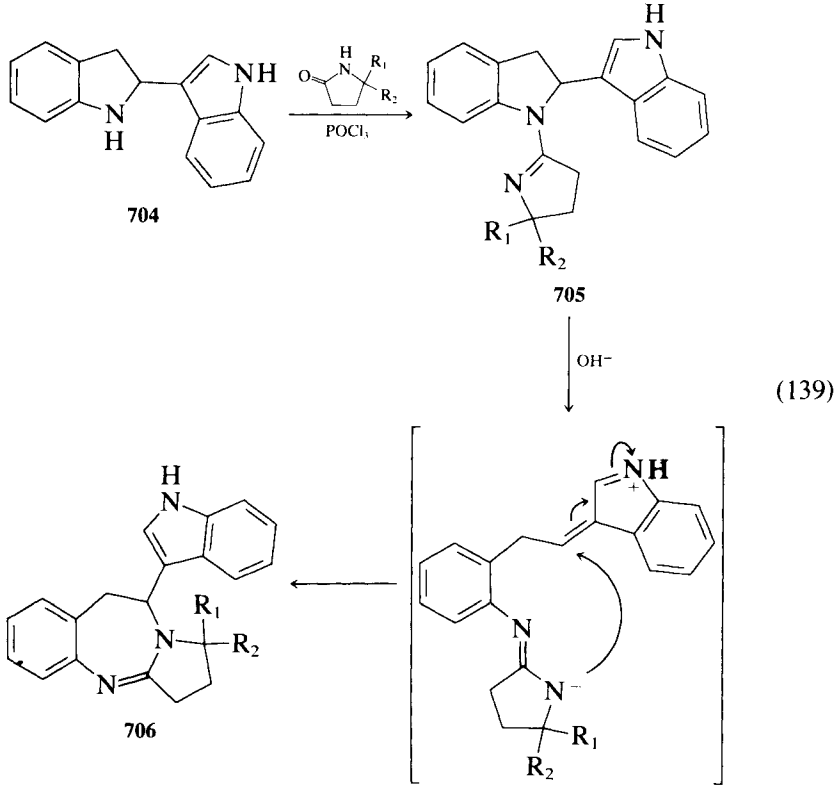
| $R_1$ | $R_2$ | $R_3$ | Y | mp (°C) |
|---|---|---|---|---|
| $CO_2Me$ | $CO_2Me$ | $CO_2Me$ | $NO_2$ | 221.5–222.5 |
| $CO_2Me$ | $CO_2Me$ | $CO_2Me$ | Cl | 161.5–162.5 |
| $CO_2Me$ | $CO_2Me$ | $CO_2Et$ | Cl | 107.5–108.5 |
| *p*-$FC_6H_4CO$ | H | $CO_2Et$ | Cl | 198–199 |

## 61. Pyrrolo[2,1-*b*][1,3]benzodiazepines (see Section XV.41)



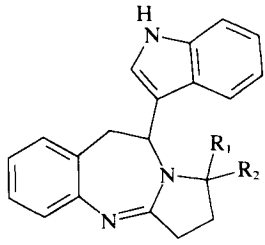

Pyrrolo[2,1-*b*][1,3]benzodiazepines were prepared as part of a series of indolines with diuretic activity. Imidoylation of the indole dimer **704** with 2-pyrrolidinone in the presence of phosphoryl chloride led to **705**, which, during workup under basic or neutral conditions, rearranged to **706** (Eq. 139).

Compounds formed in this way are listed in Table 81 (346–351).



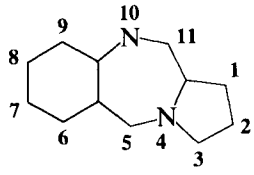

(139)

TABLE 81. PYRROLO[2,1-*b*][1,3]BENZODIAZEPINES

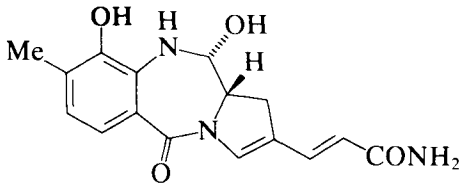


| $R_1$ | $R_2$ | Yield (%) | mp (°C) | Spectra | Refs. |
|---|---|---|---|---|---|
| H | H | 45 | 237–238 | ir, nmr, ms | 346–351 |
| H | Me | | 190–192 | nmr, ms | 346,349–351 |
| Me | Me | | 212.5–213.5 | nmr, ms | 346,349–351 |

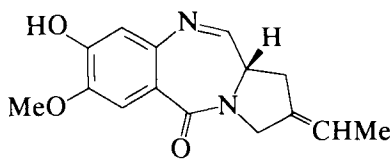
## 62. Pyrrolo[2,1-*c*][1,4]benzodiazepines (see Section XV.42)



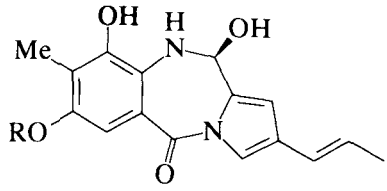
The main thrust of work in the area of pyrrolo[2,1-*c*][1,4]benzodiazepines was stimulated by the isolation of a series of antitumor antibiotics, including anthramycin (**707**) from *Streptomyces refuineus* var. thermotolerans (352), tomaymycin (**708**) from *Streptomyces achromogenes* var. tomaymyceticus (353), and sibiromycin (**709**) from *Streptosporangium sibiricum* (354).



**707**

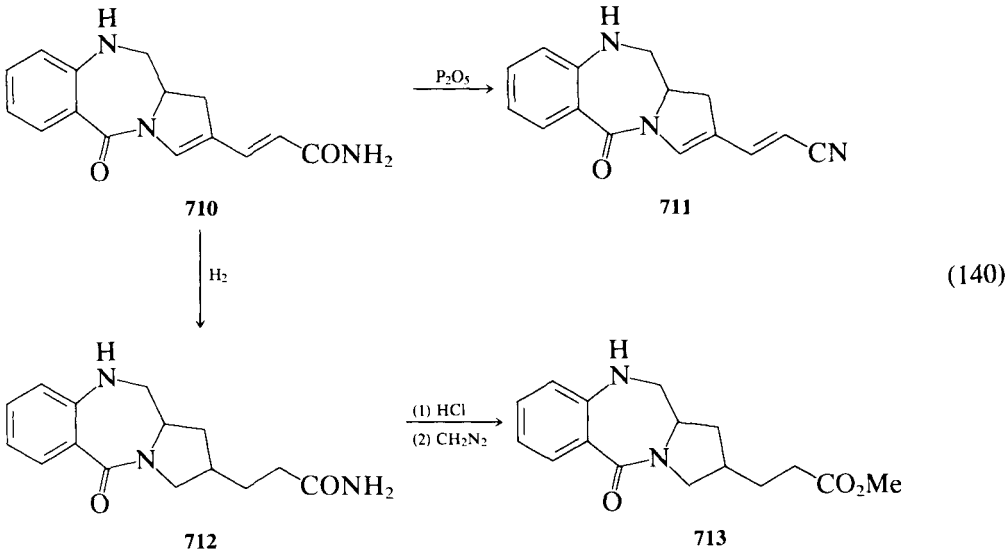


**708**



709

The initial studies on these compounds were conducted to determine their structures and to elucidate the chemical properties of the system. Also present in the fermentation broth containing **707** was the related but simpler structure **710,** called "yellow pigment" (355). Reaction of **710** with phosphorus pentoxide led to the nitrile **711** (Eq. 140). Hydrogenation of **710** afforded **712,** which was hydrolyzed and then esterified to **713.**



710 711 712 713 (140)

Crystallization of anthramycin (**707**) (Fig. 48) from acetone led to partial conversion to anhydroanthramycin (**714**). Addition of methanol to **714** afforded **715.** Reaction of **715** with diazomethane resulted in the dimethoxy product **716,** which could be degraded to the known anthranilic acid derivative **717.** Hydrogenation of **715** generated the amide **718,** which could be *O*-methylated to **719** or *O*-acetylated to **720** (355). Methyl ether **715** was esterified with acetic anhydride to **721** (R = Me). Other derivatives of **715** are listed in Table 82. On treatment with aqueous acetone, acetate **721** (R = Me) rearranged to acetamide **722.** Reaction of **722** with additional acetic anhydride generated diacetate **723** (356).

TABLE 82. PYRROLO[2,1-*c*][1,4]BENZODIAZEPINES

| Structure | Substituents | mp (°C) | Other Data | Refs. |
|---|---|---|---|---|
| **707** | | 188–194 | uv, ir<br>$[\alpha]_D^{25}$ = +930° (*c* = 1.00; DMF) | 352 |
| **708** | | 145–146.5 | uv, ir | 357,358 |
| **709** | | | | 354,362 |
| **710** | | 280–282 | nmr, ms, uv, ir<br>$[\alpha]_D^{25}$ + 883° (*c* = 1.03; DMSO) | 355 |
| **711** | | 233–234 | ir, ms | 355 |
| **712** | | | ir | 355 |
| **713** | | | nmr, uv | 355 |
| **714** | | 205–206 | ms, ir<br>$[\alpha]_D^{25}$ + 1796° (*c* = 1.00; DMA) | 342<br>355 |
| **715** | | 120 | ms, uv, ir<br>$[\alpha]_D^{25}$ + 1002° (*c* = 1.01; DMSO) | 352 |
| **716** | | 229 | nmr | 355 |
| **718** | | | ir, uv | 355 |
| **719** | | | nmr, ms | 355 |
| **720** | | | ir | 355 |
| **721** | R = Me | 184–186 | ir, uv<br>$[\alpha]_D^{25}$ + 860.7° (*c* = 1.00; DMSO) | 356 |
| **721** | R = Et | 150–154 | uv, ir | 356 |
| **721** | R = *n*-$C_3H_7$ | 240 | uv, ir | 356 |
| **721** | R = Ph | 240 | uv, ir | 356 |
| **721** | R = NHPh | 172–173 | uv, ir | 356 |
| **721** | R = NHEt | 192.5–194 | uv, ir | 356 |
| **721** | R = EtO | 191–192 | uv, ir, | 356 |
| **722** | | 240 | ir, uv,<br>$[\alpha]_D^{25}$ + 354° (*c* = 1.04; DMSO) | 356 |

(*continued*)

TABLE 82. (*Continued*)

| Structure | Substituents | mp (°C) | Other Data | Refs. |
|---|---|---|---|---|
| **723** | | 249–249.5 | $[\alpha]_D^{25} = +237.3°$ ($c = 1.00$; DMSO) | 356 |
| **724** | | | | 357–360 |
| **725** | ZR = MeO | 145–146.5 | | 357–359 |
| **725** | ZR = EtO | 134–136 | uv, ir | 358 |
| **725** | ZR = $SCH_2Ph$ | 143–145 | | 359 |
| **725** | ZR = EtS | 70–74 | | 359 |
| **725** | ZR = $NMe_2$ | 65–68 | | 359 |
| **726** | $R_2$ = Me | 88 | ir, uv | 353,357,358 |
| **726** | $R_2$ = Et | | | 353 |
| **727** | | 132–133 | | 358,360 |
| **728** | | 204–205 | | 358,360 |
| **729** | $R_2$= Me | | | 353 |
| **729** | $R_2$ = Et | | | 353 |
| **730** | $R_2$ = Me | 279–281 | ir, nmr, ms | 353 |
| **730** | $R_2$ = Et | 253–254 | ir, nmr, ms | 353 |
| **731** | $R_2$ = Et | 233–235 | ir, uv, nmr<br>$[\alpha]_D^{25} = +817°$ (MeOH) | 353,361 |
| **731** | $R_2$ = Me | 256–258 | ir, nmr | 353,361 |
| **732** | | 248–249 | ir, nmr<br>$[\alpha]_D^{22} = +1200°$ (MeOH) | 353 |
| **734** | R = **733** (HCl)<br>11-MeO | 184–187 | $[\alpha]_D^{20} = -50°$ ($H_2O$) | 362 |
| **734** | R = **733** (HCl)<br>11-MeO | 178–179 | $[\alpha]_D^{20} = +75°$ ($H_2O$) | 362 |
| **735** | | | | 362 |
| **736** | | 225–226 | ir, nmr | 362 |
| **737** | | 192–193 | nmr | 362 |
| **740** | | | uv, nmr | 362 |
| **741** | | 131–133 | ir, nmr | 362 |

| | | | | |
|---|---|---|---|---|
| **742** | | 161–162 | ir, nmr | 362 |
| **746** | | | ir, nmr | 367,368 |
| | | | $[\alpha]_D^{25} = +265°$ ($c = 0.5$; MeOH) | |
| **747** | | | ir | 367,368 |
| **748** | | | nmr | 367,368 |
| **749** | | | | 367,368 |
| **750** | *Cis/trans* mixture | 179–198 | nmr | 367,368 |
| | *Trans* isomer | 203–205 | | |
| | | | $[\alpha]_D^{25} = +553°$ ($c = 0.113$; $CHCl_3$) | |
| | *Cis* isomer | 212–213 | $[\alpha]_D^{25} = +597°$ ($c = 0.107$; $CHCl_3$) | |
| **751** | | 194–195 | $[\alpha]_D^{25} = +951°$ ($c = 0.65$; DMSO) | 367,368 |
| **752** | | | nmr | 367,368 |
| **753** | R = H; X = 8-Me, 9-OH | 278–280 | ir, ms | 369 |
| **753** | R = OH, X = 7,8-$(MeO)_2$ | 277–278 | ir, nmr, ms | 370 |
| **753** | R = OH; X = 7-MeO, 8-EtO | | ir, nmr | 370 |
| **753** | X = H, R = H | 230–231 | ir | 253–255,377,380 |
| **753** | X = H, R = OH | 229–231 | ir | 253–255,377 |
| **753** | X = H, R = OAc | 287–289 | | 377 |
| **753** | X = H, R = $O_2CCHCl_2$ | 246–248 | | 377 |
| **753** | R = H, X = 7-Cl | 222–224.5 | | 253–255 |
| **753** | R = H, X = 7-$NO_2$ | 246–248 | | 253,254 |
| **753** | X = H, R = 3-$CO_2Et$ | 188–189 | | 253–255 |
| **753** | $R_1$ = H, X = 8-Cl | 299–301 | $[\alpha]_D^{25} = +610°$ (DMF) | 383 |
| **753** | R = H, X = 7-$NO_2$ | 249–251 | | 383 |
| **754b** | | 232–233 | ir | 380 |
| **754c** | | 196–198 | ir | 380 |

(*continued*)

TABLE 82. *(Continued)*

| Structure | Substituents | mp (°C) | Other Data | Refs. |
|---|---|---|---|---|
| **755** | $R_1$ = OH, $R_2$ = X = H | 183–185 | ms, ir | 371 |
| **755** | $R_1$ = X = H, $R_2$ = EtO | 136.5–137.5 | ir, nmr, ms | 372 |
| **755** | $R_1$ = X = H, $R_2$ = MeO | 70 | ms, ir, nmr | 372 |
| **755** | $R_1$ = X = H, $R_2$ = $OCHMe_2$ | 182–185 | ms, ir, nmr | 372 |
| **755** | $R_1$ = OH, $R_2$ = MeO | 165–167 | ms | 371 |
| **755** | $R_1$ = $R_2$ = X = H | 183–184 | | 377 |
| **755** | $R_1$ = Me, $R_2$ = O | 120–122 | $[\alpha]_D^{25}$ = +486° (1% MeOH) | 382 |
| **755** | $R_1$ = Et, $R_2$ = O | 138–140 | D | 380 |
| **755** | $R_1$ = Me, $R_2$ = O, 7-Me | 137–139 | | 382 |
| **756** | R = H | 174–176<br>141–142 | ir, nmr | 378,382 |
| **756** | R = Me | 256–258 (HCl) | (L) $[\alpha]_D^{25}$ = +415° (1.3% MeOH) | |
| **756** | R = Me | 229–231 (HCl) | DL | 382 |
| **756** | R = Me | 120–122 | (D) $[\alpha]_D^{25}$ = −477° (1.24% MeOH) | 382 |
| **756** | R = Et | 233–235 (HCl) | (D) $[\alpha]_D^{25}$ = +415° (0.9% MeOH) | 382 |
| **756** | $R_1$ = Me, 7-Me | 213–215 (HCl) | D | 382 |
| **756** | $R_1$ = Me, 7-Cl | 243–245 (HCl) | DL | 382 |
| **756** | $R_1$ = Me, 7-Cl | 270–272 (HCl) | (D)$[\alpha]_D^{25}$ + 377° (1.03% MeOH) | 383 |
| **757** | $R_1$ = $R_2$ = $R_3$ = H | 152–154 | ir, nmr | 373,374 |
| **757** | $R_1$ = COMe, $R_2$ = $R_3$ = H | 154–155 | ir, nmr, ms | 373, 374, 376 |
| **757** | $R_1$ = $COCH_2Cl$, $R_2$ = $R_3$ = H | 122–123 | ir | 373 |
| **757** | $R_1$ = COMe, $R_2$ = H, $R_3$ = CHO | 104–105 | | 374,376 |
| **757** | $R_1$ = COMe, $R_2$ = H, $R_3$ = $CH=C(CONH_2)(CN)$ | 259–262 | | 374 |
| | $R_1$ = COMe, $R_2$ = H, $R_3$ = $CH=C(CN)(CO_2Et)$ | | | |

| | | | | |
|---|---|---|---|---|
| **757** | $R_1 = R_3 = H$, $R_2 = Me$ | 79–80 | ir | 375 |
| **757** | $R_1 = R_2 = R_3 = H$ | 151–154 | uv | 375 |
| **757** | $R_1 = R_2 = H$, $R_3 = COOH$ | 180–182 | uv | 375 |
| **757** | $R_1 = H$, $R_2 = Me$, $R_3 = COOH$ | 203–204 | uv | 375 |
| **757** | $R_1 = COMe$, $R_2 = H$, $R_3 = CN$ | 192–193 | ir | 376 |
| **757** | $R_1 = COMe$, $R_2 = X = H$, $R_3 = CH{=}C(CN)CO_2Et$ | 248–250 | | 376 |
| **757** | $R_1 = COMe$, $R_2 = X = H$, $R_3 = CH{=}C(CN)CONH_2$ | 259–262 | | 376 |
| **757** | $R_1 = COMe$, $R_2 = H$, $R_3 = CH{=}C(CN)COOH$ | 249–252 | | 376 |
| **757** | $R_1 = R_2 = H$, $R_3 = CH{=}C(CN)CO_2Et$ | 188–189 | | 376 |
| **757** | $R_1 = R_2 = H$, $R_3 = CH{=}C(CN)CONH_2$ | 230–231 | | 376 |
| **757** | $R_1 = R_2 = H$, $R_2 = CHO$ | 172–173 | ir | 376 |
| **757** | $R_1 = R_2 = H$, $R_3 = CN$ | | | 376 |
| **757** | $R_1 = H$, $R_2 = Me$, $R_3 = CN$ | 141–142 | ir | 376 |
| **757** | $R_1 = COMe$, $R_2 = Me$, $R_3 = CN$ | 156–157 | ir | 376 |
| **757** | $X = 7,8\text{-(MeO)}$ $R_1 = R_2 = R_3 = H$ | 114–116 | ir | 381 |
| **757** | $R_2 = R_3 = H$, $R_1 = COMe$, $X = 7,8\text{-(MeO)}_2$ | 177–179 | ir | 381 |
| **757** | $R_1 = R_2 = R_3 = H$, $X = 7,8\text{-}OCH_2O$ | 131–132 | ir | 381 |

(*continued*)

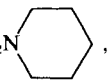
TABLE 82. (*Continued*)

| Structure | Substituents | mp (°C) | Other Data | Refs. |
|---|---|---|---|---|
| **757** | $R_2=R_3=H$, $R_1=COMe$, $X=7,8\text{-}OCH_2O$ | 222–223 | ir | 381 |
| **757** | $X=7,8\text{-}(MeO)_2$, $R_1=COMe$, $R_2=H$, $R_3=CHO$ | 203–205 | ir | 381 |
| **757** | $X=7,8\text{-}OCH_2O$, $R_1=COMe$, $R_2=H$, $R_3=CHO$ | 184–186 | ir | 381 |
| **757** | $X=7,8\text{-}(MeO)_2$ $R_1=COMe$, $R_2=H$, $R_3=CH{=}C(CN)CO_2Et$ | 194–196 | | 381 |
| **757** | $X=7,8\text{-}OCH_2O$, $R_1=COMe$, $R_2=H$, $R_3=CH{=}CNCO_2Et$ | 236–238 | | 381 |
| **757** | $X=7,8\text{-}OCH_2O$, $R_1=COMe$, $R_2=H$, $R_3=CH{=}C(CN)CONH_2$ | 302–304 | | 381 |
| **758** | $R_1=R_2=H$ | 95–96 | ir, uv, nmr | 374,375 |
| **758** | $X=H$, $R_1=Me$, $R_2=CN$ | 114–115 | ir, nmr | 375 |
| **758** | $X=R_1=H$, $R_2=CN$ | 97–98 | ir.nmr | 375 |
| **758** | $X=H$, $R_1=Me$, $R_2=CONH_2$ | 215–216 | ir, nmr | 375 |
| **758** | $X=H$, $R_1=Me$, $R_2=COOH$ | 235–236 | ir, uv | 375 |
| **758** | $X=H$, $R_1=H$, $R_2=COOH$ | 245–246 | uv | 375 |
| **758** | $R_1=Me$, $X=R_2=H$ | 96–97 | uv | 375 |
| **758** | $X=7,8\text{-}(MeO)_2$, $R_1=R_2=H$ | 111–113 | ir | 381 |
| **758** | $X=7,8\text{-}OCH_2O\text{-}$, $R_1=R_2=H$ | 142–144 | ir | 381 |
| **759** | | 223–224 | ir, nmr | 374,375 |
| **760** | $R_1=R_2=X=H$ | 108–109 | | 253–255,377 |
| **760** | $X=R_1=H$, $R_2=OH$ | 152–153 | | 255,377 |
| **760** | $X=R_2=H$, $R_1=COEt$ | 230–231 (HCl) | | 253–255 |
| **760** | $X=R_2=H$, $R_1=COCH(CH_3)OCOMe$ | 257–259 (HCl) | | 253–255 |
| **760** | $X=R_2=H$, $R_1=CHO$ | | bp 92–94°C (0.004 mm) | 253,254 |
| **760** | $R_1=R_2=H$, $X=Cl$ | 173–174 (TsOH) | | 253–255 |
| **760** | $X=H$, $R_1=COEt$, $R_2=OH$ | 260–262 (HCl) | | 253–255 |
| **760** | $R_2=X=H$, $R_1=COEt$, $3\text{-}CH_2OH$ | 242–243 (HCl) | | 253–255 |
| **760** | $R_1=COCH_2CH_2Cl$, $X=Cl$, $R_2=H$ | 215–217 (HCl) | $[\alpha]_D^{25} = -110°$ (MeOH) | 383 |

| | | | | |
|---|---|---|---|---|
| **760** | $R_1 = COCH_2CH_2N$  , X = Cl, $R_2 = H$ | | $[\alpha]_D^{25} = -84.9°$ (MeOH) | 383 |
| **760** | $R_1 = COCH_2CH_2N$  , X = Cl, $R_2 = H$ | Ditartrate | $[\alpha]_D^{25} = +32°$ (MeOH) | 383 |
| **760** | $R_1 = COCH_2CH_2N$  NMe, X = Cl, $R_2 = H$ | 159–161 (Trimaleate) | $[\alpha]_D^{25} = -59.3°$ (MeOH) | 383 |
| **760** | $R_1 = COCH_2CH_2N(C_3H_7n)_3$, X = Cl, $R_2 = H$ | Ditartrate | $[\alpha]_D^{25} = -35°$ (MeOH) | 383 |
| **760** | $R_1 = COCH_2CH_2NMe_2$, X = Cl, $R_2 = H$ | Ditartrate | $[\alpha]_D^{25} = -34°$ (MeOH) | 383 |
| **760** | $R_1 = COCH_2CH_2N_4(CH_2)_6$, X = Cl, $R_2 = H$ | Ditartrate | $[\alpha]_D^{25} = -26°$ (MeOH) | 383 |
| **760** | $R_1 = COCH_2CH_2N$  , X = Cl, $R_2 = H$ | Tartrate | $[\alpha]_D^{25} = -41°$ (MeOH) | 383 |
| **760** | $R_1 = COCH_2CH_2N$  , $R_2 = X = H$ | Ditartrate | $[\alpha]_D^{25} = -42°$ (MeOH) | 383 |
| **760** | $R_1 = COCH_2CH_2N$  , $R_2 = X = H$ | Ditartrate | $[\alpha]_D^{25} = -45°$ (MeOH) | 383 |
| **760** | $R_1 = COCH_2CH_2N$  O, $R_2 = X = H$ | Ditartrate | $[\alpha]_D^{25} = -44°$ (MeOH) | 383 |
| **760** | $R_1 = COCH_2CH_2N$  , X = 8-Cl, $R_2 = H$ | Ditartrate | $[\alpha]_D^{25} = -21°$ (MeOH) | 383 |
| **760** | $R_1 = R_2 = H$, X = 8-Cl | 131–133 | $[\alpha]_D^{25} = -237°$ | 383 |

*(continued)*

TABLE 82. (*Continued*)

| Structure | Substituents | mp (°C) | Other Data | Refs. |
|---|---|---|---|---|
| **760** | $X = 7\text{-Me}$, $R_1 = COCH_2CH_2N$  , $R_2 = H$ | Ditartrate | $[\alpha]_D^{25} = -33°$ (MeOH) | 383 |
| **761** | | 233–234 | ir, nmr | 378 |
| **769** | $R_1 = Me$, $R_2 = H$ | 223–225 | uv, ir, nmr | 379 |
| **769** | $R_1 = CH_2OMe$, $R_2 = H$ | 239–240 | uv, ir, nmr | 379 |
| **769** | $R_1 = R_2 = Me$ | 214–216 | uv, ir, nmr | 379 |
| **769** | $R_1 = CH_2OEt$, $R_2 = H$ | 151 | uv, ir, nmr | 379 |
| **770** | | 150–153 | uv, nmr | 379 |
| **773** | | 193–195 | uv, ir, nmr | 379 |
| **774** | | 145–148 | uv, nmr | 379 |

As with anthramycin (**707**), tomaymycin (**708**) was studied to determine its structure and the chemistry of the system (Fig. 49). By analogy with the ease of dehydration of **707**, tomaymycin (**708**) may have arisen from pretomaymycin (**724**) during isolation. Treatment of **708** with methanol, ethanol, benzyl mercaptan, ethyl mercaptan, or dimethyl amine afforded the adducts **725.** Alkylation of **725** with diazomethane or diazoethane led to the corresponding methyl or ethyl ethers **726a** and **726b**, respectively. Esterification of **725** with acetic anhydride generated the acetate **727**, and esterification with *p*-bromobenzoyl chloride generated the ester **728** (356–360). On heating, **726** lost methanol to give **729**, which was oxidized to **730** with *m*-chloroperbenzoic acid. Ozonolysis afforded the trione **731** (353). Confirmation of the structure **731** ($R_2 = Et$), and thus of **708**, was achieved by its synthesis via methyl 1-(2-nitro-4-ethoxy-5-methoxybenzoyl)-4-hydroxyprolinate (353,361).

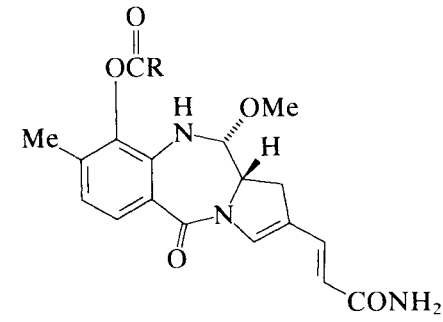
The chemistry of sibiromycin (**709**, R = **733**) was similarly investigated to confirm its structure (361,362). Reaction with methanol afforded the expected adduct **734** (Fig. 50). Dehydration of **709** led to the imine **735**, which formed the diacetate **736** on treatment with acetic anhydride. Methylation of **735** afforded the dimethoxy derivative **737**, which was degraded with base to fragments **738** and **739.** Hydrogenation of **735** led to **740**, which was converted to the derivatives **741** and **742.** The physical constants of these naturally occurring compounds and their derivatives are listed in Table 82.

Although these natural products can be obtained routinely by fermentation (363–366), a total synthesis of **707** has been achieved as shown in Fig. 51 (367,368). Acylation of L-hydroxyproline methyl ester with **743** gave amide **744.** Reduction with sodium dithionite generated the amine **745**, which underwent cyclization in acid to **746.** Chromic acid oxidation of **746** led to the ketone **747**, which was condensed with triethyl phosphonoacetate to give the $\beta,\gamma$-unsaturated ester **748** in 74% yield. Diisobutylaluminum hydride converted ester **748** to an aldehyde, which was then treated sequentially with sodium bisulfite and potassium cyanide to obtain the cyanohydrin **749.** Dehydration of **749** via its mesylate effected the formation of the conjugated nitrile **750** as a 4:1 mixture of *E* and *Z* isomers. To selectively reduce the secondary amide group, the mixture of isomeric nitriles was debenzylated and then converted with benzaldehyde to aminal **751**. Hydration of the nitrile group of **751** to an amide followed by reduction with sodium borohydride afforded **752.** Finally, deprotection in acidic methanol produced the anthramycin methyl ether (**715**).

A host of simpler analogs have been synthesized via the basic methodology for ring formation described above. Use of proline derivatives (Eq. 141) led to **753** (368,369). 2-Pyrrolidine carboxaldehyde (370) or its acetal (371) yielded compounds of general structure **755.** 2,2-Dicarbethoxypyrroline derivatives **754a** afforded the products **754b** and **754c** (Eq. 142). On decarboxylation, **754c** was also converted to **753** (X = R = H) (372).

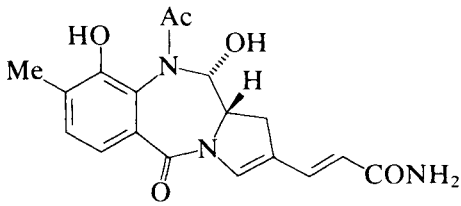
Condensation of *o*-nitrobenzyl bromide with proline ethyl ester (375), pyr-

707 recryst.



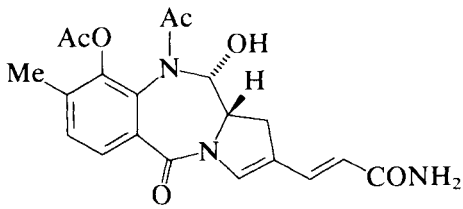
721

aq. $Me_2CO$ (R = Me)



722

$Ac_2O$



723

**Figure 48**

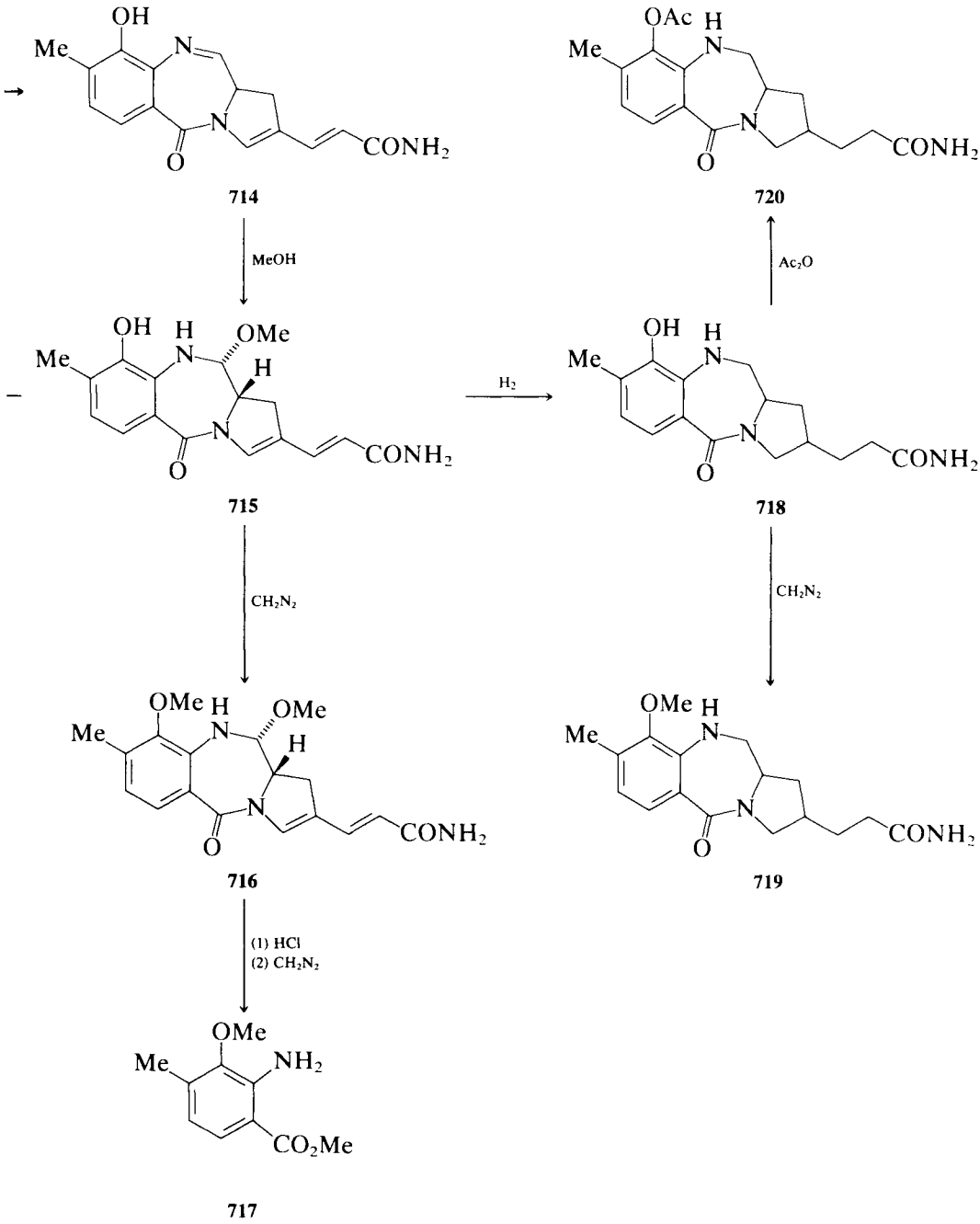
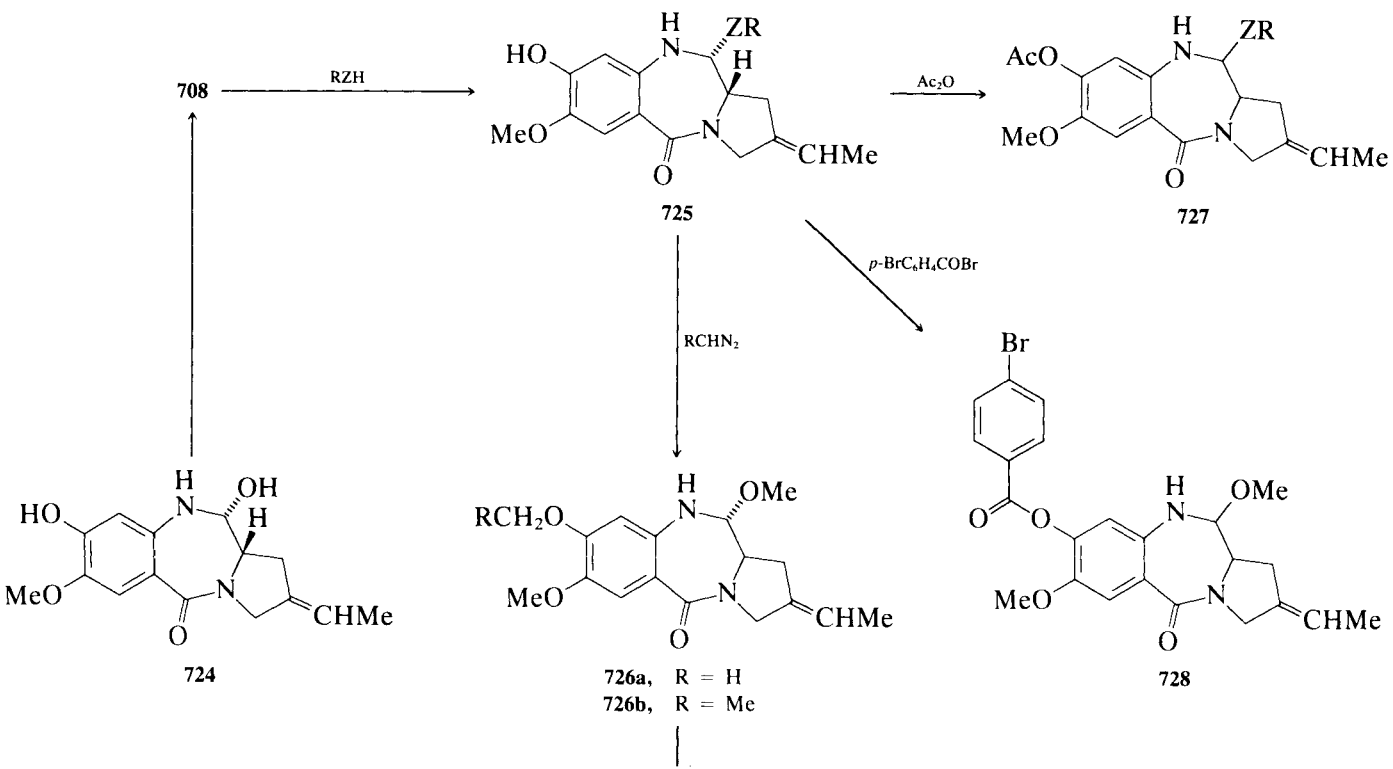



**Figure 48** ***(continued)***


708
RZH
HO
MeO
H
N
ZR
H
O
CHMe
725
Ac2O
AcO
MeO
H
N
ZR
O
CHMe
727
p-BrC6H4COBr
RCHN2
Br
O
O
MeO
H
N
OMe
O
CHMe
728
HO
MeO
H
N
OH
H
O
CHMe
724
RCH2O
MeO
H
N
OMe
O
CHMe
726a, R = H
726b, R = Me

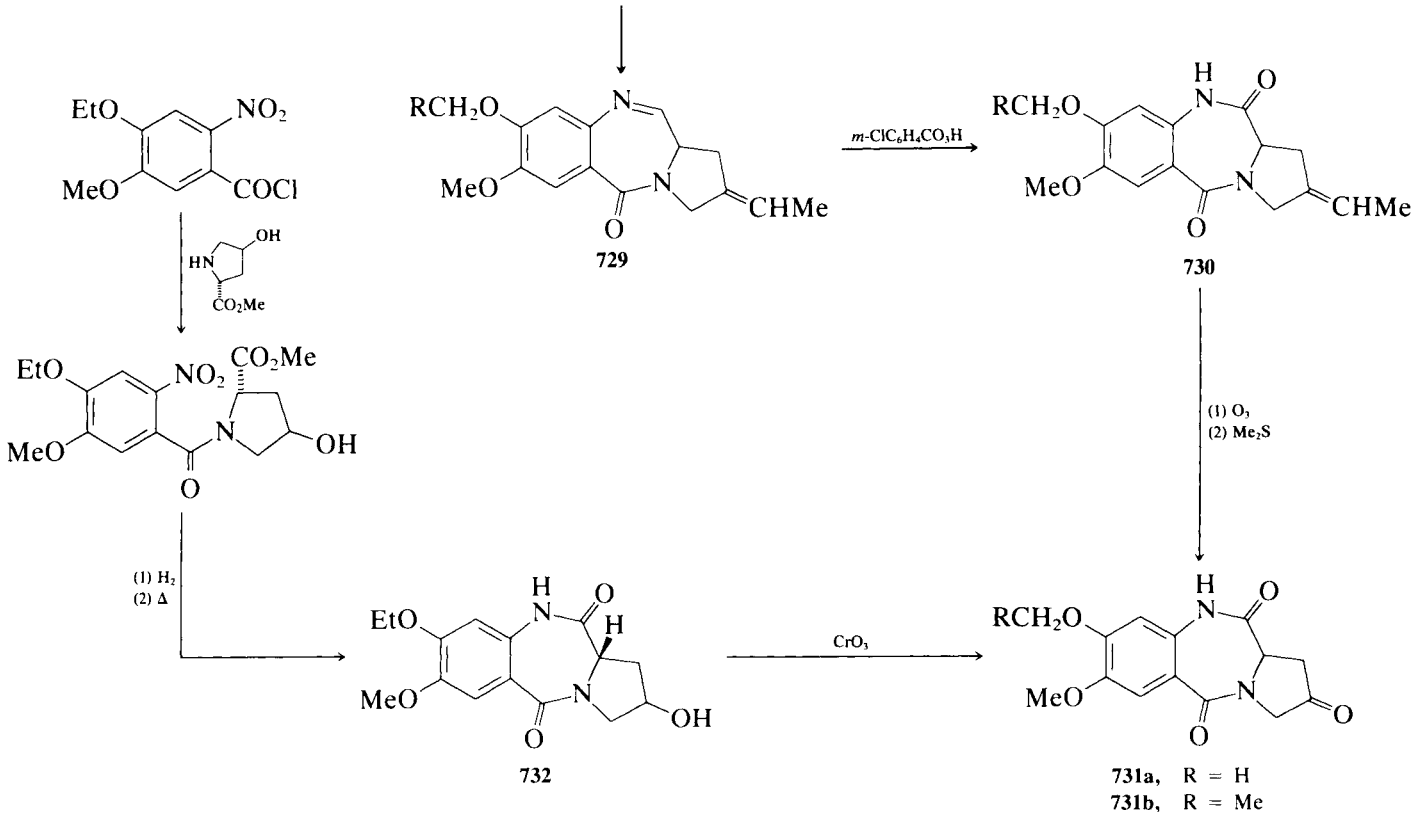
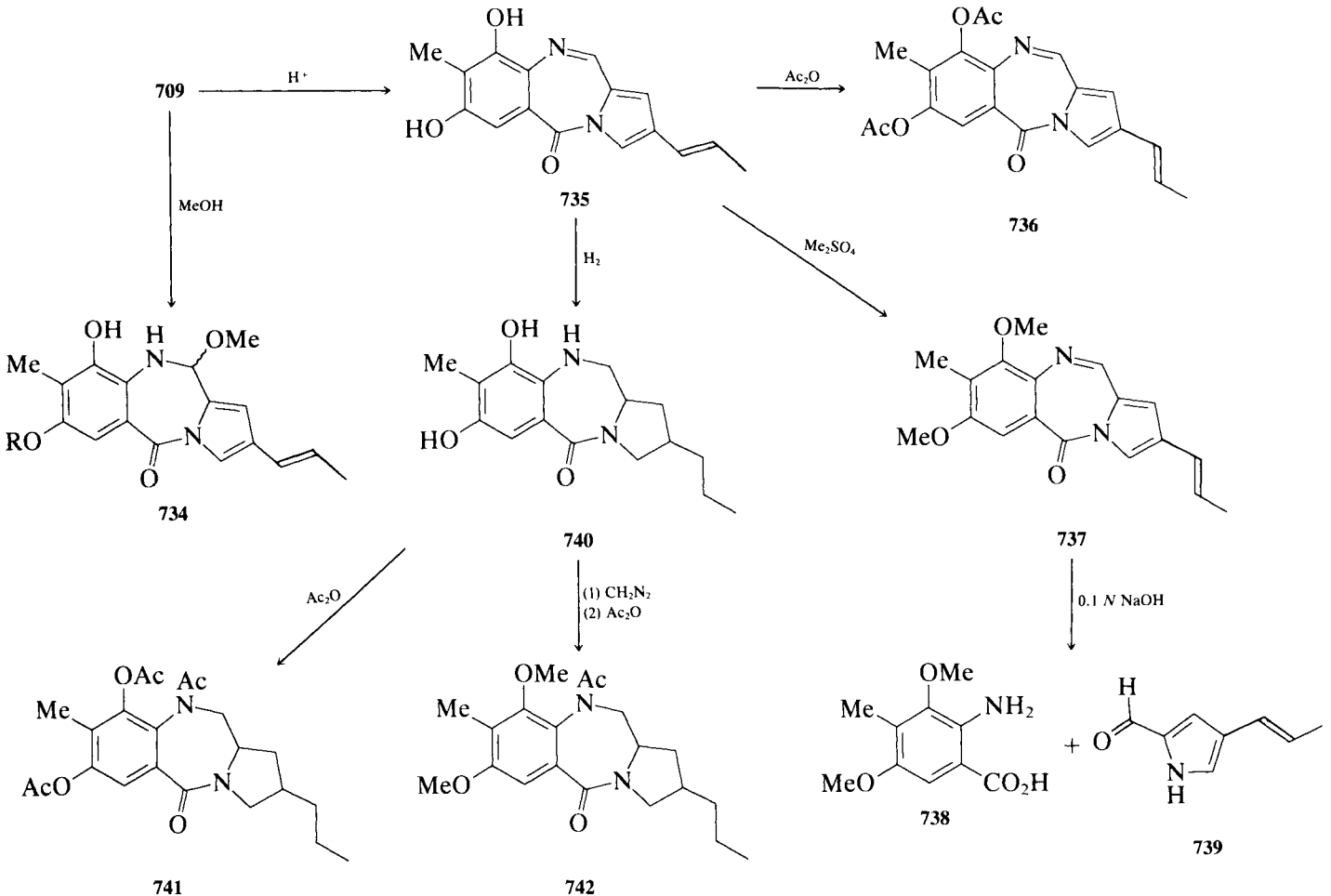

EtO
NO2
MeO
COCl
OH
HN
CO2Me
EtO
NO2
CO2Me
MeO
N
OH
O
(1) H2
(2) Δ
RCH2O
N
MeO
N
O
CHMe
729
m-ClC6H4CO3H
RCH2O
H
N
O
MeO
N
O
CHMe
730
(1) O3
(2) Me2S
EtO
H
N
O
H
MeO
N
OH
O
732
CrO3
RCH2O
H
N
O
MeO
N
O
O
731a, R = H
731b, R = Me

**Figure 49**


709
H+
MeOH
735
Ac2O
736
H2
Me2SO4
734
740
737
Ac2O
(1) CH2N2
(2) Ac2O
0.1 N NaOH
741
742
738
739

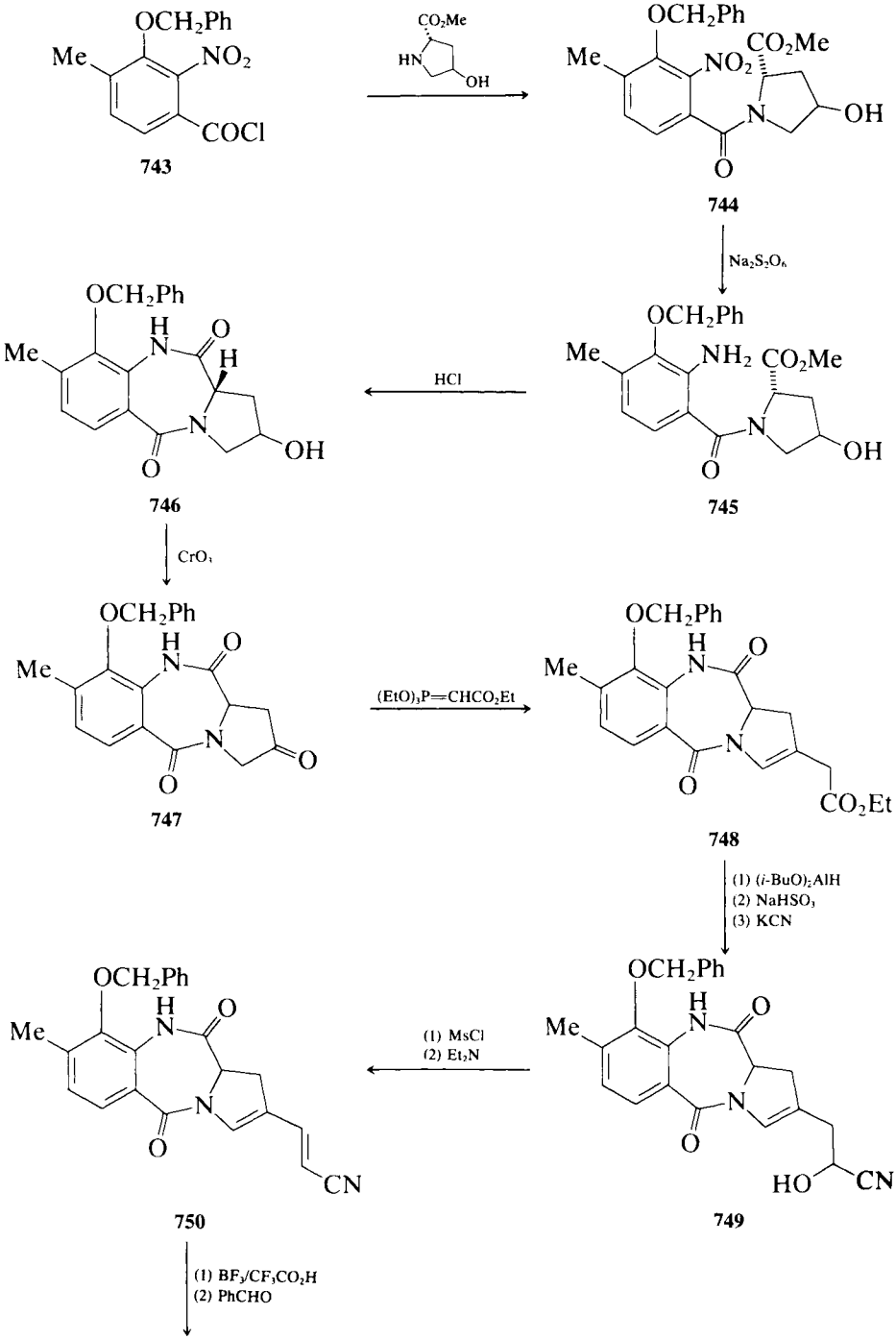



**Figure 51** (*continued on next page*)

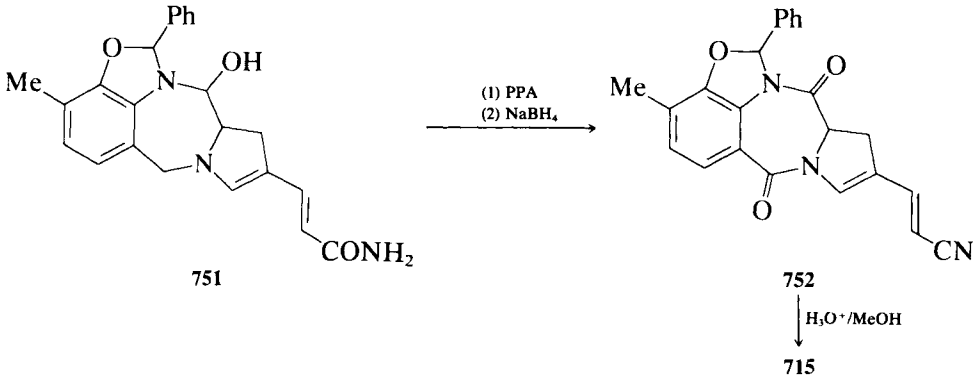
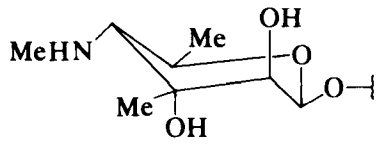
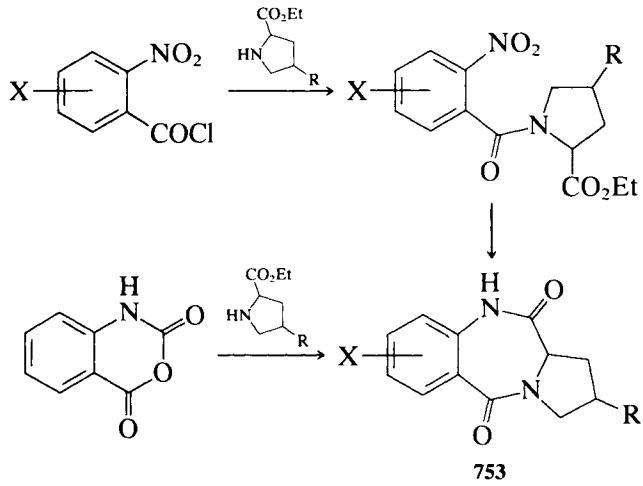



**Figure 51** ***(continued)***

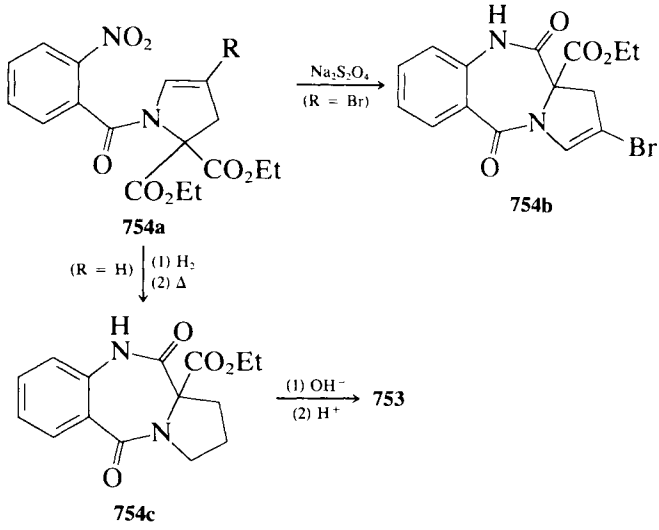



role-2-carboxaldehyde (374), its oxime (375,376), or pyrrole-2-carbonitrile (375,376) led to the products **756–760.**

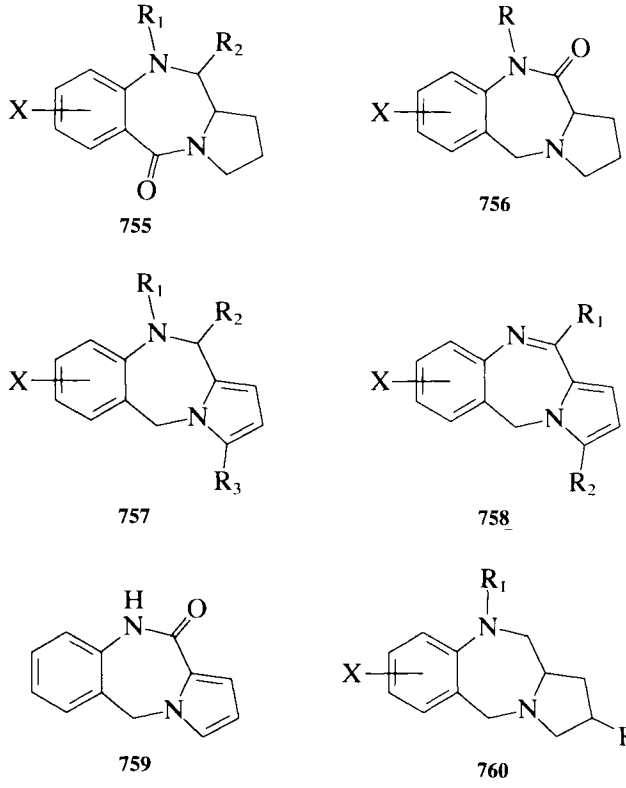
Compound **758** was also prepared from *N*-(2-acylaminobenzyl)pyrroles on treatment with phosphoryl chloride (376). Another modification avoiding




(141)


NO2
R
N
O
CO2Et
CO2Et
754a
Na2S2O4
(R = Br)
H
N
O
CO2Et
N
O
Br
754b
(R = H)
(1) H2
(2) Δ
H
N
O
CO2Et
N
O
754c
(1) OH−
(2) H+
753

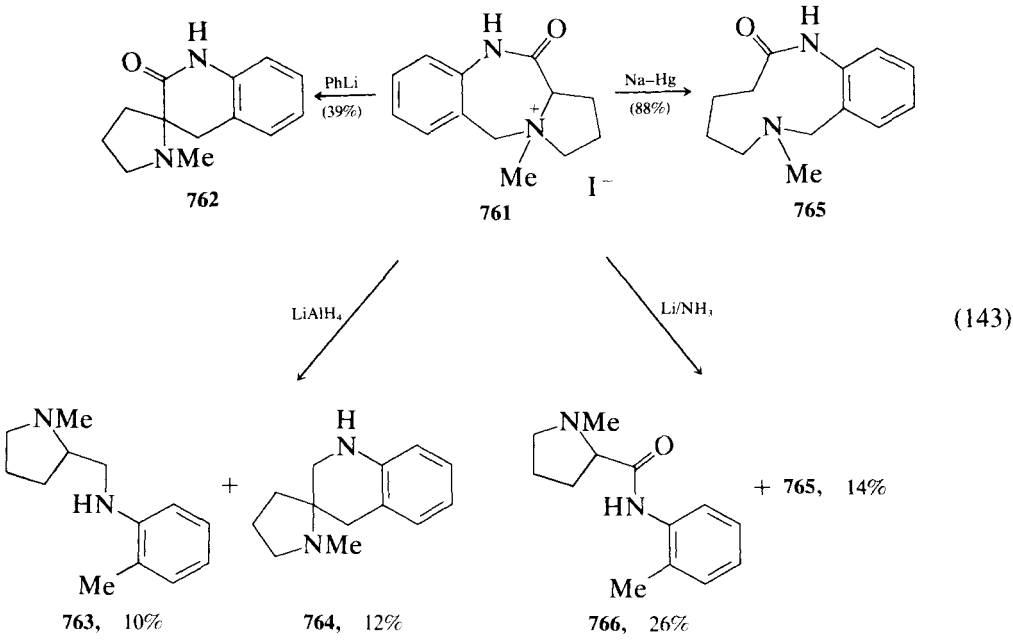
(142)


R1
N
R2
X
N
O
755
R
N
O
X
N
756
R1
N
R2
X
N
R3
757
N
R1
X
N
R2
758
H
N
O
N
759
R1
N
X
N
R2
760

the use of nitro compounds involved condensation of isatoic anhydride with proline derivatives (377,378).

Other compounds obtained from these intermediates by reduction, alkylation, or acylation are listed in Table 82 (253,254,371–377,381–383). Some of these products have analgetic antagonist, anti-inflammatory, psychomotor depressant (253,254,255) and anxiolytic properties (382,383).

Compound **756** (R = X = H) was quaternized to **761** and the latter was treated with phenyllithium to give **762,** with lithium aluminum hydride to give **763** and **764,** with sodium amalgam to give **765,** and with lithium in liquid ammonia to give **765** and **766** (Eq. 143) (378,384,385).




(143)

A different approach to this ring system made use of the chemistry of benzodiazepines (379). As shown in Fig. 52, when the 3-alkyl[1,4]-benzodiazepine 4-oxide **768** was subjected to the Polonovsky reaction, pyrrolo[2,1-*c*]benzodiazepine **769** was obtained. Other similarly prepared compounds are listed in Table 82. The proposed mechanism for this conversion is shown in Fig. 53. Reduction of **769** ($R_1$ = Me, $R_2$ = H) afforded the amine **770.** The tetrahydro analog **774** was prepared from **767** by addition of methyl acrylate to give **771,** followed by reduction to **772,** ring closure to **773,** and lithium aluminum hydride reduction (379).

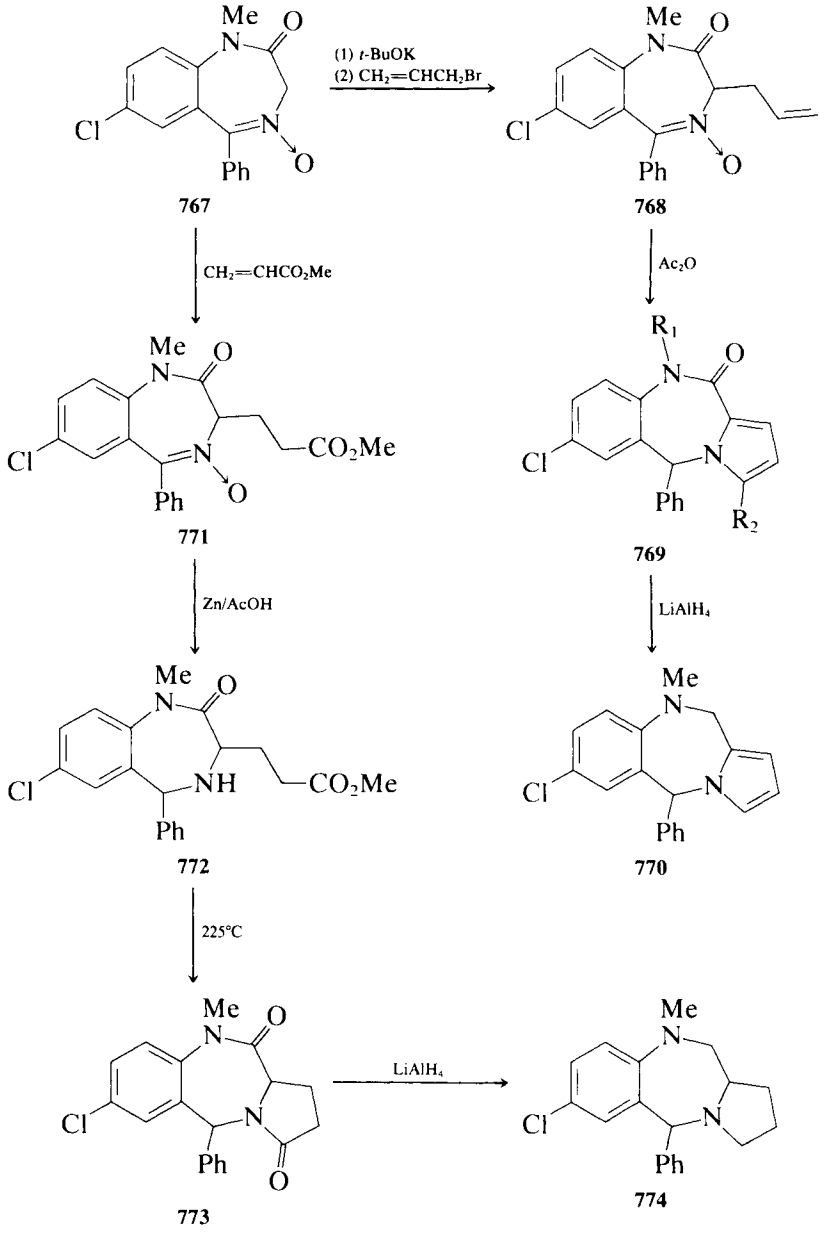
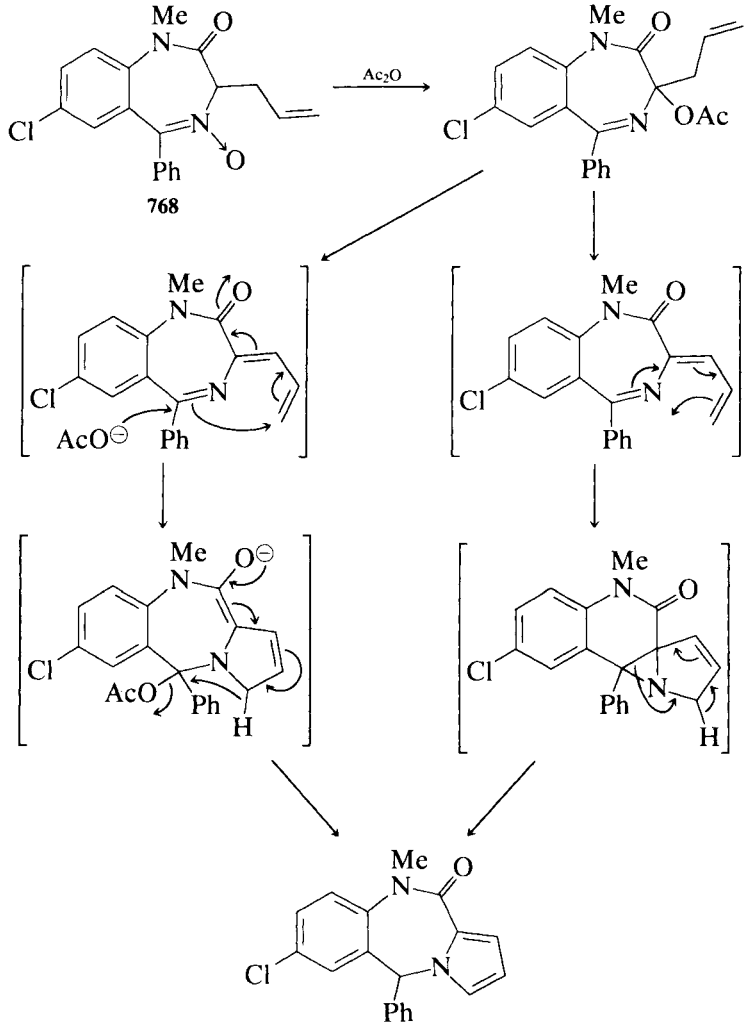

Me
N
O
Cl
N
O
Ph
767
(1) t-BuOK
(2) CH2=CHCH2Br
768
CH2=CHCO2Me
Ac2O
771
769
CO2Me
R1
R2
Zn/AcOH
LiAlH4
NH
772
770
225°C
773
774

**Figure 52**

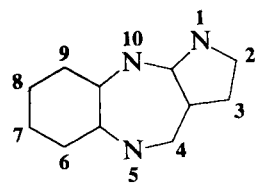



768

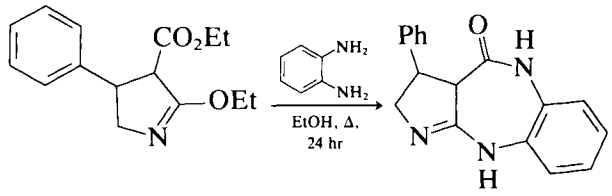
769

Figure 53

## 63. Pyrrolo[2,3-*b*][1,5]benzodiazepines



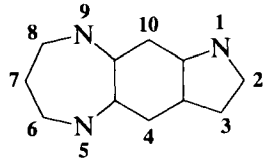
Pyrrolo[2,3-*b*][1,5]benzodiazepines were patented as tranquilizers and hypotensives. Condensation of pyrroline **775** with *o*-phenylenediamine (Eq. 144) effected the synthesis of the tricyclic structure **776.** The corresponding pyridobenzodiazepine system was also prepared (387).



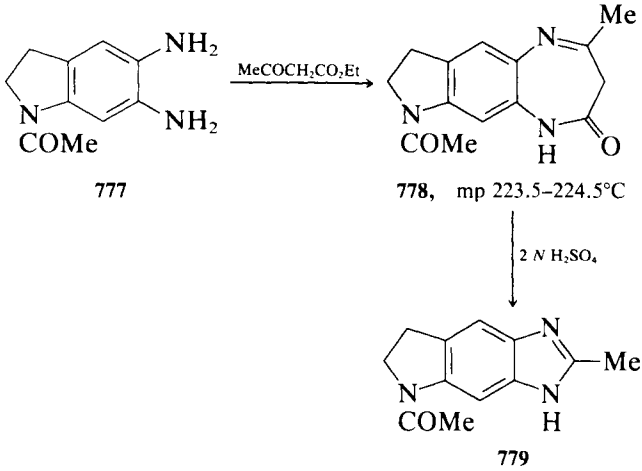

(144)

**775** **776,** mp 229–231°C

## 64. Pyrrolo[2,3-*h*][1,5]benzodiazepines




The pyrrolo[2,3-*h*][1,5]benzodiazepine ring system was formed by condensation of indoline **777** with ethyl acetoacetate in refluxing xylene (Eq. 145) to give **778** in 47% yield. The product had an ultraviolet absorption consistent with its structure [$\lambda_{max}$, nm) (log $\epsilon$): 234 (4.47), 293 (3.90), 320 (4.04)]. Reaction of **778** with 2 *N* sulfuric acid afforded the benzimidazole **779** in 56% yield (388, 389).

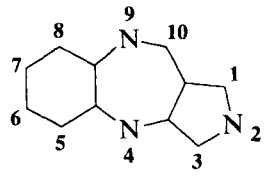



(145)

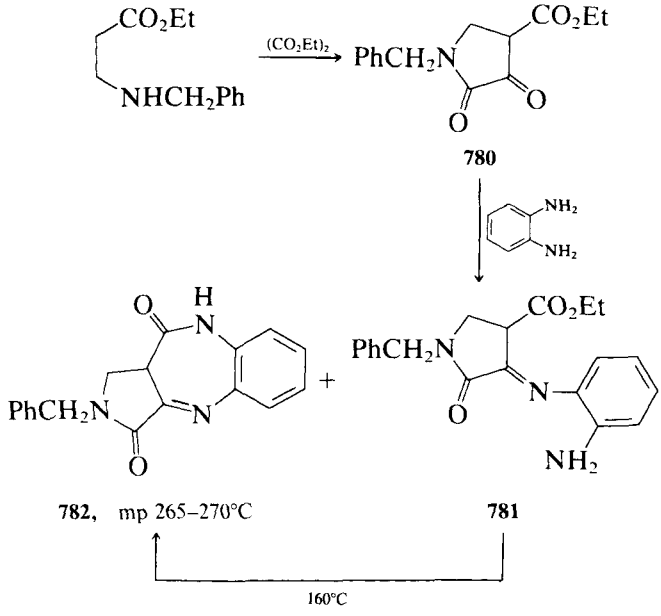
**777** **778,** mp 223.5–224.5°C

**779**

## 65. Pyrrolo[3,4-*b*][1,5]benzodiazepines

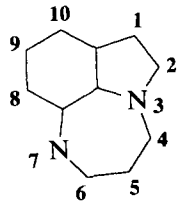


Condensation of ethyl β-benzylaminopropionate with diethyl oxalate (Eq. 146) gave 1-benzyl-4-carbethoxypyrrolidine-2,3-dione (**780**) in 46% yield. Reaction of **780** with *o*-phenylenediamine in refluxing ethanol afforded the imino adduct **781** as well as the benzodiazepine **782** as a minor product. Imine **781** was converted to **782** upon being heated at 160°C. The position of the double bond in **782** was not clearly determined. The product showed characteristic infrared bands at 1630–1680 $cm^{-1}$ (390).

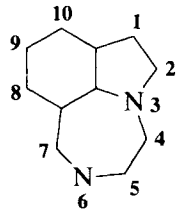


(146)

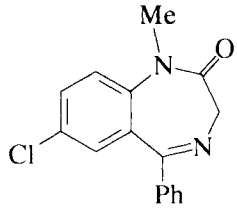
## 66. Pyrrolo[1,2,3-*ef*][1,5]benzodiazepines (see Section XV.43)



## 67. Pyrrolo[3,2,1-*jk*][1,4]benzodiazepines




Work on the pyrrolo[1,2,3-*ef*][1,5]- and pyrrolo[3,2,1-*jk*][1,4]benzodiazepine ring systems was inspired principally by the chemistry of diazepam (**783**). One approach (391) to these analogs (Fig. 54) began with a Schmidt reaction on ketone **784** to yield the ring-expanded diazepines **785** and **786** in a 1:5 ratio for R = H and a 1:1 ratio for R = Cl. An attempted Beckmann rearrangement on ketone **784** was unsuccessful. Lithium aluminum hydride




**783**

reduction gave the amines **787** and **788,** respectively. The amine **788** was converted to the amidino derivative **788a** using 1-amidino-3,5-dimethylpyrazole nitrate (392,404) and to the 6,6-dimethyl quaternary salt with methyl iodide in ether (404). Dehydrogenation of **785** and **786** (R = H) with Pd–C catalyst in refluxing decalin gave the indoles **789** and **790.** Alternatively, compounds **785** and **786** (R = Cl) could be oxidized to **789** and **790** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. Lithium aluminum hydride reduction afforded **793** and **795,** respectively. Oxidation of **795** with activated manganese dioxide (Fig. 55) generated the imine **796.** Under Mannich reaction conditions, compounds **789** and **790** were converted to amines **794** and **797,** respectively. Reduction of **797** led to **798.** Treatment of **786** and **790** with triethyloxonium fluoroborate generated **791** and **799,** which were converted to **792** and **800** by displacement with phenylmagnesium bromide. Reaction of **790** with phosphorus pentachloride followed by phenyllithium afforded the chloro compound **801.** Alkylation of **790** led to the adducts **802,** which were reduced to **803** (391–398).

Because of the low yield of **785** (R = Cl) via **784,** an alternative synthesis was devised. As shown in Fig. 56, reduction of **804** afforded the aminoin-

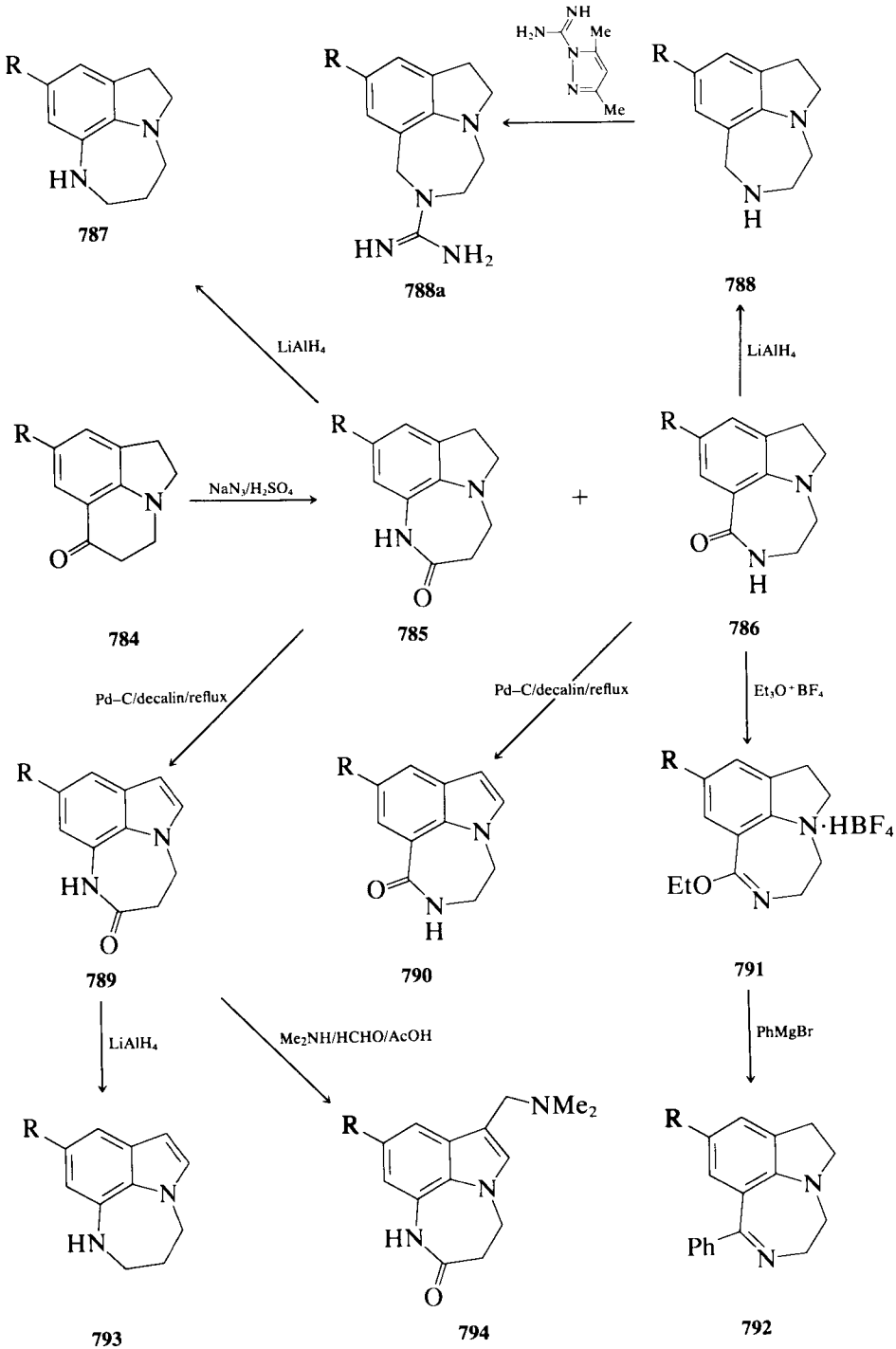

R
HN
787
HN
NH2
788a
NH
H2N
Me
Me
788
LiAlH4
LiAlH4
NaN3/H2SO4
O
784
785
786
Pd–C/decalin/reflux
Pd–C/decalin/reflux
Et3O+BF4
N·HBF4
EtO
789
790
791
LiAlH4
Me2NH/HCHO/AcOH
PhMgBr
NMe2
Ph
793
794
792

**Figure 54**

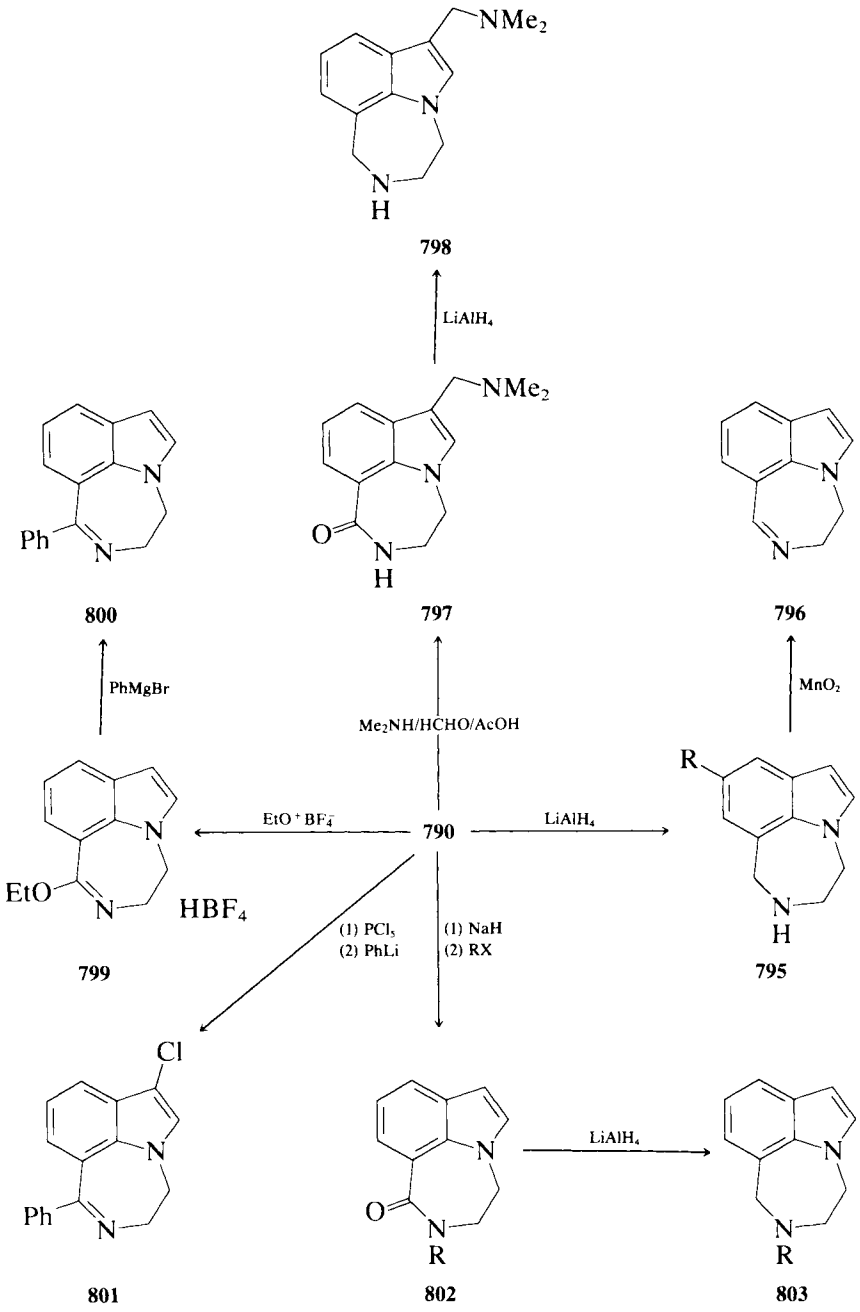

NMe2
N
N
H
798
LiAlH4
NMe2
N
O
N
H
797
Ph
N
N
800
N
796
PhMgBr
Me2NH/HCHO/AcOH
MnO2
R
N
N
H
795
EtO
N
HBF4
799
EtO+ BF4−
790
LiAlH4
(1) PCl5
(2) PhLi
(1) NaH
(2) RX
Cl
Ph
N
N
801
O
N
R
802
LiAlH4
N
N
R
803

**Figure 55**

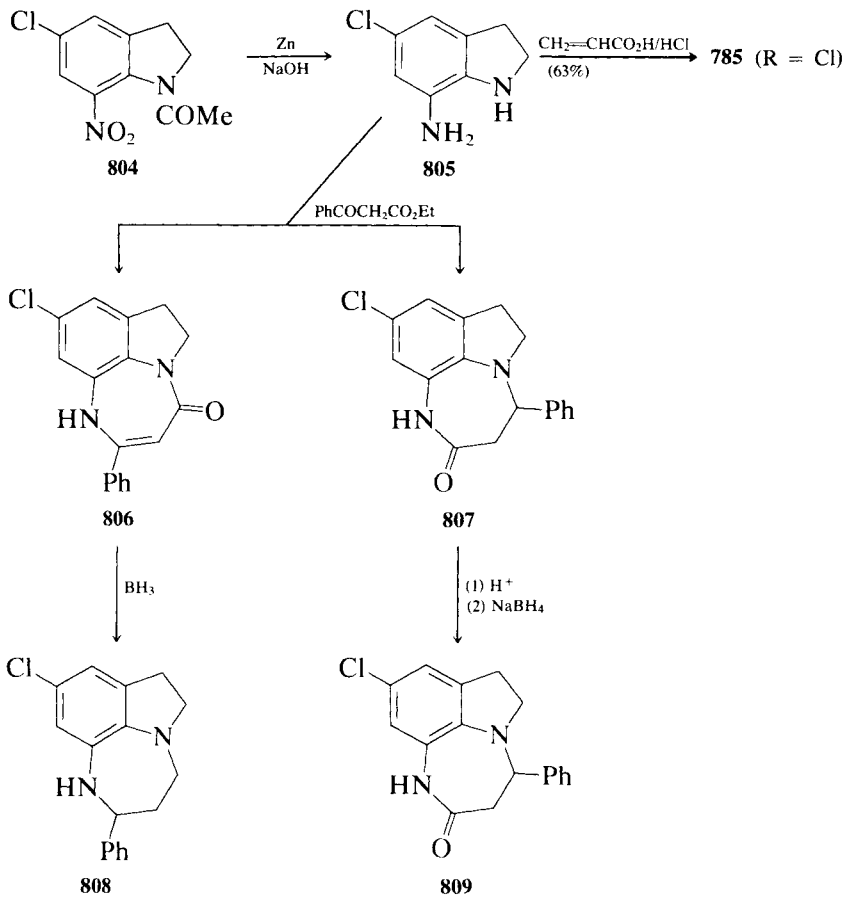



Figure 56

doline **805.** Condensation with acrylic acid led to **785** (R = Cl). Reaction with ethyl benzoylacetate produced the isomeric diazepines **806** and **807,** which were reduced to **808** and **809,** respectively (391,399–401).

Another method for the preparation of 7-phenylpyrrolo[3,2,1-*jk*]-[1,4]benzodiazepines is shown in Fig. 57. Indoline **810** was converted via 1-aminoindoline **811** to the indole **812** by the Fischer indole synthesis with 1-phenyl-2-propanone. Cleavage of **812** with sodium metaperiodate afforded **813,** which was hydrolyzed to **814.** Diazepine ring formation was achieved by reaction of **814** with bromoacetyl bromide followed by ammonia to yield **815.** Reduction led to **818.** Finally, dehydrogenation of **815** and **818** afforded the pairs of products **816** and **817** and **800** and **819,** respectively (391,399–401).

As shown in Fig. 58, ketone **820** was subjected to the Schmidt reaction to yield **821** and **822** in a ratio of 8:1. Other ketones gave only products **821a,**

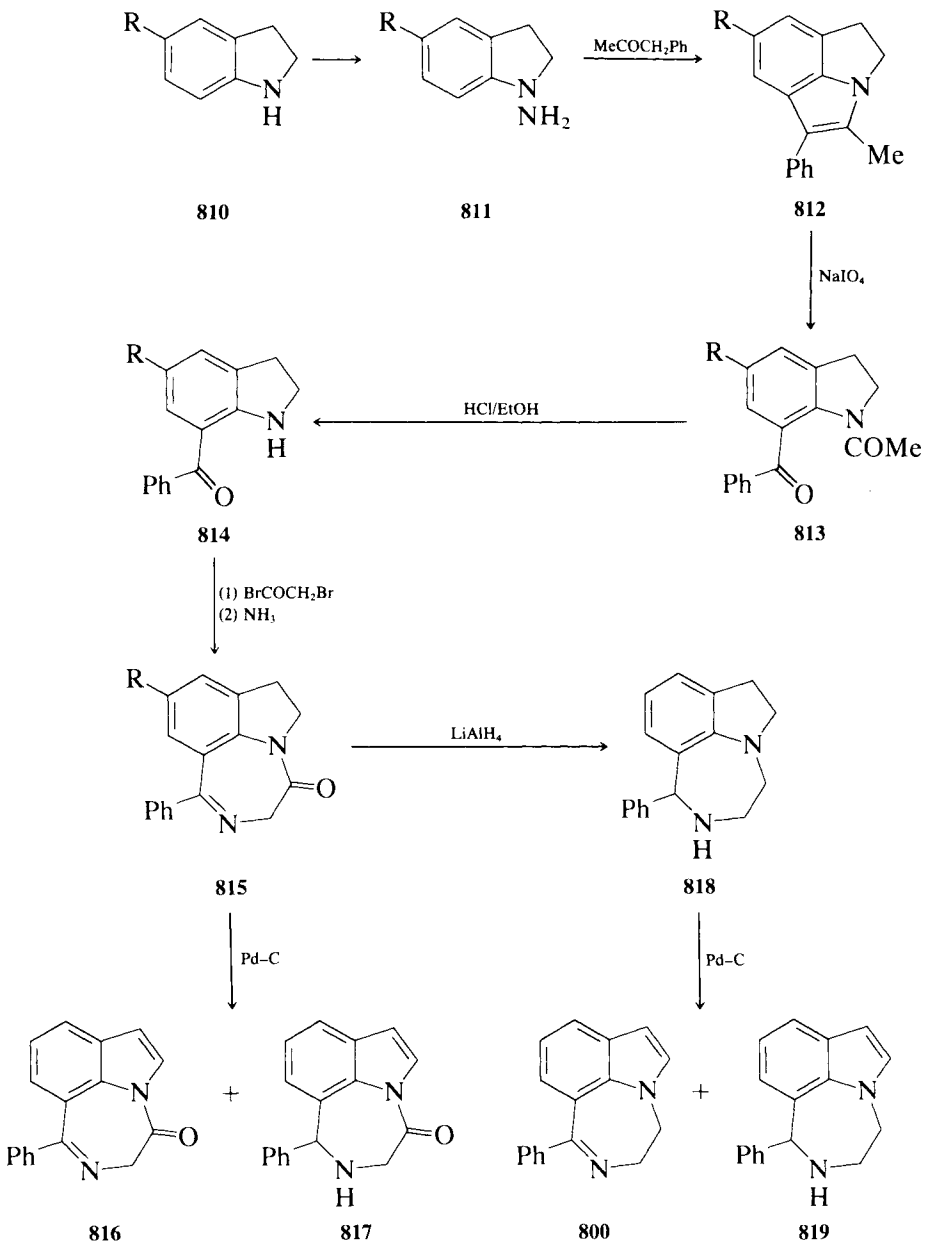
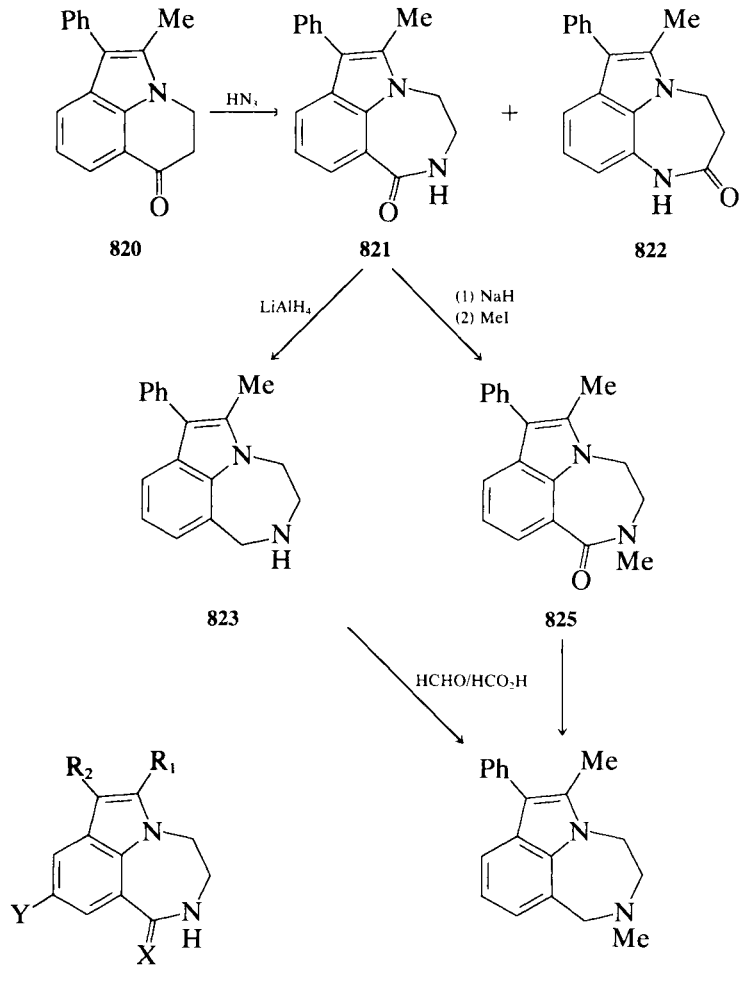

R
N
H
R
N
NH2
MeCOCH2Ph
R
N
Ph
Me
810
811
812
NaIO4
R
N
COMe
Ph
O
HCl/EtOH
R
N
H
Ph
O
813
814
(1) BrCOCH2Br
(2) NH3
R
N
O
Ph
N
LiAlH4
N
Ph
N
H
815
818
Pd-C
Pd-C
N
Ph
N
O
+
N
Ph
N
H
O
N
Ph
N
+
N
Ph
N
H
816
817
800
819

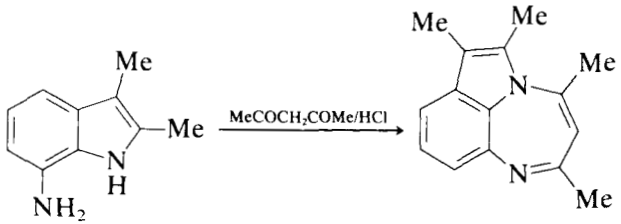
**Figure 57**




| X | Y | $R_1$ | $R_2$ | mp (°C) |
|---|---|---|---|---|
| O | H | Et | Me | 220–224 |
| O | Cl | Me | Me | 239–249 |
| $H_2$ | H | Et | Me | 288–293 (HCl) |

**Figure 58**

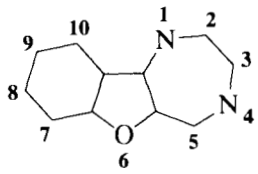
analogous to **821** (402). Conversion of **821** to **824** was achieved via lithium aluminum hydride reduction followed by Eschweiler–Clarke methylation (403). The first synthesis of the fully aromatic skeleton was completed by condensation of indole **826** with acetylacetone (Eq. 147) to generate **827,** whose hydrochloride salt (mp 353–355°C) crystallized in the form of yellow needles with a bright green fluorescence (294).



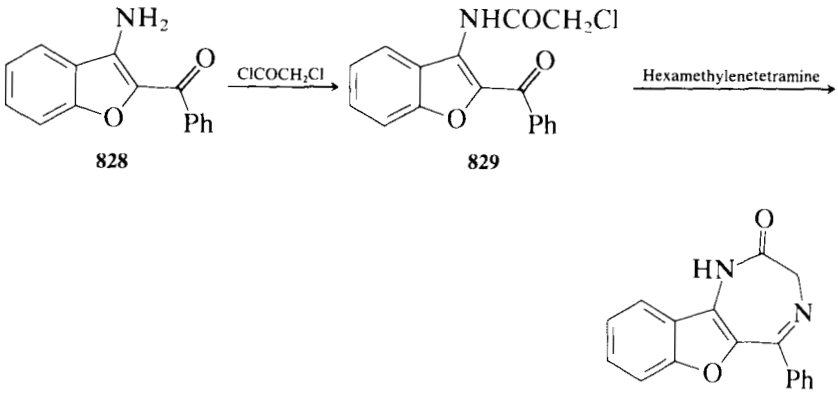

826 827 (147)

A listing of known members of the pyrrolo[1,2,3-*ef*] [1,5] benzodiazepine and pyrrolo[3,2,1-*jk*][1,4]benzodiazepine ring systems is given in Table 83.

## 68. Benzofuro[3,2-*e*][1,4]diazepines (see Section XV.45)




Benzofuro[3,2-*e*][1,4]diazepine **830** was prepared by a typical diazepine-forming procedure (Eq. 148). Thus reaction of 2-benzoyl-3-aminobenzofuran **828** with chloroacetyl chloride generated the intermediate **829** in 79% yield. Treatment of **829** with ethanolic hexamethylenetetramine led to the diazepine **830.** The structure of **830** was verified by ir and proton nmr spectral data (405).




828 829 (148)

830, mp 255°C

TABLE 83. PYRROLO[1,2,3-*ef*][1,5]BENZODIAZEPINES AND PYRROLO-[3,2,1-*jk*][1,4]BENZODIAZEPINES

| Structure | R | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|
| **785** | H | 12.7 | 163–164 | 391–395 |
| **785** | Cl | 6.3 | 169.5–170 | 391,393,395 |
| **786** | H | 60.8 | 151–152.5 | 391–394 |
| **786** | Cl | 62 | 201.5–202 | 391,392,394 |
| **787** | H | 91 | 227–231 | 391–394 |
| **787** | Cl | 72.5 | 77.5–78.5 | 391,392,394 |
| **788** | H | 79.3 | 67–68 | 391–394 |
| **788** | Cl | 74 | 281(dec.) | 391,392,394 |
| **789** | H | 81.5 | 213–214.5 | 391,395,396 |
| **789** | Cl | 53.2 | 234–235 | 391,395,396 |
| **790** | H | 68.3 | 173–174 | 391,395,936 |
| **790** | Cl | 60.8 | 231.5–232.5 | 391,395,396 |
| **791** | | 62.2 | 47.5–49 | 391,397,398 |
| **792** | | 37.1 | 245.5–246.5 | 391,397,398 |
| **793** | H | 75.6 | 79.5–80.5 | 391,395,396 |
| **794** | Cl | 84.2 | 128.5–129.5 | 391,395,396 |
| **794** | | 79.4 | 193–193.5 | 391,395,396 |
| **795** | H | 51 | 62.5–63.5 | 391,395,396 |
| **795** | Cl | 63.8 | 70–71.5 | 391,395,396 |
| **796** | | 73.7 | 171–174 | 391,397 |
| **797** | | 58.8 | 171–172.5 | 391,395,396 |
| **798** | | 82.3 | 67.5–68.5 | 391,395,396 |
| **799** | | 82.7 | 142–143.5 | 391,397,398 |
| **800** | | 43.1 | 275(dec.) | 391,397,398 |
| **801** | | 8.2 | 301.5–304 | 391,397 |
| **802** | Me | 59.5 | 105.5–106.5 | 391,395,396 |
| **802** | $(CH_2)_2NEt_2$ | 75.8 | 168–170 | 391,395,396 |
| **802** | $(CH_2)_3NMe_2$ | 60.7 | 101.5–102.5 | 391,395,396 |
| **803** | Me | 77.4 | 42.5–44 | 391,395,396 |
| **803** | $(CH_2)_2NEt_2$ | 80.2 | 244.5–246.5 | 391,395,396 |
| **803** | $(CH_2)_3NMe_2$ | 91 | 244–246 | 391,395,396 |
| **803** | $(CH_2)_3COC_6H_4F$-*p* | | 90–91 | 395,396 |
| **806** | | 44.3 | 124.5–125.5 | 391,399–401 |
| **807** | | 11.5 | 280–281 | 391,399–401 |
| **808** | | 71.8 | 208.5–209.5 | 391,399–401 |
| **809** | | 65.6 | 183–187 | 391,399–401 |
| **815** | H | 80.7 | 140–141.5 | 391,399–401 |
| **815** | Cl | 81.7 | 116–117.5 | 391,399–401 |
| **815** | $NO_2$ | 51.5 | 157–158.5 | 391,399–401 |
| **816** | | 13.7 | 151.5–152 | 391,399–401 |
| **817** | | 23.8 | 115–117 | 391,399–401 |
| **818** | | 84.7 | 102–103.5 | 391,399–401 |
| **819** | | | 276(dec.) | 391,399–401 |
| **821** | | 75 | 238–239 | 403 |
| **822** | | 9 | 233–234 | 403 |
| **823** | | 74 | 121–122 | 403 |
| **824** | | 72, 64 | 140–145 | 403 |
| **825** | | 90 | 232–233 | 403 |
| **827** | | 88 | 213–213.5 | 294 |

## 69. Furo[2,3-*b*][1,5]benzodiazepines

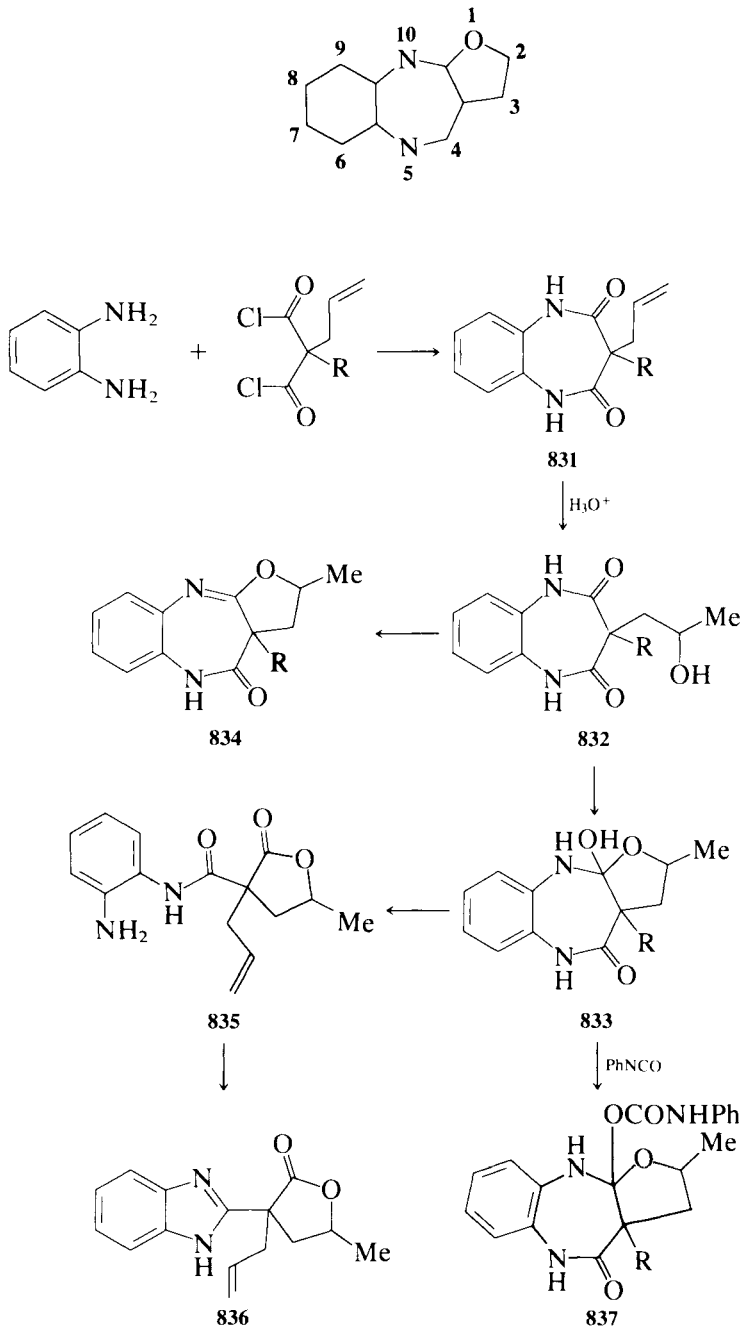
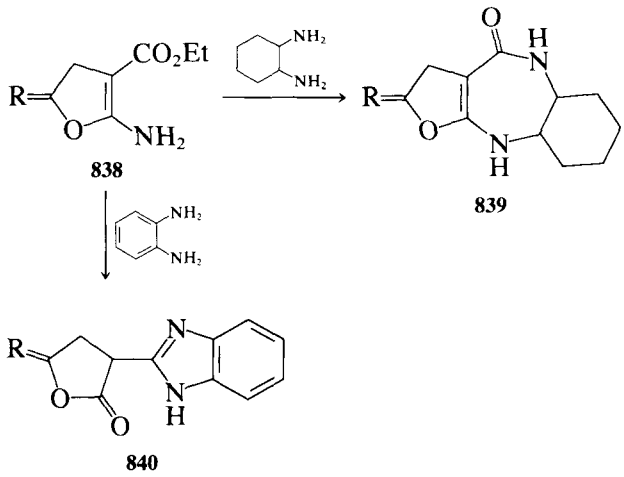



Figure 59

Two routes to furo[2,3-*b*][1,5]benzodiazepines have appeared. One method (Fig. 59) begins with 3-allylbenzodiazepine **831.** Hydration of **831** afforded the 3-(2-hydroxypropyl)benzodiazepine **832,** which cyclized to yield either **833** for small R groups or **834** for bulky ones. By adjusting the reaction times for R = allyl, either **833** (3 min, 90% yield), **835** (30 min, 89% yield), or **836** could be obtained. Reaction of **833** with phenyl isocyanate produced the urethane **837.** These compounds are listed in Table 84 (406,407).

A different approach (Eq. 149) produced reduced derivatives of this system. Condensation of **838** with 1,2-diaminocyclohexane (stereochemistry not specified) generated the tricyclic diazepine **839.** Substitution of *o*-phenylenediamine for diaminocyclohexane produced benzimidazole **840** and no diazepine. Members of this reduced ring system are listed in Table 84 (408).

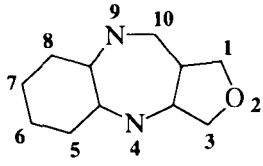



(149)

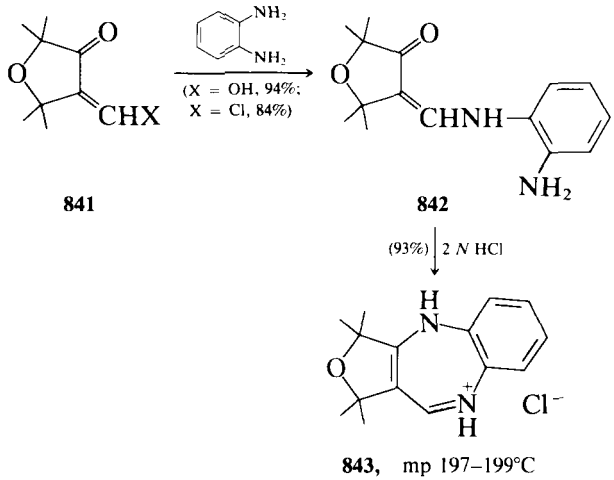
TABLE 84. FURO[2,3-*b*][1,5]BENZODIAZEPINES

| Compound | R | mp (°C) | Yield (%) | Spectra | Refs. |
|---|---|---|---|---|---|
| **833** | Allyl | 88 | 90 | | 406 |
| **837** | Allyl | 145 | | | 406 |
| **834** | Isopropyl | 192 | 86 | | 407 |
| **834** | Ph | 204 | 85 | | 407 |
| **834** | Cyclohexyl | 204 | 90 | | 407 |
| **839** | H, H | 275–278 | 53 | nmr | 408 |
| **839** | H, Me | 193–197 | 36 | nmr | 408 |
| **839** | Me, Me | 205–215 | 27 | nmr | 408 |

## 70. Furo[3,4-*b*][1,5]benzodiazepines



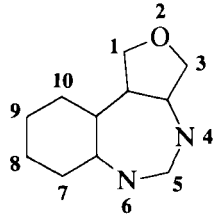
Condensation of ketone **841** with *o*-phenylenediamine (Eq. 150) afforded the adduct **842.** Cyclization to **843** occurred readily in 2 *N* hydrochloric acid (409).




**841** **842** (150)

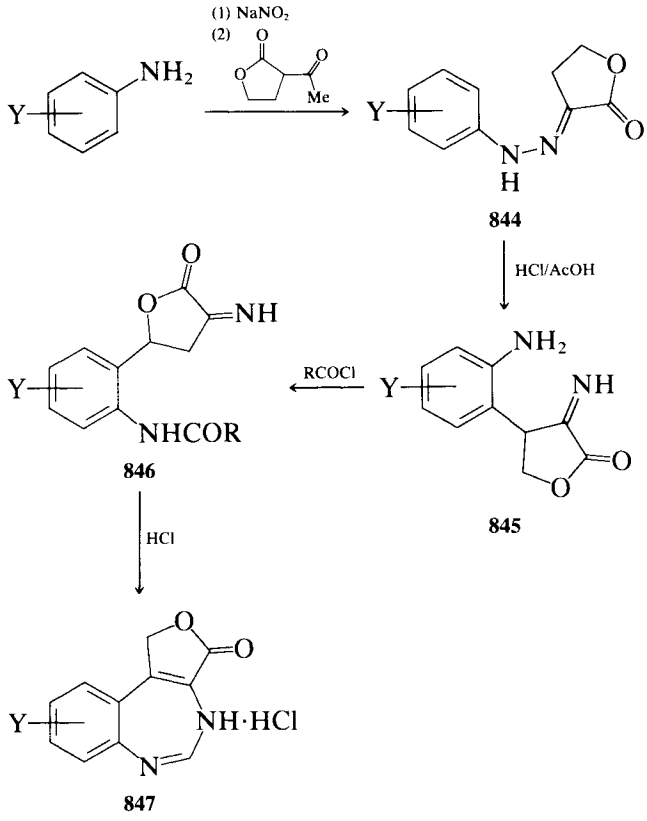
**843,** mp 197–199°C

## 71. Furo[3,4-*d*][1,3]benzodiazepines



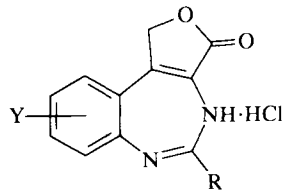
The formation of furo[3,4-*d*][1,3]benzodiazepines occurred unexpectedly when the hydrazones **844** were subjected to the conditions of the Fischer indole synthesis. Instead of the desired indoles, the intermediate furanones

**845** were isolated (Eq. 151). Acylation led to **846,** which cyclized in acid to **847** (410). Other compounds similarly prepared are listed in Table 85 (411). The free bases were not stable. Cyclization of amides **846** failed when R was a $p$-$NO_2C_6H_4$, $m$-$NO_2C_6H_4$, $EtO_2C$, $(CH_3)_3C$, $PhCH_2$, $MeOCH_2CH_2$, or $n$-$C_4H_9NH$ substituent.




(151)

TABLE 85. FURO[3,4-*d*][1,3]BENZODIAZEPINES

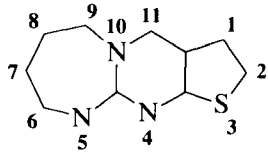



| R | Y | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|
| NHPh | H | 67 | 286–288 | 411 |
| Me | H | 91 | 263–265 | 410,411 |
| Et | H | 83 | 259–262 | 411 |

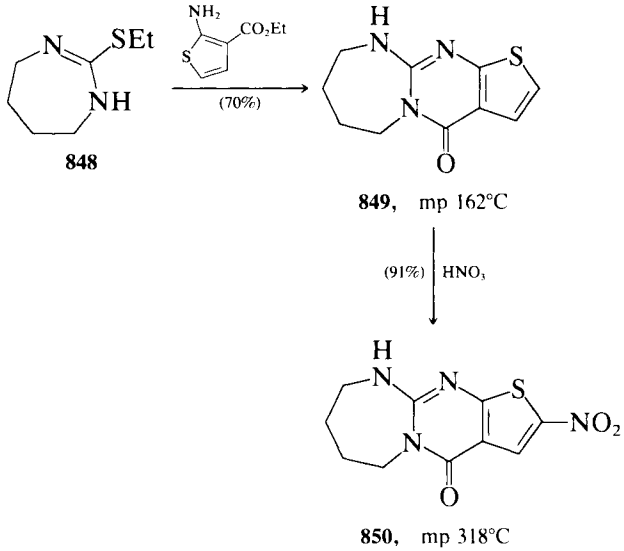
TABLE 85. (*Continued*)

| R | Y | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|
| $C_3H_7$-*n* | H | 86 | 255–257 | 411 |
| Ph | H | 79 | 248–250 | 411 |
| Me | 9-Me | 95 | 283–284 | 411 |
| Et | 9-Me | 86 | 254–256 | 411 |
| $C_3H_7$-*n* | 9-Me | 95 | 272–274 | 411 |
| Me | 9-MeO | 69 | 266–268 | 411 |
| Et | 9-MeO | 84 | 247–249 | 411 |
| $C_3H_7$-*n* | 9-MeO | 91 | 236–238 | 411 |
| Me | 8-MeO | 44 | 285–286 | 411 |
| Et | 8-MeO | 69 | 259–261 | 411 |
| $C_3H_7$-*n* | 8-MeO | 51 | 229–231 | 411 |

## 72. Thieno[2′,3′:4,5]pyrimido[1,2-*a*][1,3]diazepines

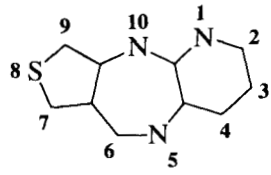



Reaction of 2-amino-3-carbethoxythiophene with **848** in *N*-methylpyrrolidone at 200°C for 30 min (Eq. 152) afforded **849,** which was patented for its anti-inflammatory properties (412,413). Nitration of **849** generated **850,** which was claimed to have trichomonicidal and amoebicidal activity (413).

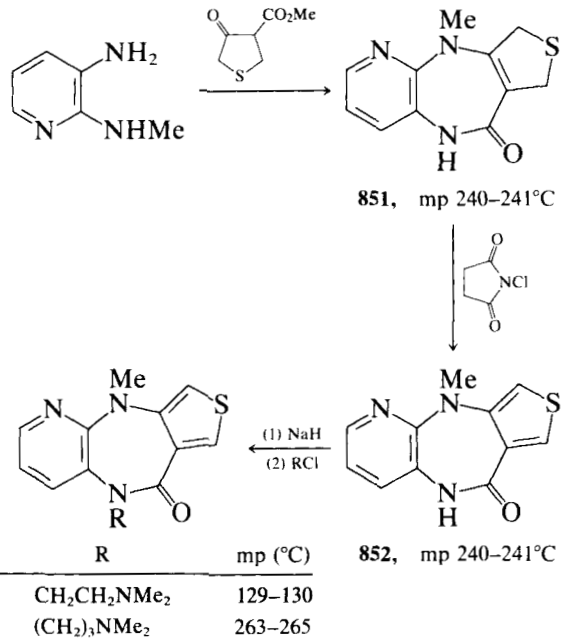



(152)

## 73. Pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepines (see Section XV.46)




Pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepines entered the literature as a minor part of a patent primarily dealing with the corresponding thienobenzodiazepine system. Condensation of 2-methylamino-3-aminopyridine with methyl tetrahydro-4-oxo-3-thiophenecarboxylate in refluxing toluene in a Dean–Stark apparatus resulted in the formation of the tricyclic compound **851** (Eq. 153). Aromatization to **852** was carried out with *N*-chlorosuccinimide in

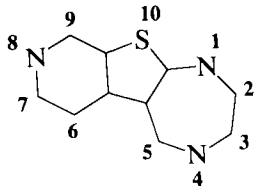



(153)

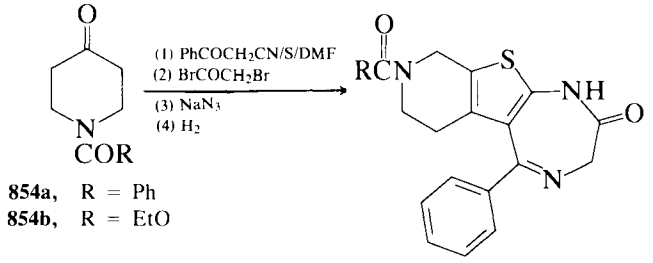
| | R | mp (°C) |
|---|---|---|
| **853a** | $CH_2CH_2NMe_2$ | 129–130 |
| **853b** | $(CH_2)_3NMe_2$ | 263–265 |

pyridine. The final products (**853**) were obtained by alkylation with sodium hydride as the base (414).

## 74. Pyrido[4′,3′:4,5]thieno[2,3-*e*][1,4]diazepines




The chemistry used to prepare pyrido[4′,3′:4,5]thieno[2,3-*e*][1,4]diazepines follows the methodology described for cyclopenta[4,5]thieno[2,3-*e*]-[1,4]diazepines (Fig. 10, Eq. 27). Thus piperidone **854** and phenylacetonitrile were transformed into the target structure **855** (Eq. 154) (60).

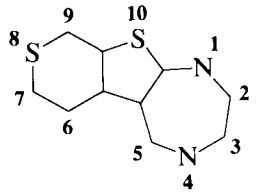



**854a**, R = Ph
**854b**, R = EtO

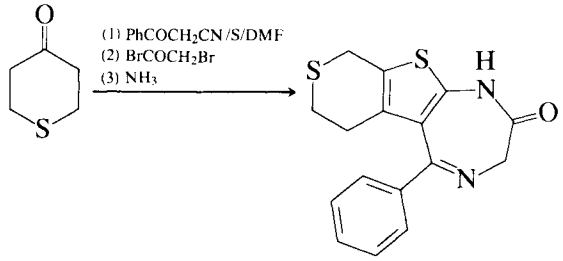
(154)

| | R | mp (°C) |
|---|---|---|
| **855a** | Ph | 213–215 |
| **855b** | EtO | 223–225 |

## 75. Thiopyrano[4′,3′:4,5]thieno[2,3-*e*][1,4]diazepines



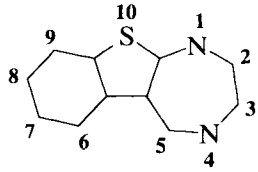

The sole example of the thiopyrano[4′,3′:4,5]thieno[2,3-*e*][1,4]diazepine ring system was prepared according to the procedure outlined in Fig. 10. Thus the starting materials tetrahydrothiopyran-4-one and phenylacetonitrile were elaborated to the tricyclic compound **856** (Eq. 155) (60).




(155)

**856,** mp 256–259°C

## 76. [1]Benzothieno[2,3-*e*][1,4]diazepines (see Section XV.48)




The [1]benzothieno[2,3-*e*][1,4]diazepine ring system was developed as part of a search for 1,4-benzodiazepine derivatives with psychotherapeutic properties similar to those of diazepam. One member, bentazepam (**860**; R = phenyl), is undergoing clinical trial. The synthesis of these compounds is described in Fig. 60. The key intermediate, **858,** prepared via **857** by established methods (59,60) (see Fig. 10 for analogous procedure), was transformed to **859** by acylation with an appropriate acid chloride. The method of conversion of **859** to **860** varied with the substituent X. For X = I, addition of ammonia led to **860.** For X = phthalimido, hydrazinolysis produced **860.** For X = azide, reduction with hydrogen afforded **860** (58,60,415–418). Alternatively, **858** could be converted directly to **860** by condensation with oxazolidine-2,5-dione. Substitution of 4-methylcyclohexanone for cyclohexanone at the start of the synthesis led ultimately to the 8-methyl derivative **864** (58,60). Reaction of **859** (X = halogen) with hydroxylamine afforded the diazepine oxide **862** (60). Alkylation of **860** or **862** with sodium hydride and an alkyl halide generated **861** and **863,** respectively (58,60,415,416). The Pummerer reaction transformed **863** to **861a,** which could be hydrolyzed to **861b** (60).

Derivatives of the basic structure **860** were prepared as shown in Fig. 61. Reduction led to **865,** which on treatment with methyl isocyanate yielded the carbamate **866** (419). Amide **860** was converted to thione **867** with phosphorus pentasulfide, and further reaction with piperidine afforded **868** (420). Addition of hydrazine led to **869,** which was converted to the triazole derivatives **870** and **871** with phosgene and orthoesters, respectively (35a,41).

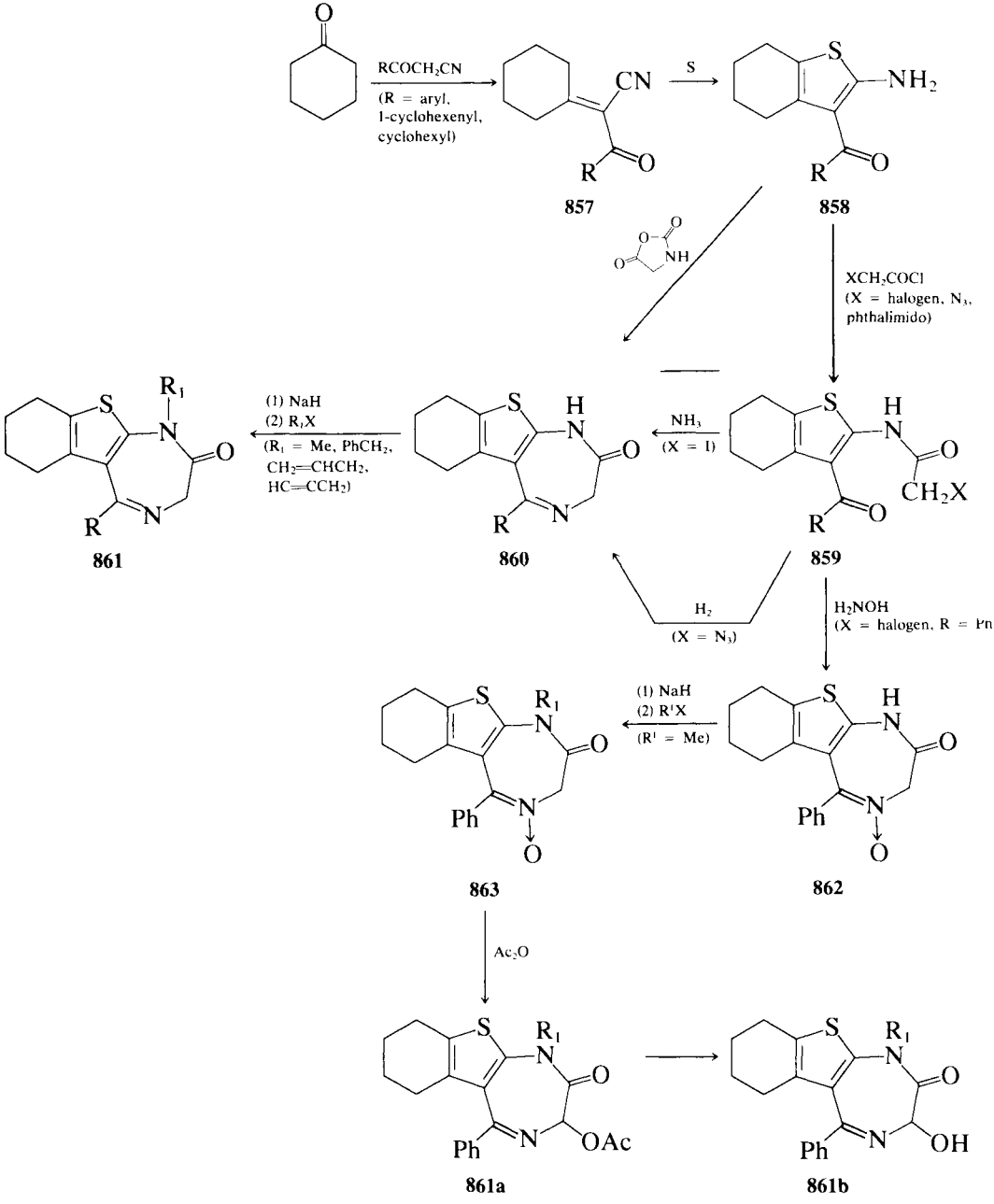
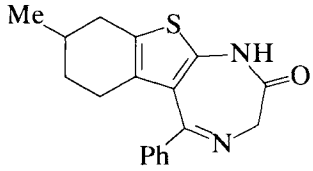

RCOCH2CN
(R = aryl, 1-cyclohexenyl, cyclohexyl)
CN
S
NH2
857
858
XCH2COCl
(X = halogen, N3, phthalimido)
(1) NaH
(2) R1X
(R1 = Me, PhCH2, CH2=CHCH2, HC≡CCH2)
NH3
(X = I)
859
860
861
H2
(X = N3)
H2NOH
(X = halogen, R = Ph)
(1) NaH
(2) R1X
(R1 = Me)
862
863
Ac2O
861a
861b

**Figure 60**



**864**

Reaction of **872** with *t*-butyl hypochlorite (Eq. 156) generated the 1-chloro adduct **873.** Thermal rearrangement led to **874,** which was transformed in low yield to the cyclohexenyl derivative **875** (60).

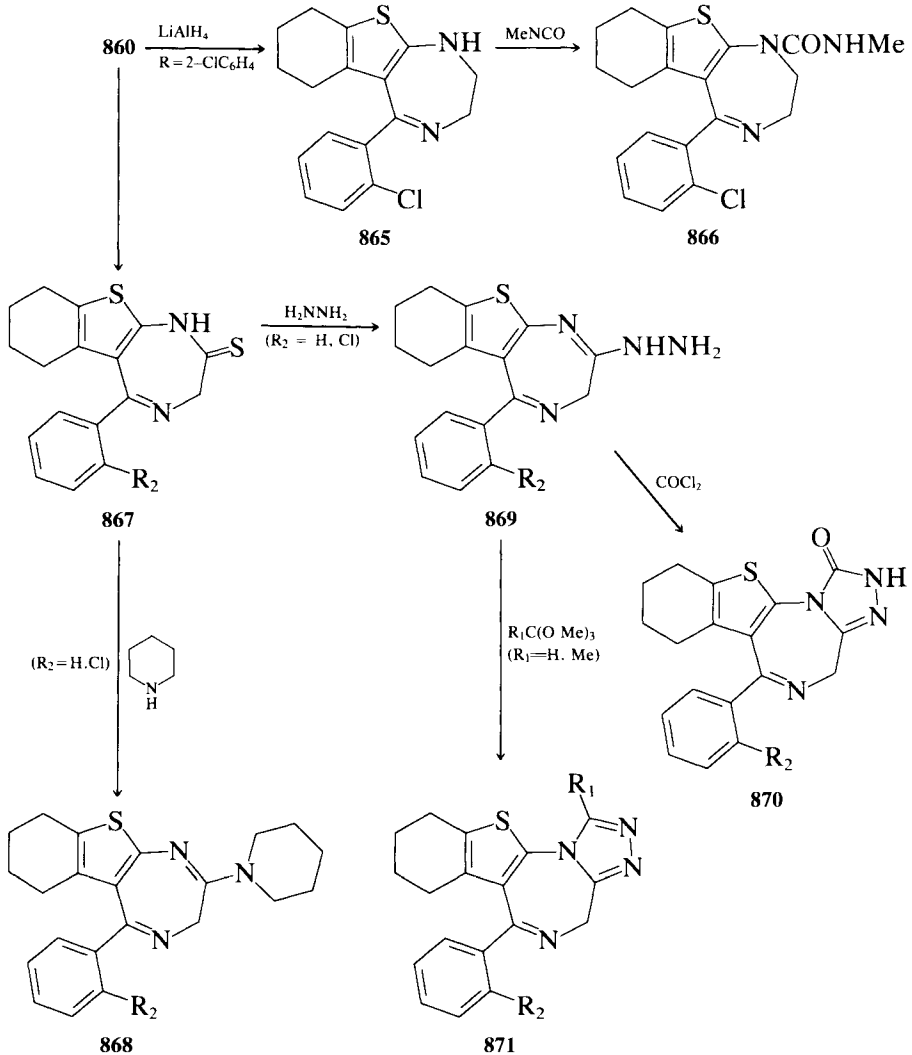
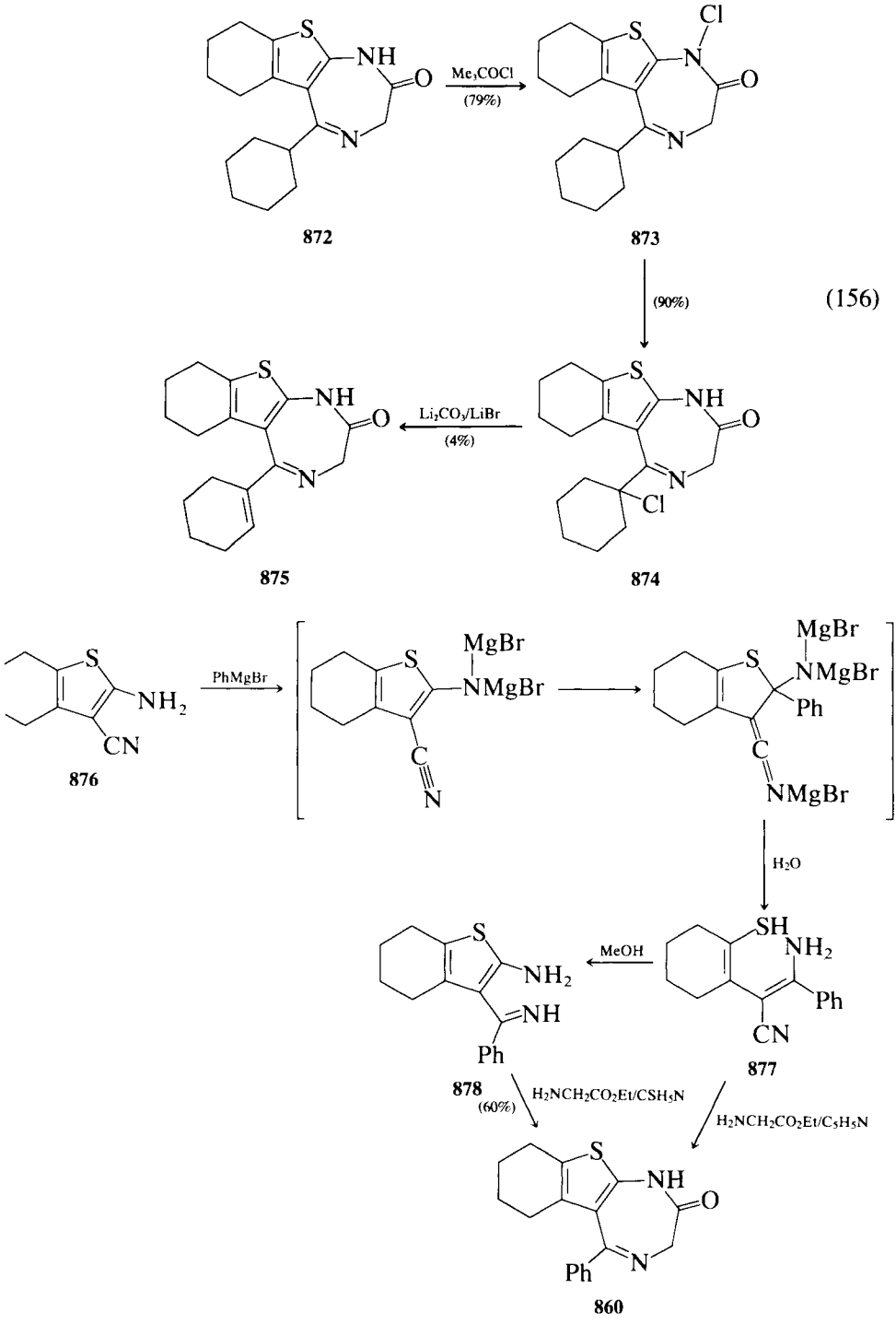


**Figure 61**




(156)

**Figure 62**

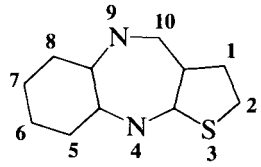
TABLE 86. [1]BENZOTHIENO[2,3-*e*][1,4]DIAZEPINES

| Structure | R | $R_1$ | $R_2$ | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| **860** | Ph | | | 60 | 249–250 | 58,60,415–418,421 |
| **860** | *o*-$FC_6H_4$ | | | 16 | 234–236 | 60,416 |
| **860** | *o*-$ClC_6H_4$ | | | 11 | 267–269 | 58,60 415,416 |
| **860** | *o*-$MeC_6H_4$ | | | 22 | 275–276 | 60 |
| **860** | *o*-$MeOC_6H_4$ | | | | 245–246 | 58,60,415 |
| **860** | *m*-$ClC_6H_4$ | | | 8 | 189–191 | 60,417,418 |
| **860** | *m*-$MeOC_6H_4$ | | | 20 | 183–186 | 60 |
| **860** | *m*-$CF_3C_6H_4$ | | | 69 | 217 | 58,415 |
| **860** | *p*-$ClC_6H_4$ | | | | 263–264 | 58,60, 415,418 |
| **860** | *p*-$MeOC_6H_4$ | | | 42 | 256–258 | 60 |
| **860** | 2-Naphthyl | | | 15 | 249–250 | 60 |
| **860** | 2-Thienyl | | | 15 | 252–254 | 60,416 |
| **860** | 2-Furyl | | | 26 | 233–235 | 60 |
| **860** | Cyclohexyl | | | 31 | 242–244 | 60 |
| **860** | 1-Cyclohexenyl | | | 4 | 225–227 | 60 |
| **861** | Ph | Me | | 70 | 129–131 | 58,60, 415,416 |
| **861** | Ph | $CH_2$–  | | 55 | 170–172 | 60 |
| **861** | Ph | $(CH_2)_3NMe_2$ | | 94 | 137–140 | 60 |
| **861** | Ph | $(CH_2)_2NEt_2$ | | 95 | 259–261 | 60 |
| **861** | 2-Furyl | $(CH_2)_2NEt_2$ | | 56 | 228–230 | 60 |
| **861** | *o*-$MeC_6H_4$ | H | | 26 | 231–233.5 | 60 |
| **861** | Ph | H | OAc | 14 | 288–290 | 60 |
| **861** | Ph | Me | OAc | 83 | 182–184.5 | 60 |

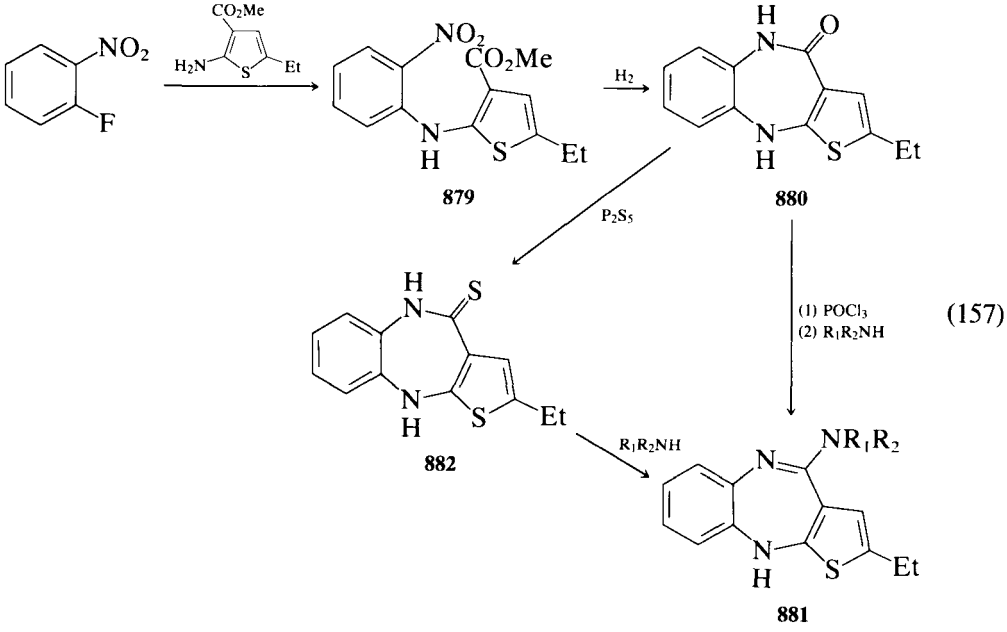
| | | | | | | |
|---|---|---|---|---|---|---|
| **861** | Ph | Me | OH | 64 | 185–186 | 60 |
| **861** | *o*-$ClC_6H_4$ | Me | H | 87 | 137 | 58,415 |
| **861** | *o*-$MeOC_6H_4$ | Me | H | 88 | 148–149 | 58,415 |
| **861** | *m*-$CF_3C_6H_4$ | Me | H | 77 | 141–141.5 | 58,415 |
| **861** | Ph | $CH_2CH{=}CH_2$ | H | 71 | 139–140 | 58 |
| **861** | Ph | $CH_2C{\equiv}CH$ | H | 70 | 137–138 | 58 |
| **861** | Ph | *n*-$C_4H_9$ | H | 82 | 101–102 | 58 |
| **861** | Ph | $CH_2Ph$ | H | 84 | 121–122 | 58 |
| **862** | Ph | | | 62 | 277–278 | 60 |
| **863** | Ph | Me | | 77 | 177–179 | 60 |
| **864** | | | | 83 | 227–229 | 58,60 |
| **865** | | | | | 228–229 | 419 |
| **866** | | | | | 190–191 | 419 |
| **867** | | | H | 50 | 265–266 | 35a,60 |
| **867** | | | Cl | | 235 | 35a,420 |
| **868** | | | | | 211–213 | 420 |
| **869** | | | H | | 212–213 | 35a |
| **869** | | | Cl | | 212–213 | 35a |
| **870** | | | | | 252–254 | 41 |
| **871** | | H | Cl | | 214–215 | 35a |
| **871** | | Me | Cl | | 120–124 | 35a |
| **871** | | H | H | | 222–223 | 35a |

An alternative synthesis of bentazepam (**860**) was achieved from aminothiophene **876** (421). Reaction with excess phenylmagnesium bromide afforded **877**, possibly via 1,4-addition of a phenyl group. Conversion of **877** to bentazepam was carried out as shown in Fig. 62 (421). Known members of the ring system are listed in Table 86.

## 77. Thieno[2,3-*b*][1,5]benzodiazepines (see Section XV.51)



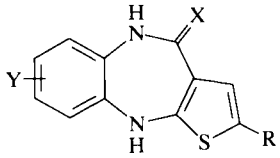

Members of the thieno[2,3-*b*][1,5]benzodiazepine ring system were patented for their neuroleptic activity and were prepared as shown in Eq. 157. Condensation of *o*-fluoronitrobenzene with 2-amino-3-carbomethoxy-5-ethylthiophene afforded **879**, which was converted to **880** by catalytic reduction of the nitro group followed by base-induced cyclization. Compounds **881** were prepared by treatment of **880** with titanium tetrachloride and an




(157)

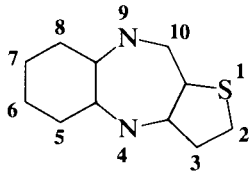
amine (usually 1-methylpiperazine), by treatment of **880** with phosphoryl chloride followed by the amine, or via thione **882** by reaction with the amine. Additional amide and thioamide derivatives are listed in Table 87, and amidino derivatives are given in Table 88 (422).

TABLE 87. AMIDE AND THIOAMIDE DERIVATIVES ON THIENO-[2,3-*b*][1,5]BENZODIAZEPINES



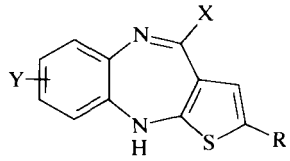
| R | X | Y | mp (°C) |
|---|---|---|---|
| 2-Et | O | 7-F | 210–212 |
| 2-Et | O | 6.8-$F_2$ | 230–232 |
| 2-Et | O | 6-F | 255–257 |
| 2-Et | O | 7-Cl | 216–218 |
| 2-Et | O | 7-$NH_2$ | 230 |
| 2-Et | O | 6-Me | 205–207 |
| 2-Et | O | 7-$SO_2NMe_2$ | 258–260 |
| 2-Et | O | 7-$NO_2$ | 264–266 |
| H | O | 7-F | 240 |
| 2,3-$(CH_2)_4$ | O | 7-F | 238 |
| 2-Et | O | 6,7-$F_2$ | 290 |
| 2-Ph | O | 7-F | 250–252 |
| 2-Me | O | 7-F | 250–252 |
| 2-Et | O | H | 218–220 |
| 2-Et | O | 7-NHAc | 264 |
| 2-Et | S | 7-F | 203–206 |
| 2-Et | S | H | 236 |
| 1-$COCH_3$, 2-Et | O | 7-F | 215–218 |

## 78. Thieno[3,2-*b*][1,5]benzodiazepines (see Section XV.53)



Thieno[3,2-*b*][1,5]benzodiazepines, patented as neuroleptics, were prepared by condensation of *o*-fluoronitrobenzene with 3-amino-2-carbomethoxythiophene (Eq. 158). The intermediate **883** was converted to **884** by catalytic reduction of the nitro group followed by cyclization with base. The

TABLE 88. AMIDINE DERIVATIVES OF THIENO[2,3-*b*][1,5]BENZODIAZEPINES



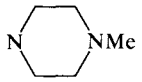
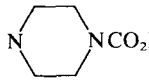
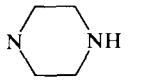
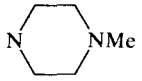
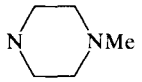
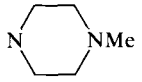
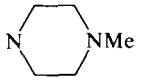
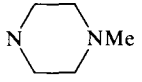
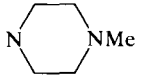
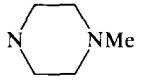
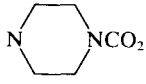
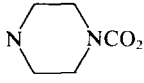
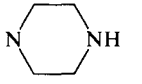
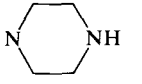
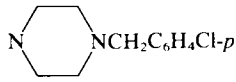
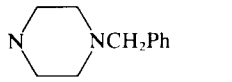
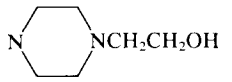
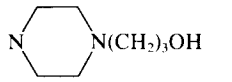
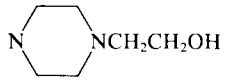
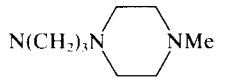
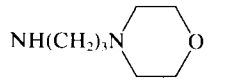
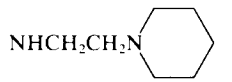
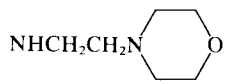
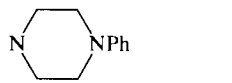
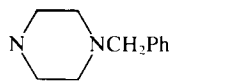
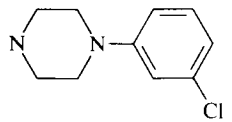
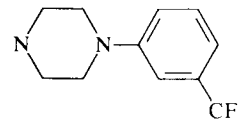
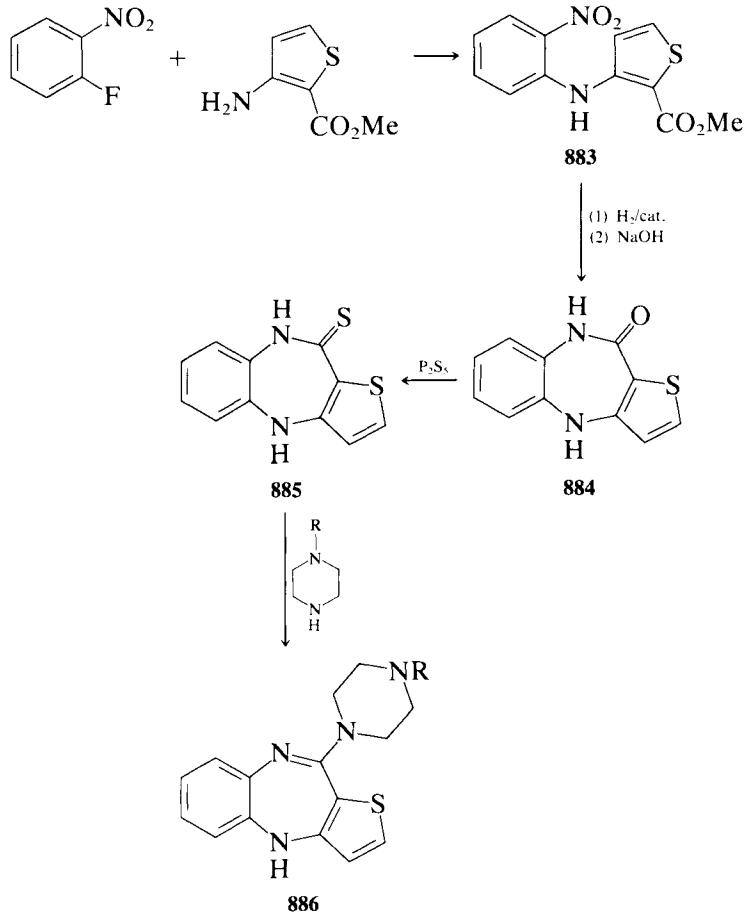
| R | Y | X | mp (°C) | Salt |
|---|---|---|---|---|
| 2-Et | 7-F |  | 175–177 | |
| 2-Et | 7-F |  | 168–171 | |
| 2-Et | 7-F |  | 138–140 | |
| 2-Et | H |  | 195–197 | |
| 2-Et | 6,8-$F_2$ |  | 243–246 | |
| 2-Et | 7-Cl |  | 235–240 | |
| 2-Et | 6-Me |  | 177–179 | |
| 2-Et | 7-$SO_2NMe_2$ |  | 225–227 | |
| 2-Me | 7-F |  | 160–162 | |
| 2-Et | 6,7-$F_2$ |  | 172 | |
| 2-Et | H |  | 169 | |
| 2-Et | 7-Cl |  | 155–158 | |
| 2-Et | H |  | 170–171 | |
| 2-Et | 7-Cl |  | 167–169 | |

TABLE 88. *(Continued)*

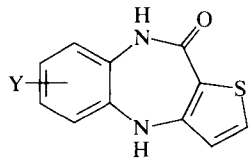
| R | Y | X | mp (°C) | Salt |
|---|---|---|---|---|
| 2-Et | 7-F |  | 166–168 | |
| 2-Et | 7-F |  | 79–80 | |
| 2-Et | 7-F |  | 173–175 | |
| 2-Et | 7-F |  | 145–148 | |
| 2-Et | H |  | 175–176 | |
| 2-Et | 7-F |  | 181 | |
| 2-Et | 7-F | $NH(CH_2)_3NMe_2$ | 193–195 | Dimaleate |
| 2-Et | 7-F |  | 182–186 | Dimaleate |
| 2-Et | 7-F | $NHCH_2CH_2OH$ | 196–198 | Maleate |
| 2-Et | 7-F | $NHCH_2CH_2NMe_2$ | 183–184 | Maleate |
| 2-Et | 7-F | $NH(CH_2)_3OH$ | 174–175 | Maleate |
| 2-Et | 7-F |  | 184–185 | Fumarate |
| 2-Et | 7-F |  | 189–203 | Fumarate |
| 2-Et | 7-F |  | 154–156 | |
| 2-Et | 7-F |  | 265–270 | |
| 2-Et | 7-F |  | 250–260 | HCl |
| 2-Et | 7-F |  | 184–187 | HCl |

target products **886** were prepared from **884** via thione **885** by reaction with a 4-substituted piperazine. The intermediate compounds are recorded in Table 89 and the products are listed in Table 90 (422).



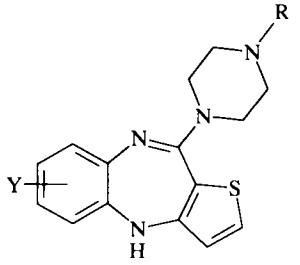

(158)

TABLE 89. THIENO[3,2-*b*][1,5]BENZODIAZEPIN-10-ONES



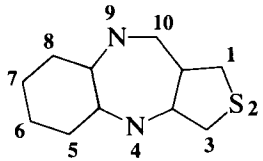

| Y | mp (°C) |
|---|---|
| H | 226 |
| 7-F | 225–230 |
| 7-Cl | 255–256 |

TABLE 90. 10-(1-PIPERAZINYL)THIENO[3,2-*b*][1,5]BENZODIAZEPINES



| Y | R | mp (°C) |
|---|---|---|
| H | Me | 202–206 |
| 7-F | Me | 206–208 |
| 7-Cl | Me | 225–226 |
| H | $CO_2Et$ | 166 |
| 7-F | $CO_2Et$ | 162–164 |
| H | H | 203–206 |
| 7-F | H | 165–167 |
| H | $(CH_2)_3OH$ | 172–173 |
| 7-F | $(CH_2)_3OH$ | 138–140 |
| 7-F | $(CH_2)_2OH$ | 205–210 |
| H | $CH_2Ph$ | 198–200 |
| 7-F | $CH_2Ph$ | 180–182 |

## 79. Thieno[3,4-*b*][1,5]benzodiazepines (see Section XV.55)



Several entries into the thieno[3,4-*b*][1,5]benzodiazepine ring system were achieved as summarized in Fig. 63. Condensation of *o*-phenylenediamine with methyl 4-oxotetrahydrothiophene-3-carboxylate yielded **887.** By starting with *N*-methyl- or *N*-ethyl-*o*-phenylenediamine, the corresponding 4-methyl or 4-ethyl analogs of diazepines **887** were obtained. These compounds are listed in Table 91. Aromatization occurred on treatment of **887** with *N*-chlorosuccinimide in pyridine or with chloranil. Alkylation of **888** led to the 9-substituted derivatives **889.** These compounds are claimed to have analgetic and antidepressant properties (414,423).

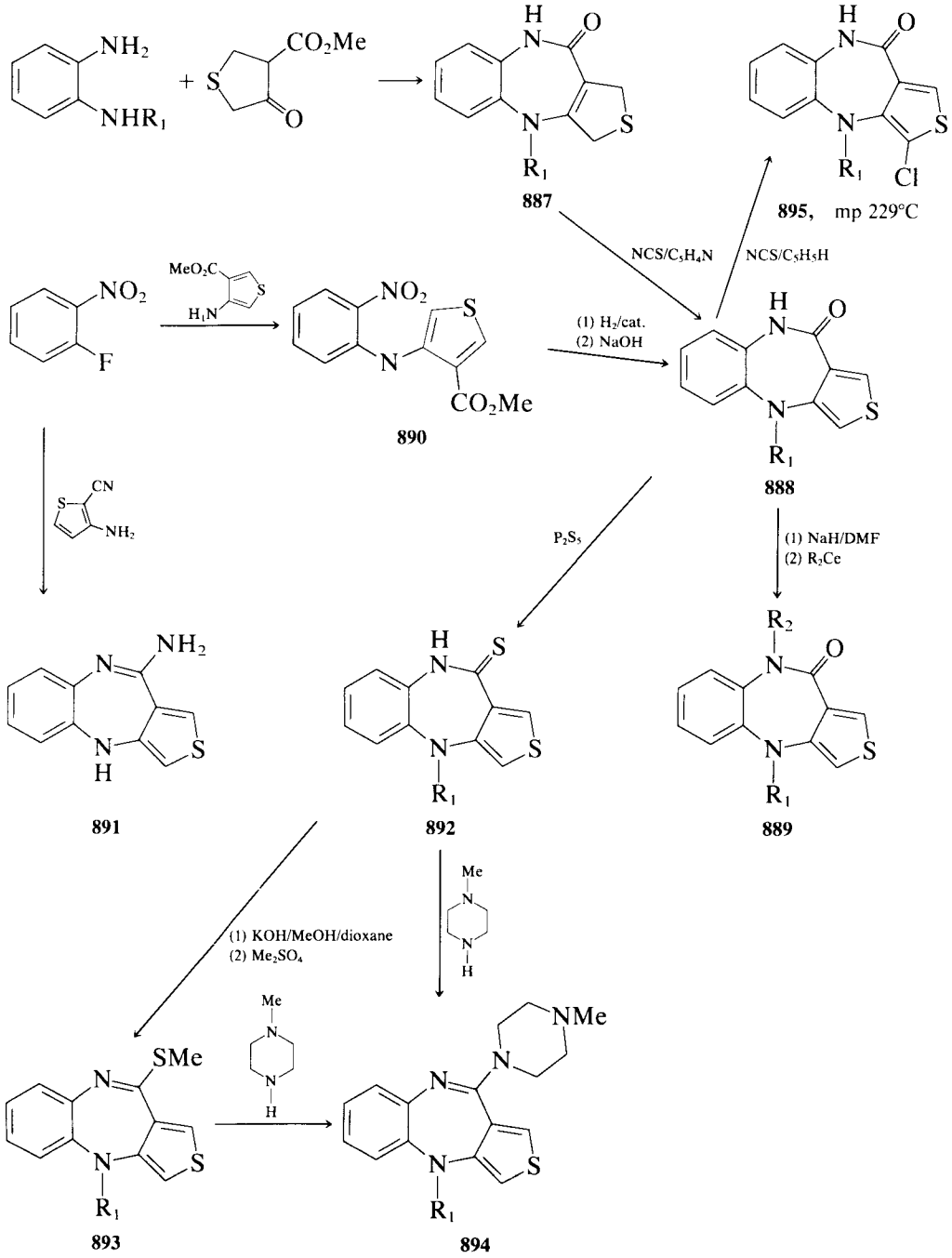
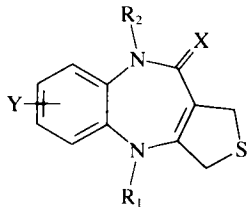

NH2
NHR1
CO2Me
O
S
H
N
O
R1
887
NCS/C5H4N
NCS/C5H5H
895, mp 229°C
Cl
MeO2C
H2N
NO2
F
890
CO2Me
(1) H2/cat.
(2) NaOH
888
CN
NH2
P2S5
(1) NaH/DMF
(2) R2Ce
R2
891
892
889
(1) KOH/MeOH/dioxane
(2) Me2SO4
Me
SMe
NMe
893
894

**Figure 63**

TABLE 91. 1,3-DIHYDROTHIENO[3,4-*b*][1,5]BENZODIAZEPIN-10-ONES AND -IMINES

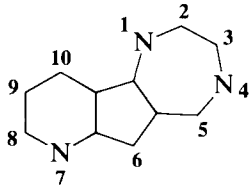


| $R_1$ | $R_2$ | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|---|
| H | H | O | H | 225–230 | 414,422,423 |
| Me | H | O | H | 196–198 | 414 |
| Et | H | O | H | 195–197 | 414 |
| Me | H | O | 6,7-$Me_2$ | 250–252 | 414 |
| Me | H | O | 6,7-$Cl_2$ | 281–283 | 414 |
| H | H | NH | H | 230–240 | 422 |
| H | H | NH | 6-$CF_3$ | 200–210 | 422 |

An alternate route to **888** involved nucleophilic substitution of *o*-fluoronitrobenzene with 3-amino-4-carbomethoxythiophene to generate **890,** followed by catalytic reduction of the nitro group and cyclization in base. Use of 3-amino-4-cyanothiophene in this reaction led directly to the 10-aminodiazepine **891.** Treatment of **888** with *N*-chlorosuccinimide led to the 3-chloro derivative **895.** These products are listed in Table 92 (414,422–424).

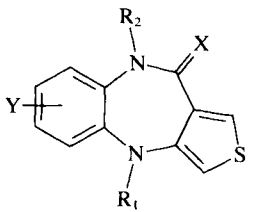
Treatment of **888** with phosphorus pentasulfide led to thione **892,** which could be converted directly to **894** by condensation with amines, usually 1-methylpiperazine. In addition, the transformation of **892** to **894** could be carried out via **893,** obtained from **892** by methylation. These and related compounds, patented for neuroleptic activity, are listed in Table 93 (422,424).

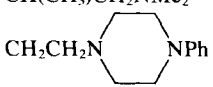
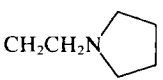
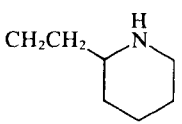
## 80. Pyrido[2′,3′:4,5]cyclopenta[1,2-*e*][1,4]diazepines



As part of an investigation of the chemistry of 6-acyl-5H-pyrindine-5,7-

TABLE 92. THIENO[3,4-*b*][1,5]BENZODIAZEPIN-10-ONES AND -THIONES



| $R_1$ | $R_2$ | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|---|
| H | H | O | H | 237–239 | 414,422,423 |
| Me | H | O | H | 225–226 | 414,423 |
| Me | $(CH_2)_2NMe_2$ | O | H | 147–149 | 414,423 |
| Me | $(CH_2)_3NMe_2$ | O | H | 52–56 | 414 |
| Me | $(CH_2)_2NEt_2$ | O | H | 92–93 | 414 |
| Me | $CH(CH_3)CH_2NMe_2$ | O | H | 280–282 (HCl) | 414 |
| Me |  | O | H | 180–183 (2HCl) | 414 |
| Et | H | O | H | 201–202 | 414 |
| Me |  | O | H | 139–141 | 414 |
| Me |  | O | H | 84–88 | 414 |

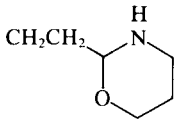
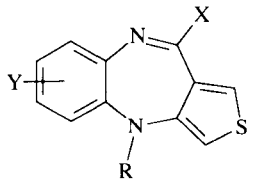
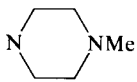
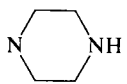
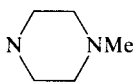
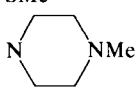
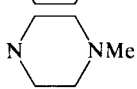
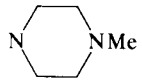
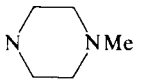
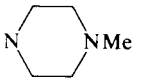
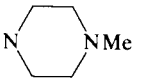
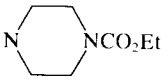
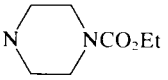
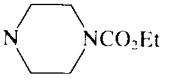
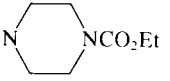
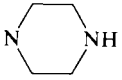
| | | | | | |
|---|---|---|---|---|---|
| Me |  | O | H | 109–111 | 414 |
| Me | $CH_2Ph$ | O | H | 137–138 | 414 |
| Et | $(CH_2)_2NMe_2$ | O | H | 75–77 | 414 |
| Et | $(CH_2)_3NMe_2$ | O | H | 154–156 ($HClO_4$) | 414 |
| Me | H | O | 6,7-$Me_2$ | 260–262 | 414 |
| Me | $(CH_2)_2NMe_2$ | O | 6,7-$Me_2$ | 119–120 | 414 |
| Me | H | O | 6,7-$Cl_2$ | 270–272 | 414 |
| Me | $(CH_2)_2NMe_2$ | O | 6,7-$Cl_2$ | 223–225 ($HClO_4$) | 414 |
| H | Me | O | H | 195–198 | 414 |
| $(CH_2)_2NMe_2$ | Me | O | H | 245–248 (HCl) | 414 |
| $CH_2Ph$ | Me | O | H | 151–153 | 414 |
| H | H | O | 6-Cl | 279–281 | 414,424 |
| H | H | O | 7-Cl | 197–198 | 414,422,424 |
| Me | H | O | 7-Cl | 244–246 | 414 |
| H | H | S | H | 210–212 | 424 |
| Me | H | S | H | 203–204 | 424 |
| H | H | S | 6-Cl | 235–237 | 424 |
| H | H | S | 7-Cl | 197–198.5 | 424 |
| Me | H | S | 7-Cl | 238–240 | 424 |
| H | H | O | 6,7-$Cl_2$ | 284–287 | 422 |
| H | H | O | 7-F | 238 | 422 |
| H | H | S | H | 221 | 422 |

TABLE 93. 11-SUBSTITUTED THIENO[3,4-*b*][1,5]BENZODIAZEPINES

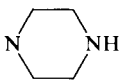
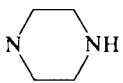
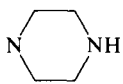
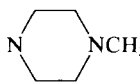
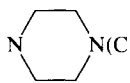
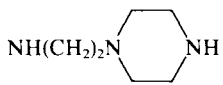


| R | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|
| H | SMe | H | 128.5–130 | 424 |
| H |  | H | 200–201 | 422,424 |
| H |  | H | 228–231 | 424 |
| H |  | H | 157–159 | 424 |
| Me | SMe | H | 113–115 | 424 |
| Me |  | H | 83–85 | 424 |
| H | SMe | 6-Cl | 152–154 | 424 |
| H | SMe | 7-Cl | 111–113 | 424 |
| H |  | 6-Cl | 148–149 | 424 |
| H |  | 7-Cl | 267–270 | 422,424 |

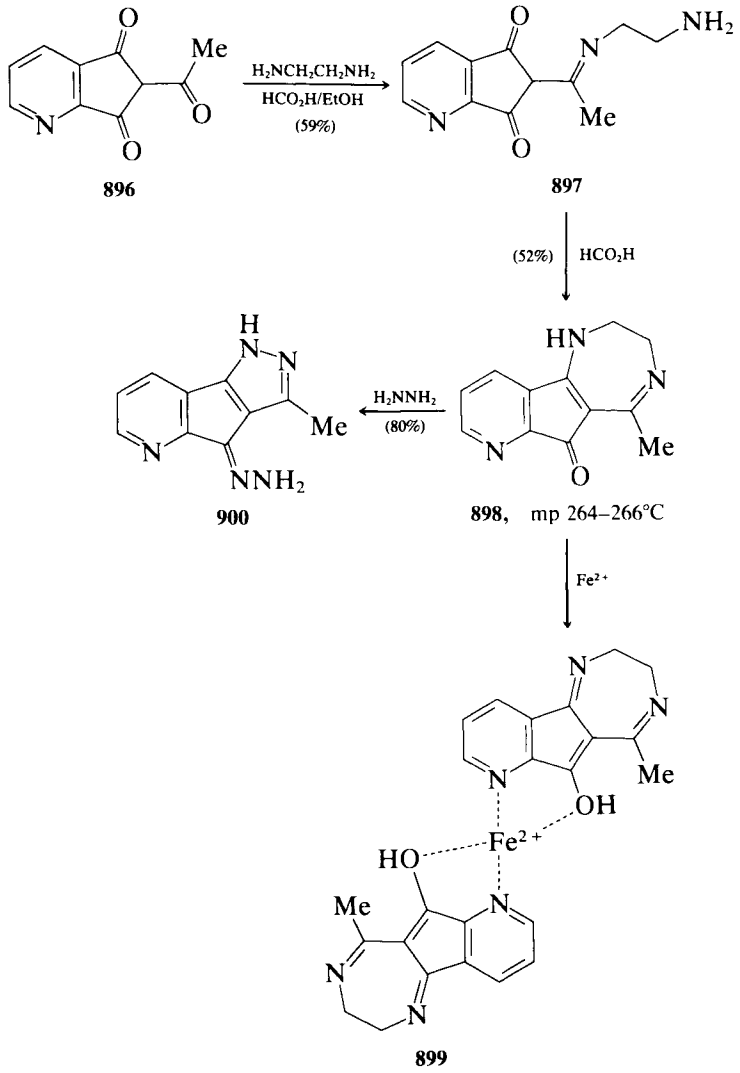
| | | | | |
|---|---|---|---|---|
| Me | SMe | 7-Cl | 156–158 | 424 |
| Me |  | 7-Cl | 212–215 | 424 |
| H | $NH_2$ | 7-Cl | 239–240 | 422 |
| H | $NH_2$ | 7-SMe | 195–197 | 422 |
| H | $NH_2$ | H | 190 | 422 |
| H | $NH_2$ | 6-$CF_3$ | 178 | 422 |
| H |  | 6-$CF_3$ | 202 | 422 |
| H |  | 7-F | 190–191 | 422 |
| H |  | 6,7-$Cl_2$ | 200–202 | 422 |
| H |  | H | 186–187 | 422 |
| H |  | 7-F | 197–199 | 422 |
| H |  | 6,7-$Cl_2$ | 213–214 | 422 |
| H |  | 7-Cl | 195–196 | 422 |
| H |  | H | 233–235 | 422 |

(*continued*)

TABLE 93. *(Continued)*

| R | X | Y | mp (°C) | Refs. |
|---|---|---|---|---|
| H |  | 7-F | 197–203 | 422 |
| H |  | 6,7-$Cl_2$ | 213–214 | 422 |
| H |  | 7-Cl | 178–179 | 422 |
| H |  | H | 221–222.5 | 422 |
| H |  | H | 184 | 422 |
| H |  | H | 182–184 | 422 |

(6H)-diones, a number of reactions with diamines were carried out (Fig. 64). Condensation of **896** with ethylenediamine gave imine **897.** Final ring closure to the diazepine **898** was effected by refluxing in propanol in the presence of formic acid. The structure of the product was supported by infrared spectral data (2300, 1640 $cm^{-1}$). In addition, **898** formed a blue-violet 2:1 complex (**899**) with ferrous ammonium sulfate and reacted with hydrazine to afford the pyrazole **900** (425).



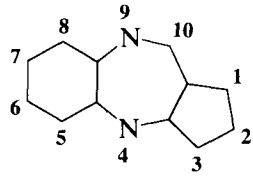

**896** **897**

**900** **898,** mp 264–266°C

**899**

**Figure 64**

## 81. Benzo[*b*]cyclopenta[*e*][1,4]diazepines (see Section XV.56)




The benzo[*b*]cyclopenta[*e*][1,4]diazepine ring system has been prepared by a variety of methods. The most general procedure began with *o*-phenylenediamine, as shown in Fig. 65. Condensation with 2-hydroxymethylenecyclopentanone or 1-chloro-2-formylcyclopentene derivatives afforded the diazepinium salts **901.** Attempts to isolate the free bases of these products failed (23,426–428). Reaction of *o*-phenylenediamine with 2-acetyl- or 2-

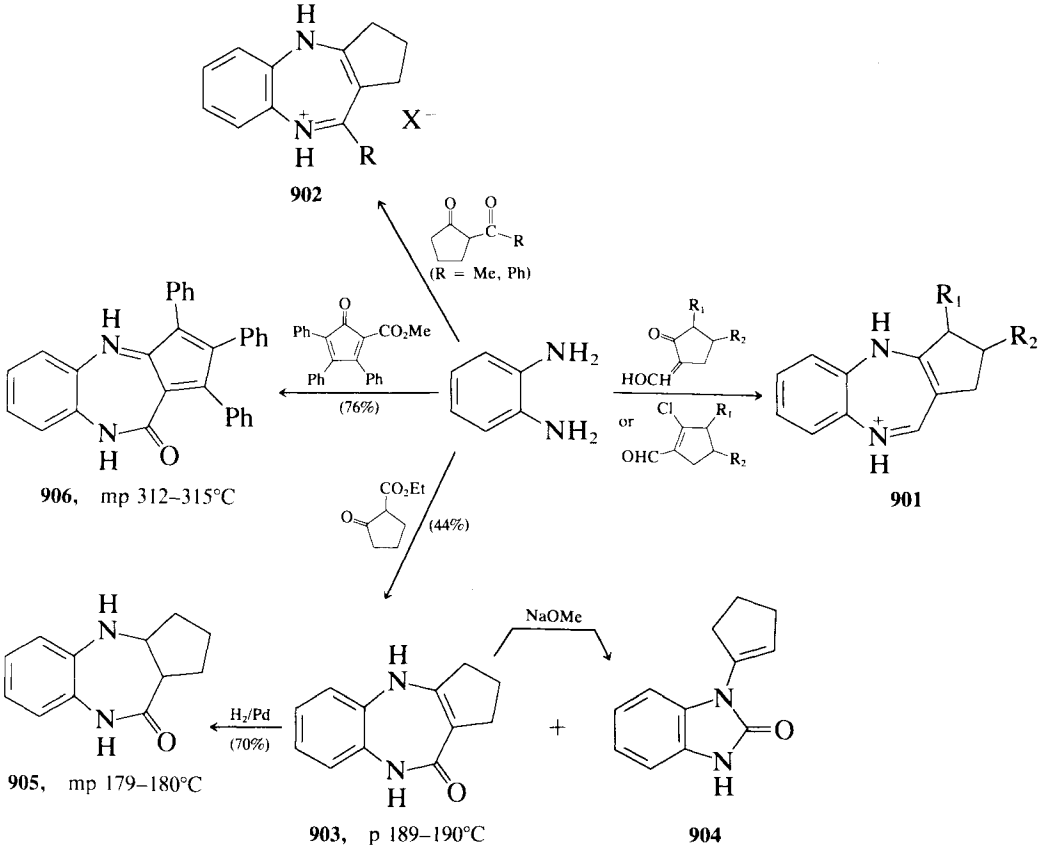
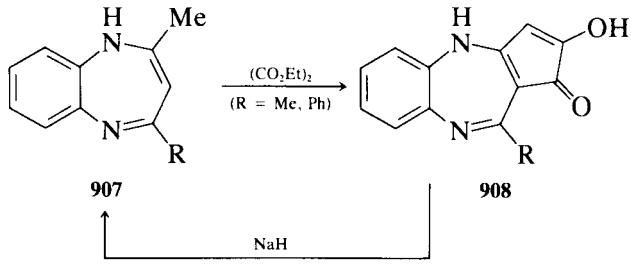



Figure 65

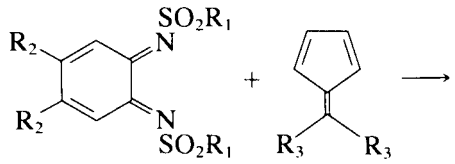
benzoylcyclopentanone generated the adducts **902** (427). Use of 2-carbethoxycyclopentanone in refluxing xylene without acid catalysis led to the benzodiazepine product **903** and to a lesser amount of the benzimidazolone **904.** Treatment of **903** with alkoxide gave rise to **904.** Hydrogenation of **903** over palladium produced **905** (429,430). Using the same methodology, condensation of *o*-phenylenediamine with 5-carbomethoxy-2,3,4-triphenylcyclopentadienone afforded the diazepine **906** (431). The compounds derived by reaction of *o*-phenylenediamine with cyclopentane derivatives are listed in Table 94.

An alternate entry into this ring system (Eq. 159) was attained by base-catalyzed condensation of benzodiazepine **907** with diethyl oxalate (432,433). The red, crystalline products **908** were characterized by ir, nmr, and uv ($\lambda_{max}$ = 475 nm) spectral data and by chemical studies. Treatment with sodium hydride regenerated the benzodiazepines **907.**

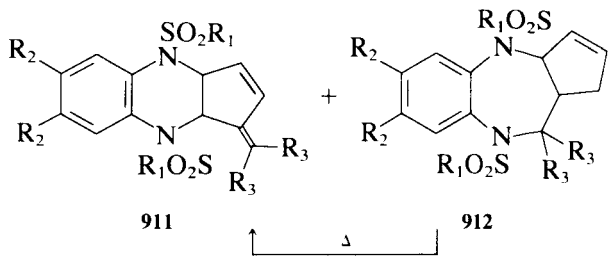



907 908 (159)

A novel method of ring formation (Eq. 160) was achieved by reaction of the *N,N'*-dibenzenesulfonyl-*o*-benzoquinonediimines **909** with the fulvene derivatives **910** (434,435). In addition to the [2 + 4] adducts **911,** the [6 + 4] tricyclic products **912** were also obtained, as specified in Table 95. Com-

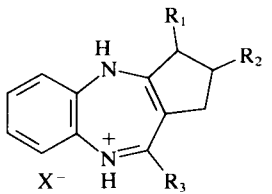



909 910



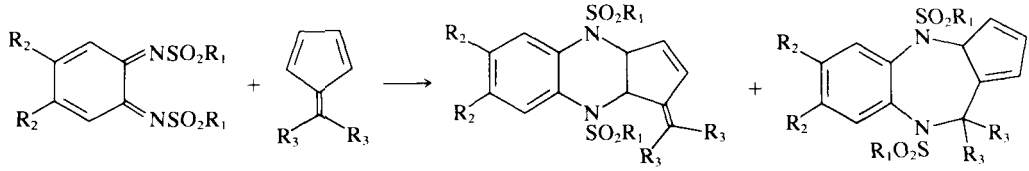

911 912 (160)

TABLE 94. 1,2,3,4-TETRAHYDROBENZO[*b*]CYCLOPENTA[*e*][1,4]DIAZEPINIUM SALTS



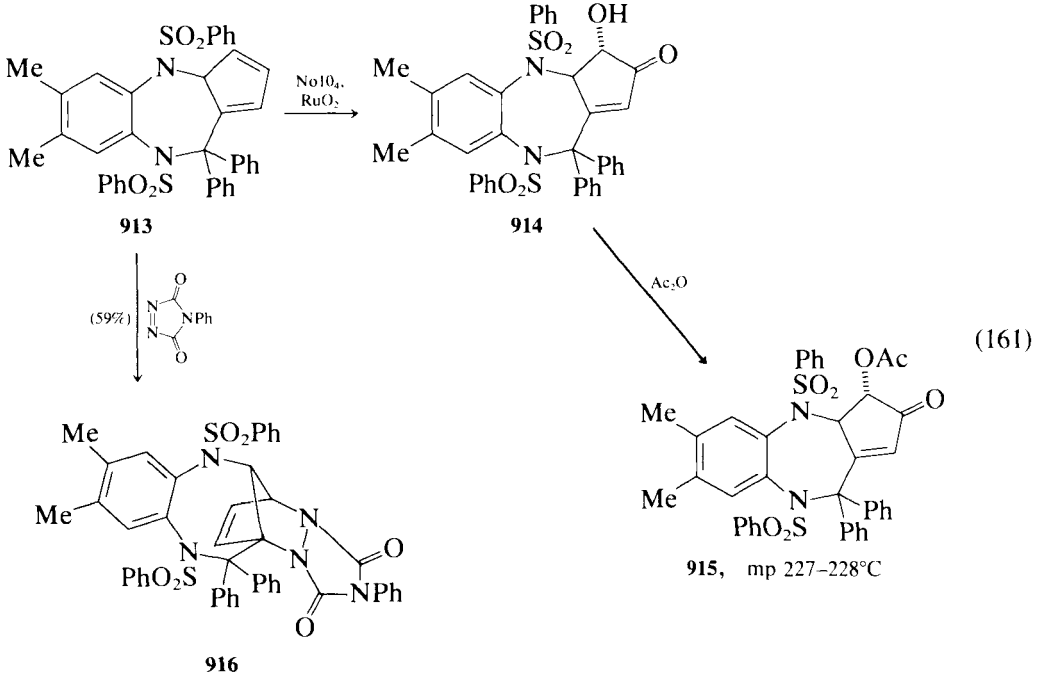

| Structure | $R_1$ | $R_2$ | $R_3$ | X | Yield (%) | mp (°C) | $\lambda_{max}$ (nm) | Color | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| **901** | H | H | H | $ClO_4$ | 82 | 221.5–222.5 | 574 | Black | 23,426,428 |
| **901** | H | H | H | Cl | 30 | 208–209 | | Dark green | 23,426,428 |
| **901** | Me | H | H | $ClO_4$ | 75 | 191–192 | 570 | Dark green | 427 |
| **901** | Ph | H | H | $ClO_4$ | 15 | 169–170 | 572 | Blue-black | 427 |
| **901** | H | Me | H | $ClO_4$ | 35 | 187–188 | 572 | Dark green | 427 |
| **901** | Me | H | H | $ClO_4$ | 83 | 251–252 | 550 | Dark green | 427 |
| **902** | H | H | Ph | $ClO_4$ | 63 | 253–254 | 564 | Black | 427 |
| **902** | H | H | Me | Cl | 75 | 248–249 | 550 | Blue-violet | 427 |
| **902** | H | H | Me | Free base | 22 | 100–101 | | Colorless | 427 |
| **902** | H | H | Ph | Cl | 55 | 194–195 | 484 | Red | 427 |

TABLE 95. REACTION OF *N,N'*-DIARYLSULFONYL-*o*-BENZOQUINONEDIIMINES WITH FULVENES



**909** **910** **911** **912**

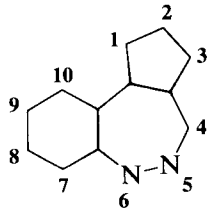
| $R_1$ | $R_2$ | $R_3$ | Yield of **911** (%) | Yield of **912** (%) | mp of **912** (°C) |
|---|---|---|---|---|---|
| Ph | Me | Ph | 51 | 49 | 181 |
| Ph | Me | *p*-$NO_2C_6H_4$ | 5 | 92 | |
| Ph | Me | *p*-$ClC_6H_4$ | 14 | 82 | 180 |
| Ph | Me | *p*-$MeC_6H_4$ | 35 | 60 | |
| Ph | Me | Me | | 28 | 162 |
| Ph | Me | Cyclopropyl | 28 | 69 | 180 |
| Ph | Cl | Ph | 38 | 62 | 172 |
| Ph | Cl | *p*-$NO_2C_6H_4$ | 25 | 70 | 178 |
| *p*-$NO_2C_6H_4$ | Me | Ph | 100 | | |
| *p*-$NO_2C_6H_4$ | Me | *p*-$ClC_6H_4$ | 50 | 50 | |
| *p*-$MeOC_6H_4$ | Me | *p*-$MeC_6H_4$ | 29 | 55 | |
| Ph | Me | *p*-$MeOC_6H_4$ | | | 136 |



**913** **914** **915**, mp 227–228°C **916** (161)

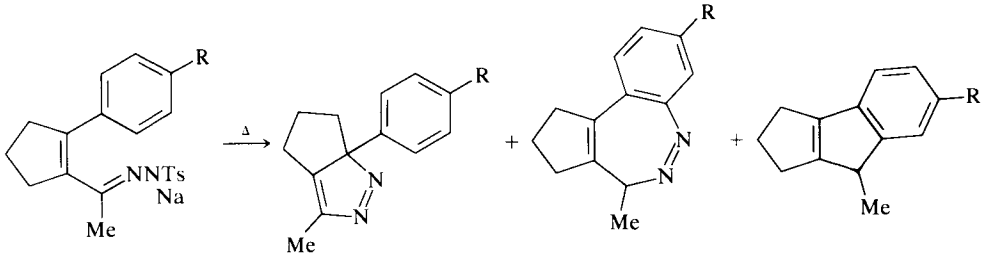
pounds **911** could also be obtained by heating **912.** The latter process presumably occurs via a 1,5-sigmatropic rearrangement. One member of the series, **913,** was oxidized to **914,** which was characterized as its acetate (**915**). Compound **913** also condensed with *N*-phenyltriazolinedione to afford the Diels–Alder adduct **916** in 59% yield (Eq. 161).

## 82. Benzo[*c*]cyclopenta[*e*][1,2]diazepines (see Section XV.57)




The benzo[*c*]cyclopenta[*e*][1,2]diazepine ring system arose from studies on the cyclization of diazoalkenes. Thermolysis of the tosylhydrazone salts **917** led to **918,** to pyrazoles **919** from 1,5-cyclization, to benzodiazepines **921** via 1,7-cyclization, and to the carbene-derived products **923.** The yields

TABLE 96. THERMOLYSIS OF THE SODIUM SALTS OF 1-ACETYL-2-ARYLCYLOPENTENE TOSYLHYDRAZONES (**917**)




**917** **919** **921** **923**

| | Yield (%) | | |
|---|---|---|---|
| R | **919** | **921** | **923** |
| H | 46 | 32 | 20 |
| Me | 43 | 37 | 20 |
| F | 36 | 38 | 26 |

of these products after reaction times just sufficient to decompose **917** are shown in Table 96. Reheating **919** at 80°C led to partial conversion to **921** (31–37% yield) and **923** (24–41% yield). The probable pathway for these transformations is summarized in Fig. 66. The corresponding diazocyclohexene system underwent cyclization only to the pyrazole product analogous to **919.** The dissimilarity between the thermal reactions of the cyclopentenyl and the cyclohexenyl systems is possibly due to the greater ring strain in **919,** which facilitates ring opening to **918** (437).

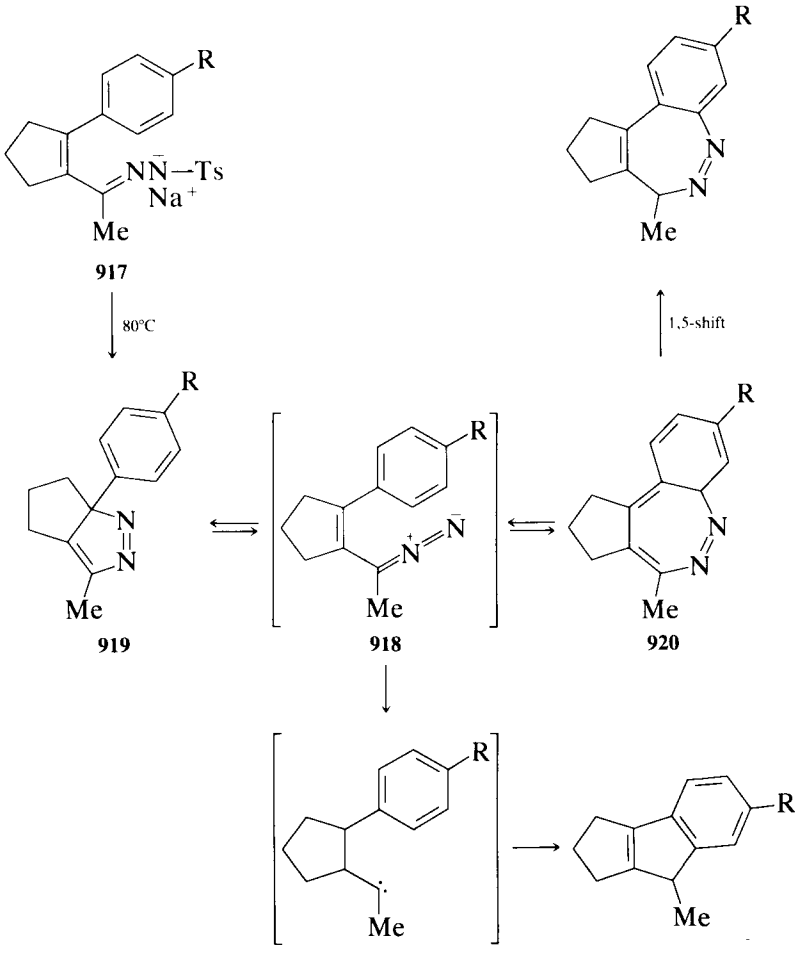
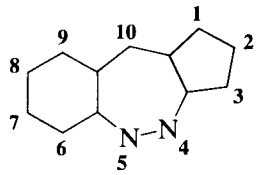
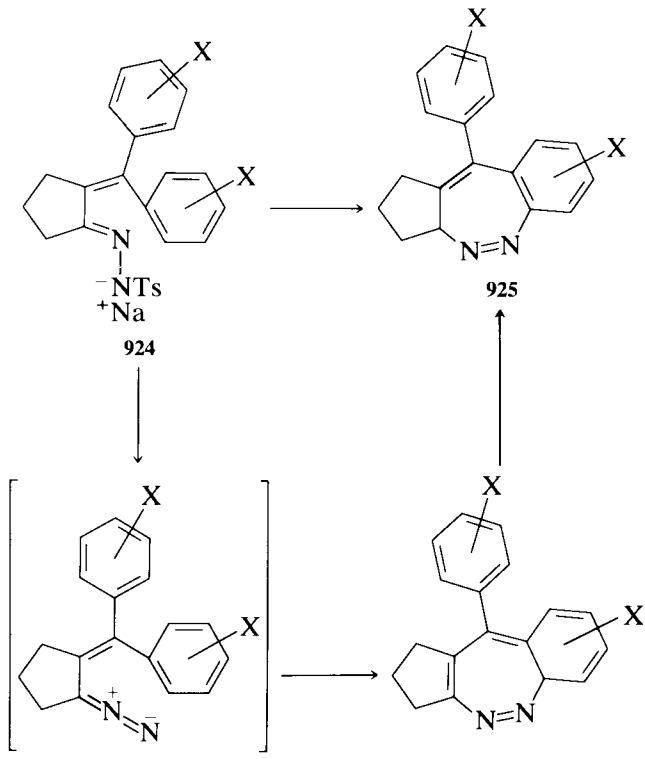



**Figure 66**

## 83. Benzo[*c*]cyclopenta[*f*][1,2]diazepines (see Section XV.58)




The benzo[*c*]cyclopenta[*f*][1,2]diazepine ring system grew out of a study of the cyclization reactions of diazoalkenes. Although the sodium salts of the tosylhydrazones of α-dialkylmethylenecyclopentanes decompose by loss

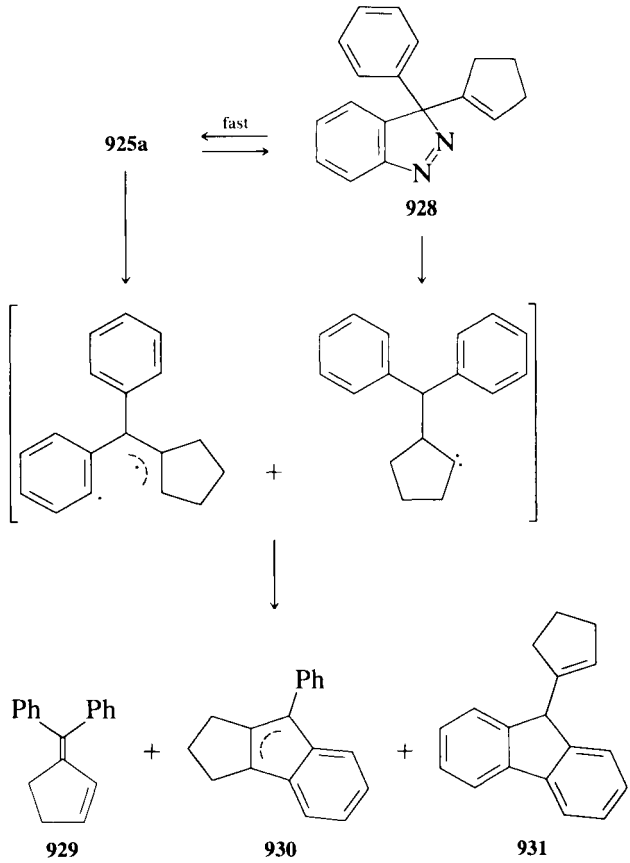



(162)

| | X | Yield (%) | mp (°C) |
|---|---|---|---|
| **925a** | H | 80 | 159–160 |
| **925b** | *p*-Me | 68 | 177–178 |
| **925c** | *p*-$CF_3$ | 56 | 106 |
| **925d** | *m*-MeO | 68 | 149–150 |
| **925e** | *p*-F | 38 | 129–132 |

of nitrogen to give dienes, and acyclic and cyclohexyl systems give exclusively pyrazoles, the corresponding diarylcyclopentyl compounds **924** undergo closure to the 1,2-benzodiazepines **925** (438,439). This process entails decomposition to the diazo intermediates **926,** which then undergo electrocyclic ring closure to **927,** followed by a 1,5-sigmatropic hydrogen shift to **925,** as shown in Eq. 162.

The benzodiazepines **925** are yellow crystalline compounds that are stable at room temperature. However, thermolysis of **925a** resulted in elimination of nitrogen and formation of alkene products **929, 930,** and **931,** as outlined in Fig. 67 (440). The product ratios of gas phase and solution processes



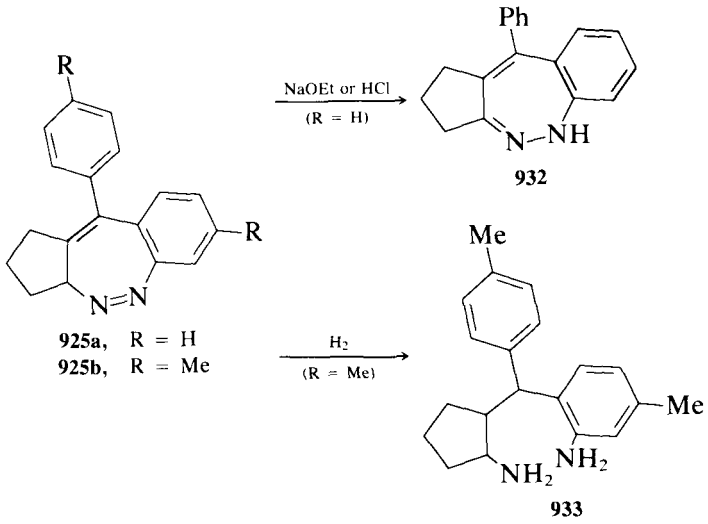

929 930 931

| Reaction Conditions | Yield (%) 929 | 930 | 931 |
|---|---|---|---|
| Gas phase | 2 | 32 | 45 |
| Chlorobenzene solution | 36 | 42 | — |
| Dodecane solution | 38 | 31 | 10 |

**Figure 67**

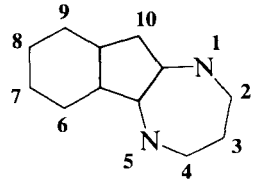
differed. A kinetic study using high-pressure liquid chromatography revealed that the equilibrium of **925a** with pyrazole **928** occurred four times faster than nitrogen loss (441).

The 1,2-benzodiazepine system also rearranged on photolysis but yielded only the alkene products **930** and **931** (440). In refluxing acid or base (Eq. 163) **925a** rearranged to the more stable isomer **932.** Benzodiazepine **925b** was converted to diamine **933** after hydrogenation (438).

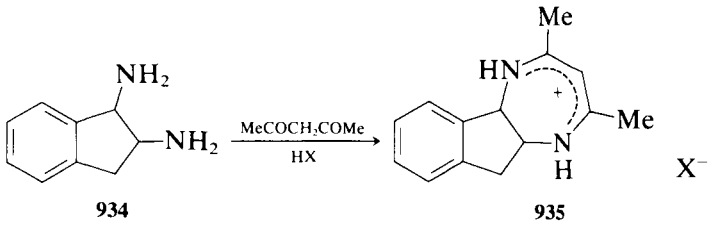



(163)

## 84. Indeno[1,2-*b*][1,4]diazepines

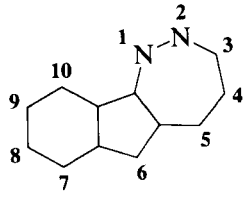



Reaction of 1,2-diaminoindane (**934**) with 2,4-pentanedione yielded the adducts **935** (Eq. 164). The products were isolated as salts, as indicated in Table 97. Spectral studies have provided insight into the preferred ring conformation of the system (443).

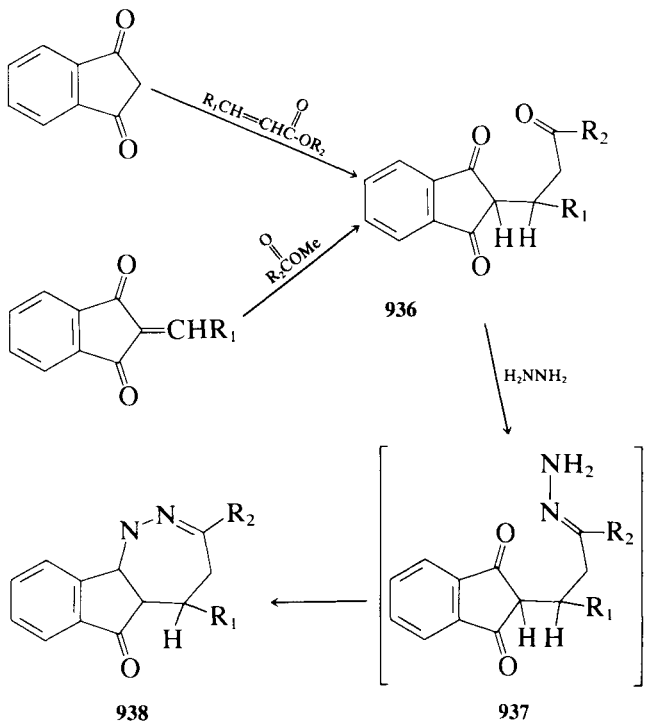



934 935 (164)

## 85. Indeno[1,2-*c*][1,2]diazepines (see Section XV.59)

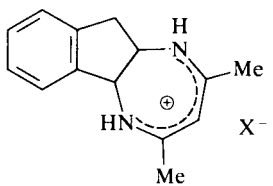



In order to form the indeno[1,2-*c*][1,2]diazepine ring system, the 1,5-diketone **936** was prepared by several methods (Eq. 165). In one procedure




(165)

TABLE 97. INDENO[1,2-*b*][1,4]DIAZEPINES

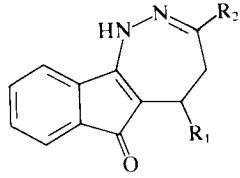



| Stereochemistry | X | Yield (%) | mp (°C) | $\lambda_{max}$ (nm) | $\epsilon \times 10^{-3}$ | Refs |
|---|---|---|---|---|---|---|
| *Cis* | $ClO_4$ | 40 | 167–174 | 326 | 12.3 | 442,443 |
| *Trans* | Cl | 71 | >300 | 323 | 12.0 | 443 |

1,3-indanedione was condensed with $\alpha,\beta$-unsaturated carbonyl compounds. A more general approach involved Michael addition of acetophenone derivatives to 2-benzylidene-1,3-indanedione. On treatment with an equimolar amount of hydrazine in refluxing ethanol or in isopropanol containing a catalytic amount of acetic acid, the 1,5-dione **936** gave the diazepines **938,** probably via the side-chain hydrazone **937.**

The products of these reactions are listed in Table 98. Supporting nmr and uv spectral data are summarized in Table 99. All attempts to alkylate or acylate **938a** or **938b** failed. The monohydrazones of **938b** (mp 248–249°C) and **938c** (mp 227°C) were obtained by refluxing with excess hydrazine in acetic acid (444). An independently reported synthesis of this ring system made use of essentially the same methodology (445). However, in contrast to the earlier claim, attempts to prepare **938** with a *p*-nitrophenyl substituent were unsuccessful (445).

TABLE 98. 4,5-DIHYDROINDENO[1,2-*c*][1,2]DIAZEPIN-6-ONES

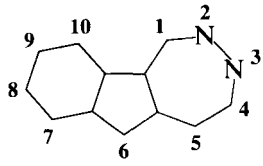



| Compound | $R_1$ | $R_2$ | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|
| **938a** | Ph | Me | 43 | 229–230 | 444,445 |
| **938b** | Ph | Ph | 66 | 224–225 | 444,445 |
| **938c** | Ph | *p*-$NO_2C_6H_4$ | 73 | 242 | 444 |
| **938d** | Ph | *p*-$AcNHC_6H_4$ | 57 | 261–262 | 444 |
| **938e** | *p*-$ClC_6H_4$ | Ph | 29 | 228 | 444,445 |
| **938f** | *p*-$ClC_6H_4$ | *p*-$NO_2C_6H_4$ | 72 | 245 | 444 |
| **938g** | Ph | 2-Pyridyl | 43 | 212–214 | 444 |
| **938h** | Ph | 1-Naphthyl | 90 | 147 | 445 |
| **938i** | *p*-$ClC_6H_4$ | 1-Naphthyl | — | 165 | 445 |
| **938j** | *p*-$MeC_6H_4$ | 1-Naphthyl | — | 192 | 445 |

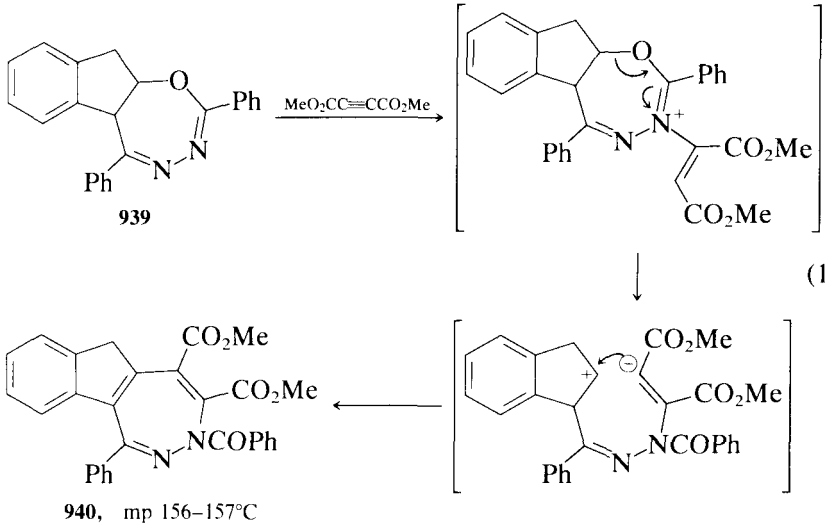
TABLE 99. ULTRAVIOLET ABSORPTION OF INDENO[1,2-*c*][1,2]DIAZEPINES

| Compound | $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$) | | | |
|---|---|---|---|---|
| **938a** | 229 (16.6) | 264 (24.2) | 286 (12.1) | 320 sh (3.6) |
| **938b** | 229 (21.4) | 265 (20.8) | 305 (12.5) | 330 sh (3.7) |
| **938c** | 223 (20.4) | 263 (24.7) | 298 (13.0) | 345 (11.4) |
| **938d** | 225 (31.5) | 265 (25.8) | 305 (13.8) | 330 sh (10.0) |
| **938e** | 228 (22.8) | 264 (18.9) | 305 (10.2) | 335 sh ( 6.0) |

## 86. Indeno[1,2-*d*][1,2]diazepines



Photolysis of 2,5-diphenyl-1,3,4-oxadiazole in the presence of indene afforded the oxadiazepine **939.** When **939** was heated with an excess of dimethyl acetylenedicarboxylate at 70–90°C for 30 min (Eq. 166), diazepine **940** was obtained in 63% yield. A possible pathway for this transformation is depicted. The structure of product **940** was supported by ir, nmr, and mass spectral data (446).



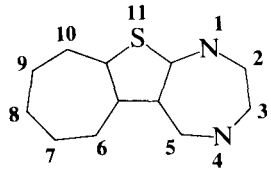
**939**

(166)

**940,** mp 156–157°C

# VII. 5,7,7-SYSTEMS

## 1. Cyclohepta[4,5]thieno[2,3-*e*][1,4]diazepines



Cyclohepta[4,5]thieno[2,3-*e*][1,4]diazepines have been prepared by methods similar to the ones used for the synthesis of the closely related cyclopenta[4,5]thieno[2,3-*e*][1,4]diazepines (58,60). The procedures are outlined in Fig. 68, which illustrates the preparation of the tricyclic diazepinones **941** (57) and **942** (55).

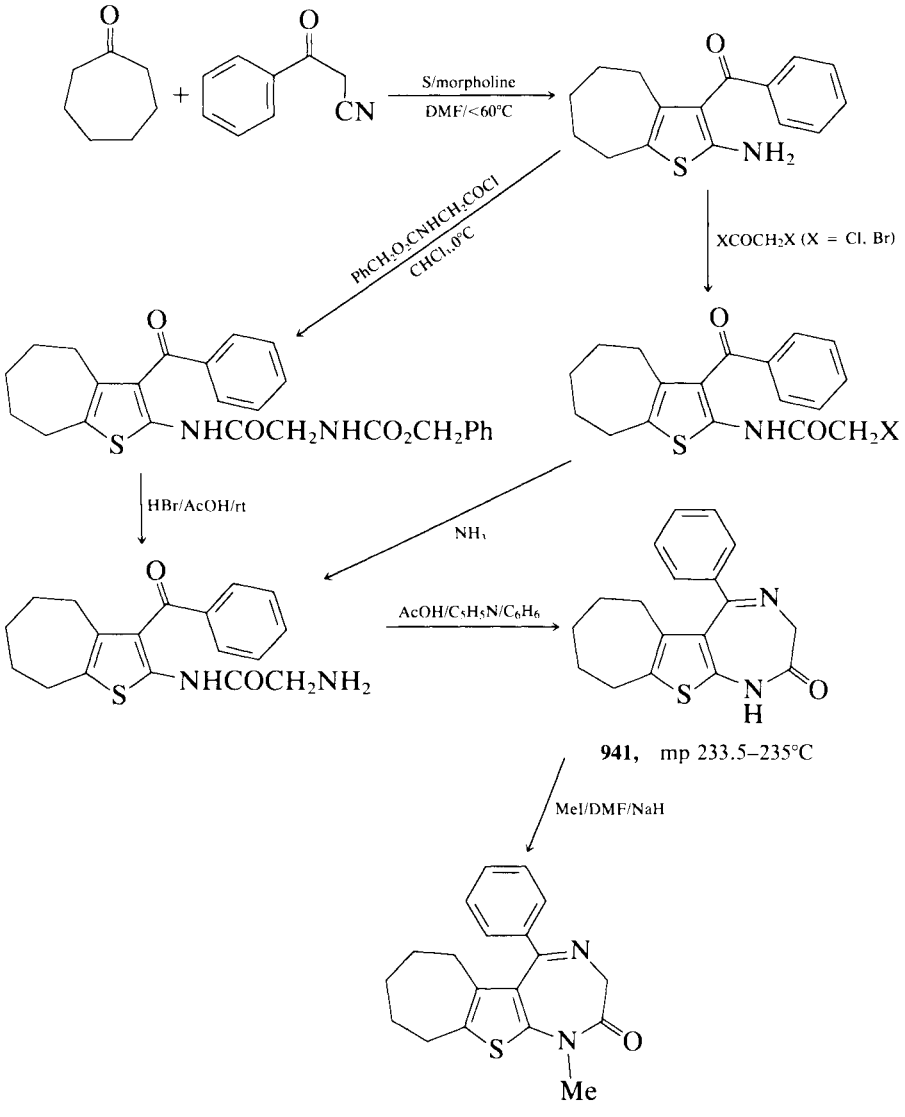
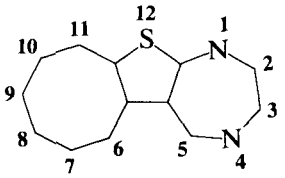


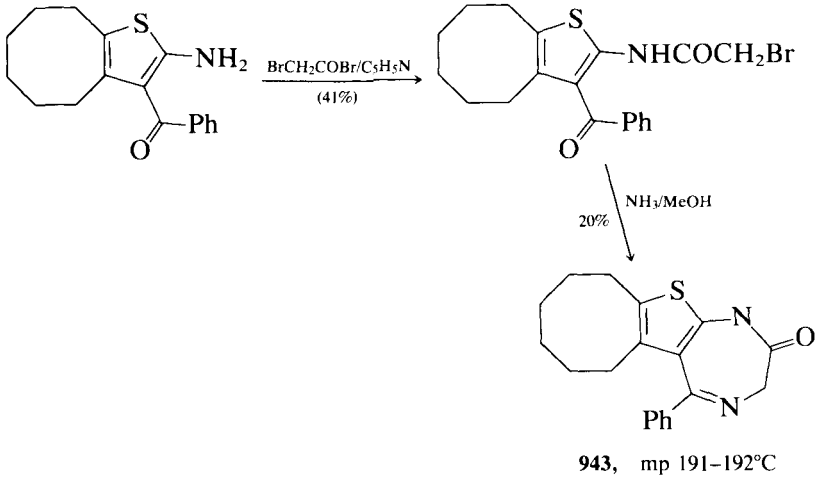

**Figure 68**

# VIII. 5,7,8-SYSTEMS

## 1. Cycloocta[4,5]thieno[2,3-*e*][1,4]diazepines




The sole known example of the cycloocta[4,5]thieno[2,3-*e*][1,4]diazepine ring system was obtained by Tinney and co-workers (60) using chemistry previously developed for the synthesis of benzodiazepines (447). The aminothiophene shown in Eq. 167 was prepared by the Gewald procedure (59). Treatment with bromoacetyl bromide in pyridine/ether followed by addition of ammonia in methanol afforded **943** in 20% yield.

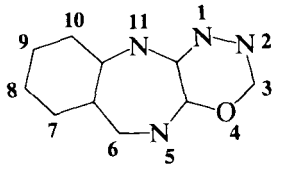



(167)

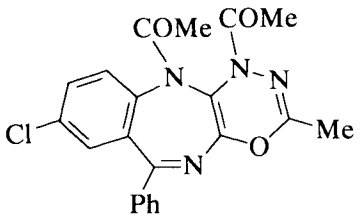
**943**, mp 191–192°C

# IX. 6,6,7-SYSTEMS

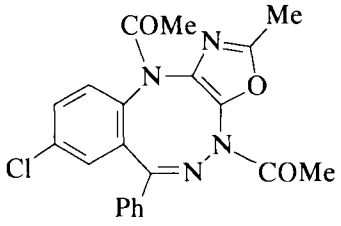
## 1. [1,3,4]Oxadiazino[5,6-*b*][1,4]benzodiazepines



In 1968 Derieg and co-workers (448) claimed the preparation of **944.** However, an X-ray crystallographic study (449) demonstrated that the correct structure for this substance was **945.**

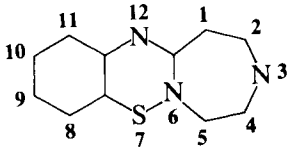


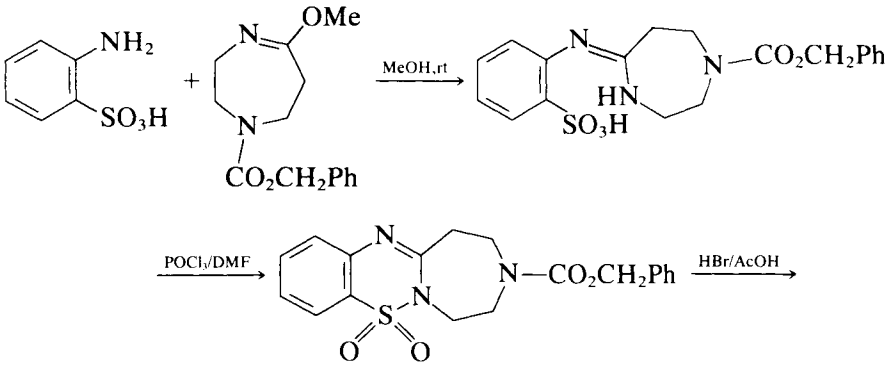
**944**



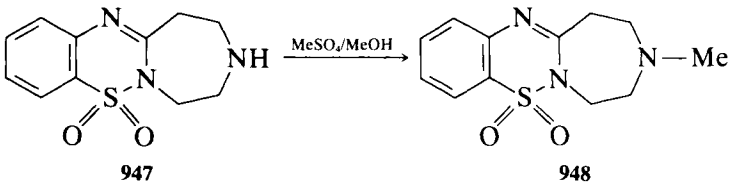
**945**

## 2. [1,4]Diazepino[1,7-*b*][1,2,4]benzothiadiazines





**946**

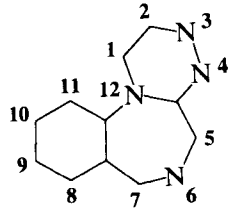


**947** **948**

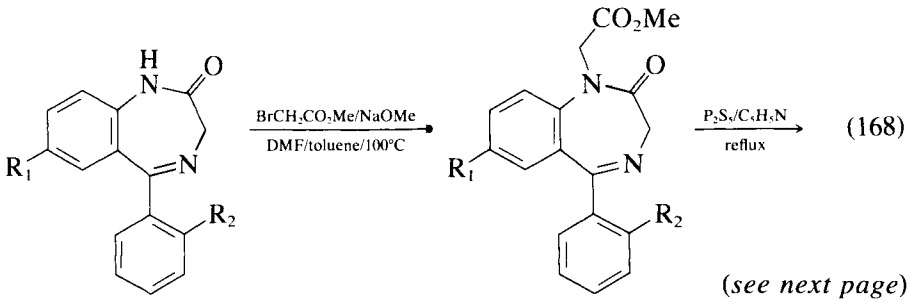
**Figure 69**

Three derivatives of the [1,4]diazepino[1,7-*b*][1,2,4]benzothiadiazine ring system (**946–948**) were claimed in a patent (450), but no preparative details, physical constants, or analytic data were provided. The synthesis is shown in Fig. 69.

### 3. [1,2,4]Triazino[4,3-*a*][1,4]benzodiazepines (see Section XVI.1)

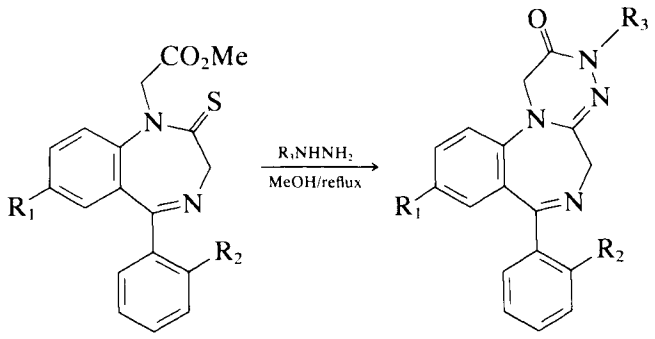



Examples of the [1,2,4]triazino[4,3-*a*][1,4]benzodiazepine ring system have been described in a series of patents (451–453). Condensation of benzodiazepinones with methyl bromoacetate in the presence of sodium methoxide gave acetic ester derivatives (Eq. 168). On treatment with phosphorus pentasulfide in pyridine, these esters gave the thiolactams, which were condensed with hydrazines to give the tricyclic triazinones **949a–f.** $N^3$-Alkylation was achieved by treatment with sodium hydride in dimethylformamide at 100°C followed by addition of an alkyl halide in xylene solution and continued heating (452). Introduction of the dimethylaminomethylene substituent (453) was achieved by treatment of the triazinobenzodiazepine **949b** with sodium hydride in dimethylformamide followed by addition of dimethylmethyleneammonium chloride to form **949g** (Eq. 169). Other examples of $N^3$-dimethylaminoalkyl derivatives obtained via this route are listed in Table 100. Sedative hypnotic, anticonvulsant, tranquilizing, and muscle relaxant properties were claimed for the products (451–453).




(168)

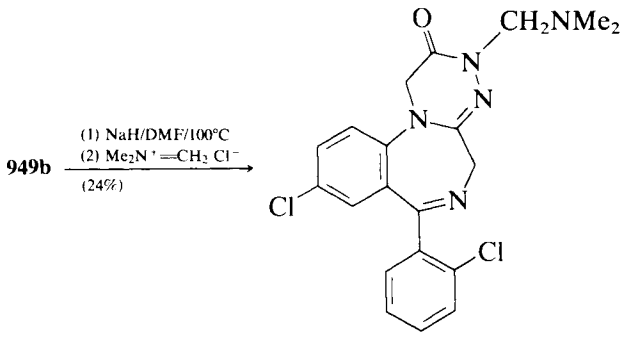
(*see next page*)




(168 *cont'd*)

**949a–f**

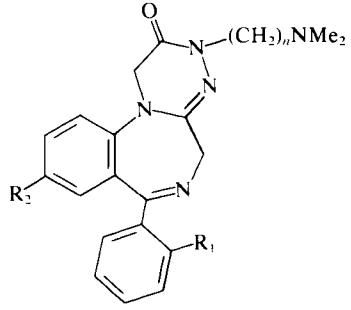
| | $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) |
|---|---|---|---|---|---|
| **949a** | Cl | H | H | 267–270 | 62 |
| **949b** | Cl | Cl | H | 232–233 | 84 |
| **949c** | Cl | Cl | Me | 170–171 | 34 |
| **949d** | H | Cl | H | 195–196.5 | 74 |
| **949e** | H | Cl | Me | Oil | 56 |
| **949f** | Cl | H | Me | 175–176 | 50 |




(169)

**949g,** mp 140–141°C

TABLE 100. 3-SUBSTITUTED [1,2,4]TRIAZINO[4,3-*a*][1,4]BENZODIAZEPIN-2-ONE DERIVATIVES

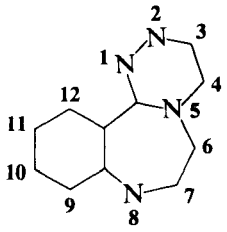



(*continued*)

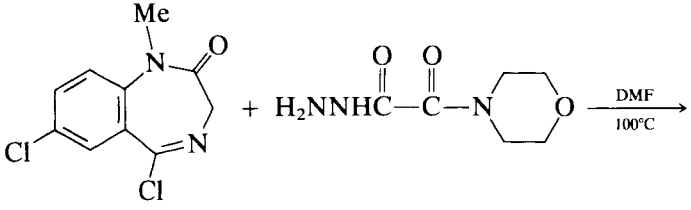
TABLE 100. (*Continued*)

| *n* | $R_1$ | $R_2$ | mp (°C) | Yield (%) |
|---|---|---|---|---|
| 2 | Cl | Cl | 166–167 | 40 |
| 3 | Cl | Cl | 144–145 | 44 |
| 2 | H | Cl | 157–158 | |
| 3 | H | Cl | 124–125 | |
| 2 | Cl | H | 168–169 | |
| 3 | Cl | H | 148–149 | |

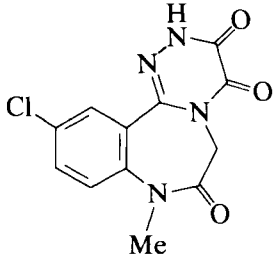
## 4. [1,2,4]Triazino[4,3-*d*][1,4]benzodiazepines (see Section XVI.2)




The [1,2,4]triazino[4,3-*d*][1,4]benzodiazepine ring system was constructed by reaction of the imidoyl chloride **950** with 4-morpholinoglyoxylic acid hydrazide (454), as shown in Eq. 170. Compound **951** was alkylated by treatment with thallous ethoxide followed by addition of the appropriate




**950**

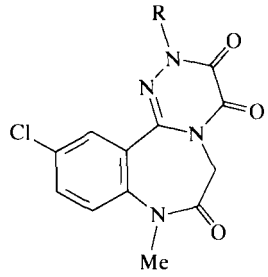


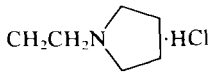
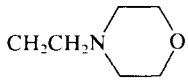

(170)

**951**, mp 342–365°C

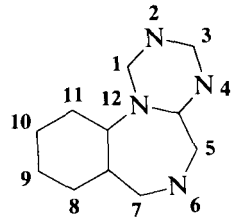
alkyl halide. Derivatives prepared in this way (Table 101) were claimed to have anti-inflammatory, sedative, and tranquilizing activity.

TABLE 101. 2-SUBSTITUTED[1,2,4]TRIAZINO[4,3-*d*][1,4]BENZODIAZEPINE-3,4,7-TRIONE DERIVATIVES

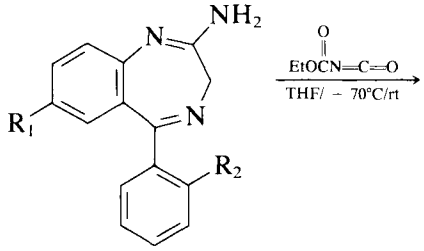


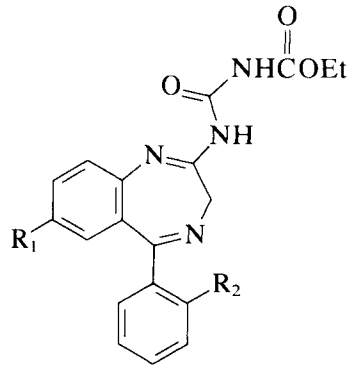
| R | mp (°C) | Yield (%) |
|---|---|---|
| $CH_2CH_2NMe_2$ | 224–225 | 24 |
| $CH_2CH_2NMe_2 \cdot HCl$ | 296–297 | |
| $CH_2CH_2CH_2NMe_2$ | 233–238 | 69 |
| $CH_2CH_2NEt_2$ | 260–262 | 73 |
|  | 300–303 | 55 |
|  | | 50 |

## 5. [1,3,5]Triazino[1,2-*a*][1,4]benzodiazepines

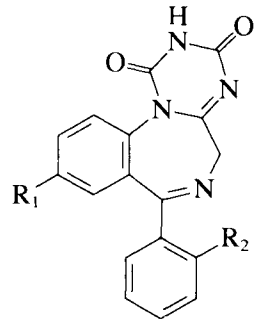


Moffett and Rudzik (455) prepared examples of the [1,3,5]triazino[1,2-*a*]-[1,4]benzodiazepine ring system from 2-amino[1,4]benzodiazepines via carbethoxyureas, as shown in Fig. 70. When a 2-methylamino derivative was used as the starting material, one of the double bonds in the product occupied a different position (Eq. 171). Methylation of **952** with one equivalent of methyl iodide and thallous ethoxide in dimethylformamide gave the



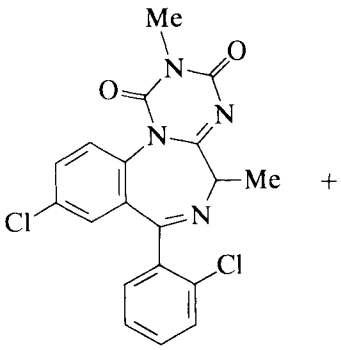

xylene/reflux




| | $R_1$ | $R_2$ |
|---|---|---|
| **952** | Cl | H |
| **953** | Cl | Cl |
| **954** | H | Cl |

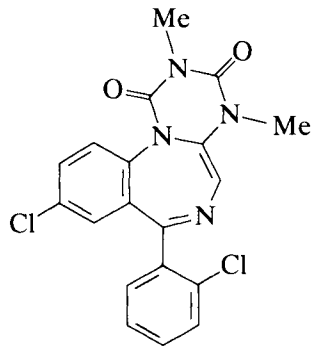
MeI/2 eq.
TlOEt/DMF
($R_1$ = $R_2$ = Cl)

MeI/1 eq.
TlOEt/DMF
($R_1$ = Cl, $R_2$ = H)

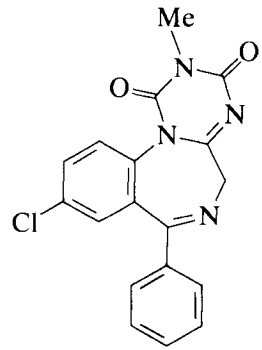



**958**

+

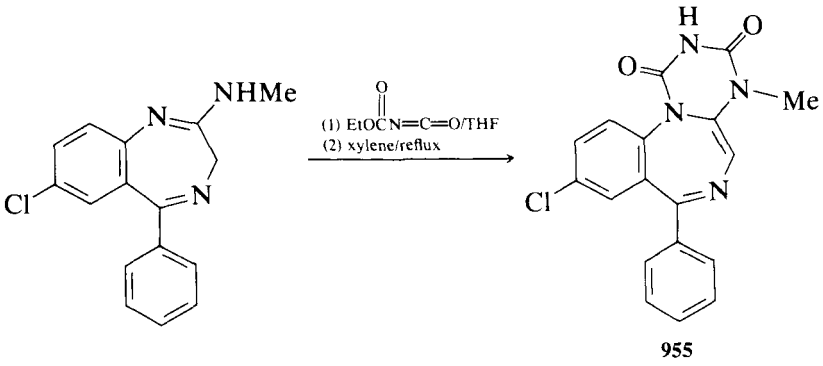



**957**




**956**

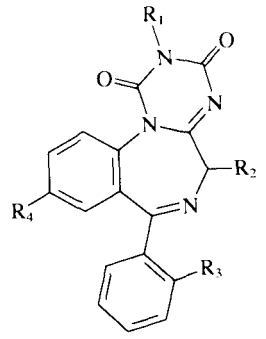
**Figure 70**




955 (171)

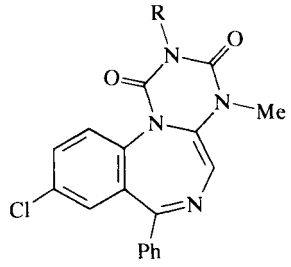
2-methyl derivative **956** (Table 102). When **953** was methylated with two equivalents of methyl iodide under similar conditions, a mixture of the dimethyl derivatives **957** and **958** were produced (Tables 102 and 103). Members of this ring system exhibited activity similar to that of diazepam in a variety of test systems.

TABLE 102. 2,5-DIHYDRO[1,3,5]TRIAZINO[1,2-*a*][1,4]BENZODIAZEPINE-1,3-DIONES



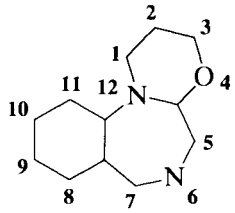
| Compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) | Spectra |
|---|---|---|---|---|---|---|
| **952** | H | H | H | Cl | 224–233 | ir, nmr, ms |
| **953** | H | H | Cl | Cl | 238–240 | ir, nmr, ms |
| **954** | H | H | Cl | H | 225–230 | ir, nmr, ms |
| **956** | Me | H | H | Cl | 211–213 | ir, uv, nmr |
| **958** | Me | Me | Cl | Cl | 226–228 | ir, nmr |

TABLE 103. 2,4-DIHYDRO[1,3,5]TRIAZINO[1,2-*a*][1,4]BENZODIAZEPINE-1,3-DIONES

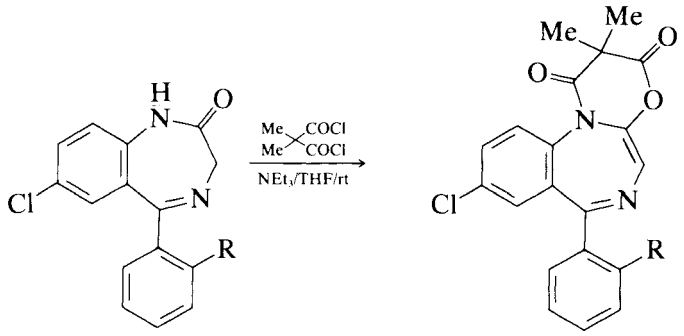


| Compound | R | mp (°C) | Spectra |
|---|---|---|---|
| **955** | H | 243–245 | ir, uv, nmr, ms |
| **957** | Me | 239–240 | ir, uv, nmr |

## 6. [1,3]Oxazino[3,2-*a*][1,4]benzodiazepines



A patent (456) describes the reaction of the benzodiazepinones shown in Eq. 172 with dimethylmalonyl chloride to give the corresponding tricyclic oxazinediones **959** and **960.**

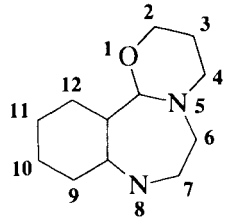


(172)

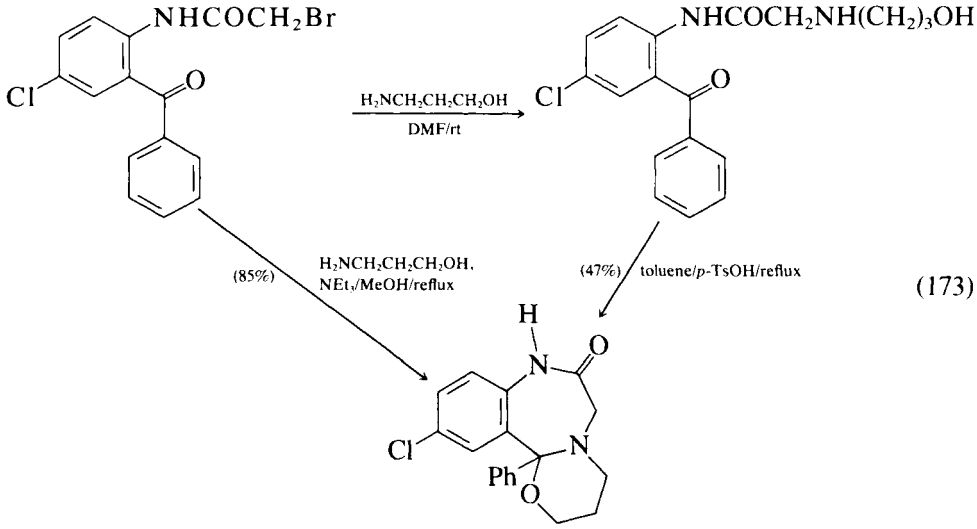
(R = H, Cl)

**959,** $R_1$ = H; mp 174°C (60%)
**960,** R = Cl, mp 188–190°C (78%)

## 7. [1,3]Oxazino[3,2-*d*][1,4]benzodiazepines (see Section XVI.3)

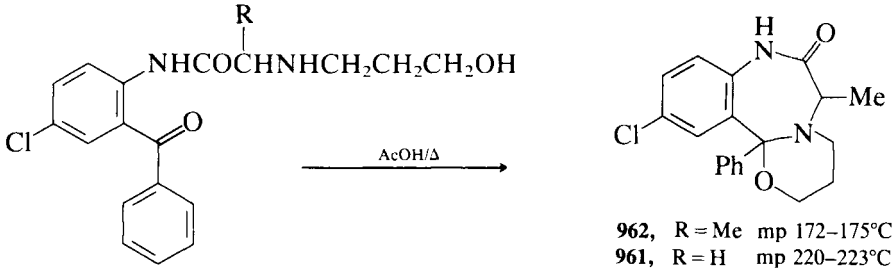



As a part of studies (206,211) designed to assess the pharmacologic effect of modifying the 4,5-double bond of diazepam, the tricyclic analog **961** was prepared according to the procedure shown in Eq. 173. In related work (206,210), double ring closure to **961** or **962** was effected with acetic acid as the catalyst (Eq. 174). Treatment of the sodium salt of **961** with methyl iodide in dimethylformamide at room temperature gave the $N^8$-methyl derivative (mp 172–175°C). Other substances of this type were prepared by similar methods (Table 104).




(173)

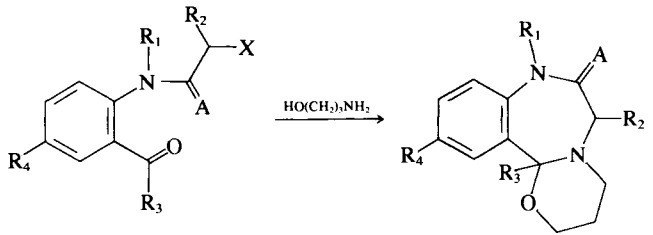
**961**, mp 213–216°C (nmr, ms)




(174)

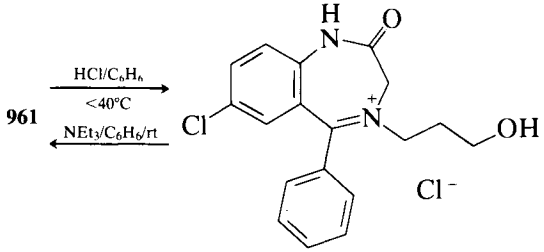
**962**, R = Me mp 172–175°C
**961**, R = H mp 220–223°C

TABLE 104. [1,3]OXAZINO[3,2-*d*][1,4]BENZODIAZEPINES PREPARED FROM o-ACYLACETANILIDE DERIVATIVES



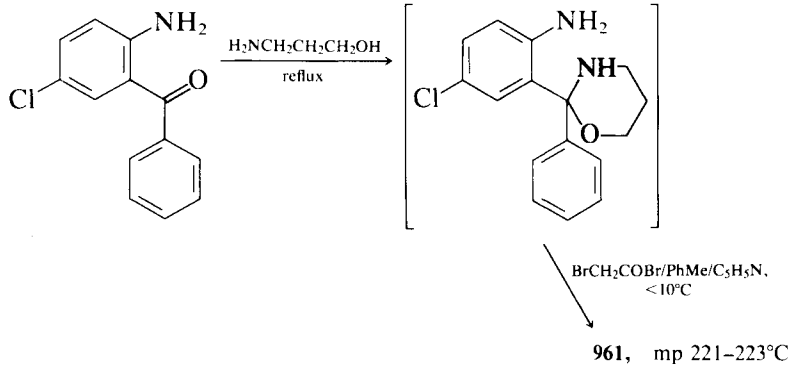

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | A | X | Reaction Conditions | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| Me | H | Ph | Cl | $H_2$ | Cl | $NEt_3$/EtOH, reflux | | 142–144 | 215 |
| H | H | H | H | O | Br | MeOH, reflux | 39 | 175–176 | 205 |
| H | Me | Ph | Cl | O | Br | NaOAc/EtOH, reflux | 18 | 172.5–176 | 206 |
| Me | H | Ph | Cl | O | Br | $CH_2Cl_2$/THF, reflux | 28 | 171.5–173 | 208 |
| H | H | Ph | Cl | O | TsO | NaOAc/MeOH, reflux | | 220.5–223 | 206 |

Under acidic conditions (Eq. 175), the tetrahydrooxazine ring of **961** was opened to give the quaternary salt **963** (225). The reaction could be reversed (225) by treating the quaternary iodide with triethylamine in benzene at room temperature. In a final variant (218), the diazepam derivative **961** could be prepared via a tetrahydrooxazine, as shown in Eq. 176. The anticonvulsant activity of **961** is significantly weaker than that of diazepam (205).




(175)

**963,** mp 230°C (dec.)

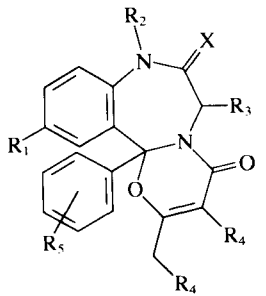



(176)

**961,** mp 221–223°C

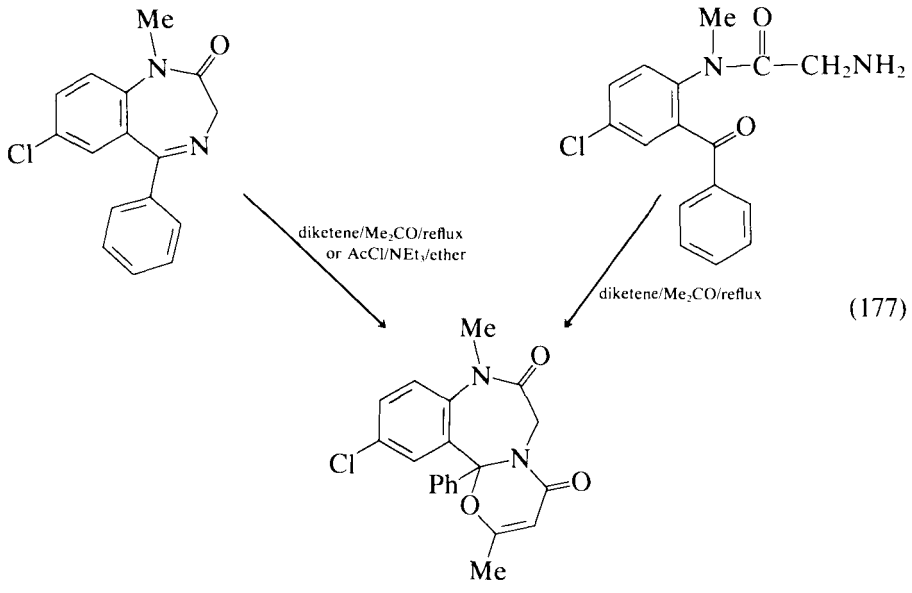
Szmuszkovicz and co-workers (457,458) reported that reaction of diazepam with diketene in acetone or with acetyl chloride and triethylamine in ether gave the tricyclic adduct **964** (Eq. 177). This compound has tranquilizing properties and has been given the generic name ketazolam. The structure of **964** was proved by X-ray crystallography; supporting infrared, ultraviolet, mass spectral, and extensive nmr data were provided as well. Analogs prepared by this method are listed in Table 105 (458). Minor variations in the synthesis have also been devised (459,460). In one of these, **964** was obtained directly (in 40% yield) from 2-(*N*-glycyl-*N*-methyl)amino-5-chlorobenzophenone and diketene in refluxing acetone (461).

TABLE 105. ANALOGS OF KETAZOLAM (**964**)



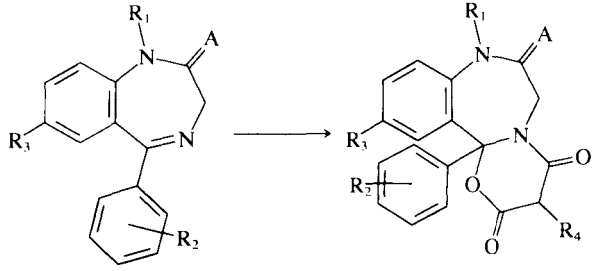
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | X | Method[a] | Yield (%) | mp (°C) | Spectra |
|---|---|---|---|---|---|---|---|---|---|
| Cl | Me | H | H | H | O | Cl | 64 | 182–183.5 | uv |
| | | | | | | Br | 44 | | |
| | | | | | | Dk | 64 | | |
| Cl | Me | H | Ph | H | O | Cl | 41 | 203–207 | uv |
| Cl | Me | H | H | 4-Cl | O | Cl | | 181–183 | uv |
| $CF_3$ | Me | H | H | H | O | Cl | | 134–136 | uv |
| Cl | Me | H | H | H | S | Cl | | 197 (dec.) | |
| CN | Me | H | H | H | O | Cl | | 154 | uv |
| $NO_2$ | Me | H | H | H | O | Dk | | 196–198 | |
| Cl | Me | H | Et | H | O | Cl | | 154–157 | uv |
| Cl | Me | H | Me | H | O | Cl | | 197–201 | uv |
| $NO_2$ | Me | H | H | 2-F | O | Dk | 26 | 199 | uv |
| Cl | Me | H | *i*-Pr | H | O | Cl | 66 | Oil | uv |
| Cl | *i*-Bu | H | H | H | O | Dk | 66 | 185–186 | uv |
| Cl | Me | OMe | H | H | O | Dk | 15 | 158–160 | uv |
| Cl | Me | H | H | 2-F | O | Dk | 30 | 175–177 | uv |
| Cl | H | H | H | H | O | Dk | 28 | 173 | uv |

[a]Cl and Br refer to preparation from the respective acid halides; Dk refers to preparation from diketene.




964 (177)

TABLE 106. [1,3]OXAZINO[3,2-*d*][1,4]BENZODIAZEPINE-2,4-DIONES BY TREATMENT OF DIAZEPAM AND ANALOGS WITH MALONIC ACIDS



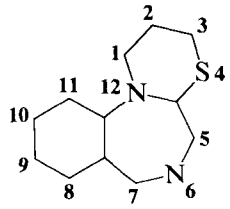

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | A | mp (°C)[a] |
|---|---|---|---|---|---|
| Me | H | Cl | H | O | 172–173 |
| Me | 2-F | Cl | H | O | 136–140 |
| Me | H | $NO_2$ | H | O | 200 |
| Me | H | Cl | Et | $H_2$ | 151 |
| Me | H | Cl | H | $H_2$ | 157 |
| H | H | Cl | Et | O | 176 |
| Me | H | Cl | Et | O | 170 |
| Me | H | $NO_2$ | Et | O | 210 |
| Me | 2-Cl | Cl | Et | O | 148 |
| Me | 2-F | Cl | Et | O | 158–162 |

[a]Decomposes.

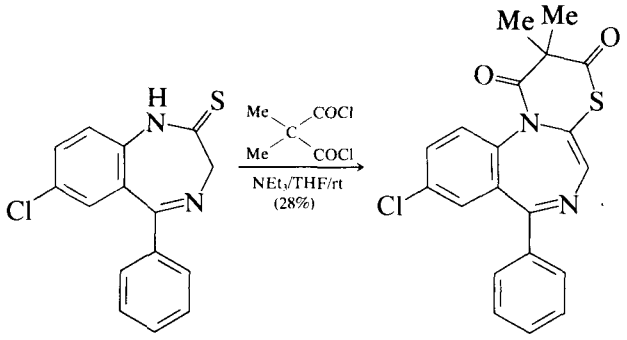
Ketazolam reverts to diazepam on attempted gas chromatographic analysis and even on dissolution in organic solvents. However, the substance is apparently quite stable on prolonged storage in the solid state (462).

Diazepam and analogs react with malonic acid in refluxing acetic anhydride (463). Substances prepared by this procedure are listed in Table 106.

## 8. [1,3]Thiazino[3,2-*a*][1,4]benzodiazepines



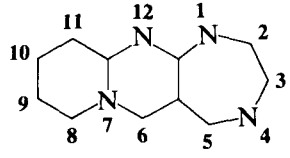
The sole example of the [1,3]thiazino[3,2-*a*][1,4]benzodiazepine structural type is compound **965**, which was prepared by reaction of the thiolactam shown in Eq. 178 with dimethylmalonyl chloride (456). This method is analogous to one that was used for the preparation of oxazine derivatives from related lactams (456).



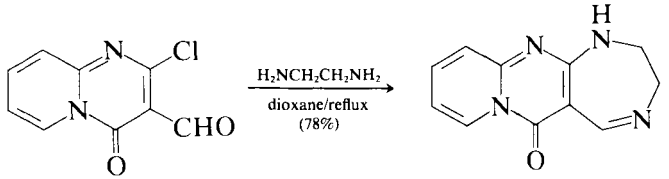
(178)

**965**, mp 210–211°C

## 9. Pyrido[1′,2′:1,2]pyrimido[4,5-*e*][1,4]diazepines



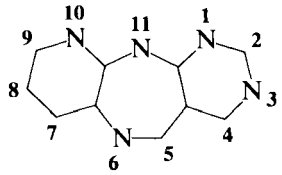
The only known substance having the pyrido[1′,2′:1,2]pyrimido[4,5-*e*]-[1,4]diazepine structure is compound **966,** which was obtained by reaction of a chloroaldehyde with ethylenediamine, as shown in Eq. 179 (464). The analogous reaction with 2-chloro-5-nitrobenzaldehyde apparently failed (464).



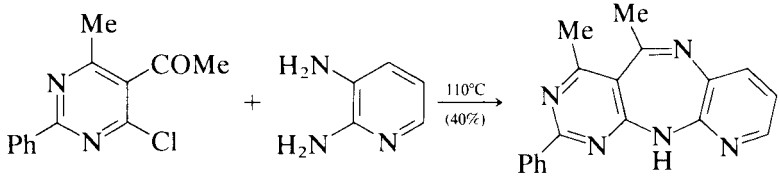

(179)

**966,** mp 310°C (ir, uv, nmr)

## 10. Pyrido[3,2-*b*]pyrimido[4,5-*e*][1,4]diazepines



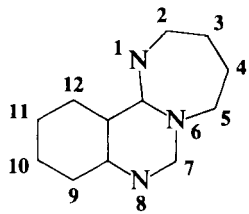

Attar and co-workers (465) prepared the only known pyrido[3,2-*b*]pyrimido[4,5-*e*][1,4]diazepine compound (**967**) by reaction of a 5-acyl-6-chloropyrimidine derivative with 2,3-diaminopyridine at 110°C in the absence of solvent (Eq. 180). Higher-melting pyrimidines could not be condensed successfully with the thermally labile diaminopyridine.



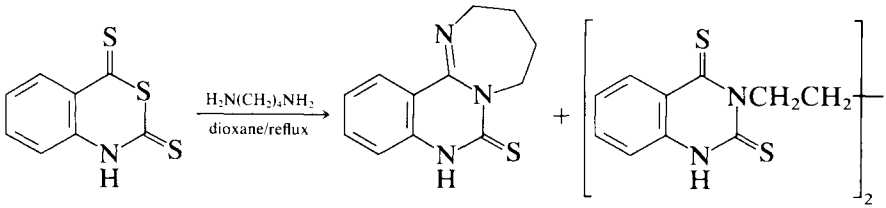

(180)

**967,** mp 195°C (ir, uv, nmr)

## 11. [1,3]Diazepino[1,2-*c*]quinazolines (see Section XVI.6)



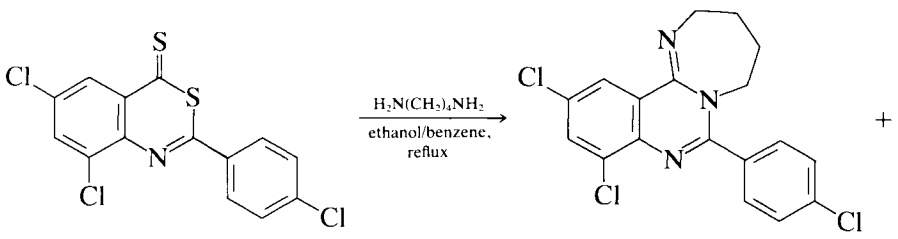
In 1973 Leistner and Wagner (466) prepared the first example of a [1,3]diazepino[1,2-*c*]quinazoline (**968**) by reaction of the dithione shown in Eq. 181 with 1,4-diaminobutane in refluxing dioxane. The tricyclic product **968** was obtained in 26% yield and was accompanied by 44% of the bis-quinazoline **969.** When the reaction was attempted in aqueous solution, only the dimeric product **969** was obtained. No analytic or spectroscopic data were provided.



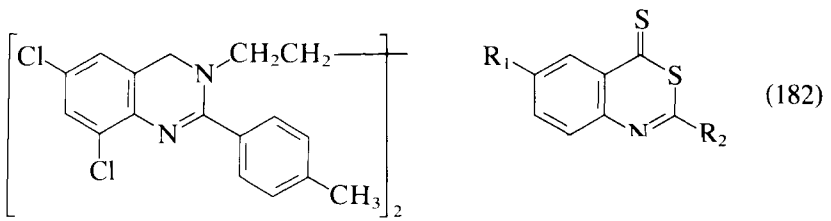

(181)

**968,** mp 154–157°C **969**

In related work (467) a second substance of this type (**970**) was prepared as shown in Eq. 182. An equal amount of the dimer **971** was also formed. Again, however, supporting physical data were not provided. When the reaction was attempted with substrates **972a** and **972b,** only dimeric products analogous to **971** were obtained.




**970,** 30%, mp 190°C

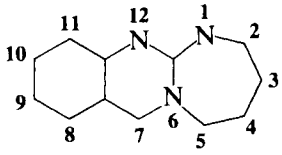


(182)

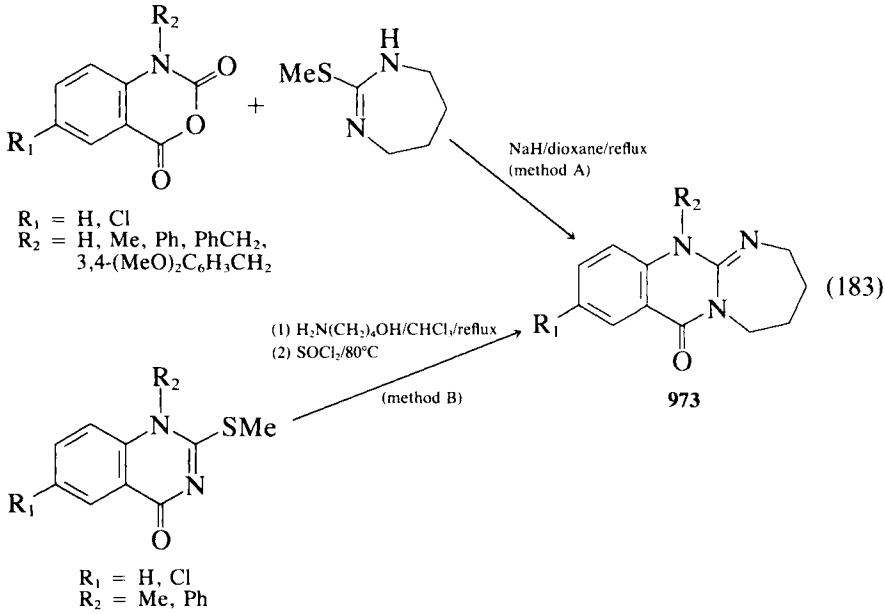
**971,** 30%; mp 138°C

**972a,** $R_1$ = Cl, $R_2$ = $CH_3$
**972b,** $R_1$ = H, $R_2$ = $C_6H_5$

## 12. [1,3]Diazepino[2,1-*b*]quinazolines

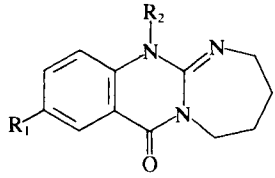


Two methods have been employed for the construction of the [1,3]diazepino[2,1-*b*]quinazoline ring system (Eq. 183). In the first (468), a suitably substituted isatoic anhydride was treated with a cyclic *S*-methylthiourea (method A). In the second, a 2-methylthioquinazolin-4-one was condensed with 4-hydroxybutylamine. Cyclization was effected with thionyl chloride (method B) (469). Substances prepared by these methods are listed in Table 107.




(183)

TABLE 107. 9,12-DISUBSTITUTED-2,4,5,12-TETRAHYDRO[1,3]DIAZEPINO[2,1-*b*]-QUINAZOLIN-7(3H)-ONES



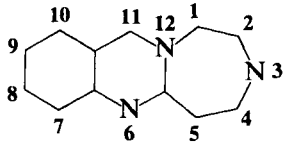
(*continued*)

TABLE 107. (*Continued*)

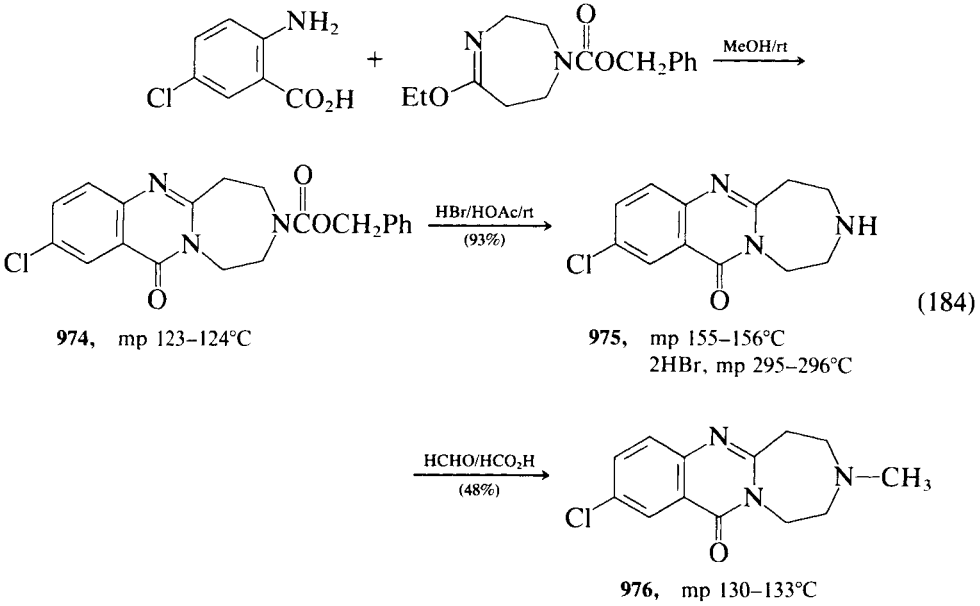
| $R_1$ | $R_2$ | Method[a] | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|
| Cl | Me | A, B | 118–119 | 22 | 468–472 |
| H | Ph | A, B | 118–123 | | 469,470,472 |
| H | H | A | 145–148 | | 470 |
| H | $PhCH_2$ | A | 103–105 | 25 | 468,471,472 |
| H | $3,4\text{-}(MeO)_2C_6H_3CH_2$ | A | 134–136 | | 471,472 |

[a]See Eq. 183.

## 13. [1,4]Diazepino[5,4-*b*]quinazolines (see Section XVI.7)




Examples of the [1,4]diazepino[5,4-*b*]quinazoline ring system are described in a single patent (473). Reaction of 5-chloroanthranilic acid with a cyclic imino ether in methanol at room temperature gave the tricyclic carbobenzyloxy derivative **974** (Eq. 184). Removal of the protecting group to give **975** was accomplished with hydrogen bromide in acetic acid at room temperature. Eschweiler–Clarke methylation gave **976.**



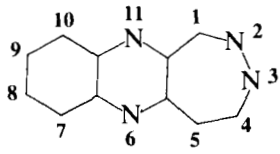

(184)

**974,** mp 123–124°C

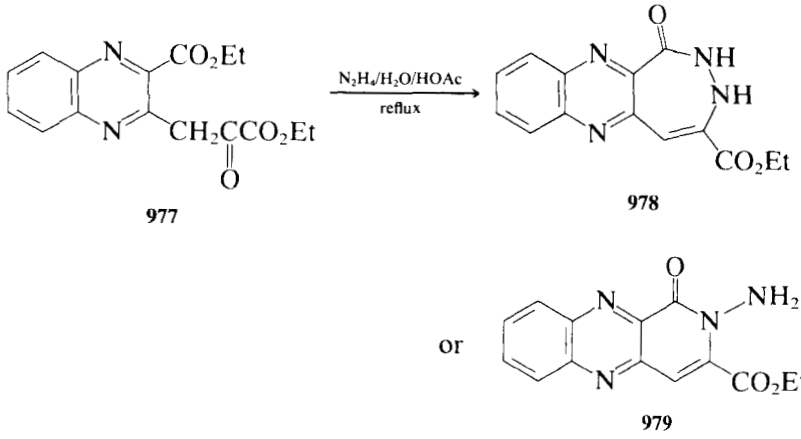
**975,** mp 155–156°C
2HBr, mp 295–296°C

**976,** mp 130–133°C

## 14. [1,2]Diazepino[4,5-*b*]quinoxalines



Treatment of the diester **977** with hydrazine in refluxing aqueous acetic acid (Eq. 185) gave a product that was formulated (474) as either **978** or **979.** Structure **978** was favored on the basis of ultraviolet spectra. The primary absorption maximum in dimethylformamide solution was at 284 nm, with secondary peaks at 310 and 415 nm. Analogs of **979** (alkyl or aryl groups instead of $NH_2$) had main absorption maxima between 465 and 410 nm.

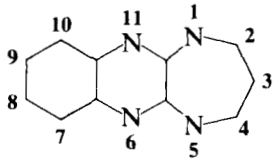


977 978 (185)

or

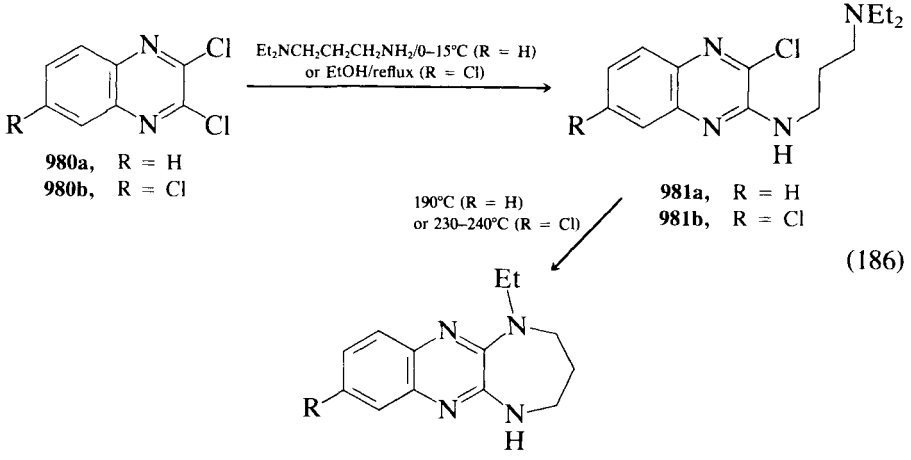
979

## 15. [1,4]Diazepino[2,3-*b*]quinoxalines



Two examples of the [1,4]diazepino[2,3-*b*]quinoxaline ring system have been prepared (475,476), as shown in Eq. 186. Reaction of the quinoxalines **980** with diethylaminopropylamine gave the monosubstituted derivatives **981,**

which on pyrolysis led to the tricyclic substances **982.** The site of substitution in **981b** was inferred by analogy with the α-piperidinopropylamino derivative, for which a satisfactory proof of structure was provided (476).



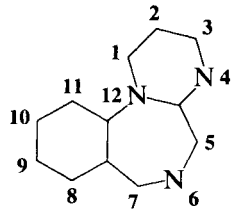

**980a,** R = H
**980b,** R = Cl

**981a,** R = H
**981b,** R = Cl

(186)

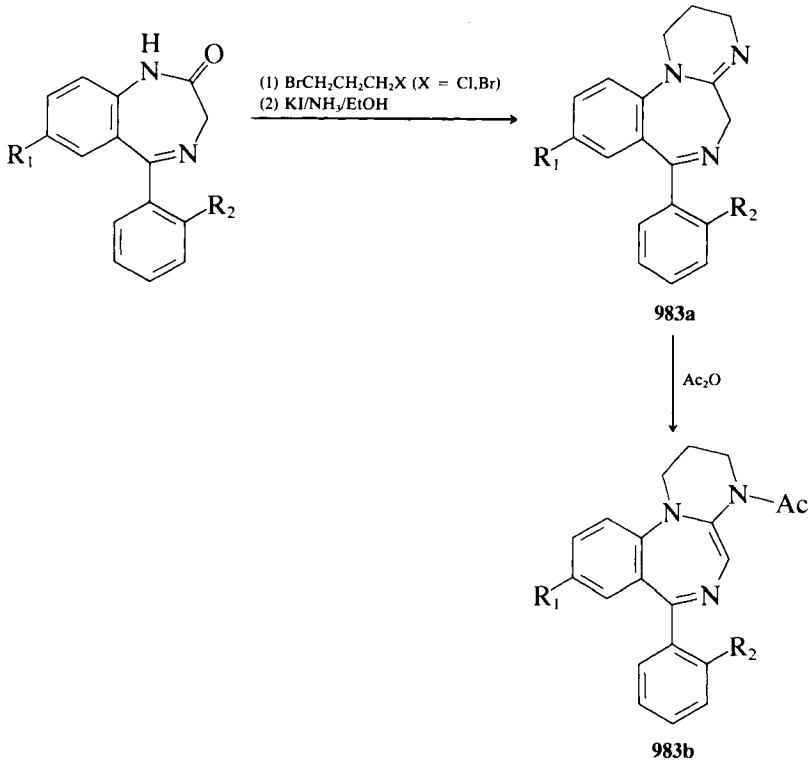
**982a,** R = H; mp 147°C
**982b,** R = Cl, 23%; mp 148°C

## 16. Pyrimido[1,2-*a*][1,4]benzodiazepines (see Section XVI.10)



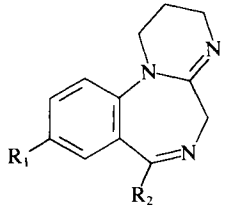
The first synthesis of pyrimido[1,2-*a*][1,4]benzodiazepines was reported in 1968 (285). *N*-Alkylation of a suitable benzodiazepinone with 1-bromo-3-chloropropane was followed by cyclization with potassium iodide and ammonia in ethanol at 75°C. A later patent (284) described the use of 1,3-dibromopropane; the resulting 3-bromopropyl intermediate could be cyclized to **983** at room temperature with addition of potassium iodide. Acetylation of **983** with acetic anhydride at room temperature gave the $N^4$-acetyl derivative **984** with concomitant double bond migration (477). These sequences are described in Eq. 187 and substances prepared by these procedures are listed in Tables 108 and 109.

There are conflicting claims in the literature as to the outcome of the reaction of 2-aminobenzodiazepines with diketene followed by cyclization of the product. One patent (478) describes the reaction of **984** with diketene




(187)

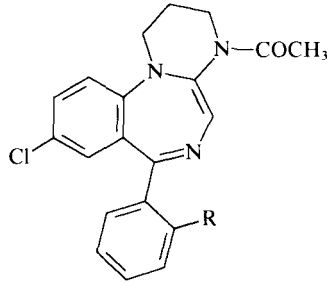
TABLE 108. 7,9-DISUBSTITUTED 1,2,3,5-TETRAHYDROPYRIMIDO [1,2-*a*][1,4]BENZODIAZEPINES




| $R_1$ | $R_2$ | Salt | Method[a] | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| Cl | Ph | | A, B | | 155–157 | 284,285 |
| Cl | Ph | HI | A | 44 | 270–275 | 285 |
| Cl | 2-$FC_6H_4$ | | A, B | | 161.5–163 | 284,285 |
| Cl | 2-$FC_6H_4$ | HI | A | 65 | 286–289 | 285 |
| | | HCl | B | | 279–280 | 284 |
| Br | 2-Pyridyl | | A | | 178–181 | 285 |
| Br | 2-Pyridyl | HI | A | 35 | 272–275 | 285 |
| $CF_3$ | Ph | | A | | 179–181 | 285 |
| $CF_3$ | Ph | HI | A | | 278–282 | 285 |
| H | Ph | | A | | 143–145 | 285 |

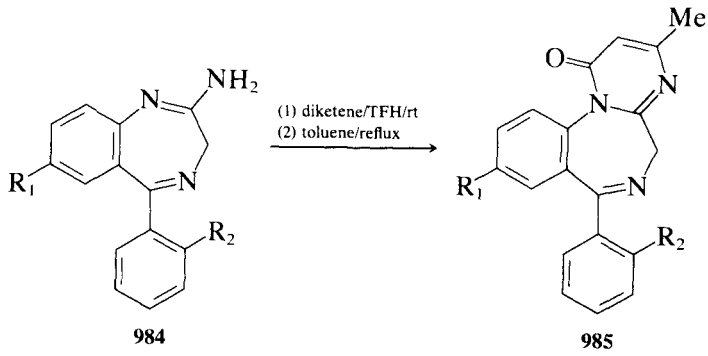
[a]Method A: $BrCH_2CH_2CH_2Cl$; method B: $BrCH_2CH_2CH_2Br$ (see text).

TABLE 109. 4-ACETYL-7-ARYL-9-CHLORO-1,2,3,4-TETRAHYDROPYRIMIDO-[1,2-*a*][1,4]BENZODIAZEPINES




| R | mp (°C) | Ref. |
|---|---|---|
| H | 224–225 | 477 |
| F | 188–190 | 477 |

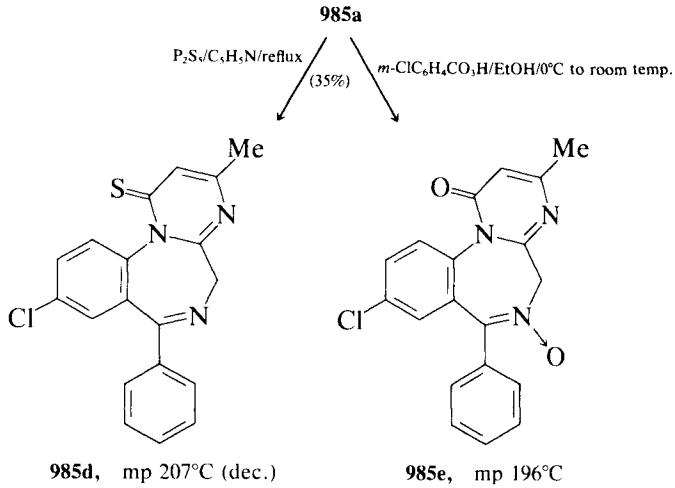
in tetrahydrofuran at room temperature followed by cyclization in refluxing toluene (Eq. 188). Conversion of **985a** to the thione **985d** and the $N^6$-oxide




**984** **985** (188)

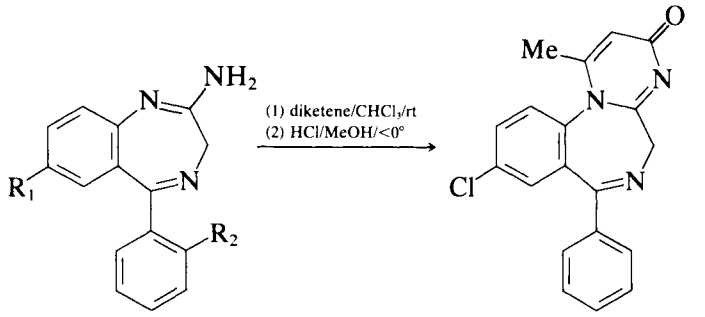
| | $R_1$ | $R_2$ | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|
| **985a** | Cl | H | 14 | 193–194 | 478 |
| **985b** | Cl | Cl | 14 | 198–200 | 478 |
| **985c** | $NO_2$ | H | — | 232.5–234 | 478 |

**985e** were also reported (Eq. 189). A later patent (479) describes reactions run with diketene in chloroform at room temperature. Cyclization was effected with methanolic hydrogen chloride below 0°C. These products were given the alternative formulation **985f** (Eq. 190). Substances prepared by this method are listed in Table 110. Melting points of potentially identical substances in the two series do not coincide. In the absence of spectroscopic data, it is impossible to make a firm structural assignment to the substances prepared by these two procedures (478,479).




**985d**, mp 207°C (dec.) **985e**, mp 196°C

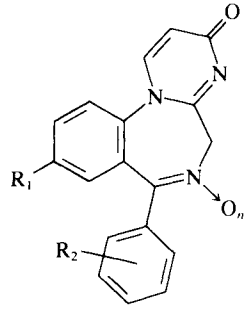
(189)




**984**, $R_1$ = Cl, $R_2$ = H **985f**, mp 232–234°C (dec.)

(190)

TABLE 110. PYRIMIDO[1,2-*a*][1,4]BENZODIAZEPIN-3-ONE DERIVATIVES



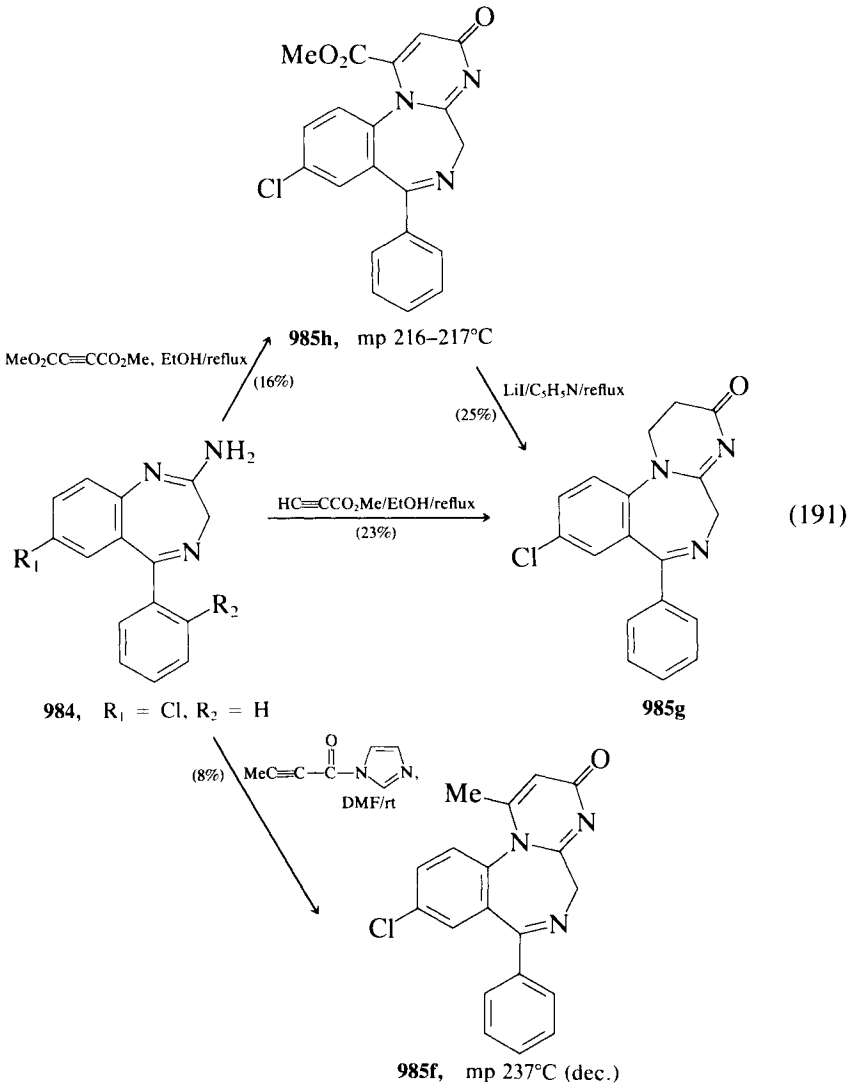

| $R_1$ | $R_2$ | *n* | mp (°C)[a] |
|---|---|---|---|
| Cl | H | 0 | 232–234[b] |
| Cl | H | 1 | 243–245[c] |
| $CF_3$ | H | 1 | 250–251 |
| $NO_2$ | H | 1 | 240–242 |

(*continued*)

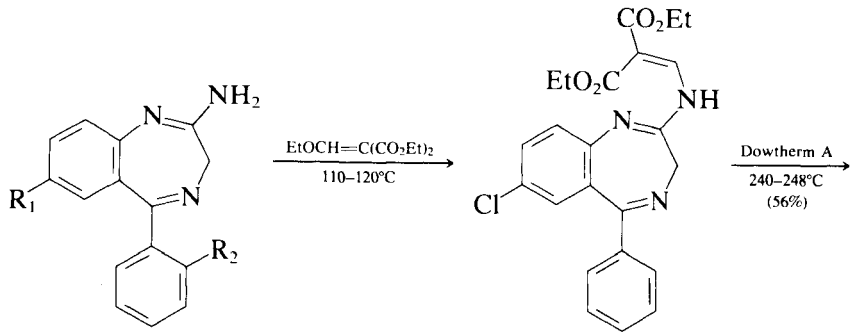
TABLE 110. (*Continued*)

| $R_1$ | $R_2$ | *n* | mp (°C)[a] |
|---|---|---|---|
| H | H | 0 | 192–193 |
| $NO_2$ | H | 0 | >280 |
| Me | H | 0 | 205–209 |
| Cl | *p*-MeO | 0 | 249–250 |
| Cl | *o*-Cl | 0 | 169–170 |

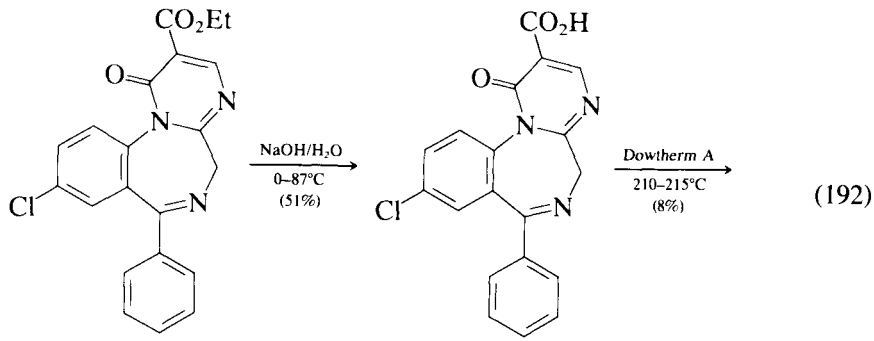
[a]Decomposes.
[b]Also prepared by treatment of the *N*-oxide with $PCl_3$ in refluxing $CHCl_3$.
[c]Prepared by oxidation of the corresponding imine with *m*-chloroperbenzoic acid in dichloromethane at room temperature.



Substances assigned structures with the carbonyl group in the 3-position have also been claimed (480). These were obtained by condensation of the amidine **984** ($R_1$ = Cl, $R_2$ = H) with $\alpha,\alpha$-acetylenic esters (Eq. 191). Reaction with methyl propiolate in ethanol or methanol at room temperature or at reflux gave the adduct **985g** in yields of up to 23%. Condensation with the imidazole derivative of $\beta$-methylpropiolic acid was accomplished in low yield, to give **985f,** the product claimed in one of the diketene procedures (Eq. 190). Again, no spectroscopic data are available, but the melting points of the substances obtained by the two procedures were very similar. Reaction with dimethyl acetylenedicarboxylate was also carried out, and the resulting



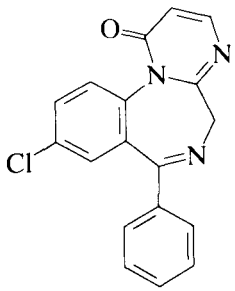

**984,** $R_1$ = Cl, $R_2$ = H




(192)

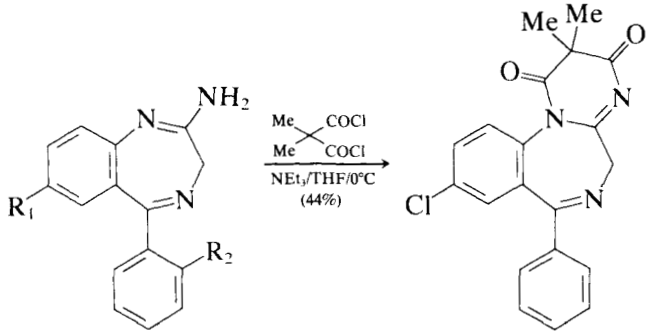
**985i,** mp 139–140°C

**985j,** mp 195°C (dec.)



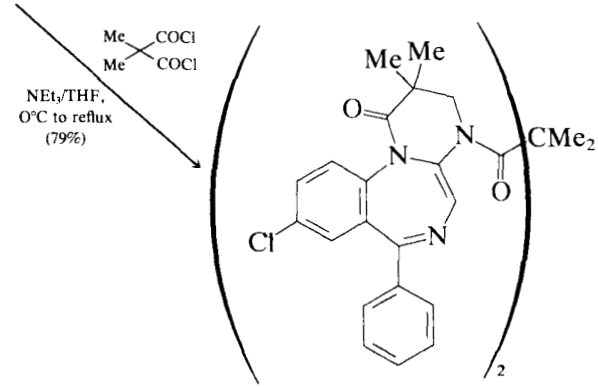

**985k,** mp 187–188.5°C

ester (**985h**) was decarbomethoxylated with lithium iodide in refluxing pyridine to give a product identical with the one obtained with methyl propiolate (Eq. 191). Use of diethyl ethoxymethylenemalonate led to tricyclic products assigned the structures **985i–k,** in which the carbonyl group is at the 1-position (Eq. 192). Again, no structural proof is available (481). Lastly, reactions with dimethylmalonyl chloride (456) led to the tricyclic adducts **985l–985n,** in which carbonyl groups are present at both the 1- and 3-positions (Eqs. 193 and 194).



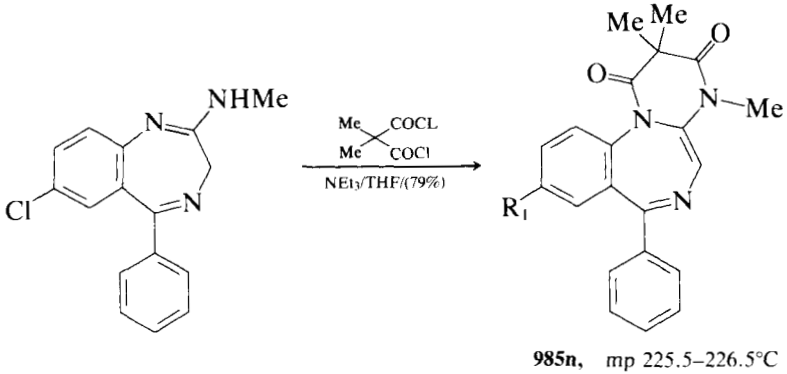

**984,** $R_1$ = Cl, $R_2$ = H

**985l,** mp 261.5–265°C




(193)

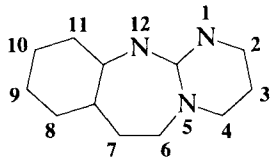
**985m,** mp 198–230°C (dec.)



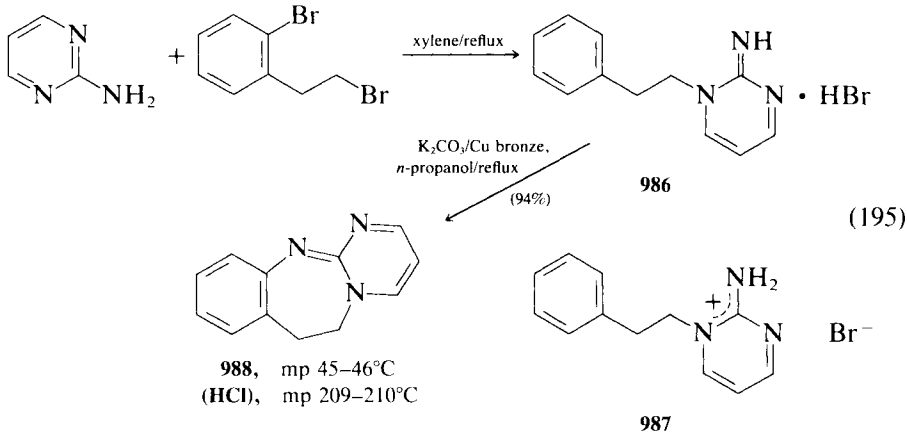

(194)

**985n,** mp 225.5–226.5°C

## 17. Pyrimido[2,1-*b*][1,3]benzodiazepines

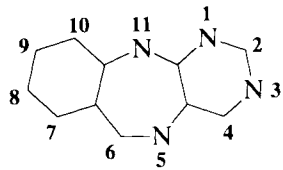


A single example of the pyrimido[2,1-*b*][1,3]benzodiazepine structural type has been prepared (Eq. 195). Reaction of 2-bromophenethylbromide with 2-aminopyrimidine in refluxing xylene gave the 1-substituted 2-pyrimidinimine hydrobromide **986.** The authors (482) cite nmr evidence suggesting that a more accurate formulation for this product is given by **987.** The free base was readily obtained and could be cyclized to **988** with copper bronze in refluxing *n*-propanol. Alternatively, the salt could be cyclized directly with copper bronze and potassium carbonate in refluxing *n*-propanol.

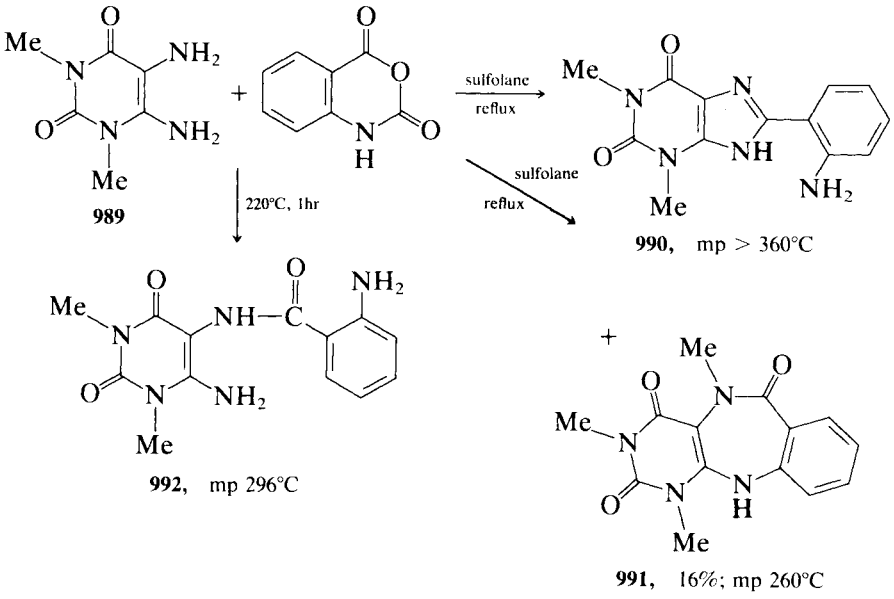



(195)

## 18. Pyrimido[4,5-*b*][1,4]benzodiazepines (see Section XVI.11)



In an initial study of the reaction of the 4,5-diaminouracil **989** with isatoic anhydride in refluxing sulfolane (Eq. 196), a mixture of the purine derivative **990** and the pyrimido[4,5-*b*][1,4]benzodiazepine **991** was obtained. Separation was effected by fractional crystallization (483). When the starting materials were heated at 220°C without solvent, only the amide **992** was produced.




**989**

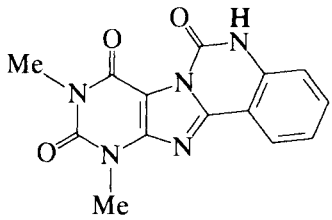
**990**, mp > 360°C

**991**, 16%; mp 260°C

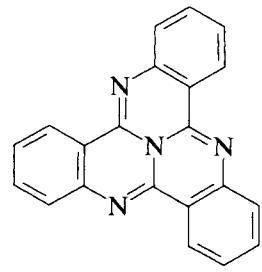
**992**, mp 296°C

(196)

When **992** was heated in sulfolane, a mixture of **990** and **991** was again produced, but when **992** was refluxed in phosphoryl chloride, only **990** was formed. In a later investigation (484), the by-products **993** and **994** were isolated in addition to **990** and **991** when **989** was treated with isatoic anhydride in refluxing sulfolane. When 6-chloro- or *N*-methylisatoic anydride was used in this reaction, products analogous to **991** were not isolated.

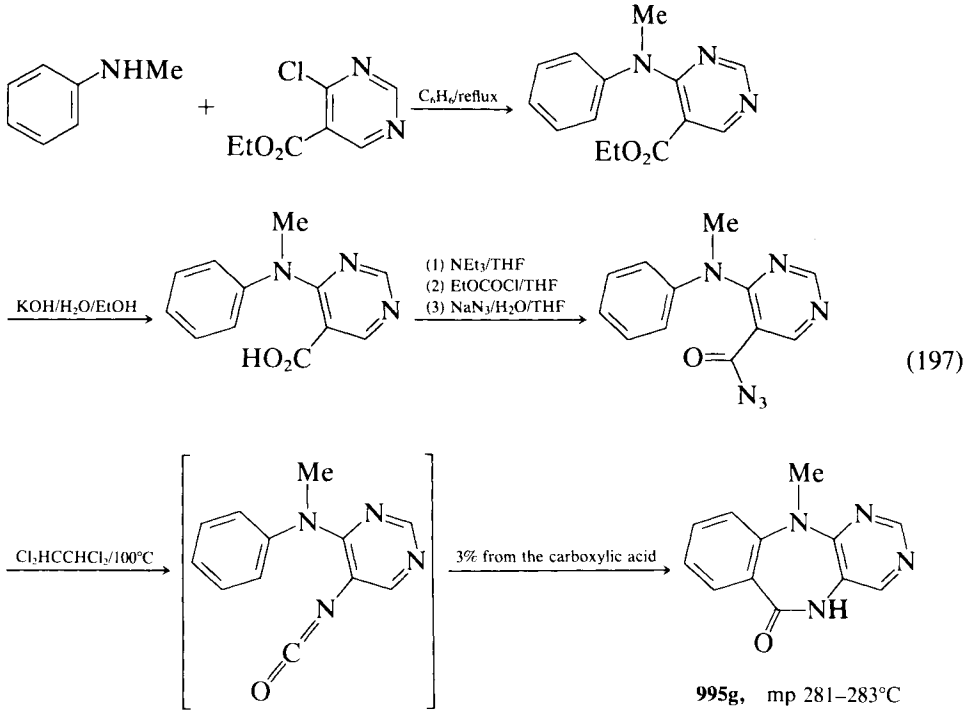


**993**, mp >320°C



**994**, mp 322°C

A conceptually similar plan was used to prepare a series of substances claimed to have antihypoxic and antipyretic activities (485). In this synthesis (Fig. 71) 4,6-dichloro-5-nitropyrimidine was condensed with an anthranilate ester. The nitro group of the resultant adduct was reduced, and the remaining chloro substituent was simultaneously hydrogenolyzed. The product was then cyclized to **995a** by heating at 160°C. The preparation of additional derivatives (**995b–995e**) is described in Fig. 71, and compounds prepared by these procedures are listed in Table 111. A similar synthesis involving cyclization of a 4-ethoxypyrimidine derivative is shown in Fig. 72. The third synthesis described by the same workers is given in Eq. 197. The key step is the *in situ* cyclization of a 4-anilino-5-isocyanatopyrimidine to give **995g.**




(197)

**995g,** mp 281–283°C

Pyrimido[4,5-*b*][1,4]benzodiazepines have also been prepared from benzodiazepinones (486). As shown in Eq. 198, reaction of benzodiazepinones with formamide in phosphoryl chloride at 110°C in a sealed vessel gave anilinopyrimidines, which could be cyclized to **996a** and **996b** with *p*-toluenesulfonic acid in refluxing ethyl acetate/ethanol or, in the case of the chloro compound, merely by heating in dimethyl sulfoxide at 70°C. The

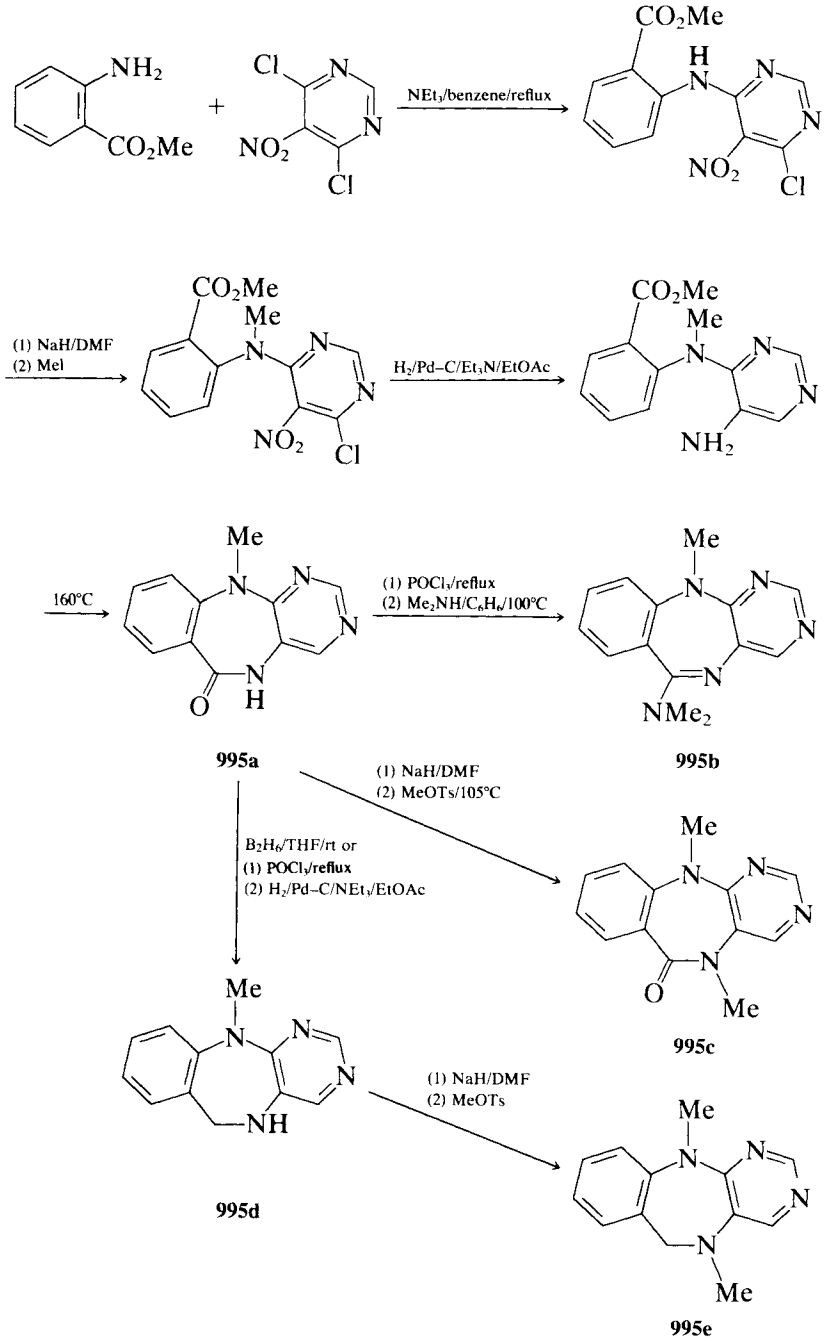
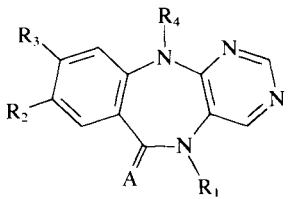

NEt3/benzene/reflux
(1) NaH/DMF
(2) MeI
H2/Pd–C/Et3N/EtOAc
160°C
(1) POCl3/reflux
(2) Me2NH/C6H6/100°C
995a
995b
(1) NaH/DMF
(2) MeOTs/105°C
B2H6/THF/rt or
(1) POCl3/reflux
(2) H2/Pd–C/NEt3/EtOAc
995c
(1) NaH/DMF
(2) MeOTs
995d
995e

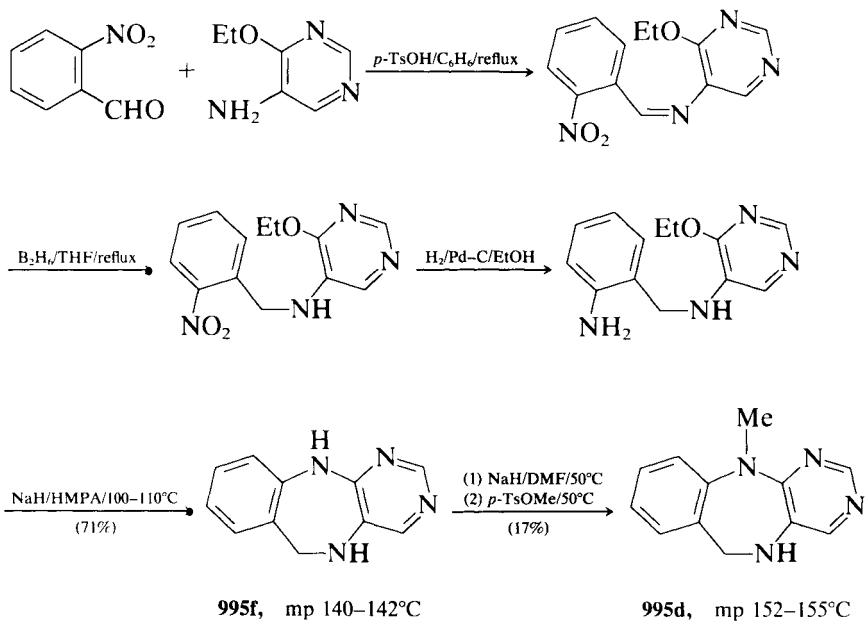
**Figure 71**

TABLE 111A. PYRIMIDO[4,5-*b*][1,4]BENZODIAZEPIN-6-ONES AND REDUCED DERIVATIVES



| $R_1$ | $R_2$ | $R_3$ | $R_4$ | A | Salt | mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|---|
| H | H | H | Me | O | | 282–284 | 82 |
| H | Cl | H | Me | O | | 318–320 | 60 |
| Me | H | H | Me | O | HCl | 214–223 (dec.) | 72 |
| H | H | H | Me | $H_2$ | | 155–157 | 93[a] |
| | | | | | | | 30[b] |
| H | Cl | H | Me | O | | 200–202 | 36 |
| Me | H | H | Me | $H_2$ | | 91–93 | |
| | | | | | HCl | 253–257 | 35 |
| H | H | H | $CH_2Ph$ | O | | 242.5–244 | 74 |
| H | H | H | $CH_2Ph$ | $H_2$ | | 118.5–119.5 | 84[a] |
| Me | Cl | H | Me | O | | 116–118 | 66 |
| Me | Cl | H | Me | $H_2$ | | 132–134 | 74 |
| H | H | Cl | Me | O | | 298–315 | 48 |
| H | H | Cl | Me | $H_2$ | | 217–218 | 25 |
| H | Me | H | Me | O | | 285–286 | 49 |
| H | Me | H | Me | $H_2$ | | 131 | 40 |

[a]Prepared by hydrogenation of the imino chloride.
[b]Prepared by borane reduction of the lactam.

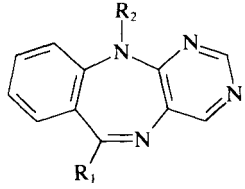



**995f,** mp 140–142°C **995d,** mp 152–155°C

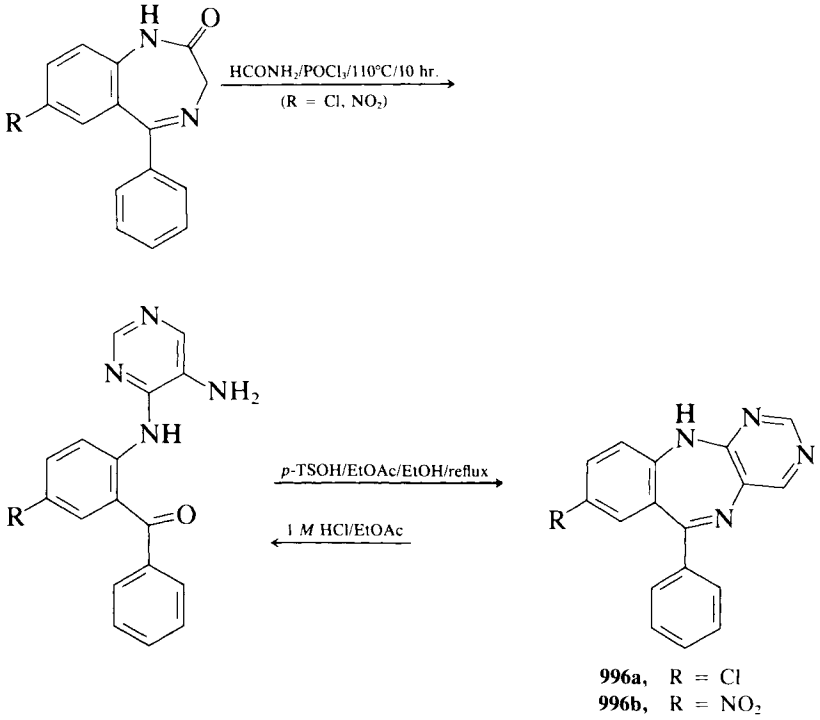
**Figure 72**

anilinopyrimidines were regenerated when **996a** and **996b** were treated with 1 *M* HCl in ethyl acetate. Thione and amidine analogs could also be used as starting materials for this sequence (Eq. 198).

TABLE 111B. PYRIMIDO[4,5-*b*][1,4]BENZODIAZEPIN-6-ONES AND REDUCED DERIVATIVES



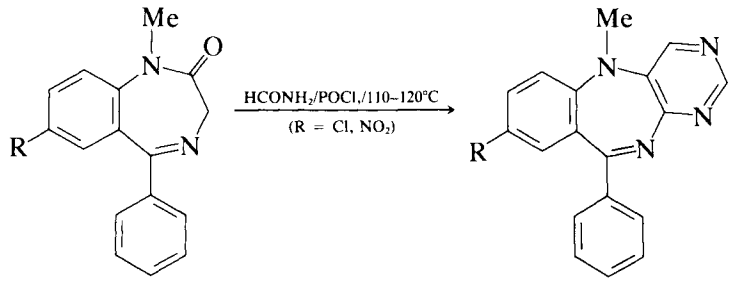

| $R_1$ | $R_2$ | mp (°C) | Yield (%) |
|---|---|---|---|
| Cl | Me | 126–128 | 43 |
| $NMe_2$ | Me | 119.5–122 | 100 |
| NH–  | Me | 268–270 | 95 |
| $NHCH_2Ph$ | Me | 245–247 | 93 |
| $NHCH_2CH_2NMe_2$ | Me | 162–163.5 | 92 |
| Cl | $CH_2Ph$ | 111.5–113 | 67 |




(198)

**996a**, R = Cl
**996b**, R = $NO_2$

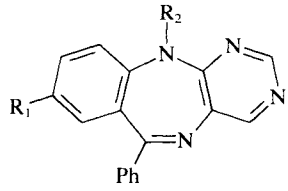
When *N*-methyl lactams were used, the tricyclic products **997a** and **997b** were formed directly (Eq. 199). The structural assignments were supported by extensive nmr, ir, and mass spectral data, and a discussion of the mechanism of the formamide/phosphoryl chloride reaction was presented. Substances prepared in this study are listed in Table 112.




(199)

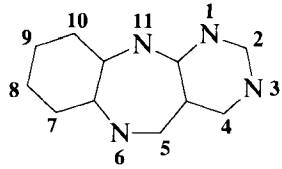
**997a**, R = Cl
**997b**, R = $NO_2$

TABLE 112. 6-PHENYLPYRIMIDO[4,5-*b*][1,4]BENZODIAZEPINE DERIVATIVES

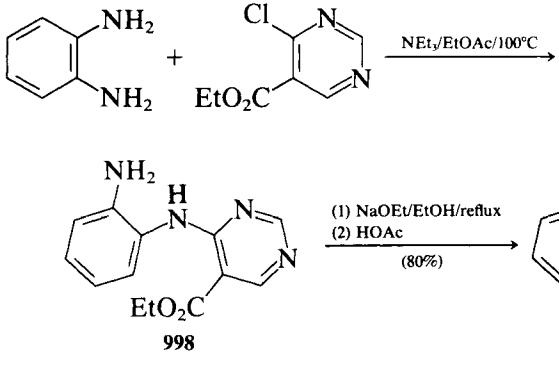


| $R_1$ | $R_2$ | mp (°C) | Yield (%) | Spectra |
|---|---|---|---|---|
| Cl | H | 240–241 | 96 | ms, nmr, uv |
| $NO_2$ | H | 261–262 | 94 | ms, nmr, uv |
| Cl | Me | 208–209 | 18 | ms, nmr, uv |
| $NO_2$ | Me | 163–164 | 24 | ms, nmr, uv |

## 19. Pyrimido[4,5-*b*][1,5]benzodiazepines (see Section XVI.12)



A single example of the pyrimido[4,5-*b*][1,5]benzodiazepine structural type has been described (487). As shown in Eq. 200, condensation of a 4-chloropyrimidine with *o*-phenylenediamine gave the 4-anilinopyrimidine **998**, which was cyclized to **999** with sodium ethoxide in refluxing ethanol. Use of *o*-nitroaniline in this sequence was not successful. Alkylation of **999** with 3-dimethylaminopropyl chloride could not be achieved.

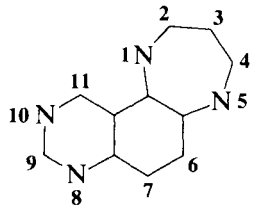


(200)

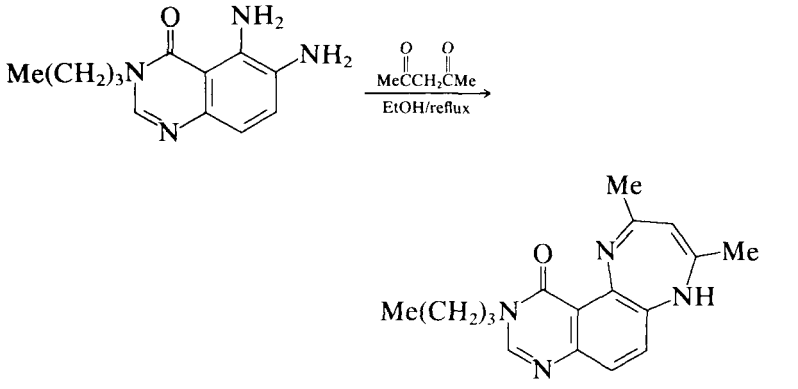
**998**

**999**, mp > 300°C (ir, uv, ms)

## 20. Pyrimido[5,4-*g*][1,5]benzodiazepines



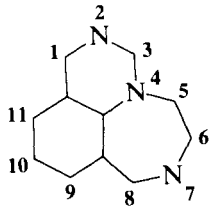
Reaction of 2,4-pentanedione with a diaminoquinazoline, as shown in Eq. 201, gave the adduct **1000** as the sole known example of the pyrimido[5,4-*g*][1,5]benzodiazepine ring system (488). Structural assignment was based on the absence of $NH_2$ absorption and the presence of NH absorptions in the ir and nmr spectra, the absence of ir carbonyl peaks (other than the one due to the quinazoline carbonyl at 1665 $cm^{-1}$), and the inability of the substance to form an enol acetate on heating with acetic anhydride at 100°C.



(201)

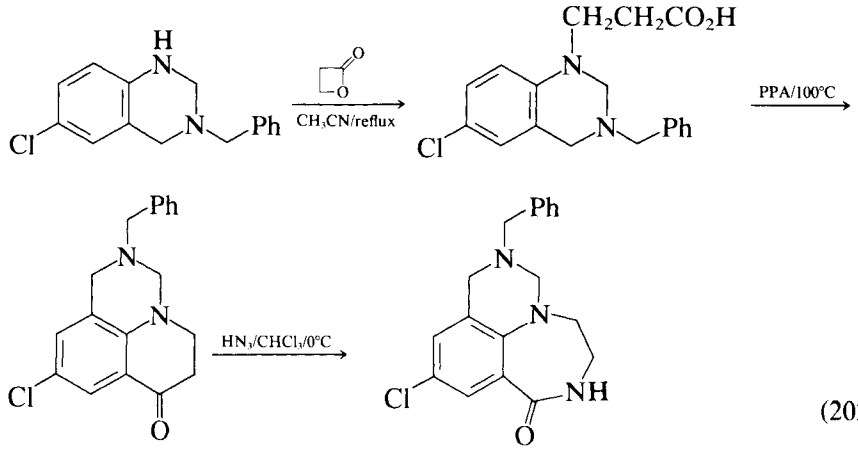
**1000,** mp 122–123°C (nmr, ir, uv)

## 21. Pyrimido[5,6,1-*jk*][1,4]benzodiazepines



Pyrimido[5,6,1-*jk*][1,4]benzodiazepines have been prepared by the fusion

of a diazepine ring onto a quinazoline precursor (489). The synthetic method employed is shown in Eq. 202, the key step being the Schmidt reaction of the tricyclic ketone **1001.** The nature of the ring-expanded product **1002** was determined from the nmr spectrum of the reduced compound **1003.**



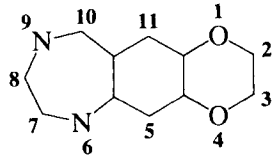

(202)

**1001**

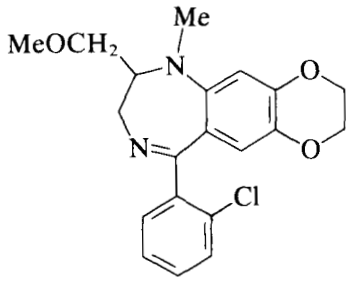
**1002,** mp 154–155°C (nmr)

**1003,** bp 158–163°C/0.002 Torr (nmr)

## 22. 1,4-Dioxino[2,3-*h*][1,4]benzodiazepines

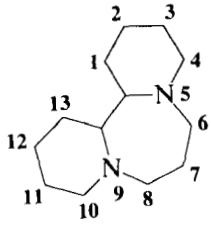


The 1,4-dioxino[2,3-*h*][1,4]benzodiazepine ring system is represented in the literature by a single entry (**1004**). No spectral or analytical data were provided (490), and the method of synthesis was not specified.

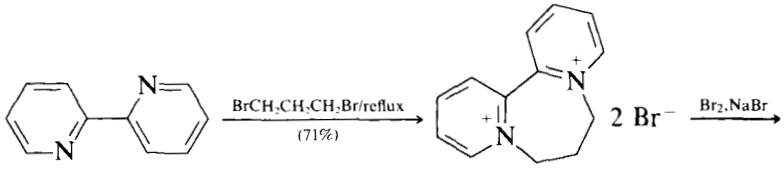


**1004a,** mp 152–155°C

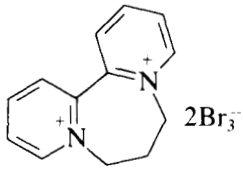
## 23. Dipyrido[1,2-*a*:2′,1′-*c*][1,4]diazepines (see Section XVI.13)



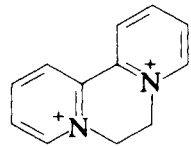
The prototype of the dipyrido[1,2-*a*:2′,1′-*c*][1,4]diazepine family was synthesized (Eq. 203) as an analog of the ethylene-bridged dipyridinium salt **1005,** a potent phytotoxic agent (491). It was concluded that the phytotoxicity of **1005** was a consequence of its redox properties, the substance apparently



**1006a,** mp > 300°C (uv);
redox potential = −548 ± 3 mV ($H_2O$) (203)



**1006b,** mp 161–163°C

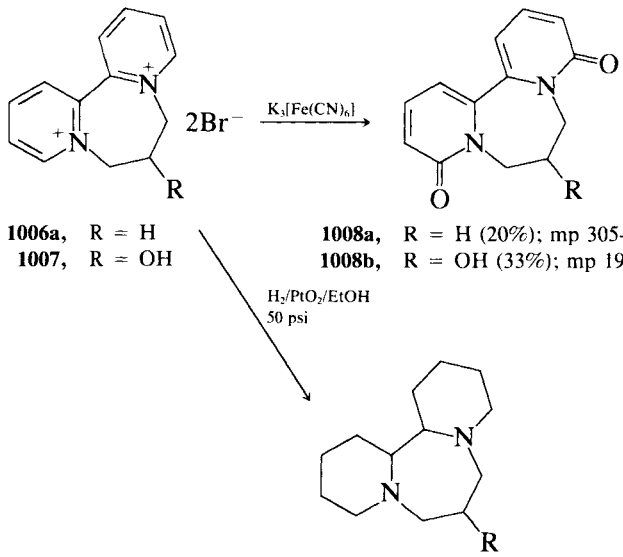


2 $Br^-$

**1005,** redox potential = $-349 \pm 3$ mV ($H_2O$)

being reduced in the plant to a free radical, stable in aqueous solution, by processes connected with photosynthesis and respiration. The trimethylene-bridged salt **1006a** was found to be a relatively weak phytotoxic agent. In keeping with this finding, it was noted that the redox potential of this substance was significantly lower than that of **1005.** The difference between **1006a** and **1005** was attributed to the inability of the aromatic rings in **1005** to assume coplanar geometry. Further examples prepared by the general method given in Eq. 203 are listed in Table 113.

Oxidation of the dipyridinium salts **1006a** and **1007** (Eq. 204) with potassium ferricyanide gave the dipyridones **1008a** and **1008b,** whereas catalytic hydrogenation resulted in the formation of perhydro derivatives **1009a** and **1009b** (494).




**1006a,** R = H
**1007,** R = OH

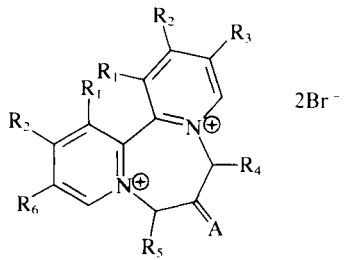
**1008a,** R = H (20%); mp 305–307°C
**1008b,** R = OH (33%); mp 194–196°C

(204)

**1009a,** R = H (94%); mp 270–272°C (ms),
picrate, mp 237–239°C,
methiodide, mp 247–248°C

**1009b,** R = OH (95%); mp 253–285°C
dipicrate, mp 232–234°C
dimethiodide, mp 221–223°C

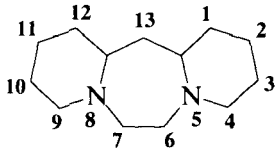
TABLE 113. BIS(QUATERNARY)DIPYRIDO[1,2-*a*:2′,1′-*c*][1,4]DIAZEPINE BROMIDES



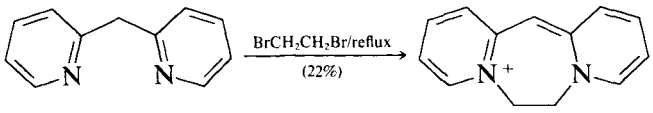

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | A | Yield (%) | mp (°C) | Other Data | Refs. |
|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | H | H | H | O | 64 | 240–250 (hydrate) | nmr, uv | 492 |
| H | H | H | Me | Me | H | O | 74 | 210–260 (dihydrate) | nmr, uv | 492 |
| Me | H | H | H | H | H | $H_2$ | | 310–313 | nmr, uv | 493 |
| H | Me | H | H | H | H | $H_2$ | | 335–340 | nmr, uv | 493 |
| H | H | Me | H | H | Me | $H_2$ | | >300 (dec) | nmr, uv | 493 |
| H | H | H | H | H | H | H, OH | 21 | >360 | | 494 |
| H | H | H | Me | H | H | $H_2$ | 30 | 271–272 | | 494 |
| H | H | OH | H | H | H | $H_2$ | 60–80 | >330 | nmr, uv | 495 |
| H | H | MeO | H | H | H | $H_2$ | 60–80 | 230 | nmr, uv, reduction potential | 495 |

Because of its unique redox properties, **1006a** has been used to study the oxidation potential of the photochemically generated reducing material in isolated chloroplasts (496) and in systems containing bacterial chromatophores (447) or isolated chlorophyll (498). Electron transfer from the cation radical of **1006a** to cytochrome c (499), and from the same cation radical to flavin adenine dinucleotide (500), has been examined. A polarographic study of the reduction of **1006a** has also been reported (501), and the substance was found to enhance the catalytic activity of the molybdenum V-cysteine complex for acetylene reduction (502). There are patents claiming the use of **1006a** in photographic emulsions (503) and developers (504). The bromine addition product **1006b**, patented for use as a herbicide and defoliant, was prepared by the addition of a bromine/sodium bromide solution to an aqueous solution of **1006a** (505).

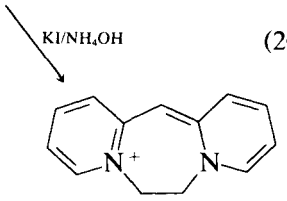
## 24. Dipyrido[1,2-*d*:2′,1′-*g*][1,4]diazepines




Treatment of di(2-pyridyl)methane with 1,2-dibromoethane under reflux gave the monoquaternary bromide **1010a**, which was readily converted to the iodide **1010b** (506). It was noted that the bromide **1010a** (Eq. 205) gave an intense green fluorescence in ethanol solution at room temperature. In an earlier publication (507), absorption, emission, and polarized excitation




**1010a**, mp 200°C (dec.)

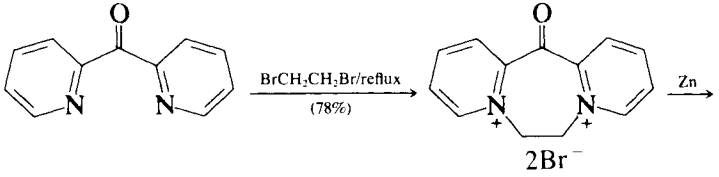



(205)

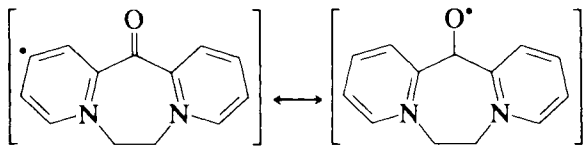
**1010b**, mp 223–224°C (dec.)

spectra for **1010a** were presented. Calculated values for the electronic transitions were compared with those obtained experimentally. The results of an nmr study (508) suggested that the molecule exists in a twisted rather than a planar conformation.

When di(2-pyridyl)ketone was refluxed with 1,2-dibromoethane (509), the bisquaternary salt **1011** was formed (Eq. 206). When **1011** in aqueous solution

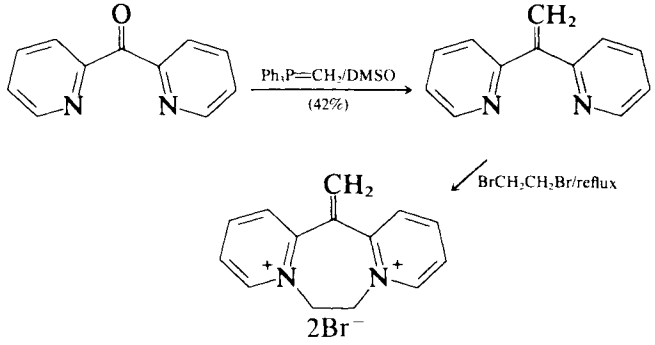



**1011,** mp 292°C (dec.) (uv, ir, nmr)



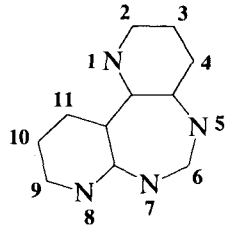

**1012** **1013** (206)

was reduced with zinc dust, a red coloration, sensitive to air, was produced. It was suggested that this was due to the formation of a radical cation. Two of the possible resonance forms (**1012** and **1013**) are shown in Eq. 206. When the sequence was repeated with 1,1-di(2-pyridyl)ethylene (510), a bisquaternary salt (**1014**) was again obtained (Eq. 207). However, no evidence for radical cation formation was obtained when **1014** was reduced with zinc dust or by polarography.

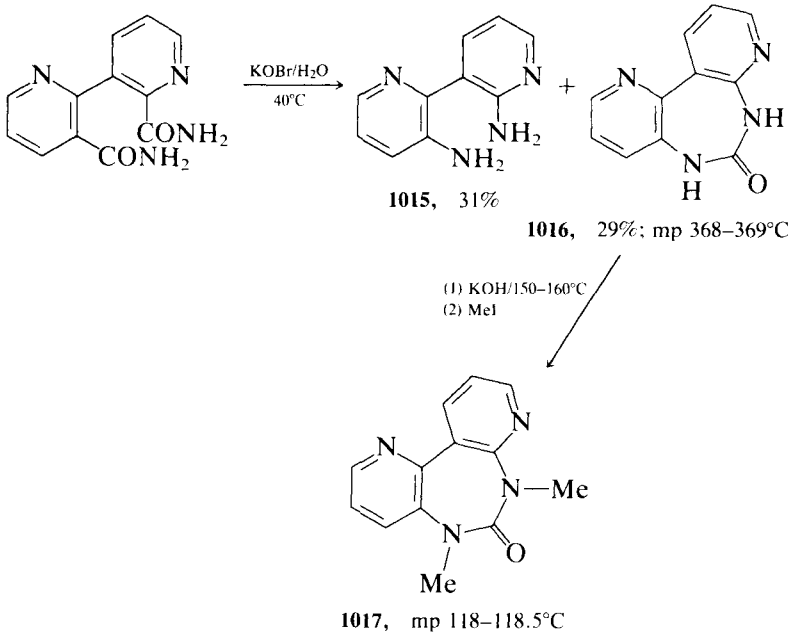



**1014,** mp 180°C (dec.) (uv, nmr) (207)

## 25. Dipyrido[2,3-*d*:2′,3′-*f*][1,3]diazepines



A single study on derivatives of the dipyrido[2,3-*d*:2′,3′-*f*][1,3]diazepine ring system has been reported (511). When the diamide shown in Eq. 208 was subjected to the conditions of the Hofmann reaction, the expected diamine **1015** was accompanied by the tricyclic urea **1016.** The diamine **1015** could also be converted to **1016** by treatment with urea at 190–205°C. The *N,N′*-dimethyl urea **1017** was obtained by methylation of **1016.**



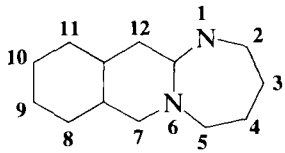

**1015,** 31%

**1016,** 29%; mp 368–369°C (dec.)

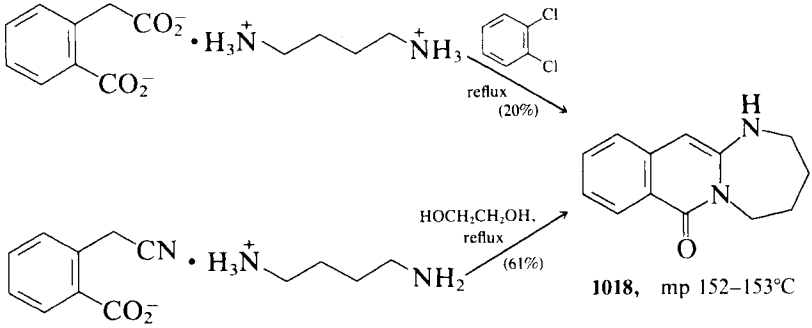
(208)

**1017,** mp 118–118.5°C

## 26. [1,3]Diazepino[1,2-*b*]isoquinolines



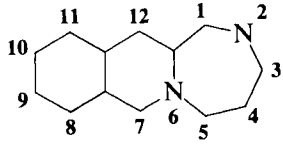
Only one [1,3]diazepino[1,2-*b*]isoquinoline (**1018**) has been reported (Eq. 209). It was prepared by two closely related procedures. In the first (512) the 1,4-diaminobutane salt of homophthalic acid was heated; in the second (513) the acidic component was 2-cyanomethylbenzoic acid.



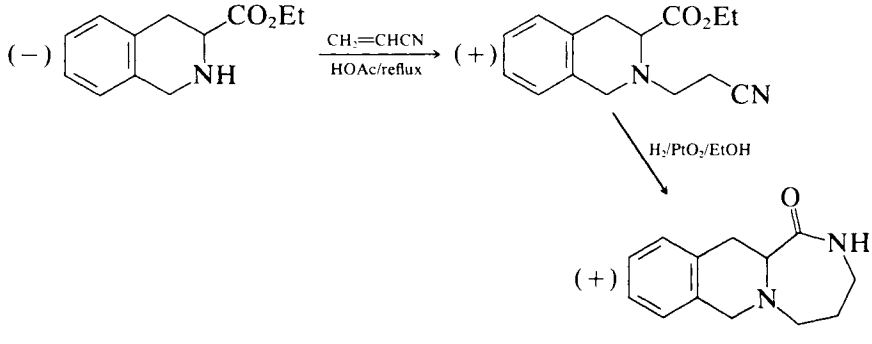

(209)

**1018**, mp 152–153°C

## 27. [1,4]Diazepino[1,2-*b*]isoquinolines



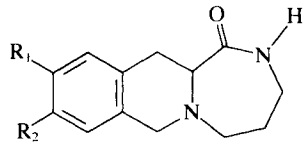

As described in a patent (514), Michael addition of ethyl 1,2,3,4-tetrahydro-3-isoquinoline carboxylate to acrylonitrile gave the adduct shown in Eq. 210. Hydrogenation gave the tricyclic lactam **1019** directly. Further examples prepared in the same manner are listed in Table 114.




(210)

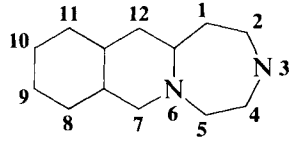
**1019**, mp 202–204°C,
bp 140–175°C/2 mm

TABLE 114. 2,3,4,5,12,12a-HEXAHYDRO[1,4]DIAZEPINO[1,2-*b*]ISOQUINOLIN-1(7H)-ONE AND ANALOGS

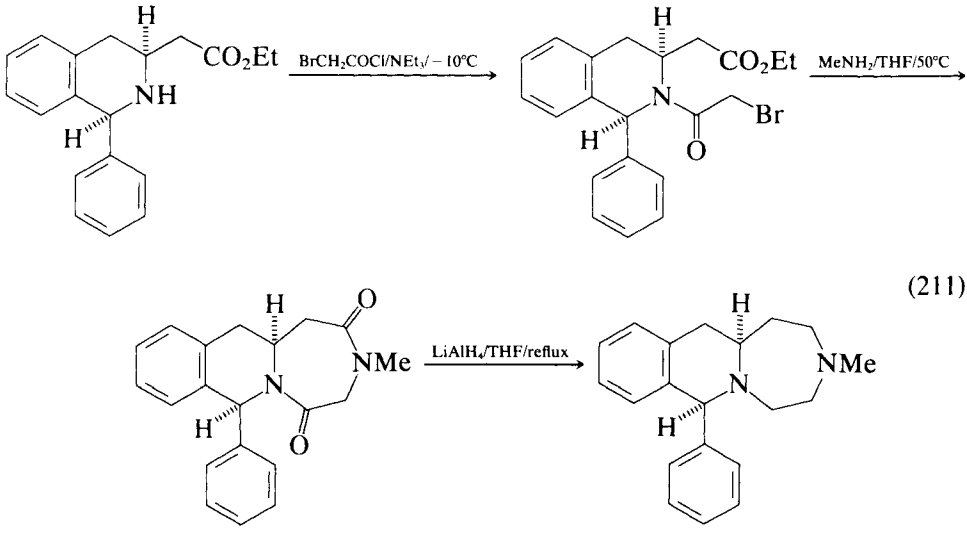


| $R_1$ | $R_2$ | mp (°C) | Other Data |
|---|---|---|---|
| H | H | 192–194 | Racemic |
| MeO | MeO | 212–215 | Racemic |
| | | 201–203 | $[\alpha]_D^{26} = -20°$ ($c$ = 0.1; EtOH) |
| F —$OCH_2O$— | H | 187–189 | Racemic |

## 28. [1,4]Diazepino[1,7-*b*]isoquinolines



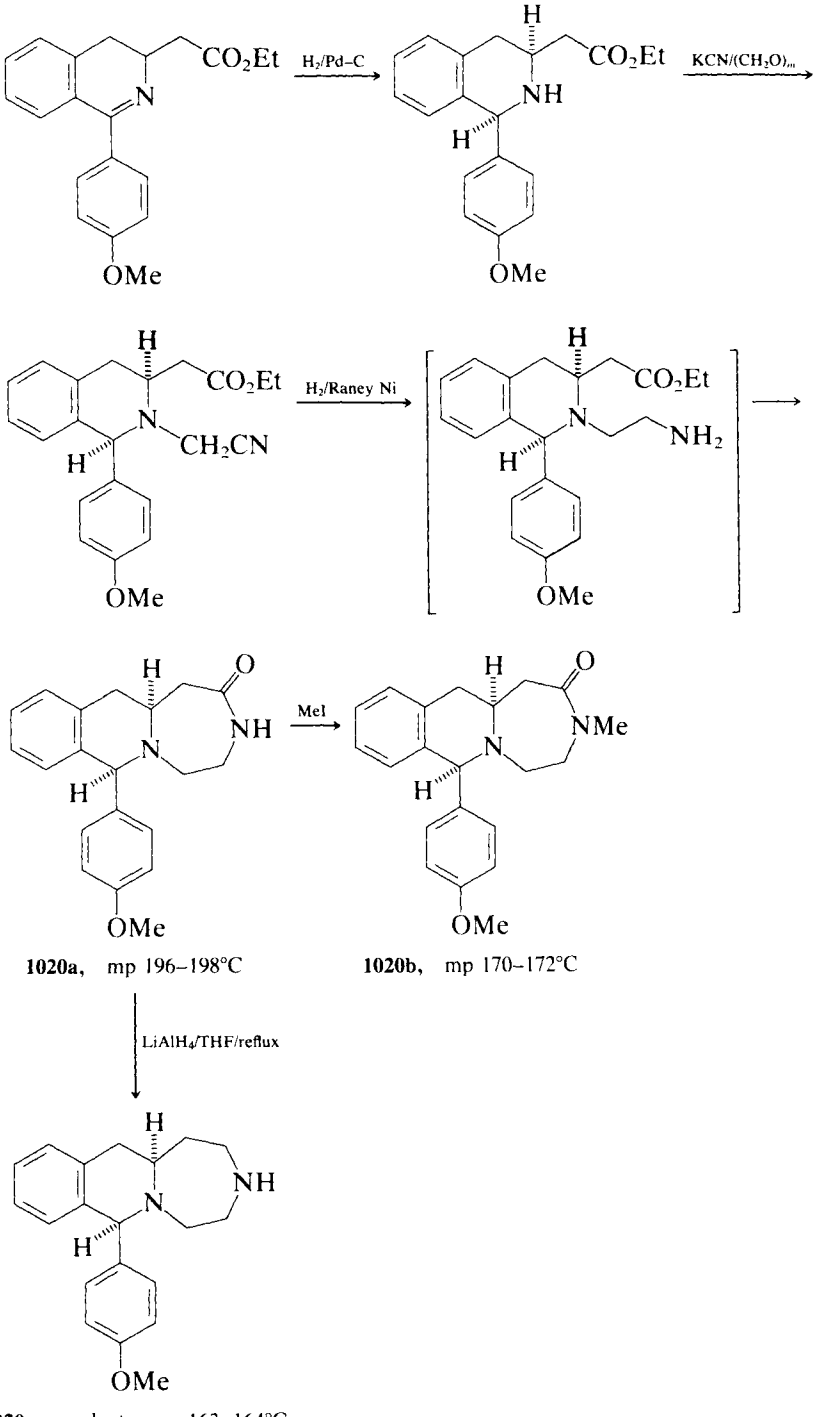
The only information on [1,4]diazepino[1,7-*b*]isoquinolines is contained in a patent (515). The synthetic sequences outlined in Fig. 73, Eq. 211, and Fig. 74 are illustrative. Reduction of the diazepinones **1020a, 1020d,** and




(211)

**1020d,** mp 208–211°C

**1020e,** maleate, mp 184–186°C

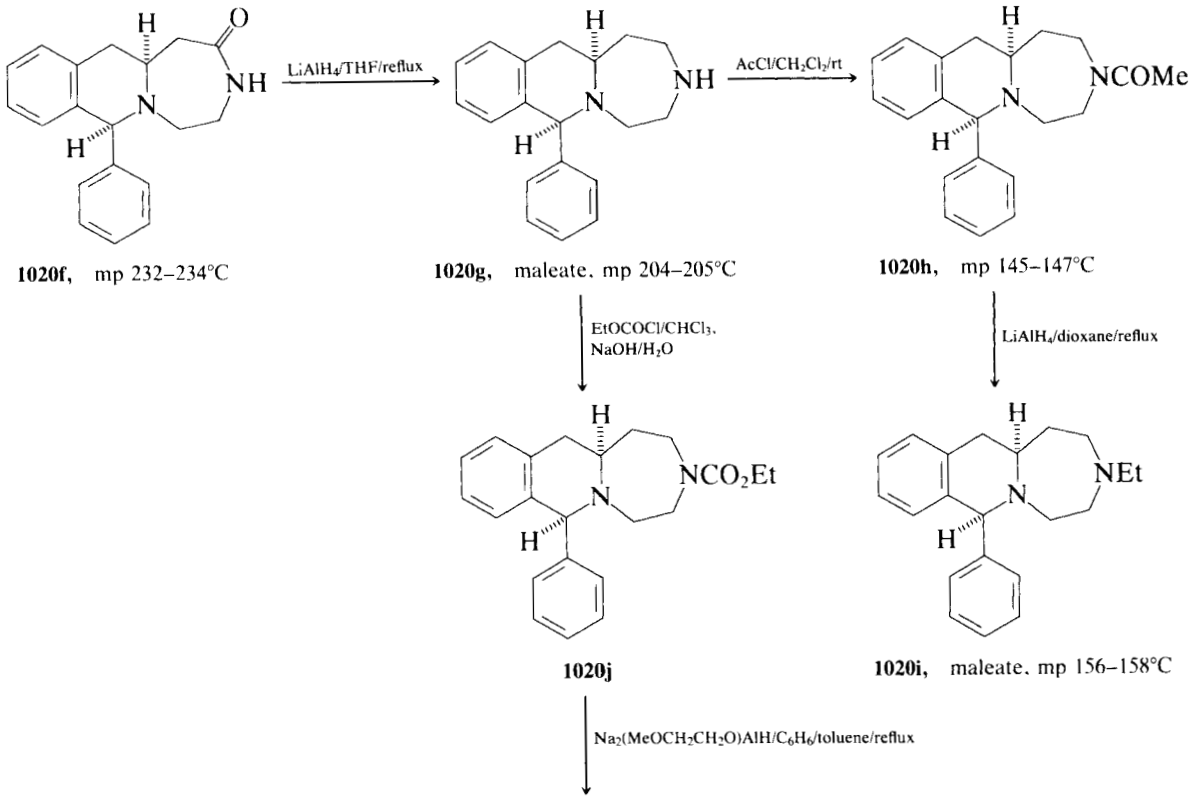



**1020a**, mp 196–198°C

**1020b**, mp 170–172°C

**1020c**, maleate, mp 163–164°C

**Figure 73**




**1020f,** mp 232–234°C

**1020g,** maleate, mp 204–205°C

**1020h,** mp 145–147°C

**1020j**

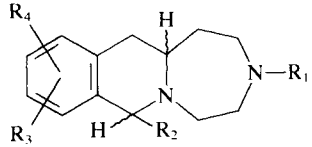
**1020i,** maleate, mp 156–158°C

**1020e**

**Figure 74**

**1020f** was accomplished with lithium aluminum hydride to give the diazepines **1020c, 1020e,** and **1020g,** respectively. Alkylation of **1020a** with methyl iodide afforded the $N^3$-substituted product **1020b.** Reaction of diazepine **1020g** with acetyl chloride yielded the $N^3$-acetyl derivative **1020h,** whereas acylation with ethyl chloroformate led to the carbamate ester **1020j,** which could be reduced to **1020e** with sodium methoxyethoxyaluminum hydride. Table 115 lists additional members of this ring system.

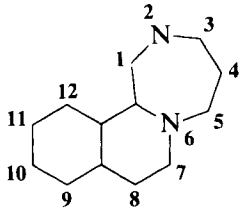
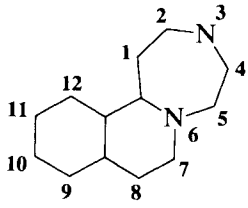
TABLE 115. 7-SUBSTITUTED 1,2,3,4,5,7,12,12*a*-OCTAHYDRO[1,4]DIAZEPINO-[1,7-*b*]ISOQUINOLINE DERIVATIVES



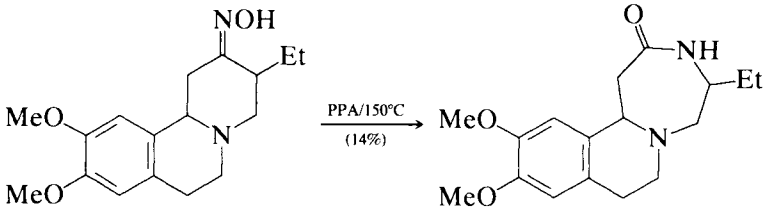

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Relative Configuration of $H_7$ and $H_{12a}$ | Salt[a] | mp (°C) |
|---|---|---|---|---|---|---|
| Me | Ph | 10-MeO | H | *Cis* | m | 159–161 |
| Me | Ph | 9-OMe | H | *Cis* | m | 173–175 |
| Me | *p*-$ClC_6H_4$ | H | H | *Cis* | m | 186–188 |
| Me | *p*-$ClC_6H_4$ | H | H | *Trans* | dh | 198–201 |
| Me | *m*-$ClC_6H_4$ | H | H | *Cis* | m | 172–174 |
| Me | *o*-$ClC_6H_4$ | H | H | *Cis* | f | 192–195 |
| Me | Ph | 10-Cl | H | *Cis* | m | 192–193 |
| Me | Ph | H | H | *Trans* | f | 210–212 |
| Me | Ph | 9-Me | H | *Cis* | m | 191–192 |
| Me | Ph | 10-Me | H | *Cis* | m | 171–173 |
| Me | Ph | 9-MeO | 10-MeO | *Cis* | m | 178–179 |
| Me | Bz | H | H | *Cis* | m | 149–150 |
| Me | Ph | 9-Cl | H | *Cis* | m | 200–201 |
| Me | Ph | 9-Cl | H | *Trans* | f | 182–184 |
| Me | *p*-$ClC_6H_4CO$ | H | H | *Cis* | b | 85–87 |
| Me | *m*-$MeOC_6H_4$ | H | H | *Cis* | m | 161–162 |
| Me | 3,4-$(MeO)_2C_6H_3$ | H | H | *Cis* | m | 174–175 |
| Me | *p*-$MeOC_6H_4CO$ | H | H | *Cis* | m | 120–121 |
| Me | *o*-$MeOC_6H_4$ | H | H | *Cis* | m | 134–137 |
| Me | *p*-$MeOC_6H_4$ | H | H | *Cis* | m | 163–164 |
| H | Ph | H | H | *Cis* | m | 204–205 |
| H | Ph | 9-MeO | H | *Cis* | m | 188–190 |
| H | *p*-$ClC_6H_4$ | H | H | *Cis* | m | 201–202 |
| H | Ph | 10-Cl | H | *Cis* | m | 196–197 |
| H | Ph | H | H | *Trans* | f | 176–178 |
| H | *p*-$MeOC_6H_4$ | H | H | *Cis* | m | 186–188 |
| H | Ph | 10-Me | H | *Cis* | m | 209–210 |
| H | Ph | 9-Me | H | *Cis* | m | 188–189 |
| Et | Ph | H | H | *Cis* | m | 158–160 |
| Me | Ph | H | H | *Cis* | m | 184–185 |

[a] b = Base; dh = dihydrochloride; f = fumarate; m = maleate.

## 29. [1,4]Diazepino[2,1-*a*]- and [1,4]Diazepino [7,1-*a*]isoquinolines

These ring systems will be discussed in one section, since there are certain reactions in which substances derived from the two systems are formed simultaneously. According to a patent (516), Beckmann rearrangement of the oxime shown in Eq. 212 with polyphosphoric acid at 150°C gives the [7,1-*a*] product **1021.** Structural proof was not provided, and the stereochemistry of the starting ketone and rearranged product was not specified.

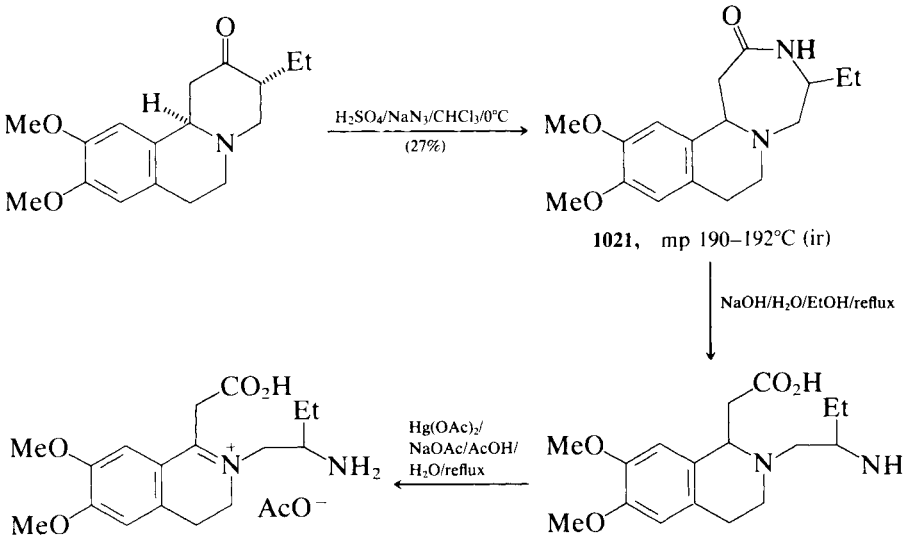



(212)

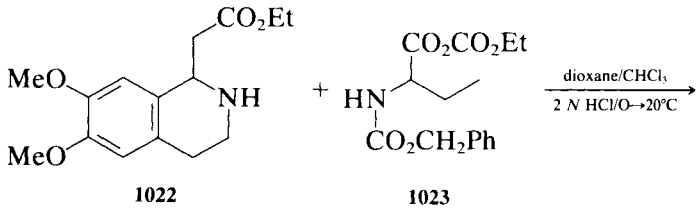
**1021**, mp 185–192°C

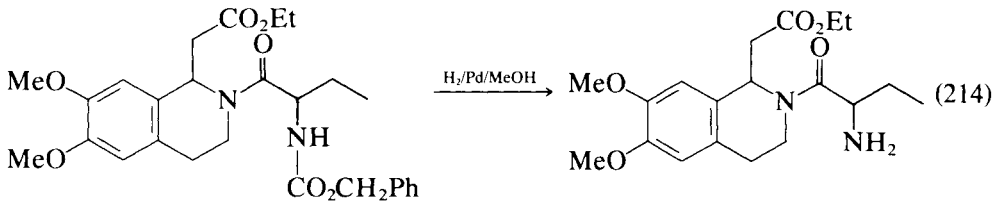
A later publication from Battersby and co-workers (517) described a more detailed investigation of the reaction. The relative stereochemistry of the starting ketone was defined as shown in Eq. 213. When this ketone was subjected to the Schmidt reaction, a product was obtained which had a melting point essentially identical to that of the compound described earlier (516). Mercuric acetate dehydrogenation of the amino acid derived from the Schmidt product (517) gave a substance that was readily decarboxylated. On this basis, the Schmidt product was formulated as the [7,1-*a*] isomer (Eq. 213). The configuration of the ethyl group was not specified, and it was stated that equilibration (of the starting ketone) might well occur under the conditions of the reaction.

Another route to this ring system began with the ester **1022.** Reaction with the mixed carbonic anhydride **1023** (Eq. 214) followed by reductive cleavage of the benzyloxycarbonyl group and thermal ring closure gave the dilactam **1024** as a mixture of diastereoisomers. Attempted selective reduction of the 5-oxo group in **1024** was not successful.

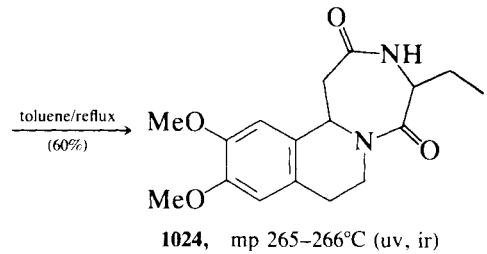

O
Et
H
MeO
MeO
N
$H_2SO_4/NaN_3/CHCl_3/0°C$
(27%)
O
NH
Et
MeO
MeO
N
1021, mp 190–192°C (ir)
NaOH/$H_2O$/EtOH/reflux
$CO_2H$
Et
MeO
MeO
N
$NH_2$
Hg(OAc)$_2$/
NaOAc/AcOH/
$H_2O$/reflux
$CO_2H$
Et
MeO
MeO
N
$NH_2$
$AcO^-$

(213)

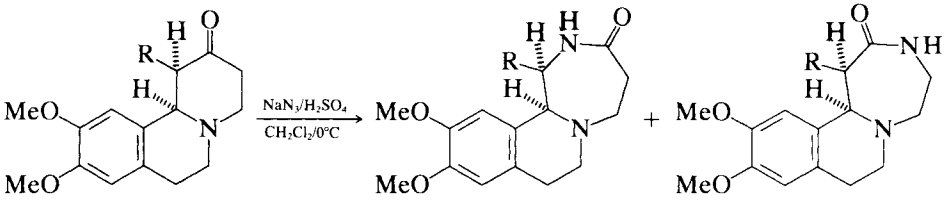

$CO_2Et$
MeO
MeO
NH
1022
+
$CO_2CO_2Et$
HN
$CO_2CH_2Ph$
1023
dioxane/$CHCl_3$
2 N HCl/O→20°C


$CO_2Et$
O
MeO
MeO
N
NH
$CO_2CH_2Ph$
$H_2$/Pd/MeOH
$CO_2Et$
O
MeO
MeO
N
$NH_2$

(214)


toluene/reflux
(60%)
O
NH
MeO
MeO
N
O
1024, mp 265–266°C (uv, ir)

A French group (518) has studied the effect of α-alkyl substitution on the direction of ring expansion of the tricyclic ketone **1025** (Eq. 215). Both the ketone **1025** and the α-methyl derivative **1026** gave two lactams on Schmidt reaction. Each compound yielded mixtures of *syn*- and *anti*-oximes, which were converted to the corresponding tosylates. One tosylate, isolated from ketone **1025** in pure state, gave the [2,1-*a*] lactam on Beckmann rearrangement. This lactam was also obtained from a pure oxime isomer that was isolated by preparative thin-layer chromatography or repeated silica gel column chromatography. Oxime tosylate mixtures derived from ketones **1025** and **1026** gave mixtures of the two possible lactams **1027** and **1029,** and **1028** and **1030,** respectively. Fractional recrystallization of the lactam mixture derived from **1026** gave a pure sample of the lactam **1028.**




(215)

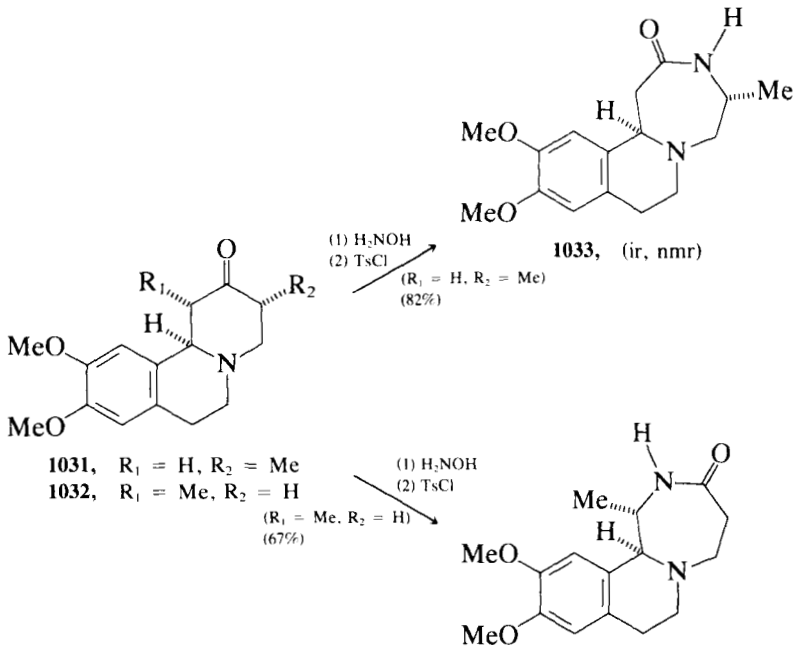
**1025,** R = H
**1026,** R = Me

**1027,** R = H; mp 183–185°C (ir, nmr)
**1028,** R = Me; mp 157.5–160°C (ir, nmr)

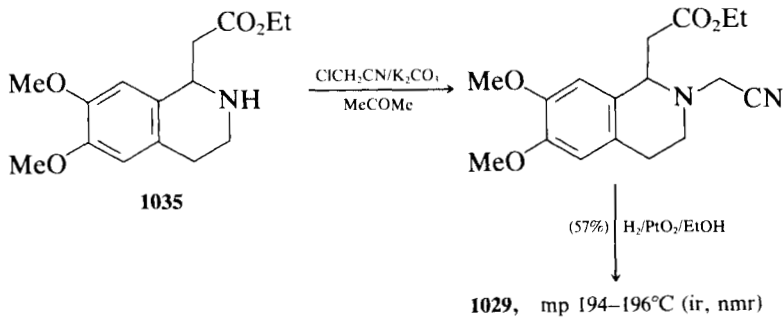
**1029,** R = H
**1030,** R = Me

Two other ketones, **1031** and **1032,** were examined (Eq. 216). Each one gave only a single oxime, and the oximes were converted to the single lactams **1033** and **1034,** respectively, via the tosylate procedure or the Schmidt reaction. Those substances in which the keto group was flanked by an equatorial methyl group gave rise to only one lactam isomer. When the methyl group had the axial configuration or was absent, mixtures of lactams were produced.

As it was not possible to obtain a pure sample of lactam **1029** from these reactions, it was decided to prepare this substance by an alternative route. Reaction of the tetrahydroisoquinoline acetic ester **1035** with chloroacetonitrile, followed by hydrogenation, gave the desired lactam together with some starting material resulting from hydrogenolysis (Eq. 217). The various lactams obtained in this study (518) were reduced with lithium aluminum hydride; the products are listed in Table 116. According to a related patent (519), the isobutyl derivative **1036** could be prepared by the Schmidt reaction and reduced to **1037** with lithium aluminum hydride (Eq. 218).



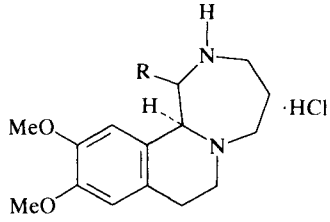

(216)



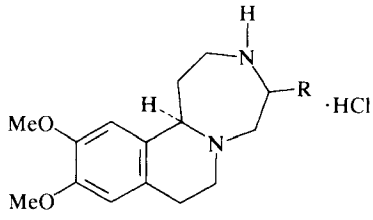

(217)

In a reinvestigation of the work of Battersby (517), Begley and Whittaker (520) examined once again the Schmidt reaction of the ketone **1020** (Fig. 75). The Battersby lactam was obtained in 90% yield, together with 1.5% of a product not previously reported. When the Schmidt reaction was carried out by gradual addition of the sodium azide to a solution of **1020** in concentrated sulfuric acid (conditions that would be relatively favorable for acid-

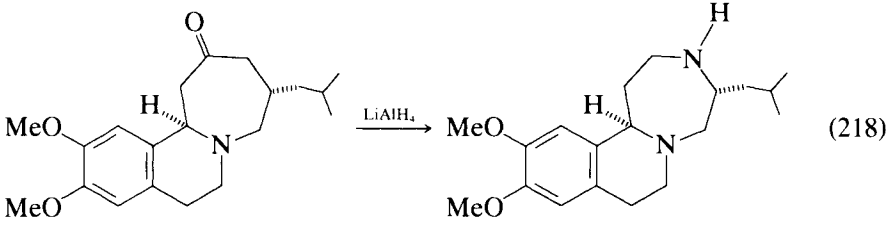
TABLE 116. REDUCTION PRODUCTS OF [1,4]DIAZEPINO[2,1-*a*]- AND [1,4]DIAZEPINO[7,1-*a*]ISOQUINOLINE LACTAMS



| R | mp (°C) | Yield (%) | Spectra |
|---|---|---|---|
| H | 207–208 | 63 | ir |
| β-Me | 168–173 | 73 | ir, nmr |
| α-Me | 182–186.5 | 76 | ir, nmr |



| | | | |
|---|---|---|---|
| H | 175–179 | 68 | ir |
| α-Me | 176–183 | 75 | ir |



**1036,** HCl, mp 176–178°C (ir) **1037,** 2 HCl, mp 199–203°C (ir) (218)

catalyzed epimerization of the starting ketone), the yield of the minor product was raised to 5%. The structure of the major product was determined to be **1038** by means of an X-ray crystallographic study of the hydrobromide. This structure is analogous to that assigned to the products **1033** derived from the corresponding α-methyl ketone **1031** by the French group (518).

Lactam **1038** was converted to the methiodide and thence to the quaternary hydroxide **1039b.** Heating this substance at 180°C under reduced pressure did not give the expected Hofmann elimination product **1040,** but yielded instead the same lactam mixture as was obtained from the original Schmidt reaction. It was thus concluded that the two lactams were epimers, arising

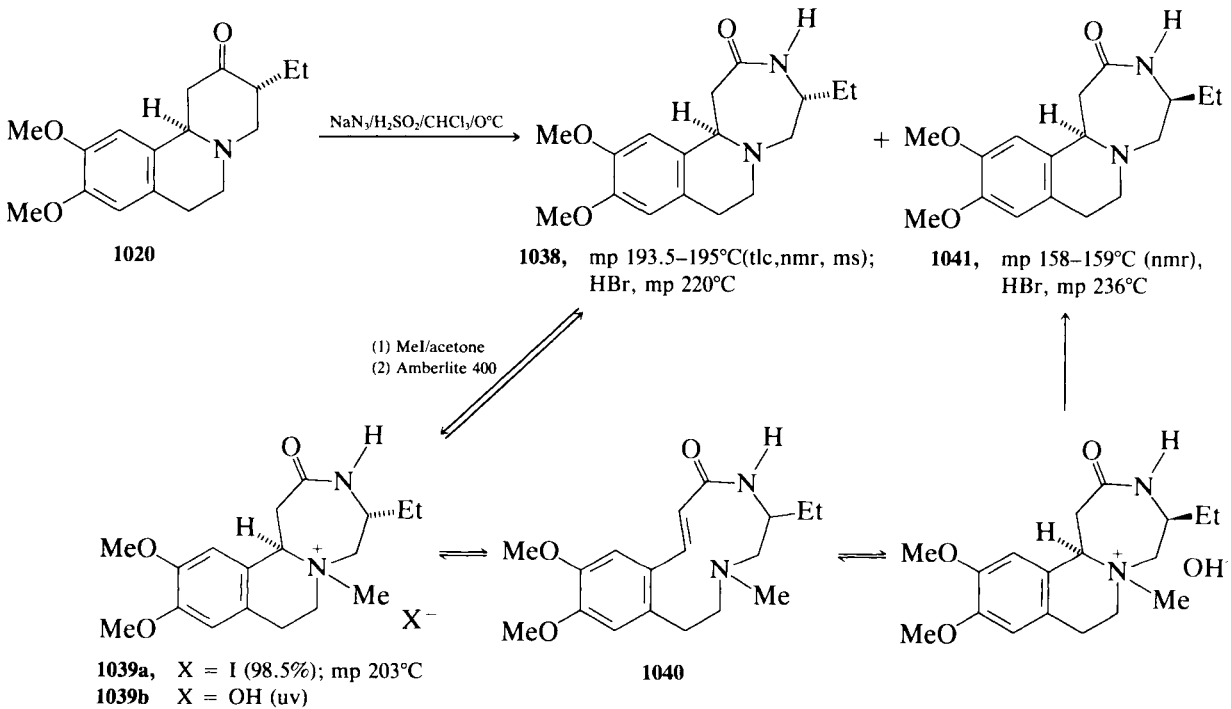
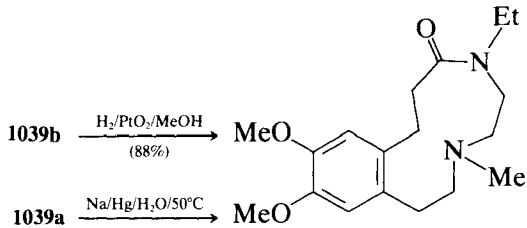

MeO
MeO
Et
H
O
N
NaN3/H2SO2/CHCl3/0°C
1020
1038, mp 193.5–195°C(tlc,nmr, ms);
HBr, mp 220°C
+
1041, mp 158–159°C (nmr),
HBr, mp 236°C
(1) MeI/acetone
(2) Amberlite 400
Me
X⁻
OH
1039a, X = I (98.5%); mp 203°C
1039b X = OH (uv)
1040

**Figure 75**

by epimerization at $C_{12b}$ via the reversible formation of the anticipated Hofmann product **1040** (the structures shown in Fig. 75 represent racemates, so that epimerization at $C_{12b}$ has been depicted as occurring at $C_4$). The minor product from the Schmidt reaction was thus shown to be **1041,** and was stated to have arisen from the starting ketone in which the ethyl group had epimerized. Presumably, in keeping with the data of the French group (518), the benzo[*a*]quinolizine system of the epimerized ketone exists in the *cis* conformation, so that the ethyl group retains its equatorial configuration, and the Schmidt reaction remains completely regiospecific.

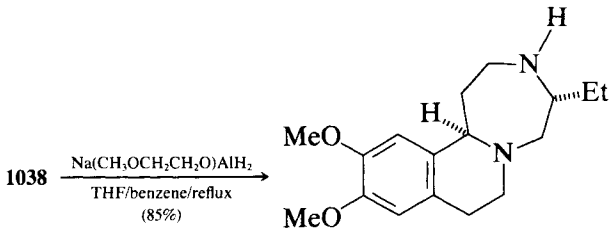
Support for the intermediacy of the ring-opened species **1040** was afforded by the demonstration that catalytic hydrogenation of the quaternary hydroxide **1039b** over platinum gave the 11-membered-ring lactam **1042** (Eq. 219). This substance was also obtained from the quaternary iodide **1039a** on




(219)

**1042,** mp 156.5–157.5°C (ms, ir, nmr); HBr, mp 253–255°C; methiodide, mp 275°C

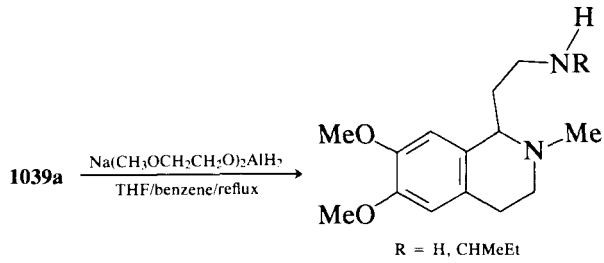
treatment with sodium amalgam. The lactam **1038** was reduced smoothly to a secondary amine (**1043**) with sodium bis(2-methoxyethoxy)aluminum hydride (Eq. 220). Treatment of the methiodide with the same reagent gave rise to ring-opened isoquinolines, as depicted in Eq. 221.




(220)

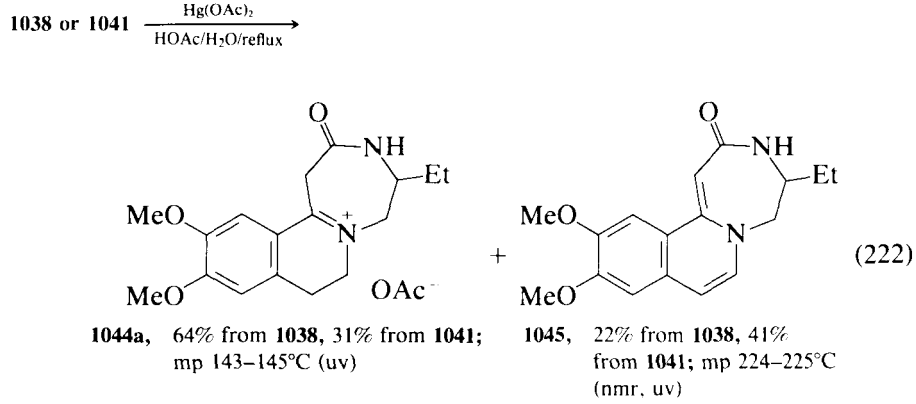
**1043,** HBr, mp 203°C

Oxidation of the lactams **1038** or **1041** with mercuric acetate (Eq. 222) gave the dehydrogenation product **1044a** (converted to the anhydro base **1044b**) together with a second product, isolated as the anhydro base **1045.** Since the salt **1044a** was inert to these oxidation conditions, it was suggested




(221)

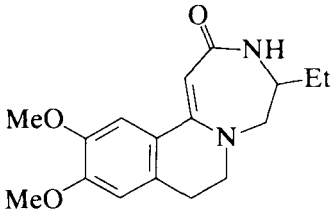
that **1045** arose from the iminium salt **1046.** Prolonged heating of the lactam **1038** with carbon tetrachloride at 100°C also gave a mixture of the two oxidation products. The amide bond in both oxidation products proved to be very labile to base, and the resulting carboxylic acids were rapidly decarboxylated at 100°C, in a manner reminiscent of the observations made by the Battersby group (517).



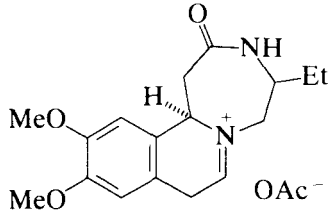

(222)

**1044a,** 64% from **1038,** 31% from **1041;** mp 143–145°C (uv)

**1045,** 22% from **1038,** 41% from **1041;** mp 224–225°C (nmr, uv)

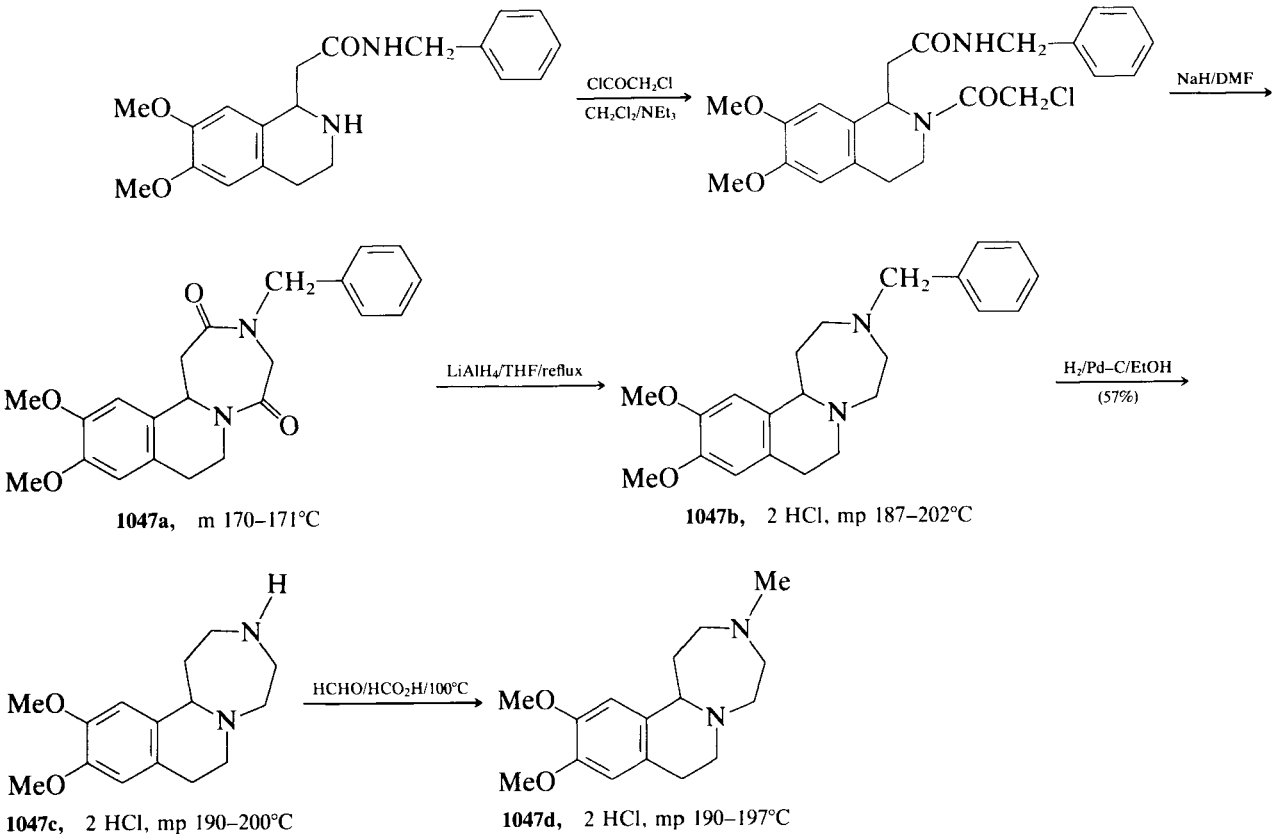



**1044b,** mp 171–172°C (nmr, uv)




**1046**

Further examples of the [7,1-*a*] system are compounds **1047a–h,** which were synthesized from 1,2,3,4-tetrahydroisoquinoline-1-acetic acid derivatives by the methods shown in Fig. 76. A list of substances prepared by these procedures is given in Table 117.




**1047a,** m 170–171°C

**1047b,** 2 HCl, mp 187–202°C

**1047c,** 2 HCl, mp 190–200°C

**1047d,** 2 HCl, mp 190–197°C

**Figure 76**

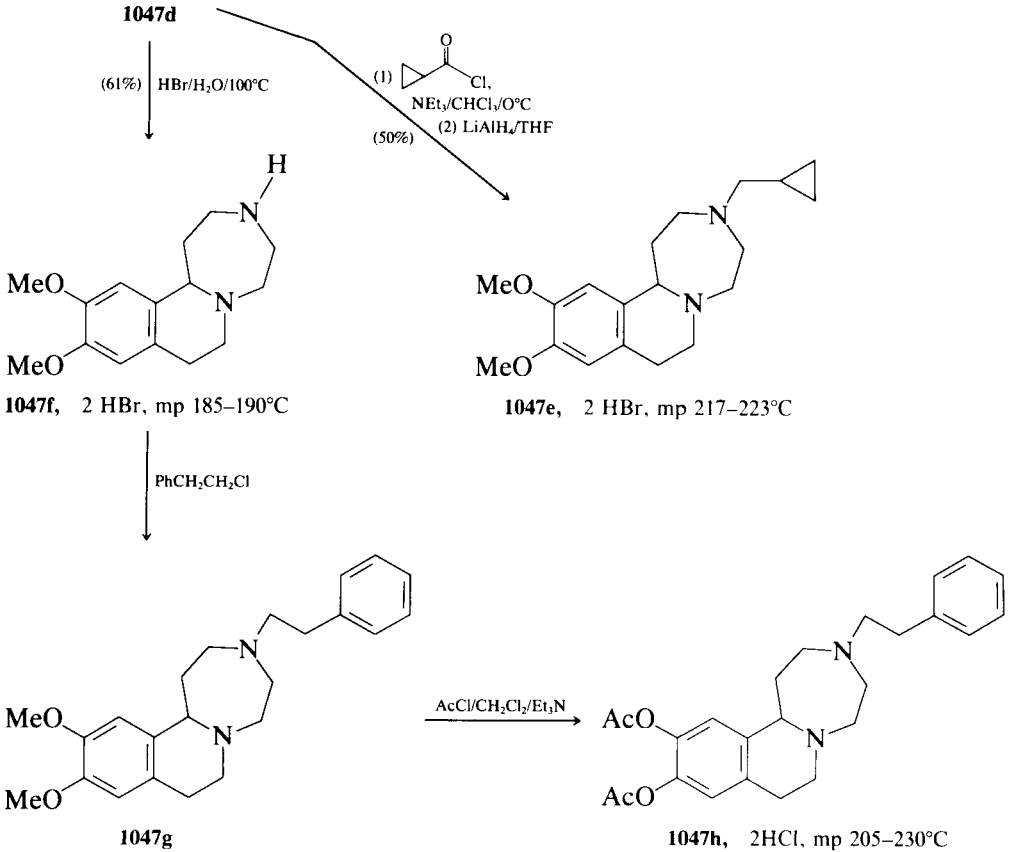
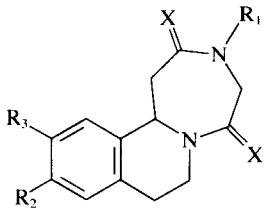



**Figure 76** (*cont'd*)

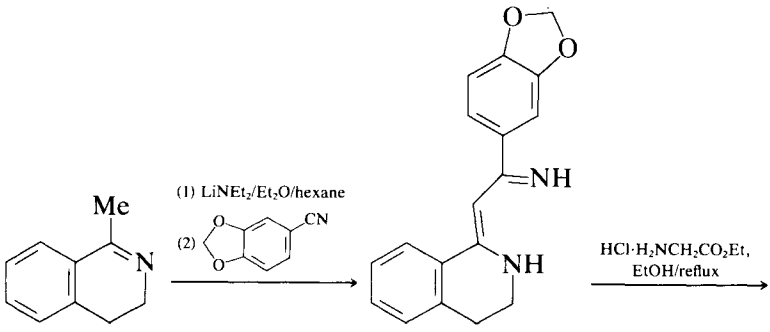
TABLE 117. [1,4]DIAZEPINO[7,1-*a*]ISOQUINOLINE-2,5-DIONES AND REDUCTION PRODUCTS



| | $R_2$ | $R_3$ | X | Salt | mp (°C) | Yield (%) | Other Data |
|---|---|---|---|---|---|---|---|
| $CH_2CH_2Ph$ | MeO | MeO | O | | 151–152 | 69 | |
| $CH_2CH_2Ph$ | MeO | MeO | $H_2$ | 2HCl | 215–222 (dec.) | 61 | |
| $CH_2CH_2Ph$ | MeO | MeO | O | | 131–133 | 78 | (R) $[\alpha]_D^{25} = +109.1°$ ($c = 1.39$; 95% EtOH) |
| $CH_2CH_2Ph$ | MeO | MeO | $H_2$ | 2HCl | 224–230 | 71 | (R) $[\alpha]_{436}^{25} = -21.9°$ ($c = 1.26$; $H_2O$) |
| $CH_2CH_2Ph$ | MeO | MeO | O | | 133–134 | 74 | (S) $[\alpha]_D^{25} = -108.4°$ ($c = 1.16$; 95% EtOH) |
| $CH_2CH_2Ph$ | MeO | MeO | $H_2$ | 2HBr | 222–228 | 69 | (S) $[\alpha]_{436}^{25} = +22.0°$ ($c = 1.20$; $H_2O$) |
| $CH_2CH_2Ph$ | OH | OH | $H_2$ | 2HBr | 178–188 | | |
| $CH_2CH_2Ph$ | OH | OH | $H_2$ | 2HBr | 194–199 | 69 | (R) $[\alpha]_{365}^{25} = -34.7°$ ($c = 1.35$; $H_2O$) |

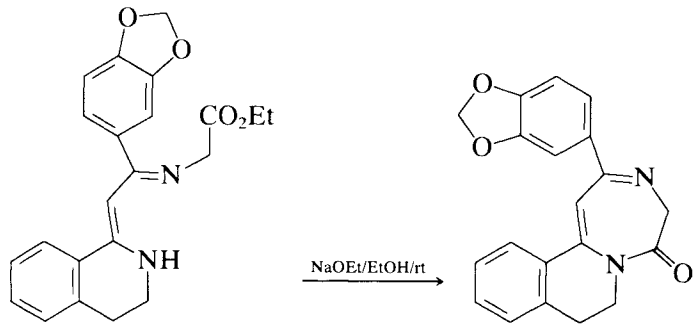
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $CH_2CH_2Ph$ | OH | OH | $H_2$ | 2HCl | 174–179 | | (R) $[\alpha]_{436}^{25} = -36.8°$ ($c = 1.03$; MeOH) |
| $CH_2CH_2Ph$ | OH | OH | $H_2$ | 2HCl | 210–217 | | (R) $[\alpha]_{365}^{25} = -86°$, $[\alpha]_{435}^{25} = -37°$ ($c = 1.06$; MeOH) |
| $CH_2CH_2Ph$ | OH | OH | $H_2$ | 2HBr | 177–187 | 61 | (S) $[\alpha]_{365}^{25} = +34.7°$ ($c = 1.25$; $H_2O$) |
| $CH_2CH_2Ph$ | MeO | H | O | | 119–121.5<br>130.5–131.5 | 81 | |
| $CH_2CH_2Ph$ | OH | H | $H_2$ | 2HBr | 225–235 | | |
| $CH_2CH_2Ph$ | H | H | O | | 106–108 | 35 | |
| $CH_2CH_2Ph$ | H | H | $H_2$ | 2HBr | 201–211 | 81 | |
| $CH_2Ph$ | H | H | $H_2$ | 2HCl | 175–185 | 62 | |
| H | H | H | $H_2$ | 2HCl | 180–225 | 93 | |
| 3,4-$(MeO)_2C_6H_3$ | H | H | $H_2$ | 2HBr | 212–232 | 45 | |
| $CH_2CH_2Ph$ | MeO | H | $H_2$ | 2HBr | 212–225 | | $[\alpha]_D^{25} = +17.8°$ ($c = 1.2$; MeOH) |
| $CH_2CH_2Ph$ | MeO | H | $H_2$ | 2HBr | 214–225 | | $[\alpha]_D^{25} = -17.5°$ ($c = 1.1$; MeOH) |
| $CH_2CH_2Ph$ | OH | H | $H_2$ | 2HBr | 236–244 | | $[\alpha]_{436}^{25} = +19.5°$ ($c = 1.05$; $H_2O$) |
| $CH_2CH_2Ph$ | OH | H | $H_2$ | 2HBr | 234–241 (dec.) | | $[\alpha]_{436}^{25} = -19.3°$ ($c = 1.03$; $H_2O$) |

A novel approach has been used to prepare substances in the [7,1-*a*] series (522). Condensation of 1-methyl-3,4-dihydroisoquinoline with 3,4-methylenedioxyphenylacetonitrile gave an imine (Eq. 223) which, on treatment with glycine ethyl ester hydrochloride followed by base-catalyzed cyclization of the *N*-substituted imine **1048,** gave the tricyclic lactam **1049.** Additional compounds prepared by this procedure are listed in Table 118. A thiolactam

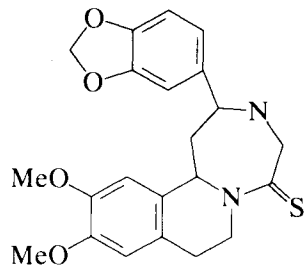



**1047,** mp 105–107°C

(223)



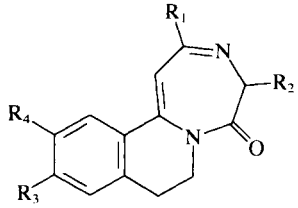

**1048** **1049,** (nmr)




**1050,** mp 182–184°C
HCl, mp 223–226°C

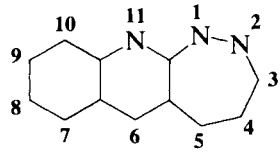
analog (**1050**) was prepared from the corresponding lactam with phosphorus pentasulfide in refluxing pyridine.

TABLE 118. 2-ARYL-7,8-DIHYDRO[1,4]DIAZEPINO[7,1-*a*]ISOQUINOLIN-5(4H)-ONES



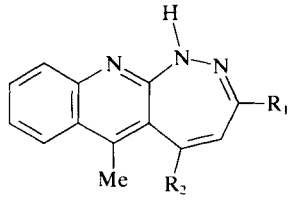
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Salt | mp (°C) |
|---|---|---|---|---|---|
| 3,4,5-$(MeO)_3C_6H_2$ | H | MeO | MeO | | 214–215 |
| | | | | HCl | 237–238 |
| 3,4-$(OCH_2O)C_6H_3$ | H | MeO | MeO | | 214–215 |
| | | | | HCl | 188–190 |
| 3,4-$(OCH_2O)C_6H_3$ | Me | Me | Me | | 138–140 |
| | | | | HCl | 180–181 |
| 3,4-$(OCH_2O)C_6H_3$ | Et | Me | Me | HCl | 184–187 |
| 3,4-$(OCH_2O)C_6H_3$ | *i*-Pr | MeO | MeO | HCl | 189–193 |
| Ph | H | MeO | MeO | | 104–106 |
| | | | | HCl | 162–164 |
| 4-$FC_6H_4$ | H | MeO | MeO | | 156–157 |
| | | | | HCl | 151–152 |
| 4-$ClC_6H_4$ | H | MeO | MeO | | 196 |
| | | | | HCl | 175–176 |
| 4-$MeOC_6H_4$ | H | MeO | MeO | | 174–175 |
| | | | | HCl | 168–170 |
| 3,4-$(MeO)_2C_6H_3$ | H | MeO | MeO | | 98–99 |
| | | | | HCl | 131–132 |
| 2-Thienyl | H | MeO | MeO | | 183–185 |
| | | | | HCl | 194–195 |
| 3,4-$(OCH_2O)C_6H_3$ | H | —$OCH_2O$— | | HCl | 183–185 |
| | | | | | 270–271 |

## 30. [1,2]Diazepino[3,4-*b*]quinolines



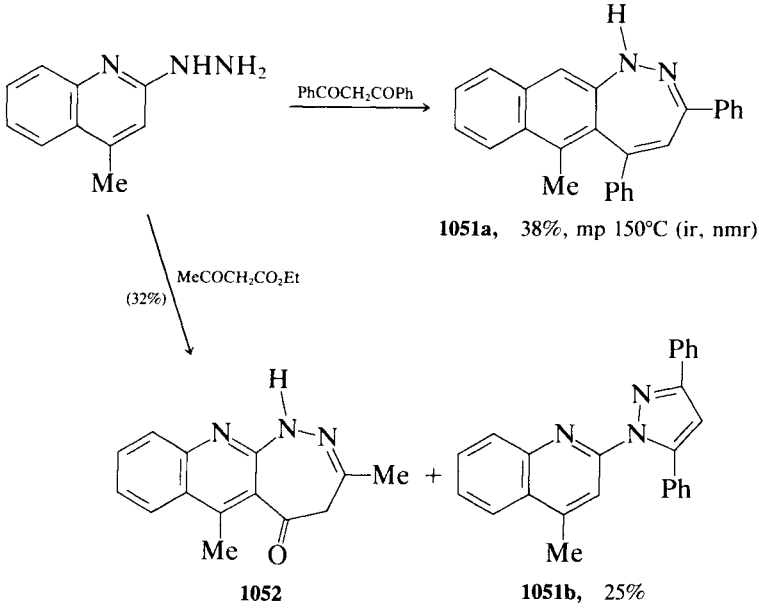
Condensation of 2-hydrazino-4-methylquinoline with β-diketones in refluxing glycerol in the presence of fused sodium acetate (523) gave the 1,2-diazepino[3,4-*b*]quinolines listed in Table 119. When dibenzoylmethane was

TABLE 119. 3,5-DISUBSTITUTED 6-METHYL[1,2]DIAZEPINO[3,4-*b*]QUINOLINE DERIVATIVES



| $R_1$ | $R_2$ | Yield (%) | mp (°C) | Spectra |
|---|---|---|---|---|
| Me | Me | 71 | 107 | ir, nmr |
| Ph | Me | 69 | 130 | ir, nmr |
| Ph | Ph | 38 | 81 | ir, nmr |

used, diazepine **1051a** was accompanied by the pyrazole **1051b** as a by-product (Eq. 224). Ethyl acetoacetate gave the tricyclic diazepinone **1052.**

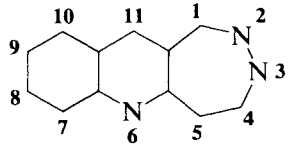


**1051a,** 38%, mp 150°C (ir, nmr)

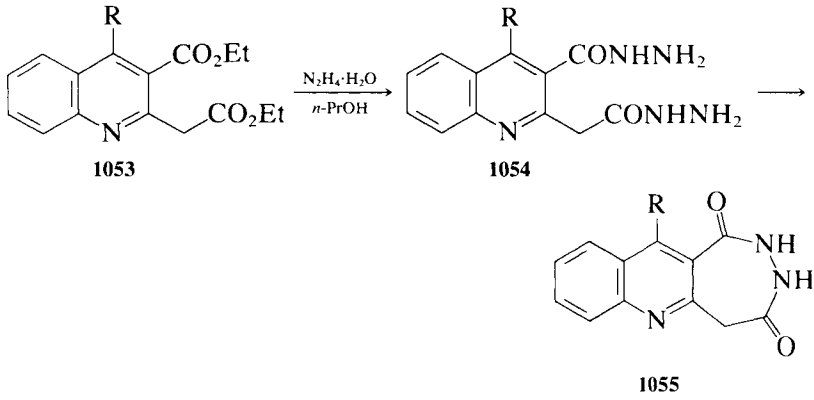
(224)

**1052** **1051b,** 25%

## 31. [1,2]Diazepino[5,4-*b*]quinolines

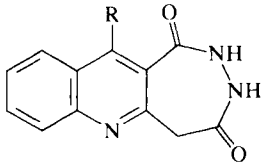


Reaction of the diesters **1053** (Eq. 225) with hydrazine hydrate gave the somewhat unstable hydrazides **1054,** which had uv spectra reminiscent of the diesters. Treatment of **1054** with bases (unspecified) or acids, or simply exposure to a protic solvent, gave the tricyclic diazepines **1055** (524), which had characteristic long-wavelength ultraviolet absorption maxima. A list of substances prepared in this way is given in Table 120.




(225)

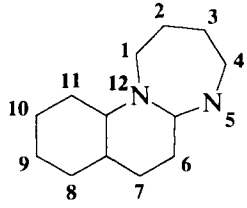
TABLE 120. 11-SUBSTITUTED [1,2]DIAZEPINO[5,4-*b*]QUINOLINE-1,4-DIONE DERIVATIVES



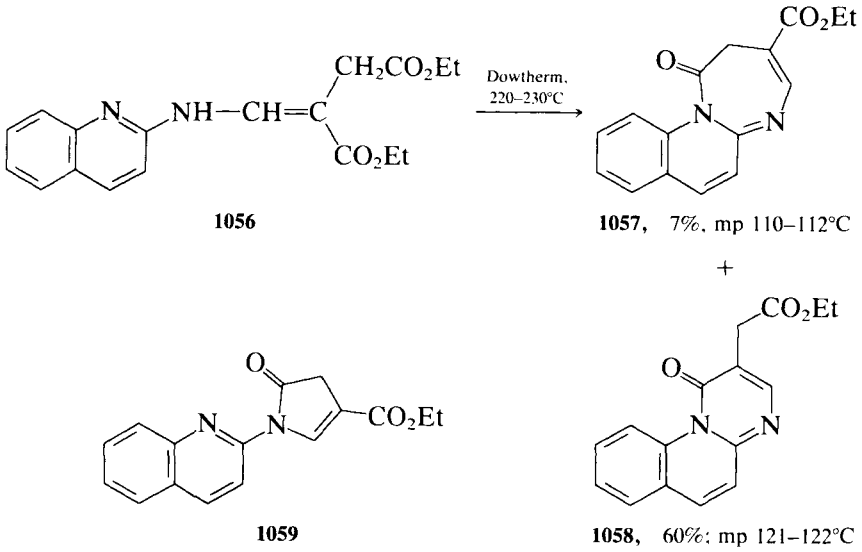
| R | mp (°C)[a] | Yield (%) | Spectra |
|---|---|---|---|
| Me | 220 | 80 | uv |
| Ph | 220 | 85 | uv |
| *p*-$MeC_6H_4$ | 230 | 85 | uv |

[a]Decomposes.

## 32. [1,3]Diazepino[1,2-*a*]quinolines

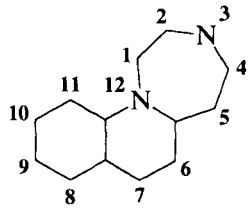


A German patent (525) describes the thermal cyclization of **1056** to the diazepinoquinoline **1057** and the fused pyrimidine **1058,** as shown in Eq. 226. However, in the equivalent British patent (526) no mention is made of the diazepinoquinoline. Instead, the product is formulated as the quinolylpyrrole **1059,** with the same yield (7%) and melting point (110–112°C) being quoted in both cases. As the British patent had a later filing date, and the cyclization to a fused diazepine appears to be a relatively unlikely reaction, it may be concluded that no derivative of the [1,3]diazepino[1,2-*a*]quinoline system has been prepared to date.




(226)

## 33. [1,4]Diazepino[1,7-*a*]quinolines




Only one study on the synthesis of derivatives of the [1,4]diazepino[1,7-*a*]quinoline ring system has been published (527). Michael addition of either benzylmethylamine or dibenzylamine to 2-vinylquinoline gave the aminoethyl derivatives **1060** (Fig. 77). Bouveault–Blanc reduction produced the tetrahydroquinolines **1061** without debenzylation. Condensation with ethy-

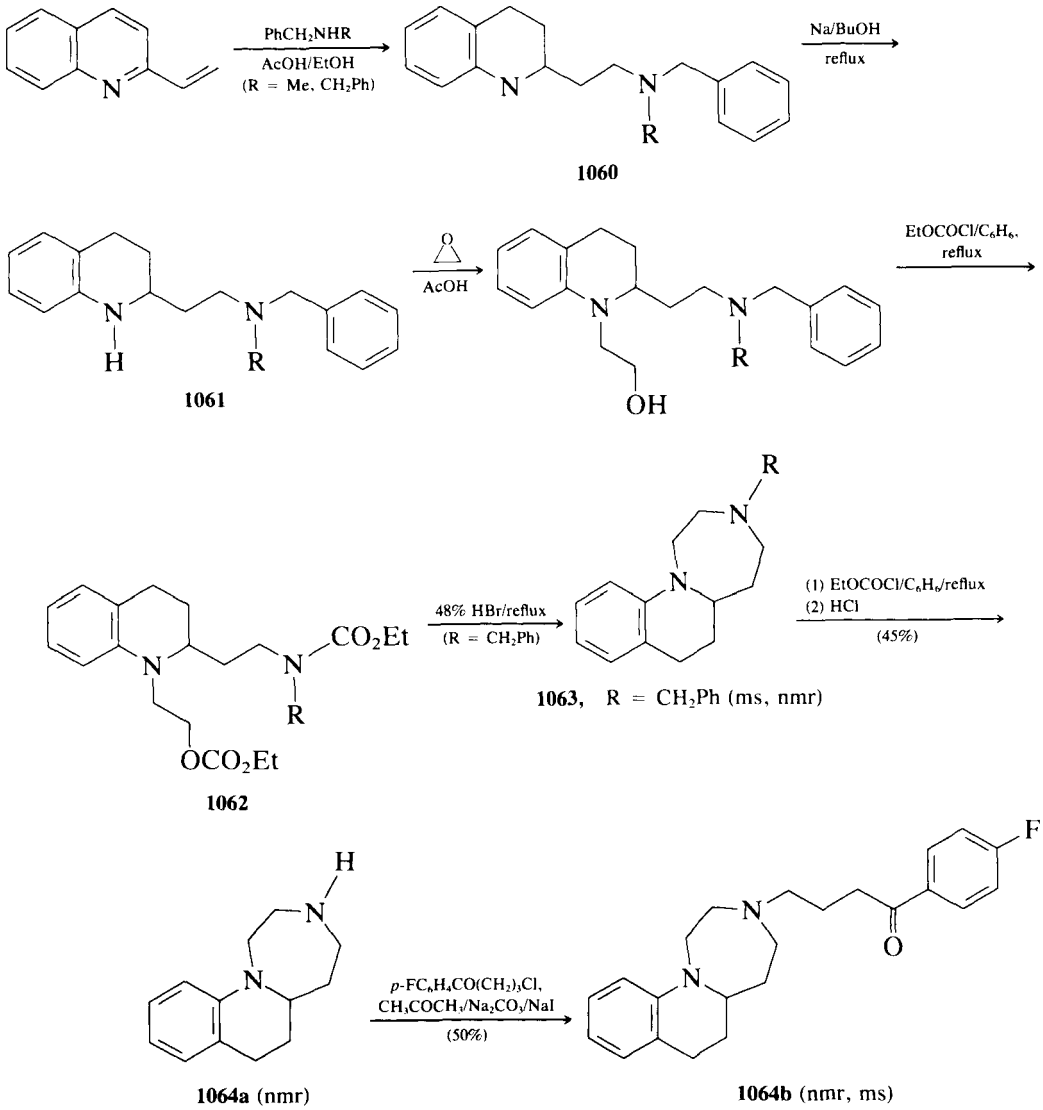
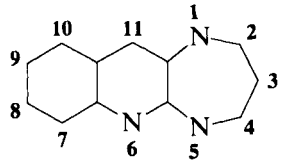


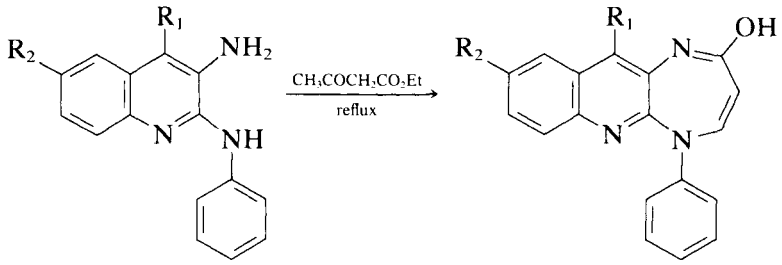

**Figure 77**

lene oxide gave the 1-$\beta$-hydroxyethyl derivatives, which were debenzylated with ethyl chloroformate to give the *N,O*-dicarbethoxy derivatives **1062.** Cyclization was effected with 48% HBr. The *N*-benzyl compound **1063** was debenzylated by the ethyl chloroformate procedure, and the resulting carbamate **1064a** was hydrolyzed with hydrochloric acid. Condensation with $\omega$-chloro-*p*-fluorobutyrophenone gave **1064b.** The substances were prepared as potential hypotensive/CNS agents, but no interesting biological activity was found.

## 34. [1,4]Diazepino[2,3-*b*]quinolines

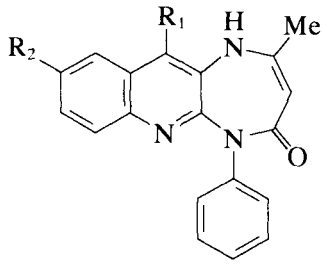


Reaction of 3-amino-2-anilinoquinolines with refluxing ethyl acetoacetate gave products formulated (528) as the [1,4]diazepino[2,3-*b*]quinolines **1065** (Eq. 227). No justification for the enolized amide formulation was presented, and, in fact, the infrared spectrum included a band at 3450 $cm^{-1}$, which could be assigned to the NH function. The more likely alternative formulation (**1066**) apparently was not considered for these substances.



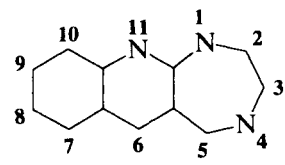

(227)

| | $R_1$ | $R_2$ | Yield (%) | mp (°C) | Spectra |
|---|---|---|---|---|---|
| **1065a** | Ph | Cl | 82 | 273–275 | ir, uv |
| **1065b** | Ph | H | 84 | 274–276 | ir, uv |
| **1065c** | Me | H | 86 | 218–220 | ir, uv |

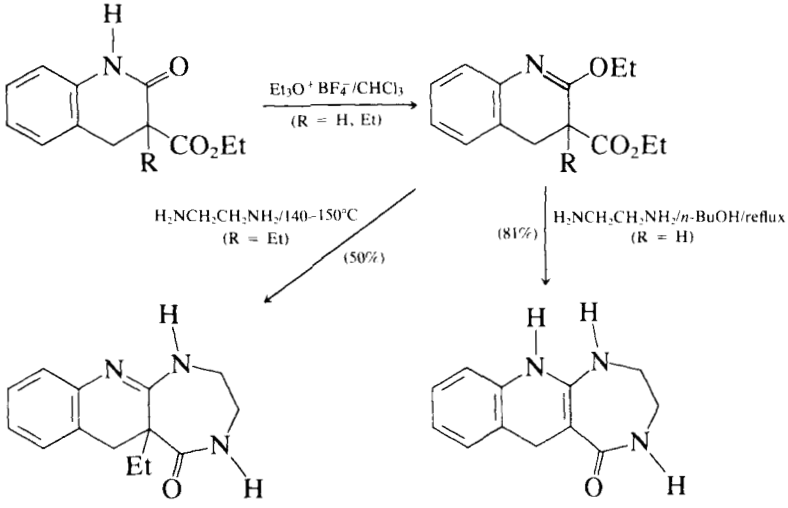



**1066**

## 35. [1,4]Diazepino[5,6-*b*]quinolines



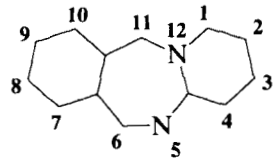
The preparation of two examples of the [1,4]diazepino[5,6-*b*]quinoline structural type is described in a Russian patent (529). The 2-ethoxy-3,4-dihydroquinoline starting materials were prepared by reaction of the 3,4-dihydrocarbostyrils with triethyloxonium tetrafluoroborate (Fig. 78). Heating these imino ethers with ethylenediamine gave the desired tricyclic derivatives **1067a** and **1067b.**




**1067b,** mp 191–192°C **1067a,** 81%; mp 197–199°C

**Figure 78**

## 36. Pyrido[1,2-*b*][2,4]benzodiazepines




Treatment of the betaine **1068** with phosphorus oxychloride or the corresponding ester **1069** with sodium methoxide in methanol gave the tricyclic lactam **1070** (Fig. 79) (530). Hydrogenation of **1070** with platinum oxide in

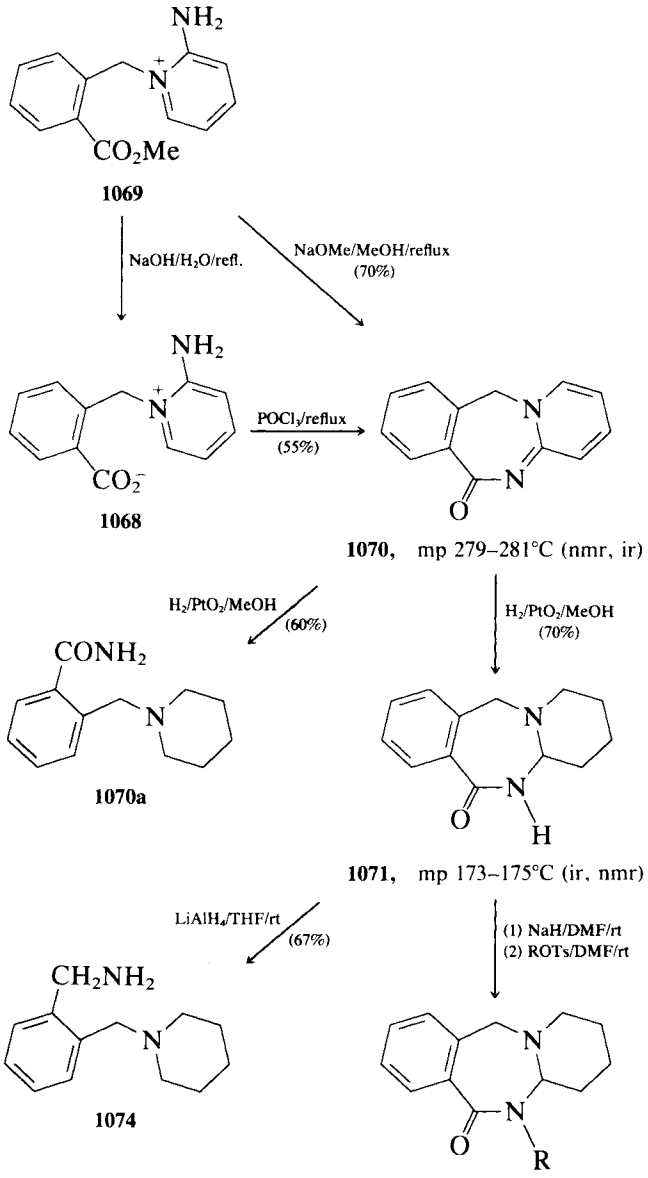
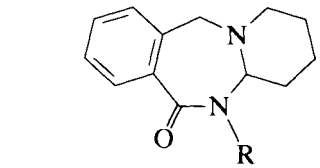
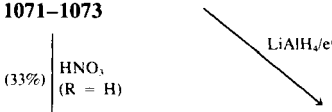

NH2
CO2Me
1069
NaOH/H2O/refl.
NaOMe/MeOH/reflux
(70%)
CO2−
1068
POCl3/reflux
(55%)
1070, mp 279–281°C (nmr, ir)
H2/PtO2/MeOH
(60%)
H2/PtO2/MeOH
(70%)
CONH2
1070a
1071, mp 173–175°C (ir, nmr)
LiAlH4/THF/rt
(67%)
(1) NaH/DMF/rt
(2) ROTs/DMF/rt
CH2NH2
1074
1072, R = Me (39%); HCl, mp 180–183°C
1073, R = Et (47%); HCl, mp 175–176.5°C

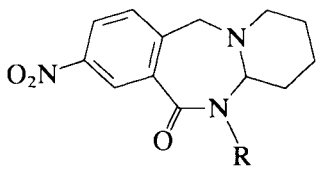
**Figure 79**

methanol at atmospheric pressure gave the hexahydro derivative **1071,** whereas hydrogenation at elevated temperature and pressure led to the cleavage product **1070a.** *N*-Alkylation of **1071** was accomplished by treatment with sodium hydride followed by addition of an alkyl tosylate. When the lactam **1071** was reduced with lithium aluminum hydride in tetrahydrofuran at room temperature, the carbinolamine was cleaved to the 1-benzylpiperidine **1074.** The lactam function of **1071** and its *N*-alkyl derivatives (**1072** and **1073**) could be reduced with lithium aluminum hydride in refluxing ether to obtain the corresponding amines **1071a, 1072a,** and **1073a** (Eq. 228). Nitration of **1071** gave the 8-nitro derivative **1071b** in 33% yield.

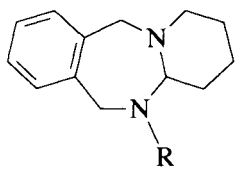


**1071–1073**



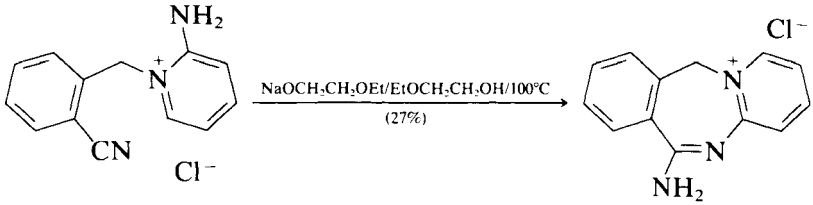
**1071b,** mp 193–195°C



**1071a,** R = H (70%); bp 104–106°C/0.1 mm Hg
**1072a,** R = Me (45%); bp 96–102°C/0.05 mm Hg
**1073a,** R = Et (63%); bp 120°C/0.1 mm Hg

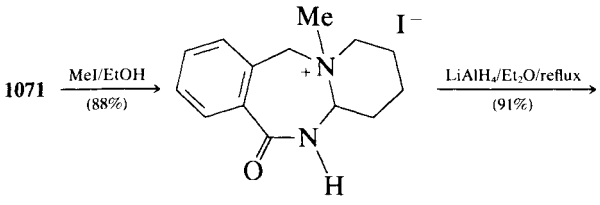
(228)

When the initial cyclization reaction was carried out with an aminonitrile (Eq. 229), the amino-substituted tricyclic derivative **1075** was formed. Treatment of **1071** with methyl iodide gave the methiodide **1071c,** which on lithium aluminum hydride treatment gave the diazacycloundecene **1076,** possibly via Hofmann elimination (Eq. 230).



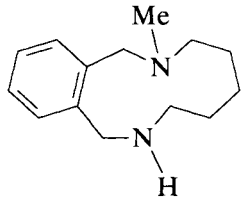

(229)

**1075,** HCl, mp 230–235°C (ir, uv)



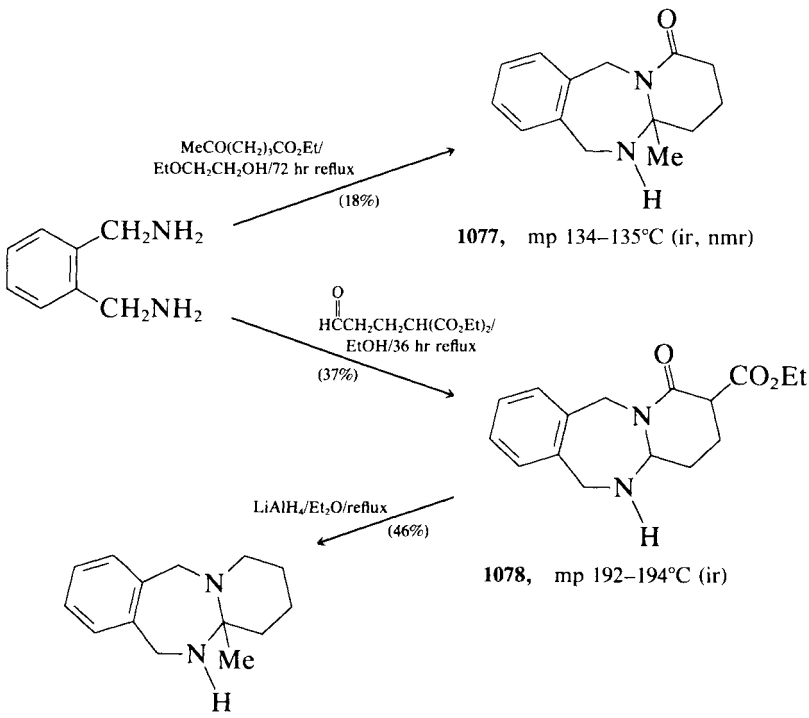

**1071c,** mp 231–233°C (ir)

(230)




**1076,** mp 68–69°C (ir, nmr)

A second synthetic approach was devised in order to provide access to 4a-substituted derivatives (343). Reaction of *o*-phenylenebismethylamine with ethyl 5-oxohexanoate or diethyl 3-oxopropylmalonate gave the desired tricyclic derivatives **1077** and **1078,** respectively (Eq. 231). The malonate de-




(231)

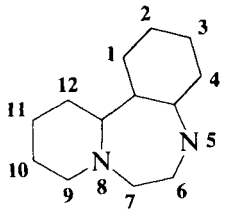
**1077,** mp 134–135°C (ir, nmr)

**1078,** mp 192–194°C (ir)

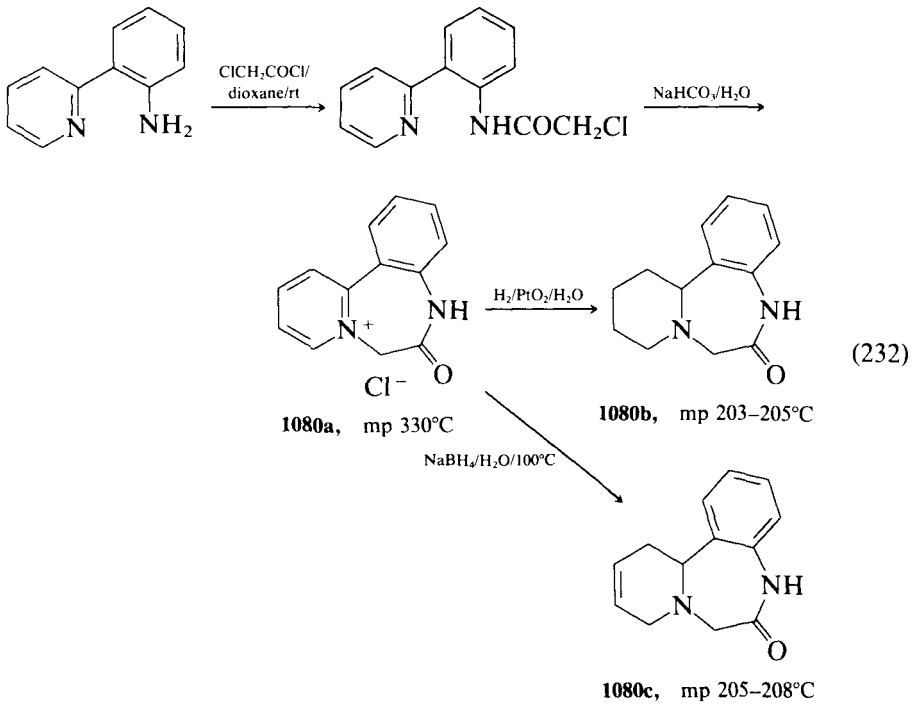
**1079,** bp 160–170°C/0.1 mm Hg (ir)

rivative proved to be a much more reactive substrate in this reaction. The 4a-substituted derivative **1078** was reduced with lithium aluminum hydride to give the tricyclic aminal **1079.**

## 37. Pyrido[1,2-*d*][1,4]benzodiazepines

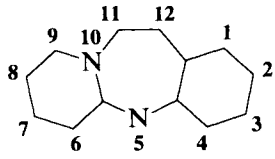



Synthetic studies on derivatives of the pyrido[1,2-*d*][1,4]benzodiazepine ring system are described in two patents. In the first (531), 2-(*o*-aminophenyl)pyridine was treated with chloroacetyl chloride, and the resulting quaternary salt was cyclized to **1080a** with aqueous sodium bicarbonate (Eq. 232). In the second patent (532) catalytic hydrogenation and sodium borohydride reduction of the tricyclic quaternary salt to **1080b** and **1080c,** respectively, was described.

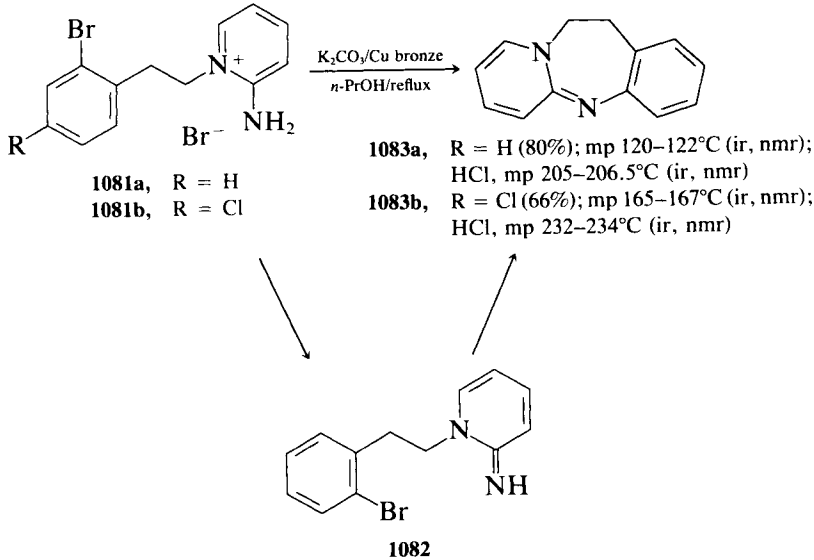



(232)

## 38. Pyrido[2,1-*b*][1,3]benzodiazepines

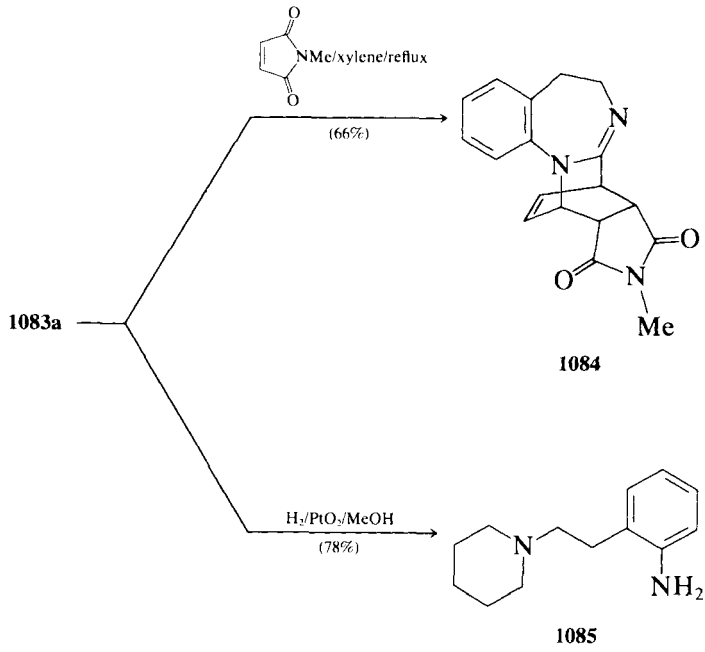



Two derivatives of the pyrido[2,1-*b*][1,3]benzodiazepine ring system have been prepared (533). The pyridinium salts **1081a** and **1081b** could be cyclized to **1083a** and **1083b**, respectively, with potassium carbonate and copper bronze in refluxing *n*-propanol (Eq. 233). Pyridinium salt **1081a** or the related pyridinimine **1082** could be cyclized in a variety of basic media (potassium carbonate in dimethylformamide at 100°C, potassium carbonate in refluxing aqueous *n*-propanol, potassium carbonate in refluxing xylene, sodium methoxide in refluxing methanol, or sodium hydroxide in refluxing aqueous methanol), but copper bronze catalysis was necessary in each instance. The tricyclic derivative **1083a** underwent a Diels–Alder reaction with *N*-meth-



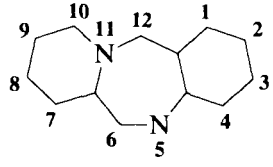

(233)

ylmaleimide (534) and hydrogenolysis with platinum oxide in methanol (535) to form **1084** and **1085**, respectively (Eq. 234).




(234)

## 39. Pyrido[2,1-*c*][1,4]benzodiazepines




The earliest reported method of synthesis of pyrido[2,1-*c*][1,4]-benzodiazepine derivatives (536) is shown in Fig. 80. Ethyl pipecolinate was condensed with 2-nitrobenzyl chloride to give the adduct **1086.** Hydrogenation of **1086** gave the amino ester **1087,** which was cyclized in dilute hydrochloric acid at reflux to the tricyclic lactam **1088a.** The methiodide and *N*-oxide derivatives **1088b** and **1088c** were prepared by standard methods. Compounds obtained by these procedures are listed in Table 121.

In a related study (541) the analogous *N*-benzoylpipecolinic ester **1089** was cyclized under acidic conditions to give the dicarbonyl derivative **1090a** (Eq. 235). Alternatively, these bislactams could be synthesized by reaction of an isatoic anhydride with a nipecotic acid derivative (253). This approach is illustrated by the preparation of compound **1090b** (Eq. 236). Compounds obtained via these routes are listed in Table 122.

The mono- or dilactams described above could be reduced with lithium

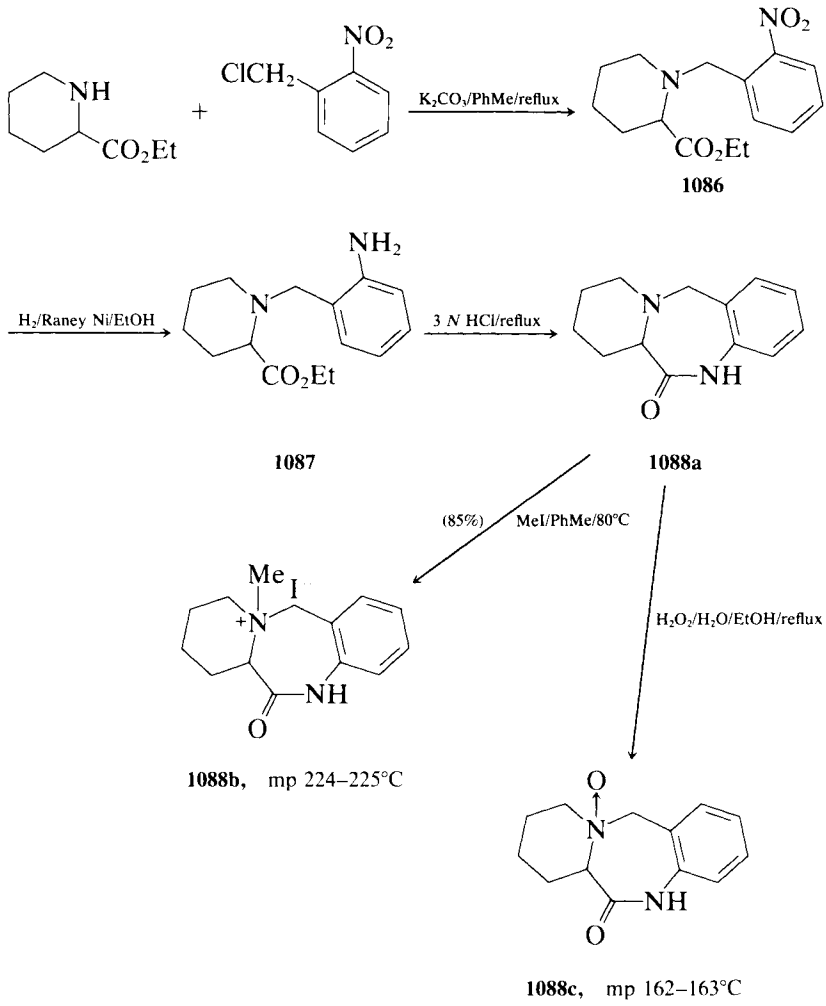
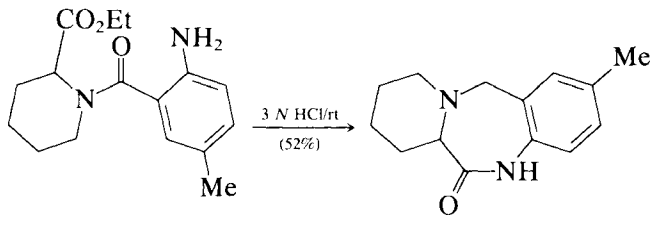
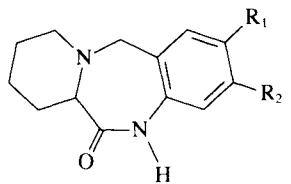



**Figure 80**



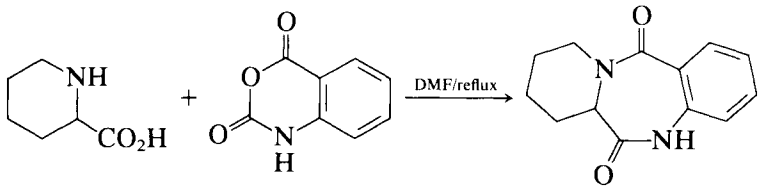

(235)

TABLE 121. PYRIDO[2,1-*c*][1,4]BENZODIAZEPIN-6-ONE DERIVATIVES



| $R_1$ | $R_2$ | Salt | Yield (%) | mp (°C) | Other Data | Refs. |
|---|---|---|---|---|---|---|
| H | H | | 70 | 182–183 | | 536,537 |
| H | H | HCl | | >250 | | |
| Cl | H | | 59 | 224–225 | (R) $[\alpha]_D^{27} = -332°$ | 536,538 |
| | | | | 169–170[a] | ($c = 1.575$; DMSO) | |
| Cl | H | | | 169–172[a] | (S) $[\alpha]_D^{28} = +359°$ | |
| | | | | | ($c = 2.58$; DMSO) | |
| Cl | H | | | 176.5–177[b] | (R) $[\alpha]_D^{27} = -384°$ | |
| | | | | | ($c = 2.135$; DMSO) | |
| Cl | H | | | 175–176[b] | (S) $[\alpha]_D^{27} = +372°$ | |
| | | | | | ($c = 1.95$; DMSO) | |
| Cl | H | MeI | | 246–248 | | 536,538 |
| H | CN | | 26 | 134 | | 536 |
| H | MeO | | | 205–207 | | 536 |
| H | Me | | 40 | 231–232 | | 536,537 |
| MeO | MeO | | 22 | 203–204[c] | | 536 |
| H | $CF_3$ | | | 185–186 | | 536 |
| H | Cl | | | 182–183 | | 536 |
| Cl | Cl | | | 199–200[d] | | 536,539 |
| Me | Me | | | 229–230[d] | | 536,539 |
| —$OCH_2O$— | | | | 265–266[d] | | 540 |

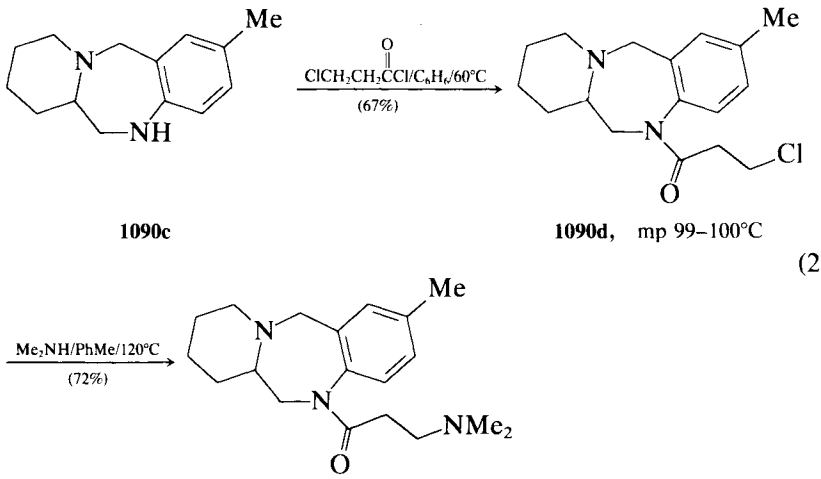
[a]Prepared by synthesis.
[b]Prepared by resolution.
[c]Cyclization with $NaOH/H_2O/EtOH$, reflux.
[d]Cyclization with $NaOH/H_2O/EtOH$ (reflux) and with 3 *N* HCl (reflux).




(236)

**1090b**

aluminum hydride to give the diamines listed in Table 123. These diamino compounds (541) could be acylated, and the acyl groups could be modified further. This approach is exemplified by the conversion of **1090c** to **1090d** and **1090e,** as shown in Eq. 237. Compounds prepared by these methods are listed in Table 124.



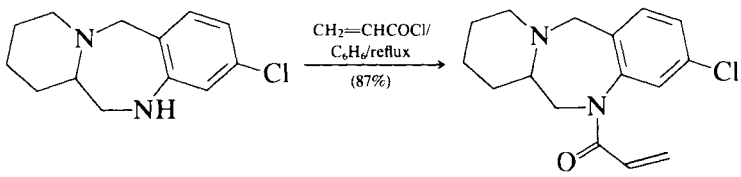

**1090c** **1090d,** mp 99–100°C

(237)

**1090e,** mp 69–70°C

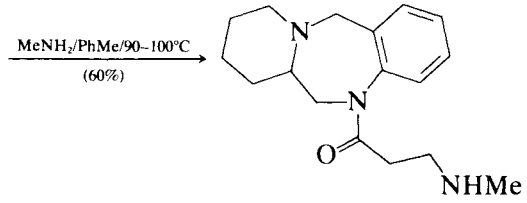
$N^5$-Acyl derivatives could also be obtained by first preparing an acryloyl derivative, with subsequent Michael addition of an amine (541). The conversion of diamine **1090f** to the acryloyl and aminoacyl derivatives **1090g** and **1090h,** respectively, exemplifies this route (Eq. 238). Further examples are listed in Table 125.

Analogs lacking the carbonyl group in the side chain were prepared either by lithium aluminum hydride reduction of the $N^5$-acyl derivatives or by direct alkylation (543). Examples of these reactions include the formation of **1090i** from **1090e** and of **1090j** and **1090k** from **1090f** (Fig. 81). Further examples are listed in Table 126.



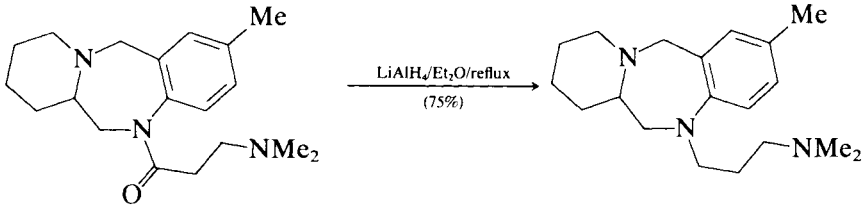

**1090f** **1090g**, mp 119–120°C

(238)

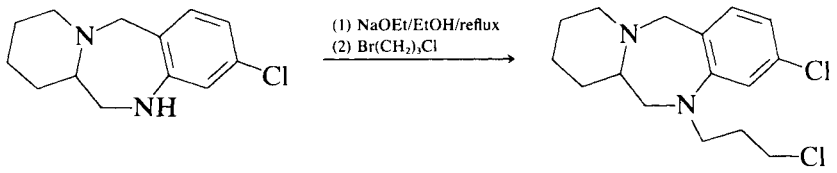



**1090h**, mp 74–75°C

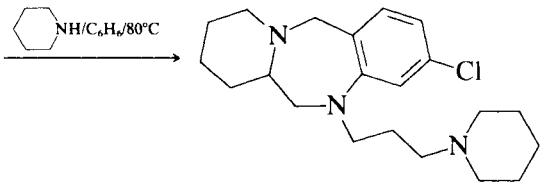
The tricyclic secondary amines **1090c** could be *N*-nitrosated (542,544), and the resultant nitroso derivative **1090l** could be reduced to hydrazine




**1090e** **1090i**, bp 157–158°C/0.08 mm



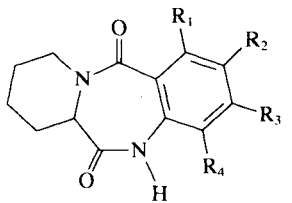

**1090f** **1090j**




**1090k**, bp 190–191°C/0.01 mm

**Figure 81**

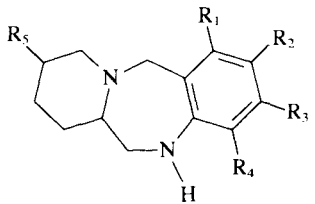
TABLE 122. PYRIDO[2,1-*c*][1,4]BENZODIAZEPINE-6,12-DIONE DERIVATIVES




| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| H | Me | H | H | 52 | 242–243 | 537,541 |
| H | H | Cl | H | | 315–316[a] | 537,541 |
| H | Me | Me | H | 30[a] | 255–256 | 537,541 |
| H | Cl | H | H | 67[a,b] | 283–284 | 253,537,541 |
| Cl | H | H | H | | 209–210 | 541 |
| H | H | H | Cl | | 185–186 | 541 |
| H | H | H | Me | 39[c] | 229–230 | 537 |
| H | Cl | H | Cl | 50[d] | 199–200 | 537 |
| H | I | H | H | 72[d] | 236–237 | 537 |
| H | H | H | H | 32[e] | 227–229 | 253 |
| H | $NO_2$ | H | H | 28[e] | 292.5–300 | 253 |
| H | H | H | H ($\Delta^{8,9}$) | 38[b] | 232–235 | 253 |
| H | H | H | H (9-COOH) | | 271–273.5 | 546 |

[a]Also cyclized with $NaOH/H_2O/EtOH$ at 100°C in indicated yield.
[b]Spontaneous cyclization on hydrogenation of nitro ester.
[c]Cyclization with 2 *N* $H_2SO_4$ under reflux.
[d]Cyclization with $NaOH/H_2O/EtOH$ at 100°C.
[e]Isatoic anhydride method.

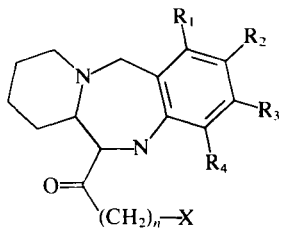
TABLE 123. 5,6,6a,7,8,9,10,12-OCTAHYDROPYRIDO[2,1-*c*][1,4]BENZODIAZEPINES

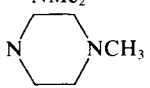
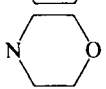


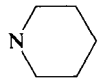
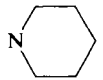
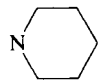
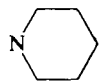
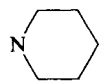
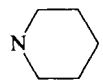

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Yield (%) | mp (°C) | Spectra | Refs. |
|---|---|---|---|---|---|---|---|---|
| H | Cl | H | H | H | 60[a], 93[b] | 131–132 | (HCl) | 537,541,542 |
| | | | | | | 280–283 | | 253 |
| H | Me | Me | H | H | 40[a,b] | 116–117 | | 541 |
| H | H | Cl | H | H | 63[a,b] | 131–132 | | 540,541 |
| H | Me | H | H | H | 92[a] | 119–120 | | 537,541 |
| H | H | MeO | H | H | 86[b] | 104–105 | | 537,540,541 |
| H | H | $CF_3$ | H | H | [b] | 105–106 | | 542 |
| H | —$OCH_2O$— | H | H | H | [b] | 285–296 | | 542 |
| H | H | Me | H | H | 47[b] | 110 | | 537,540 |
| H | H | H | H | H | 91[a] | 105–107 | ir, nmr | 253,378 |
| H | H | H | H | $CH_2OH$ | 82[c] | 222.5–226 | | 253 |
| H | H | H | H | H ($\Delta^{8,9}$) | 99[a] | | | 253 |

[a]Reduction of dione with LAH/THF under reflux.
[b]Reduction of monolactam with LAH/THF under reflux.
[c]Reduction of dione with LAH/ether/THF under reflux.

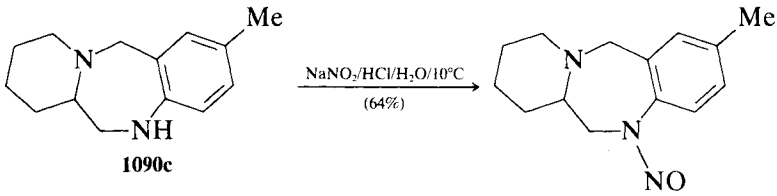
TABLE 124. 6-ACYLPYRIDO[2,1-*c*][1,4]BENZODIAZEPINE DERIVATIVES




| $R_1$ | $R_2$ | $R_3$ | $R_4$ | *n* | X | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|---|---|
| H | Me | H | H | 2 | Cl | 99–100 | 67 | 537,541 |
| H | Cl | H | H | 2 | Cl | 95–96 | 82 | 537,541 |
| H | Me | H | H | 2 | $NMe_2$ | 69–70 | 72 | 537,541 |
| H | Me | H | H | 2 |  | 64–65 | 35 | 537,541 |
| H | Me | H | H | 2 |  | 168–172(HCl) | 55 | 537,541 |

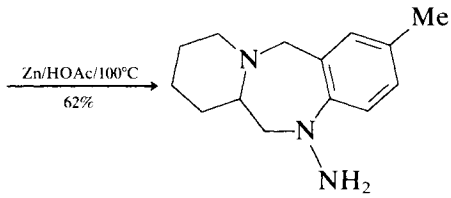
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| H | H | Cl | H | 2 | $NMe_2$ | 184–186/0.03 | | 541 |
| H | Me | Me | H | 2 | $NMe_2$ | 209–210/0.15<br>83–84 | | 541 |
| H | H | Cl | H | 2 |  | 209/0.15 | 65 | 537,541 |
| H | Cl | H | H | 2 |  | 99–100 | 51 | 537,541 |
| H | Cl | H | H | 1 | Br | 110 | 69 | 541 |
| H | Cl | H | H | 1 |  | 208–210/0.2 | 35 | 541 |
| H | H | Cl | H | 1 |  | 190–192/0.1 | 63 | 541 |
| H | H | Cl | H | 3 |  | 200–202/0.01 | | 541 |
| H | H | Cl | H | 4 |  | 234–236/0.1 | | 541 |

**1090m** (544,545), as shown in Eq. 239. Further examples of substances prepared via this route are listed in Table 127. The lactam **1091a** was $N^5$-



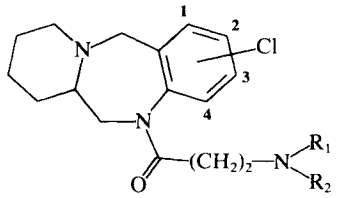

**1090c**

**1090l**, mp 68–69°C,
bp 172–174°C/0.2 mm Hg;
HCl, mp 204–205°C;
sulfate, mp 182–183°C (239)



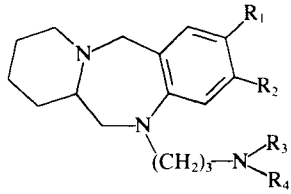

**1090m**, mp 83–84°C;
HCl, mp 158–160°C

TABLE 125. 5-AMINOACYLPYRIDO[2,1-*c*][1,4]BENZODIAZEPINE DERIVATIVES



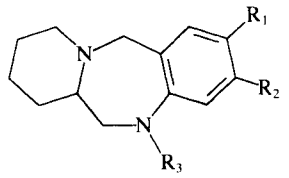

| $R_1$ | $R_2$ | Position of Cl | mp (°C) or bp (°C/torr) |
|---|---|---|---|
| Me | Me | 3 | 184–186/0.03 |
| Et | Et | 3 | 190–191/0.01 |
| H | H | 3 | 121–122 |
| —$(CH_2)_4$— | | 3 | 57–58 |
| —$(CH_2CH_2N(CH_3)CH_2CH_2)$— | | 3 | 79–80 |
| —$(CH_2CH_2OCH_2CH_2)$— | | 3 | 109–110 |
| —$(CH_2)_5$— | | 1 | 97–98 |
| —$(CH_2)_5$— | | 4 | 94–95 |

TABLE 126. 5-AMINOALKYLPYRIDO[2,1-*c*][1,4]BENZODIAZEPINE DERIVATIVES



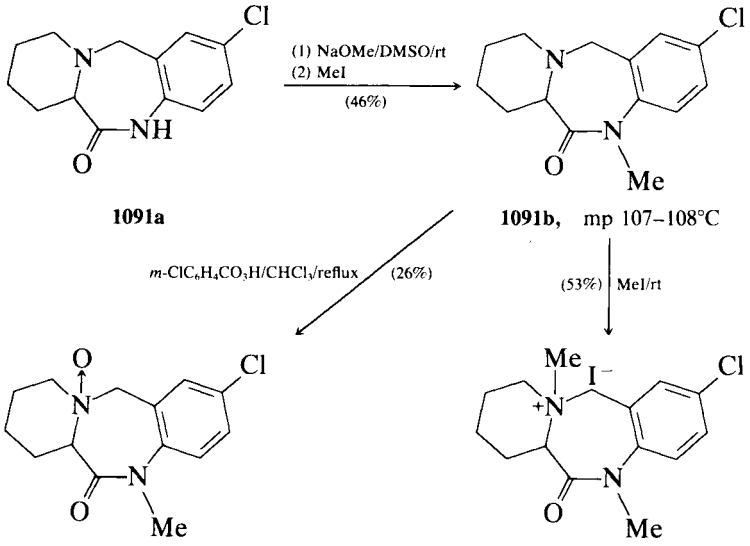
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| Me | H | Me | Me | 157–158/0.08 | 75 | 537,543 |
| H | Cl | Me | Me | 163–165/0.03 | 50 | 537,543 |
| Me | Me | Me | Me | 183–185/0.05 | 81 | 537,543 |
| H | Cl | —$(CH_2)_5$— | | 190–191/0.1 | 73 | 537,543 |

TABLE 127. 5-NITROSO-5,6,6a,7,8,9,10,12-OCTAHYDROPYRIDO[2,1-*c*] [1,4]BENZODIAZEPINES AND DERIVED 5-AMINO COMPOUNDS



| $R_1$ | $R_2$ | $R_3$ | Salt | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| Cl | H | NO | HCl | 104–105<br>137–139 | | 542,544 |
| H | $CF_3$ | NO | | 92–93 | 50 | 542,544 |
| —$OCH_2O$— | | NO | | 52–53 | 52 | 542,544 |
| H | Cl | NO | | 190–192/0.1 | 42 | 542,544 |
| H | Me | NO | | 174–175/0.05 | | 542 |
| Me | Me | NO | HCl | 96–97<br>193–194 | 56 | 542,544 |
| Me | Me | NO | | 62–63 | 52 | 542,544 |
| Br | H | NO | | 96–97 | 32 | 544 |
| H | Me | $NH_2$ | | 98 | 62 | 544,545 |
| Cl | H | $NH_2$ | | 115–116 | 70 | 544,545 |
| H | $CF_3$ | $NH_2$ | | 119–121 | | 545 |
| —$OCH_2O$— | | $NH_2$ | | 91–92 | 49 | 544,545 |

methylated to **1091b,** and the latter product was converted to the *N*-oxide **1091c** and the methiodide **1091d,** as shown in Eq. 240 (546). Further examples



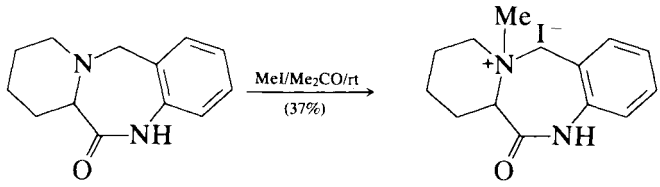

**1091a** **1091b,** mp 107–108°C

**1091c,** mp 197–198°C **1091d,** mp 283–284°C

(240)

are listed in Table 128. In addition, the amines were acylated by standard methods (253) to obtain the products listed in Table 129.

In a second investigation of the reaction of lactam **1088a** with methyl iodide in acetone at room temperature (Eq. 241), the stereoisomeric meth-



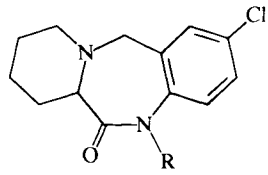

**1088a**

**1092a,** mp 241–243°C (ir, nmr)
**1092b,** mp 157–159°C (ir, nmr)

(241)

iodides **1092a** and **1092b** were isolated (378). As shown in Fig. 82, when either **1092a** or **1092b** was treated with sodium amalgam, the diazaundecanone derivative **1093** was obtained. However, with lithium in liquid ammonia or with lithium aluminum hydride, cleavage of the benzylamine bond occurred to give the piperidine derivatives **1094** and **1095.** Treatment of the methiodides with phenyllithium yielded the spiro derivative **1096** (Fig. 82).

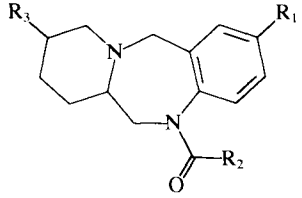
TABLE 128. 5-SUBSTITUTED PYRIDO[2,1-*c*][1,4]BENZODIAZEPIN-6-ONE DERIVATIVES



| R | mp (°C) or bp (°C/torr) | Salt | Yield (%) | Other Data |
|---|---|---|---|---|
| Me | 107–108 | | 39[a] | |
| Me | 107–108 | | 54[b] | |
| Me | 109–110 | | | (+)-Isomer by resolution: $[\alpha]_D^{27} = +385°$ ($c$ = 1.8; EtOH) |
| Me | 110–111 | | | (−)-Isomer by resolution: $[\alpha]_D^{25} = -368°$ ($c$ = 2.16; EtOH) |
| Et | 58–59 | | | |
| | 152–154/0.015 | | | |
| $CH_2CH{=}CH_2$ | 214 | HCl | 72 | |
| *i*-Pr | 150–155/0.065 | Maleate | 36 | |
| | 157–158 | | | |
| *n*-Bu | 154–157/0.1 | Maleate | 75 | |
| | 137–138 | | | |
| $CH_2Ph$ | 180/0.008 | HCl | 81 | |
| | 200–202 | | | |
| $(CH_2)_3NMe_2$ | 190/0.003 | Maleate | 70[c] | |
| | 136–137 | | | |

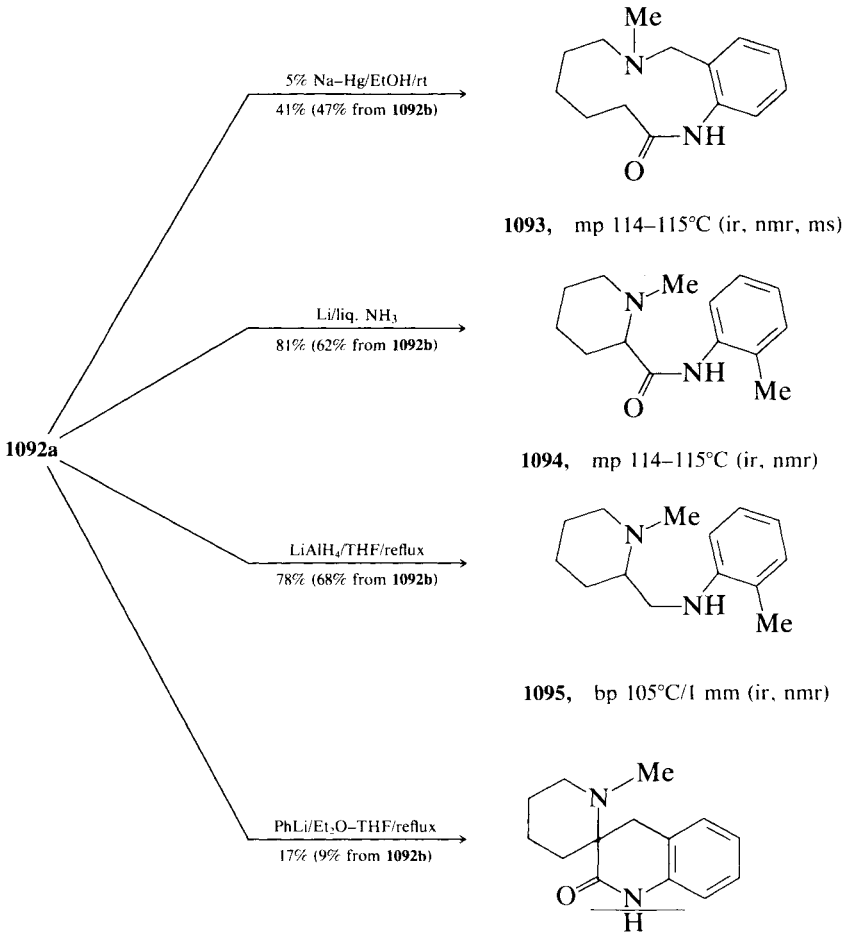
[a](1) KOBu-t/DMSO, room temperature; (2) $Me_2SO_4$.
[b](1) KOBu-t/DMSO, room temperature; (2) MeI.
[c](1) NaH/dioxane, reflux; (2) $Me_2N(CH_2)_3Cl$.

TABLE 129. 5-ACYLPYRIDO[2,1-*c*][1,4]BENZODIAZEPINE DERIVATIVES



| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) | Method |
|---|---|---|---|---|---|
| H | Me | H | 261–263 | 90 | $MeCOCl/CHCl_3$, 10°C |
| H | Et | H | 246–248 | 63 | $(EtCO)_2O/H_2SO_4$, rt |
| H | Ph | H | 257–259 | 81 | $PhCOCl/CHCl_3$, 10°C |
| Cl | Et | H | 227.5–230[a] | 47 | $EtCOCl/CHCl_3$, 10°C |
| H | Et | $EtCO_2$ | 201–203 | | $(EtCO)_2O/H_2SO_4$, rt |
| H | Et | H($\Delta^{8,9}$) | 150–152[a] | 86 | |

[a]*p*-Toluenesulfonate salt.




**1093,** mp 114–115°C (ir, nmr, ms)

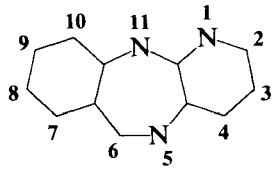
**1094,** mp 114–115°C (ir, nmr)

**1095,** bp 105°C/1 mm (ir, nmr)

**1096,** mp 157–159°C (ir, nmr, ms)

**Figure 82**

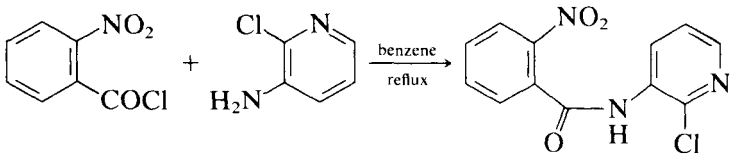
## 40. Pyrido[2,3-*b*][1,4]benzodiazepines (see Section XVI.16)



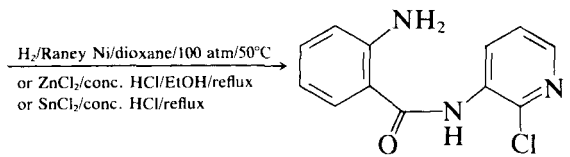

The first synthesis of pyrido[2,3-*b*][1,4]benzodiazepine derivatives (547,548) is described in Fig. 83. Reaction of 3-amino-2-chloropyridine with 2-nitro-

benzoyl chloride gave the adduct **1097.** The nitro group was reduced by catalytic hydrogenation, or with zinc chloride or stannous chloride, to give the aniline **1098**, which was cyclized thermally to the tricyclic lactam **1099a.** The 8-methyl and 9-chloro analogs (**1099b** and **1099c**) were prepared similarly.

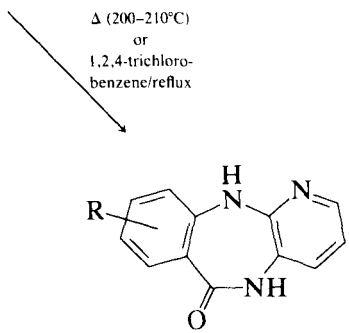
The tricyclic lactams **1099a–c** were alkylated by abstraction of the lactam proton with a basic reagent followed by treatment with an alkyl halide (548,549). Derivatives prepared in this manner are listed in Table 130. A selected number of these $N^5$-substituted products were reduced with lithium aluminum hydride in refluxing tetrahydrofuran (550,551) to give the diamines listed




**1097**




**1098**



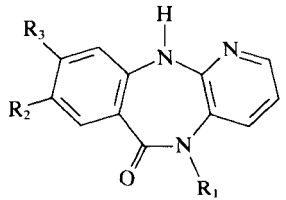

**1099a,** R = H (60% yield without solvent, 82% using trichlorobenzene); mp 286–288°C; HBr, mp 280°C

**1099b,** R = 8-Me (70% without solvent); mp 257–258°C

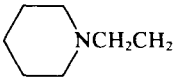
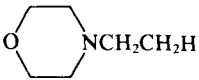
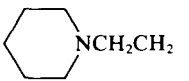
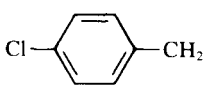
**1099c,** R = 9-Cl (68% without solvent); mp >340°C

***Figure 83***

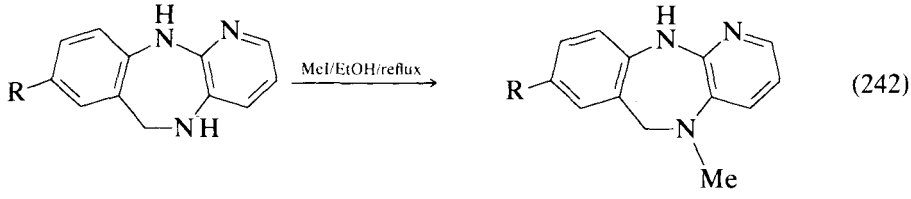
TABLE 130. 5-SUBSTITUTED PYRIDO[2,3-*b*][1,4]BENZODIAZEPIN-6-ONE DERIVATIVES



| $R_1$ | $R_2$ | $R_3$ | Salt | mp, (°C) or bp, (°C/torr) | Basic Reagent | Halide | Yield (%) | Refs. |
|---|---|---|---|---|---|---|---|---|
| Me | H | H | | 210–213 | $NaOH/H_2O$/ EtOH, reflux | I | 90 | 549 |
| Et | H | H | | 129–131 | $NaOH/H_2O$/ EtOH, reflux | I | 97 | 549 |
| *n*-Pr | H | H | | 178–180 | $NaOH/H_2O$/ EtOH, reflux | Br | 69 | 549 |
| Me | H | Cl | | 225–226 | *n*-BuONa/ *n*-BuOH, 70°C | I | 47 | 549 |
| Et | H | Cl | | 180–181 | *n*-BuONa/ *n*-BuOH, 70°C | I | 68 | 549 |
| $Me_2NCH_2CH_2$ | H | H | | 135–137 | EtONa/EtOH/ PhMe, reflux | Cl | 70 | 549 |
| | | | HCl | 278 | | | | 549 |
| $Me_2N(CH_2)_3$ | H | H | | 90–93<br>185–187/0.04 | EtONa/EtOH/ xylene, reflux | Cl | 79 | 549 |
| | | | 2HCl | 225–226 | | | | 549 |
| $Me_2NCH_2CH_2$ | H | Cl | | 148–151 | *n*-BuONa/*n*-BuOH/ xylene, reflux | Cl | | 549 |
| | | | HCl | 269–271 | | | 33 | 549 |
| *n*-Pr | H | Cl | | 164 | $NaOH/H_2O$/ *i*-PrOH, reflux | Br | 65 | 549 |
| Me | Me | H | | 184–186 | $NaOH/H_2O$/ *i*-PrOH, reflux | I | 70 | 549 |
| Et | Me | H | | 198–200 | $NaOH/H_2O$/ *i*-PrOH, reflux | I | 75 | 549 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $Me_2NCH_2Ch_2$ | Me | H | 215–220/.04 | NaOEt/EtOH | Cl | 49 | 549 |
| $Me_2N(CH_2)_3$ | H | Cl | 130–132 | NaOEt/EtOH/ *i*-PrOH, reflux | Cl | 24 | 549 |
|  | H | Cl | 153–154 | KOH/*i*-PrOH/ EtOH, reflux | Cl | 31 | 549 |
| *i*-Bu | H | H | 206–207 | $NaOH/H_2O$/ *i*-PrOH, reflux | Br | 58 | 549 |
| $Me_2N(CH_2)_3$ | Me | H | 99–101 197/0.06 | NaOEt/EtOH/ PhMe, reflux | Cl | 30 | 549 |
|  | H | H | 151–152 | KOH/*i*-PrOH, reflux | Cl | 49 | 549 |
| $CH_3OCH_2CH_2$ | H | H | 151–153 | *i*-PrOK/*i*-PrOH/ xylene, reflux | I | 75 | 549 |
| $Cl(CH_2)_3$ | H | H | 151 | EtOH/KOH, reflux | Br | 67 | 549 |
|  | H | H | 70–72 206–210/0.01 | *t*BuOK/*t*-BuOH/ dioxane, reflux | Cl | 40 | 549 |
| *n*-Bu | H | H | 159–160 | *t*-BuOK/*t*-BuOH/ dioxane, reflux | Cl | | 549 |
| $MeOCH_2CH_2$ | H | Cl | 180–181 | *t*-BuOK/*t*-BuOH/ dioxane, reflux | Cl | | 549 |
| *n*-Bu | Me | H | 124–126 | *t*-BuOK/*t*-BuOH/ dioxane, reflux | Cl | | 549 |
| $PhCH_2$ | H | H | 155–156 | NaOEt/EtOH/ xylene, reflux | Cl | 65 | 549 |
| $PhCH_2$ | H | Cl | 191 | $NaOH/H_2O$/ *i*-PrOH, reflux | Cl | | 548 |
|  | H | H | 169–171 | $NaOH/H_2O$ *i*-PrOH, reflux | Cl | | 548 |

in Table 131. Two of the $N^6$-substituted diamines, **1100c** and **1100d,** were also obtained from the unsubstituted diamines **1100a** and **1100b** by selective alkylation of the more reactive monoarylamine nitrogen (552), as shown in Eq. 242.

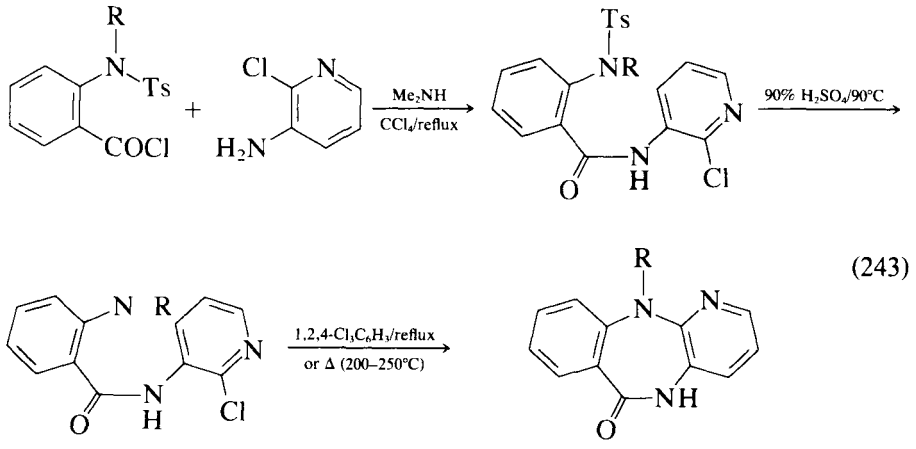



(242)

**1100a,** R = H
**1100b,** R = Me

**1100c,** R = H (65%); mp 95°C; HI, mp 173–174°C
**1100d,** R = Me (50%); mp 119–120°C; HI, mp 222–224°C; HCl, mp 185–186°C

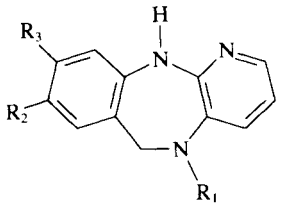
A patent (553) subsequently described a synthesis leading to $N^{11}$-substituted derivatives such as **1099d** and **1099e** (Eq. 243). Instead of starting with 2-nitrobenzoyl chloride (547,548), this approach used *N*-tosylated secondary amines. The protecting group was removed with 90% sulfuric acid at 90°C. An alternative procedure (553) made use of *N*-alkyl isatoic anhydrides as starting materials (Eq. 244). Heating the anhydrides in a solvent with a 3-amino-2-chloropyridine gave the tricyclic lactams **1099f–h** directly. These $N^{11}$-alkyl derivatives could be alkylated further on the lactam nitrogen by the method described above (Table 132).




(243)

**1099d,** R = Me (65%); mp 215–216°C
**1099e,** R = Et (57%); mp 190–193°C

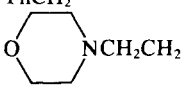
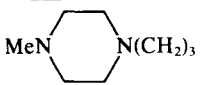
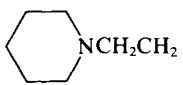
TABLE 131. 5-SUBSTITUTED PYRIDO[2,3-*b*][1,4]BENZODIAZEPINE DERIVATIVES

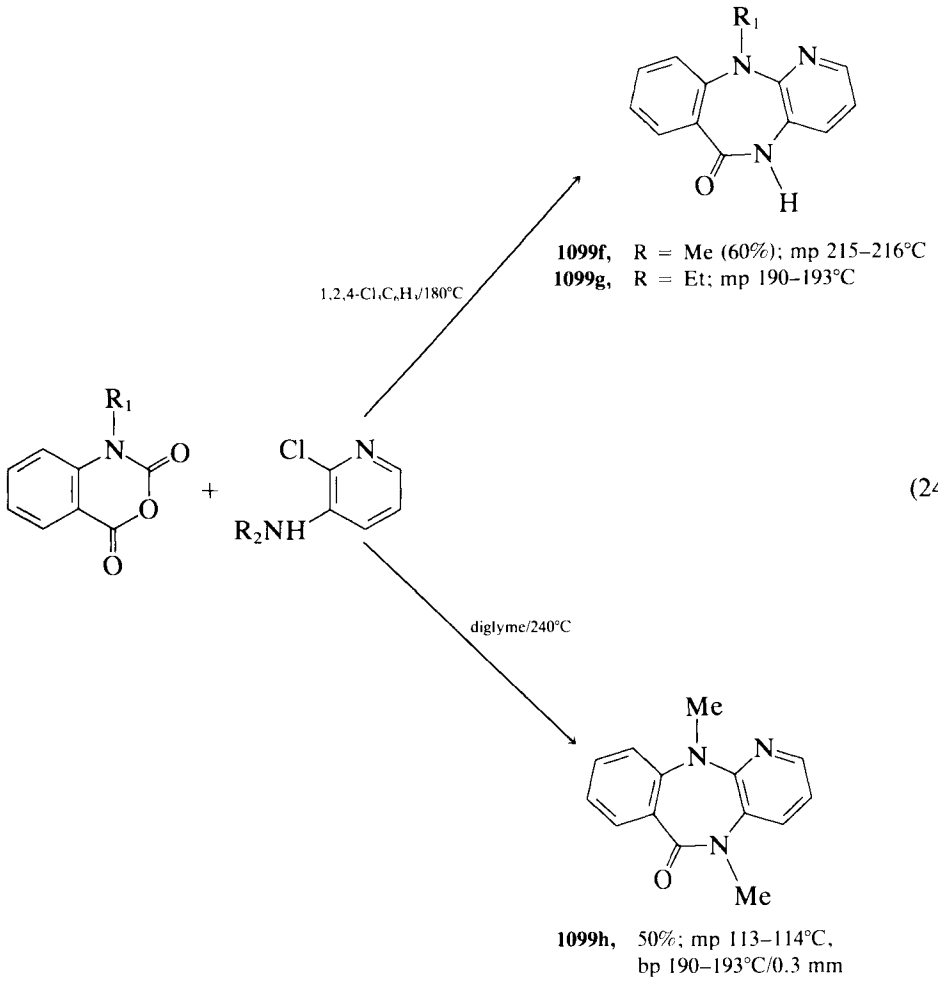


| $R_1$ | $R_2$ | $R_3$ | Salt | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| Et | H | H | | 84–86 | 60 | 550 |
| | | | | 150–153/0.08 | | |
| H | H | H | | 144–145 | | 550 |
| Me | H | H | | 95 | | 550 |
| H | Me | H | | 159–160 | | 550 |
| Me | Me | H | | 120–123 | | 550 |
| | | | HCl | 228–230 | | 550 |
| Et | Me | H | | 114–116 | | 550 |
| *i*-Bu | H | H | | 95–97 | | 550 |
| | | | 2HCl | 230 | | 551 |
| $MeOCH_2CH_2$ | H | H | | 83–86 | | 550 |
| *n*-Pr | H | H | | 155–160/0.01 | | 550 |
| *n*-Bu | H | H | | 150–152/0.02 | | 550 |
| *n*-Bu | Me | H | | 83–86 | | 550 |
| H | H | Cl | | 182–182 | | 551 |
| Me | H | Cl | | 104–106 | | 551 |
| Et | H | Cl | | 92–94 | | 551 |

(*continued*)

TABLE 131. *(Continued)*

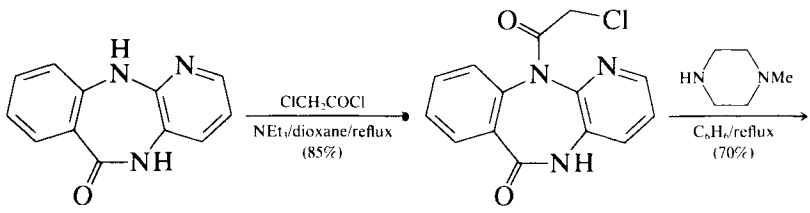
| $R_1$ | $R_2$ | $R_3$ | Salt | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| *n*-Pr | H | Cl | | 78–79 | | 551 |
| | | | | 173–175/0.05 | | |
| | | | HCl | 198–21 | | 551 |
| $PhCH_2$ | H | Cl | | 136 | | 551 |
| $Me_2NCH_2CH_2$ | H | Cl | | 99–101 | | 551 |
| $Me_2N(CH_2)_3$ | H | H | | 180/0.15 | | 551 |
| | | | | 89–91 | | |
| $PhCH_2$ | H | H | | 138–139 | | 551 |
|  | H | H | | 138–139 | | 551 |
|  | H | H | | 214/0.01 | | 551 |
|  | H | H | | 208–210/0.04 | | 551 |




(244)

$N^{11}$-Aminoacetyl derivatives were prepared by reaction of the tricyclic substrates with chloroacetyl chloride followed by treatment with a secondary amine (554). The products (Table 133) were patented as antiulcer agents. In the example shown in Eq. 245, the unsubstituted lactam **1099a** was converted to the 11-chloroacetyl derivative **1099i**, which on treatment with *N*-methylpiperazine gave compound **1099j** (pirenzepin). Extensive pharmacologic and toxicologic evaluation of this substance has been undertaken (555) in preparation for clinical testing. Other examples are listed in Table 133. In a later patent (556) the synthesis of a number of *N*,*N*-bis(allyl) derivatives obtained by this approach was described. These are listed in Table 134.

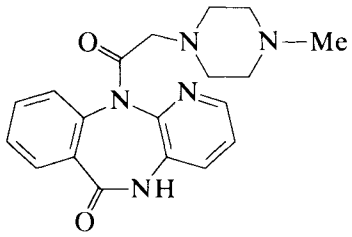
A somewhat different synthesis of the tricyclic ring system was used to prepare 2-chloro derivatives (557). In the example shown in Fig. 84, the




**1099a**

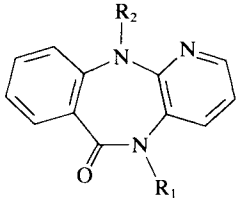
**1099i**, mp 212–213°C

(245)

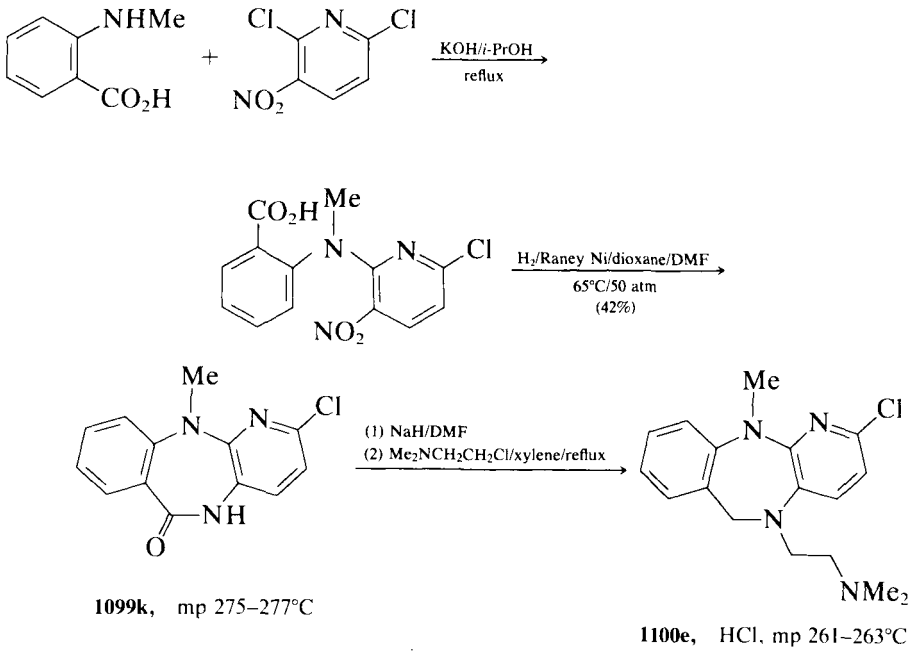



**1099j**, mp 226–228°C;
2 HCl, mp 257–259°C;
sesquifumarate, mp 219–220°C

TABLE 132. 6,11-DISUBSTITUTED PYRIDO[2,3-*b*][1,4]BENZODIAZEPIN-6-ONE DERIVATIVES




| $R_1$ | $R_2$ | mp (°C) | Basic Reagent | Yield (%) |
|---|---|---|---|---|
| Me | Me | 113–114 | KOH/$H_2O$/EtOH, reflux | 78 |
| Me | Et | 101–102 | KOMe/dioxane/ *t*-BuOH, reflux | 72 |
| Me | Pr | 98–100 | KOMe/dioxane/ *t*-BuOH, reflux | 65 |
| Me | $CH_2CH{=}CH_2$ | 89–90 | KOMe/dioxane/ *t*-BuOH, reflux | 57 |
| Et | Me | 127–128 | KOMe/dioxane/ *t*-BuOH, reflux | 58 |
| Et | Et | 95–97 | KOMe/dioxane/ *t*-BuOH, reflux | 76 |
| Et | $CH_2CH{=}CH_2$ | 135–137 | KOMe/dioxane/ *t*-BuOH, reflux | 56 |



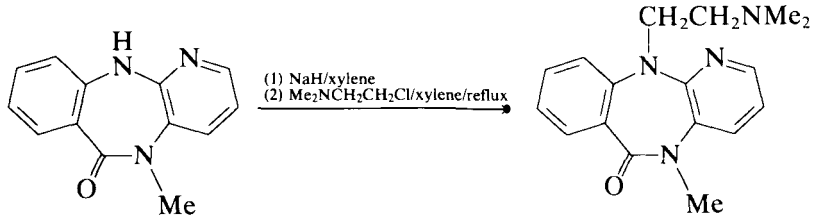

**1099k,** mp 275–277°C

**1100e,** HCl, mp 261–263°C

**Figure 84**

triamine **1100e** was prepared by $N^5$-alkylation of lactam **1099k.** The product was patented as a combination with (2-morpholinoethyl)bisabolyl ether as an antiulcer agent (558); other examples prepared by the same method are listed in Table 135.

$N^{11}$-Alkylation of tricyclic lactams was accomplished by treatment with sodium hydride followed by reaction with an aminoalkyl halide in refluxing xylene (559). One example (Eq. 246) is the conversion of lactam **1100f** to



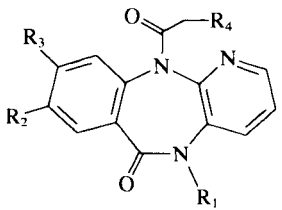

(246)

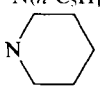
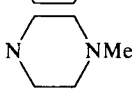
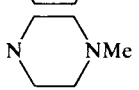
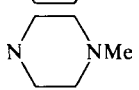
**1100f**

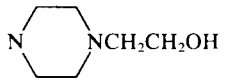
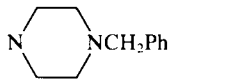
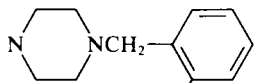
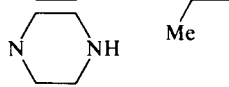
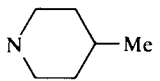
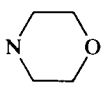
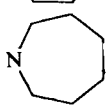
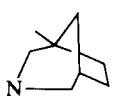
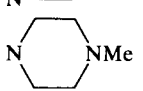
**1100g,** mp 109–110°C,
bp 171–173°C/0.006 Torr

the 11-dimethylaminoethyl derivative **1100g.** Other products obtained via this route are listed in Table 136. These substances were patented as bronchospasmolytic agents.

TABLE 133. 11-ACYLPYRIDO[2,3-*b*][1,4]BENZODIAZEPIN-6-ONE DERIVATIVES

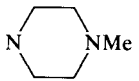
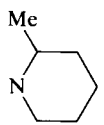
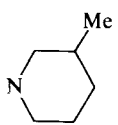
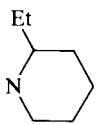
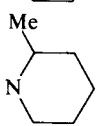
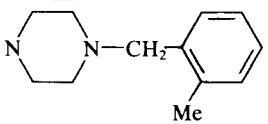


| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Salt | mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| Me | H | H | Cl | | 203–205 | 80 |
| H | Cl | H | Cl | | 211–212 | 65 |
| H | H | Cl | Cl | | 223–225 | 25 |
| Et | H | H | Cl | | 169–170 | 60 |
| H | Me | H | Cl | | 120–124 | 55 |
| H | H | H | $NEt_2$ | | 152–153 | 54 |
| Me | H | H | $NEt_2$ | | 137–138 | 30 |
| H | H | H | $N(n\text{-}Pr)_2$ | | 212–213 | 30 |
| H | H | H | $N(n\text{-}Bu)_2$ | | 177–179 | 33 |
| H | H | H | $N(i\text{-}Bu)_2$ | | 226–227 | 37 |
| H | H | H | $N(n\text{-}C_5H_{11})_2$ | | 157–158 | 35 |
| H | H | H |  | | 217–218 | 43 |
| Me | H | H |  | 2HCl | 227 | 40 |
| H | Cl | H |  | | 254–256 | 56 |
| H | H | Cl |  | 2HCl | 205–207 | 36 |

| | | | | | | |
|---|---|---|---|---|---|---|
| H | H | H |  | | 213–214 | 25 |
| H | H | H |  | | 216–217 | 40 |
| H | H | H |  | | 218–220 | 35 |
| H | H | H |  | 2HCl | 229–230 | 30[a] |
| H | H | H |  | | 202–203 | 50 |
| H | H | H |  | | 249–250 | 40 |
| H | H | H |  | | 222 | 38 |
| H | H | H |  | | 207–209 | 70 |
| H | H | H |  | | 252–254 | 30 |
| Et | H | H |  | | 174–175 | 60 |

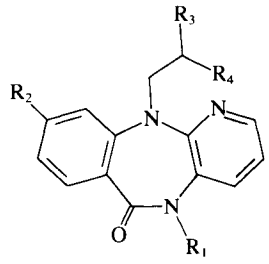
(*continued*)

TABLE 133. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Salt | mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| H | Me | H |  | HCl | 236–237<br>169–170 | 36 |
| H | H | H |  | 2HCl | 253–254 | 80 |
| H | H | H | $NMe_2$ | | 241–242 | 45 |
| Me | H | H | $NMe_2$ | | 251–252 | 55 |
| H | H | H |  | | 203–204 | 45 |
| H | H | H |  | | 214–215 | 58 |
| H | H | H |  | | 218–219 | 62 |
| Me | H | H |  | | 173–174 | 68 |
| Me | H | H |  | | 191–192 | 85 |

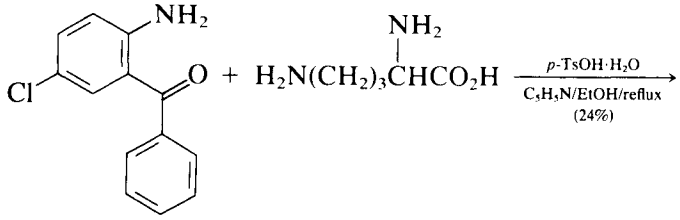
[a]Prepared from the *N*-benzylpiperazine by catalytic hydrogenolysis with Pd/C in methanol/acetic acid at 50°/50 atm.

TABLE 134. 11-SUBSTITUTED PYRIDO[2,3-*b*][1,4]BENZODIAZEPIN-6-ONE DERIVATIVES



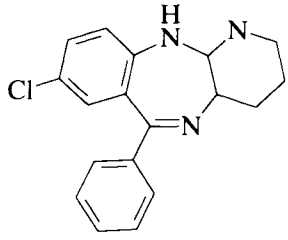
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) | Yield (%) |
|---|---|---|---|---|---|
| H | H | H | $N(CH_2CH{=}CH_2)_2$ | 165–167 | 80 |
| Me | H | H | $N(CH_2CH{=}CH_2)_2$ | 103–105<br>121–123(HCl) | 43 |
| Et | H | H | $N(CH_2CH{=}CH_2)_2$ | 133–135 | 60 |
| H | Cl | H | $N(CH_2CH{=}CH_2)_2$ | 163–164 | 53 |
| H | H | H | $CH_2N(CH_2CH{=}CH_2)_2$ | 156–158 | 62 |
| Me | H | H | $CH_2N(CH_2CH{=}CH_2)_2$ | 94–95 | 56 |
| H | H | Me | $N(CH_2CH{=}CH_2)_2$ | 231 | 20 |

The tricyclic diazepam analog **1101** was prepared (560) by reaction of the 2-aminobenzophenone **102** with L-ornithine (Eq. 247).



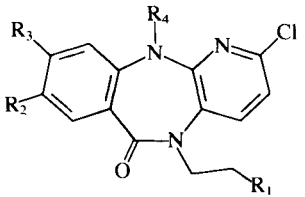
**1102**

(247)



**1101**, mp 214–218°C (ms)

TABLE 135. 11-ALKYL-5-AMINOALKYLPYRIDO[2,3-*b*][1,4]BENZODIAZEPIN-6-ONES



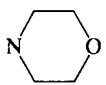
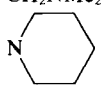
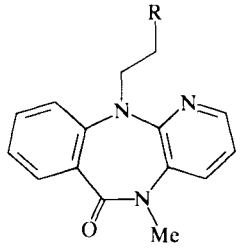
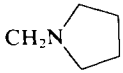
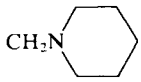
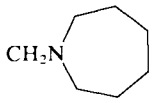
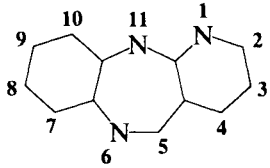

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Salt | mp (°C) |
|---|---|---|---|---|---|
|  | H | H | Me | HCl | 223–226 |
| $CH_2NMe_2$ | H | H | Me | | 180–182 |
|  | H | H | Me | HCl | 246–248 |
| $NMe_2$ | H | H | Et | HCl | 240–242 |
| $NMe_2$ | Me | H | Me | HCl | 268–270 |
| $NMe_2$ | Cl | H | Me | HCl | 272–274 |
| $NMe_2$ | H | Cl | Me | HCl | 258–260 |

TABLE 136. 11-AMINOALKYL-5-METHYLPYRIDO[2,3-*b*][1,4]BENZODIAZEPIN-6-ONE DERIVATIVES

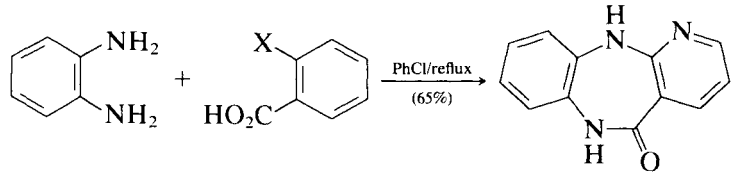


| R | mp (°C) or bp (°C/torr) |
|---|---|
| $NEt_2$ | 197–199/0.07 |
| $N(i\text{-}Pr)_2$ | 196–199/0.07 |
| $CH_2NMe_2$ | 202–205/2.5 |
| $CH_2NEt_2$ | 212–214/0.2 |
| $CH_2N(i\text{-}Pr)_2$ | 217–220/0.1 |
|  | 119–121<br>218–221(HCl) |
|  | 198–200/0.06 |
|  | 195–198/0.06 |

## 41. Pyrido[2,3-*b*][1,5]benzodiazepines (see Section XVI.17)

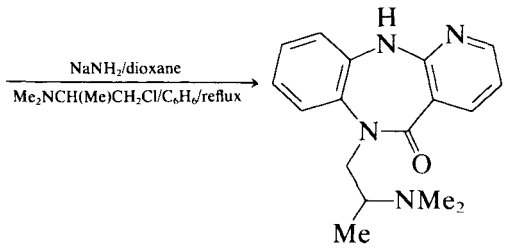


The method of preparation of essentially all pyrido[2,3-*b*][1,5]benzodiazepine derivatives reported to date was first described by a French group (561). In the example given in Eq. 248, 2-halonicotinic acid was heated with *o*-phenylenediamine at 130°C to give the tricyclic lactam **1103.** This synthesis has the disadvantage that if an unsymmetrically substituted *o*-phenylenediamine is used, either a mixture or a product of uncertain structure results. Sodium amide–mediated alkylation of the lactam nitrogen led to dialkylaminoalkyl




(X = Cl.Br) **1103**, mp 295°C

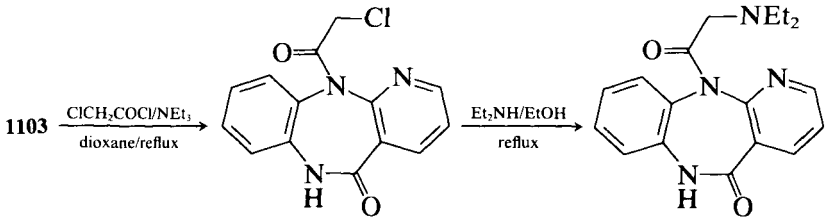
(248)




**1104**, mp 120°C

derivatives patented as antidepressant agents. One member of the series that has been studied extensively in animals and appears to be active clinically (562) is compound **1104** (propizepine). Analogous substances prepared by these procedures are listed in Table 137.

Compounds containing an 11-dialkylaminoacetyl substituent were prepared as shown in Eq. 249. The tricyclic lactam **1103** was treated with

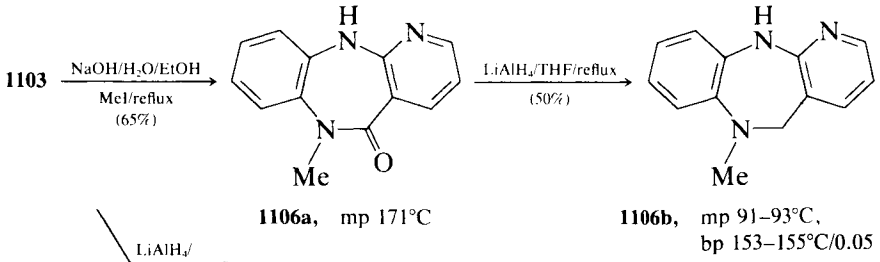



(249)

**1105a**, mp 223–225°C **1105b**, mp 172–174°C

chloroacetyl chloride, and the resulting chloro compound **1105a** was treated with diethylamine (568) to obtain the diethylaminoacetyl derivative **1105b.** Additional substances prepared by this method are listed in Table 138.

Another patent describes a series of 6-alkyl derivatives lacking the lactam carbonyl function (569). The preparation of compounds **1106b–d** (Eq. 250) is illustrative. Additional compounds prepared by this approach are listed



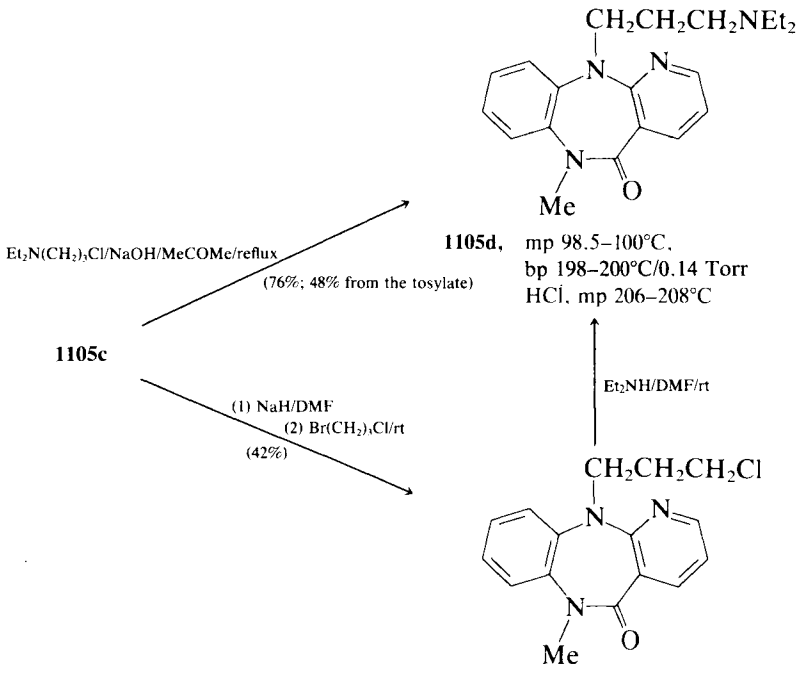

**1106a,** mp 171°C

**1106b,** mp 91–93°C,
bp 153–155°C/0.05 Torr

**1106c,** mp 125–126°C,
bp 135–140°C/0.05 Torr

**1106d,** mp 111–112°C

(250)

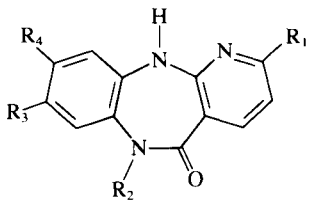


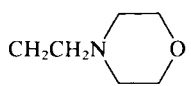

**1105d,** mp 98.5–100°C,
bp 198–200°C/0.14 Torr
HCl, mp 206–208°C

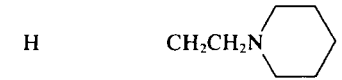
**1105e,** mp 102–103.5°C

(251)

TABLE 137. PYRIDO[2,3-*b*][1,5]BENZODIAZEPIN-5-ONE DERIVATIVES

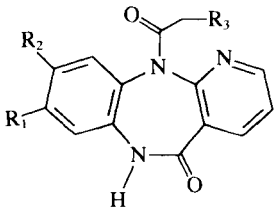


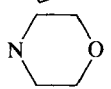
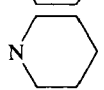
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Salt | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|---|
| H | H | H | H | | 295 | 65 | 561, 563, 564 |
| H | H | Me | Me | | 292 | | 561 |
| H | H | Cl | Cl | | <350 | | 561 |
| H | $CH_2CH_2NEt_2$ | H | H | | 135 | | 561 |
| | | | | HCl | | | 561 |
| H | $CH_2CMe_2NMe_2$ | H | H | | 186–186 | | 561 |
| | | | | HCl | | | 561 |
| H |  | H | H | | 164 | | 561 |
| | | | | HCl | 220–225 | | 561 |
| H | $CH_2CHMeNMe_2$ | Cl | Cl | | 163–164 | | 561 |
| H | $CH_2CH_2NMe_2$ | H | H | | 96 | 80 | 561 |
| | | | | HCl | | | 561 |

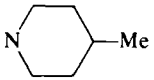
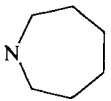
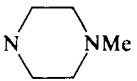
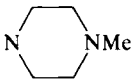
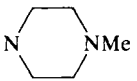
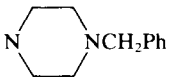
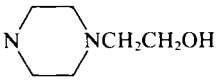
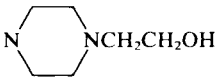
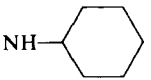
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| H |  | H | H | | 135 | | 561 |
| H | $(CH_2)_3NMe_2$ | H | H | | 108 | | 561 |
| H | $CH_2CH_2NMe_2$ | Me | Me | | 151 | | 561 |
| H | $CH_2CH_2NEt_2$ | Me | Me | | 108 | | 561 |
| H | $(CH_2)_3NMe_2$ | Me | Me | | 148 | | 561 |
| H | $CH_2CHMeNMe_2$ | Me | Me | | 200 | | 561 |
| H | $CH_2CH_2NMe_2$ | Cl | Cl | | 132 | | 561 |
| H | H | Cl[a] | H | | >300 | 51 | 564 |
| H | H | Me[a] | H | | >240 | 57 | 564 |
| H | H | Me | Me | | 295 | 60 | 564 |
| Me | H | H | H | | 276–278 | 85 | 565, 566 |
| | | | | HCl | 256–258 | | 566 |
| Me | $(CH_2)_3NMe_2$ | H | H | | 132–134 | | 566, 567 |
| Me | $CH_2CH_2NMe_2$ | H | H | | 153–155 | | 566, 567 |
| Me | H | Me | Me | | 274–276 | | 566 |
| | | | | HCl | 294–296 | | 566 |
| Me | $CH_2Ph$ | H | H | | 235–236 | | 566 |
| Me | $CH_2CH_2NEt_2$ | H | H | | 95–97 | | 566 |
| | | | | 2HCl | 228–230 | | 566 |
| Me | $CH_2CH_2NMe_2$ | Me | Me | | 175–176 | | 566 |
| Me | $(CH_2)_3NMe_2$ | Me | Me | | 166–167 | | 566 |

[a]Position of substituent not established; possible alternative: $R_3$ = H, $R_2$ = Cl or Me.

TABLE 138. 11-ACYLPYRIDO[2,3-*b*][1,5]BENZODAZEPIN-5-ONE DERIVATIVES

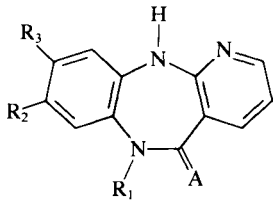


| $R_1$ | $R_2$ | $R_3$ | mp (°C) |
|---|---|---|---|
| Me[a] | H | Cl | 215 |
| Me | Me | Cl | 242–245 |
| H | H | $NMe_2$ | 212–213 |
| Me | Me | $NMe_2$ | 235–236 |
| Me | Me | $NEt_2$ | 199–200 |
| H | H | $N(n\text{-}Pr)_2$ | 171–172 |
| Me | Me | $N(n\text{-}Pr)_2$ | 151–153 |
| H | H | $N(n\text{-}Bu)_2$ | 153–154 |
| Me[a] | H | $N(n\text{-}Bu)_2$ | 162–163 |
| Me | Me | $N(n\text{-}Bu)_2$ | 182–183 |
| H | H | $N(i\text{-}Bu)_2$ | 176–177 |
| Me | Me | $N(i\text{-}Bu)_2$ | 174–175 |
| H | H | $N[(CH_2)_4CH_3]_2$ | 118–120 |
| H | H | $N(CH_2CH{=}CH_2)_2$ | 135–136 |
| H | H |  | 230–231 |
| H | H |  | 243–244 |
| H | H |  | 257 |

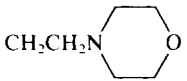
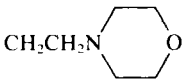
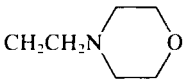
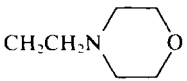
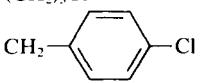
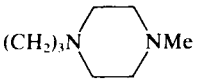
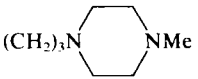
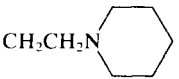
| | | | |
|---|---|---|---|
| H | H |  | 217–218 |
| H | H |  | 219–220 |
| H | H |  | 216–218 |
| Me[a] | H |  | 222 |
| Me | Me |  | 230–231 |
| H | H |  | 213–215 |
| H | H |  | 200–201<br>215–216 (HCl) |
| Me | Me |  | 232–234 |
| H | H |  | 105–106 (HCl) |
| H | H |  | 179–181 |

[a]Position of substituent not established; possible alternative: $R_1$ = H, $R_2$ = Me.

TABLE 139. 6-SUBSTITUTED PYRIDO[2,3-*b*][1,5]BENZODIAZEPIN-5-ONE DERIVATIVES AND CORRESPONDING REDUCTION PRODUCTS

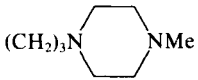
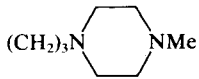
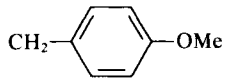
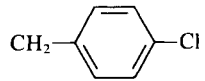
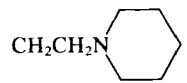
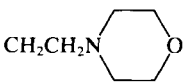
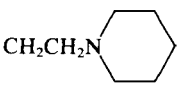
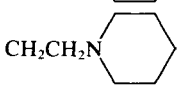


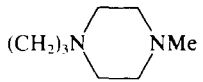
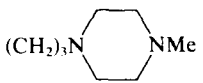
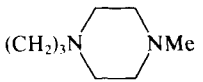
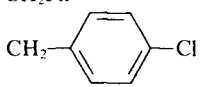
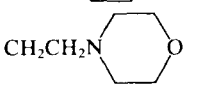
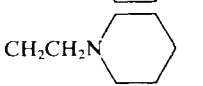
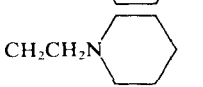
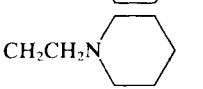
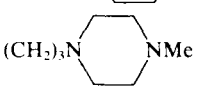
| $R_1$ | $R_2$ | $R_3$ | A | mp, (°C) or bp, (°C/torr) | Yield (%) |
|---|---|---|---|---|---|
| Et | H | H | O | 148–151 | 85 |
| Et | H | H | $H_2$ | 135–139/0.05 | |
| $CH_2Ph$ | H | H | O | 178–180 | 74 |
| | | | | 240–245/0.06 | |
| $CH_2Ph$ | H | H | $H_2$ | 111–112 | |
| | | | | 180–190/0.05 | |
| Me | Me[a] | H | O | 208 | |
| Me | Me[a] | H | $H_2$ | 100 | |
| | | | | 155–160/0.05 | |
| $CH_2CH_2NMe_2$ | H | H | O | 185–187/0.06 | 58 |
| | | | | 240 (HCl) | |
| $CH_2CH_2NMe_2$ | H | H | $H_2$ | 160–165/0.08 | |
| $CH_2CH_2NMe_2$ | Cl[a] | H | O | 112 | |
| | | | | 185–195/0.05 | |
| $CH_2CH_2NMe_2$ | Cl[a] | H | $H_2$ | 169–171/0.0025 | |
| $(CH_2)_3NMe_2$ | H | H | O | 101–102 | 63 |
| | | | | 180–200/0.05 | |
| | | | | 219–220 (HCl) | |
| $(CH_2)_3NMe_2$ | H | H | $H_2$ | 87–88 | |
| Me | Me | Me | O | 202–204 | 75 |
| Me | Me | Me | $H_2$ | 152–154 | |
| $CH_2CH_2NMe_2$ | Me | Me | O | 145–147 | 60 |
| $CH_2CH_2NMe_2$ | Me | Me | $H_2$ | 171–174/0.07 | |

| | | | | |
|---|---|---|---|---|
| Et | Me | Me | O | 162–163 |
| Et | Me | Me | $H_2$ | 145–147/0.03 |
| Et | Cl[a] | H | O | 179–181 |
| Et | Cl[a] | H | $H_2$ | 125–127 |
| $CH_2CH_2NMe_2$ | Me[a] | H | O | 105 |
| $CH_2CH_2NMe_2$ | Me[a] | H | $H_2$ | 157–159/0.02 |
|  | H | H | O | 161–162 |
|  | H | H | $H_2$ | 187–189/0.04 |
|  | Me | Me | O | 149–150 |
|  | Me | Me | $H_2$ | 193–196/0.02 |
| $CH_2CHMe_2$ | H | H | O | 125–127 |
| $CH_2CH{=}CH_2$ | H | H | O | 105–107 |
| $MeOCH_2CH_2$ | H | H | O | 125–126 |
| $(CH_2)_3Cl$ | H | H | O | 128–130 |
|  | H | H | O | 205–207 |
|  | H | H | O | 132–133 |
| $(CH_2)_3NMe_2$ | Cl[a] | H | O | 212/0.13 |
|  | Cl[a] | H | O | 164–166 |
| $(CH_2)_3NMe_2$ | Me | Me | O | 143–145 |
|  | Me | Me | O | 147–148 |

(*continued*)

TABLE 139. (*Continued*

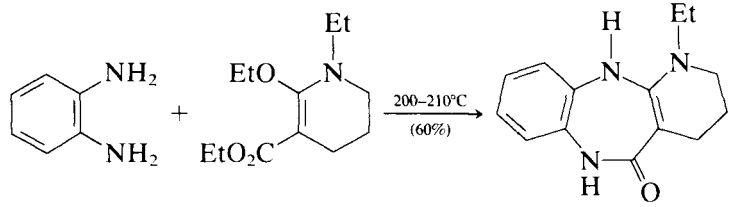
| $R_1$ | $R_2$ | $R_3$ | A | mp, (°C) or bp, (°C/torr) | Yield (%) |
|---|---|---|---|---|---|
|  | Me | Me | O | 129–131 | |
| $(CH_2)_3NMe_2$ | Me[a] | H | O | 98–100<br>192–193/0.05 | |
|  | Me[a] | H | O | 118–119<br>224–226/0.04 | |
|  | H | H | O | 193–195 | |
| $CH_2Ph$ | Me[a] | H | O | 135–136 | |
|  | Me[a] | H | O | 174–176 | |
|  | H | H | O | 193–196/0.05 | |
| Me | Cl[a] | H | O | 184–186 | |
| Et | Me[a] | H | O | 119–122 | |
| $CH_2CH{=}CH_2$ | Me[a] | H | O | 133–135 | |
| $CH_2CH{=}CH_2$ | Me | Me | O | 148–149 | |
|  | Me[a] | H | O | 147 | |
|  | Cl[a] | H | O | 170–171 | |
|  | Me[a] | H | O | 156–157 | |
| $CH_2CMe{=}CH_2$ | Me | Me | O | 197–200 | |

| | | | | |
|---|---|---|---|---|
| $CH_2CH{-}CH_2$ | Cl[a] | H | O | 167–169 |
|  | Cl[a] | H | $H_2$ | 210–212/0.025 |
|  | Me[a] | H | $H_2$ | 197/0.05 |
| $(CH_2)_3NMe_2$ | Me | Me | $H_2$ | 196–197/0.07 |
|  | Me | Me | $H_2$ | 203–206/0.03 |
| Me | Cl[a] | H | $H_2$ | 140–142 |
| Et | Me[a] | H | $H_2$ | 136/0.03 |
| $CH_2Ph$ | Me[a] | H | $H_2$ | 138–140 |
|  | Me[a] | H | $H_2$ | 120–121 |
|  | Me[a] | H | $H_2$ | 200–202/0.02 |
|  | Me[a] | H | $H_2$ | 194–195/0.03 |
|  | Cl[a] | H | $H_2$ | 190/0.015 |
|  | H | H | $H_2$ | 174/0.04 |
|  | H | H | $H_2$ | 185–190/0.03 |
| $CH_2CH{=}CH_2$ | H | H | $H_2$ | 184–185 (HBr) |
| $CH_2CH{=}CH_2$ | Me[a] | H | $H_2$ | 150–152/0.07 |
| $CH_2CH{=}CH_2$ | Me | Me | $H_2$ | 147–148/0.005 |

[a]Position of substituent not established; possible alternative: $R^3$ = H, $R_2$ = Cl or Me.

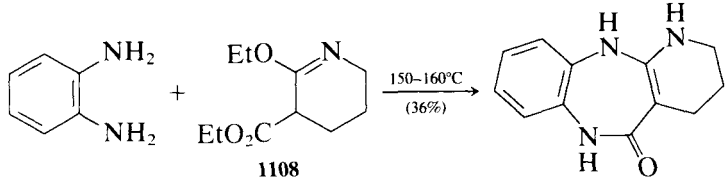
in Table 139. In yet another variation (570) a number of $N^{11}$-aminoalkyl derivatives, such as **1105d** and **1105e,** were prepared from the *N*-methyl lactam **1105c** (Eq. 251) A list of the products obtained in this study is given in Table 140. These substances were patented as antiasthma agents.

2-Ethoxytetrahydronicotinic acid esters were used as starting materials for the synthesis of a tricyclic ring system (571) fundamentally similar to the one described at the beginning of this section (561). Use of the *N*-ethyl starting material gave the tricyclic lactam **1107** (Eq. 252). The product derived from **1108** (Eq. 253) was assigned structure **1109** despite the fact that the ultraviolet spectrum differed from that of **1107.** In a subsequent patent (387a),



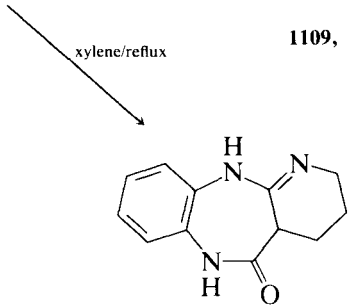

(252)

**1107,** mp 191–192°C (uv, ir)




**1108**

**1109,** mp 247–248°C (uv, ir)

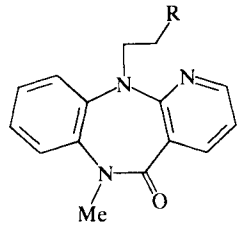


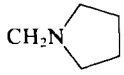
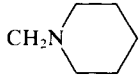
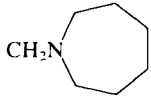

(253)

**1110,** mp 255–258°C

the reaction of **1108** with *o*-phenylenediamine was described again. The reaction was run in refluxing xylene instead of at 150–160°C in the absence of solvent. This time the product was formulated as the double bond isomer **1110,** but supporting spectroscopic evidence was not given.

TABLE 140. 11-AMINOALKYL-6-METHYLPYRIDO[2,3-*b*][1,5]BENZODIAZEPIN-5-ONE DERIVATIVES



| R | bp (°C/torr) | Method[a] | Yield (%) |
|---|---|---|---|
| $CH_2N(Et)(i\text{-}Pr)$ | 185–187/0.05 | A, B | 51 |
| $CH_2N(i\text{-}Pr)_2$ | 200–203/0.08 | A, B | 79 |
| $NMe_2$ | 163–164/0.01 | A | |
| $CH_2NMe_2$ | 180–183/0.03 | A | |
| $CH_2NHMe$ | 182/0.05 | A, C | 38 |
| $CH_2NHEt$ | 193–195/0.12 | A, C | 23 |
| $CH_2NH(i\text{-}Pr)$ | 183–185/0.05 | A, C | 39 |
| $NEt_2$ | 183–186/0.06 | A, B | 52 |
| $CH_2N(n\text{-}Pr)_2$ | 192–195/0.04 | A, B | 65 |
| $N(i\text{-}Pr)_2$ | 188–191/0.07 | A, B | 71 |
|  | 203–206/0.15 | A, B | 63 |
|  | 200–202/0.09 | A, B | 63 |
|  | 238–242/0.05 | A, B | 62 |
|  | 183–185/0.06 | A, B | 72 |
| $N(Me)(CH_2Ph)$ | 212–216/0.06 | B | 75 |
| $NHMe$ | 184–186/0.07 | C | 22 |
| $CH_2N(Me)(CH_2Ph)$ | 225–230/0.05 | B | 71 |
| $CH_2N(Et)(CH_2Ph)$ | 235–238/0.12 | B | 56 |
| $CH_2N(i\text{-}Pr)(CH_2Ph)$ | 222–227/0.06 | B | 72 |

[a]Method A: Two-step preparation: reaction of tricyclic lactam with alkylidene dihalide followed by reaction with an amine. Method B: Direct preparation from tricyclic lactam and dialkylaminoalkyl halide. Method C: Debenzylation of *N*-benzylamine by hydrogenolysis with $H_2$/Pd–C/MeOH.

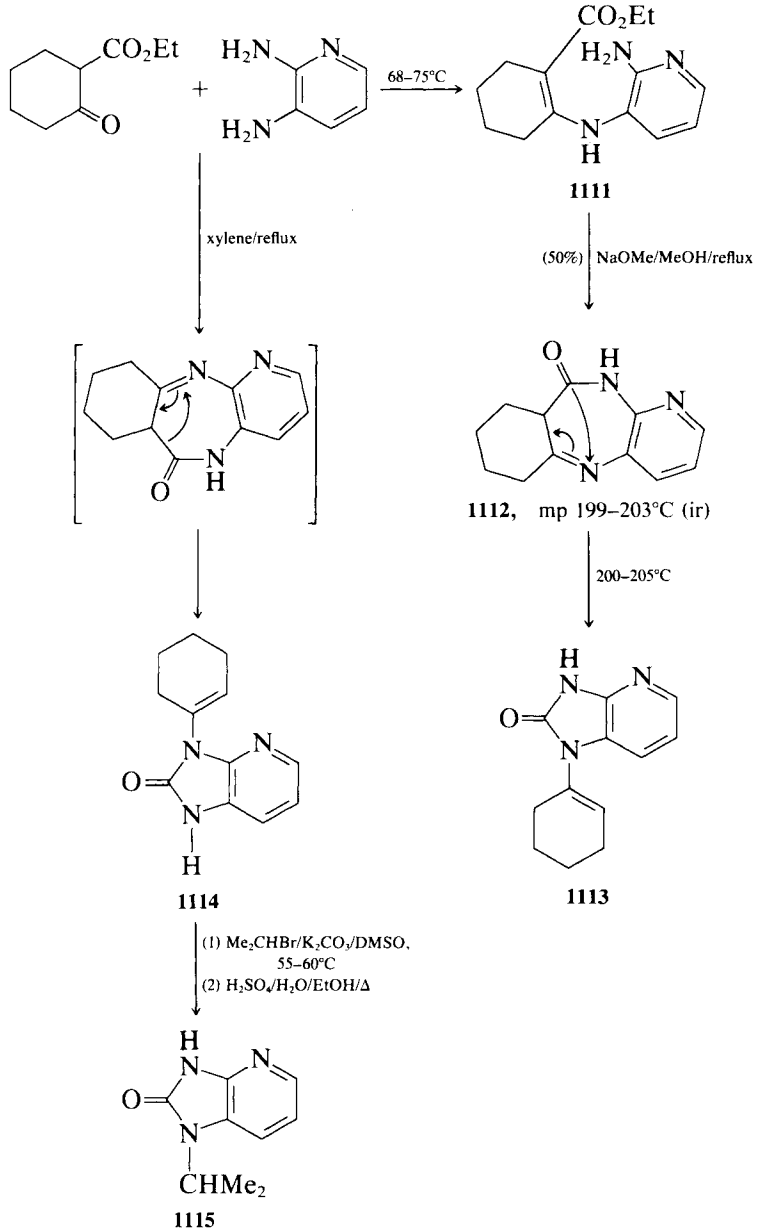
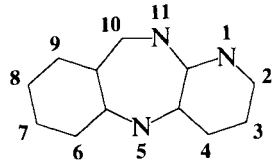

CO2Et
H2N
N
H2N
68–75°C
CO2Et
H2N
N
N
H
1111
xylene/reflux
(50%) NaOMe/MeOH/reflux
O
H
N
N
N
O
N
H
1112, mp 199–203°C (ir)
200–205°C
H
N
N
O
N
1113
1114
(1) Me2CHBr/K2CO3/DMSO, 55–60°C
(2) H2SO4/H2O/EtOH/Δ
CHMe2
1115

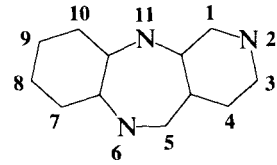
**Figure 85**

## 42. Pyrido[3,2-*b*][1,4]benzodiazepines

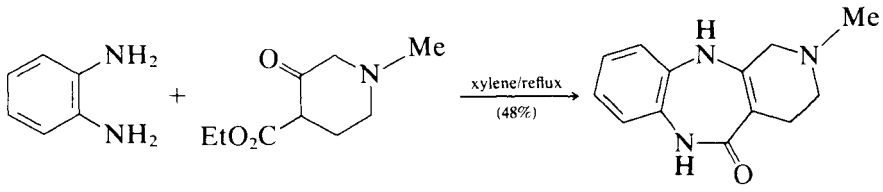


Reaction of 2,3-diaminopyridine with 2-carbethoxycyclohexanone at 68–75°C gave the β-aminoacrylate **1111,** which was cyclized to the pyrido[3,2-*b*][1,4]benzodiazepine derivative **1112** under basic conditions (572). As shown in Fig. 85, pyrolysis of **1112** at 200°C gave the bicyclic imidazolone **1113.** When the initial condensation was carried out in refluxing xylene, no tricyclic product was obtained, but a bicyclic imidazolone (**1114**) isomeric with **1113** was formed. This suggested that the tricyclic intermediate in the refluxing xylene reaction was isomeric with **1112.** The structure of **1114** was confirmed by conversion to the known isopropyl derivative **1115.** These transformations confirmed the identity of **1112.**

## 43. Pyrido[3,4-*b*][1,5]benzodiazepines (see Section XVI.18)



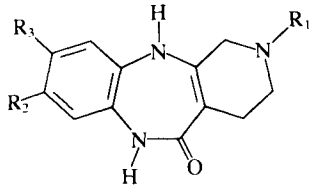
Reaction of ethyl 1-methyl-3-piperidone-4-carboxylate with *o*-phenylenediamine in refluxing xylene (573) gave the tricyclic lactam **1116** (Eq. 254). Analogs prepared by this general method are listed in Table 141.



(254)

**1116,** mp 207°C;
picrate, mp 206–207.5°C

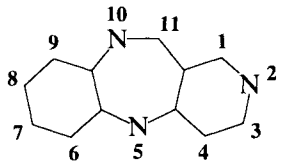
TABLE 141. 2-SUBSTITUTED PYRIDO[3,4-*b*][1,5]BENZODIAZEPIN-5-ONE DERIVATIVES



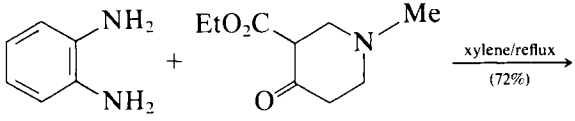
| $R_1$ | $R_2$ | $R_3$ | Yield (%) | mp (°C) |
|---|---|---|---|---|
| *n*-Bu | H | H | 69 | 110–111 |
| $CH_2Ph$ | H | H | 81 | 148–149 |
| $CH_2CH_2Ph$ | H | H | 69 | 111–112 |
| *n*-Bu | Me | Me | 66 | 105–106 |
| $CH_2CH_2Ph$ | MeO | MeO | 46 | 96–97 |
| $CH_2CH_2Ph$ | Cl[a] | H | 38 | 156–157 |
| $CH_2CH_2Ph$ | H | Cl[a] | 18 | 128–130 |

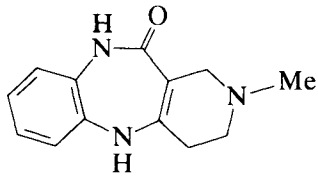
[a]These two isomers were obtained from one reaction; structural assignment is arbitrary.

## 44. Pyrido[4,3-*b*][1,5]benzodiazepines (see Section XVI.19)



Reaction of ethyl 1-methyl-4-piperidone-3-carboxylate with *o*-phenylenediamine in refluxing xylene (574) gave the tricyclic lactam **1117** (Eq. 255). Analogs prepared by this general method are listed in Table 142.

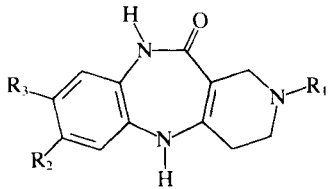


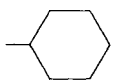




(255)

**1117**, mp 182–184°C;
HCl, mp 252–254°C

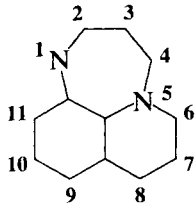
TABLE 142. 10-SUBSTITUTED 1,2,3,4,5,10-HEXAHYDROPYRIDO[4,3-*b*][1,5]BENZODIAZEPIN-11-ONES



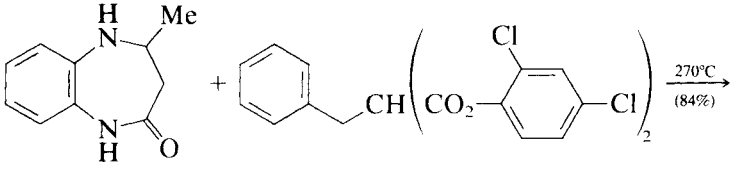
| $R_1$ | $R_2$ | $R_3$ | Yield (%) | Salt | mp (°C) |
|---|---|---|---|---|---|
| Et | H | H | 59 | | 139–140 |
| | | | | Tartrate | 65 |
| *n*-Bu | H | H | 61 | | 146–147 |
| | | | | Oxalate | 179 |
| $CH_2CH{=}CH_2$ | H | H | 66 | | 144–145 |
| | | | | Picrate | 197 |
| Ph | H | H | 83 | | 248–250 |
| | | | | Oxalate | 253 |
| | | | | Phosphate | 280 |
| | | | | HBr | 295 |
|  | H | H | 41 | | 127–128 |
| $CH_2Ph$ | H | H | 75 | | 165–166 |
| | | | | HCl | 243 |
| $CH_2CH_2Ph$ | H | H | 66 | | 183–184 |
| | | | | Phosphate | 203–204 |
| | | | | Picrate | 105 |
| $CH_2Ph$ | Me[a] | H | 42 | | 129–130 |
| | | | | HCl | 260 |
| $CH_2Ph$ | H | Me[a] | 13 | | 117–118 |
| Me | MeO | MeO | 48 | | 173–174 |
| | | | | HCl | 259 |
| Ph | Cl[a] | H | 65 | | 219–220 |
| | | | | Picrate | 183 |
| Ph | H | Cl[a] | 8 | | 233–235 |

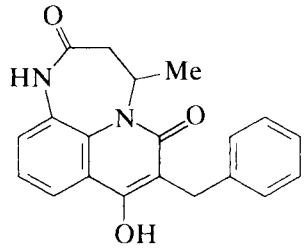
[a]Two isomeric products formed in one reaction; structural assignment is arbitrary.

## 45. Pyridol[1,2,3-*ef*][1,5]benzodiazepines



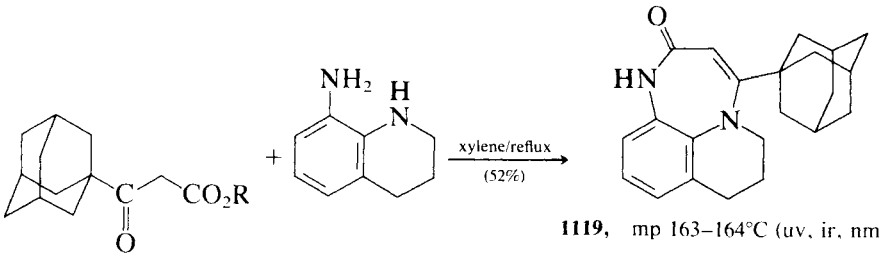

The first synthesis of a pyrido[1,2,3-*ef*][1,5]benzodiazepine derivative was reported by Ziegler and co-workers (575) in 1962. Heating the benzodiazepinone shown in Eq. 256 with a malonic ester derivative gave the tricyclic product **1118** in good yield. Another synthesis (430) involved the reaction of a β-ketoester (Eq. 257) with 8-amino-1,2,3,4-tetrahydroquinoline to give the adduct **1119**.




(256)

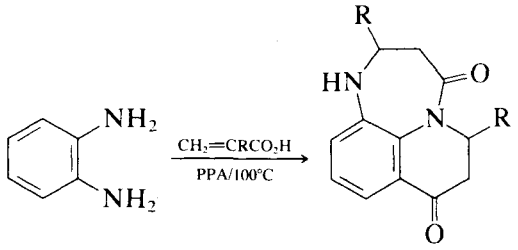
**1118**, m 243°C




(257)

**1119**, mp 163–164°C (uv, ir, nmr)

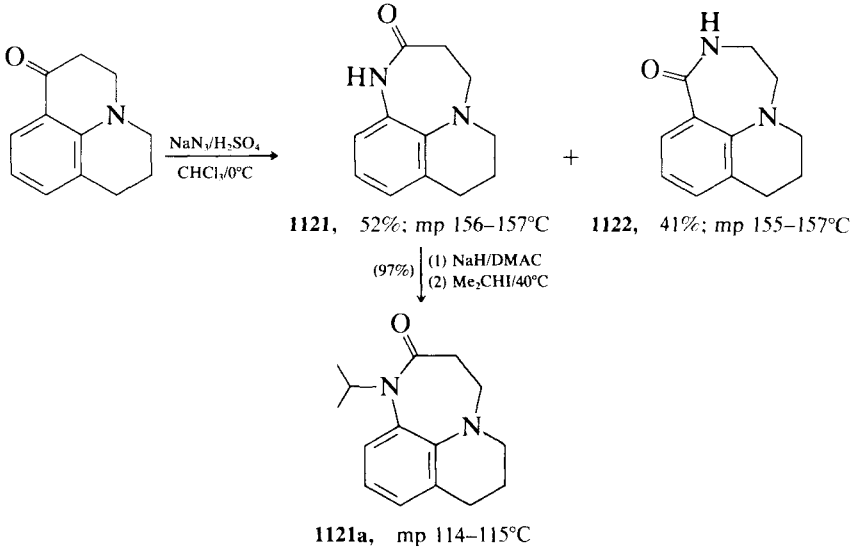
Merchant and Chothia (576) treated *o*-phenylenediamine with acrylic or methacrylic acid in the presence of polyphosphoric acid to obtain transient bis Michael adducts that underwent immediate cyclization to **1120a** and **1120b**, respectively (Eq. 258). A patent (577) describes the Schmidt reaction




(258)

**1120a**, R = H (19%); mp 204–205°C (ir, nmr, ms); 2,4-DNP, mp 283–284°C
**1120b**, R = Me (15%); mp 174–175°C (ir, nmr)

of various 2,3,6,7-tetrahydro-1H,5H-benzo[*ij*]quinolizin-1-ones. In the simplest example (Eq. 259) the reaction gave a 93% yield of a mixture of almost equal amounts of the two isomeric lactams **1121** and **1122**, which were separated by column chromatography. Alkylation of the amide nitrogen of **1121** by treatment with sodium hydride in dimethylacetamide and addition of isopropyl iodide yielded **1121a**. Additional substances prepared by these methods are listed in Table 143. Details of lactams in the isomeric series will be found under the appropriate heading.

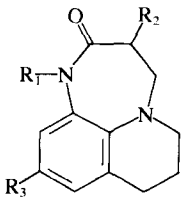



**1121**, 52%; mp 156–157°C **1122**, 41%; mp 155–157°C

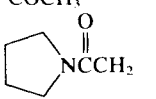
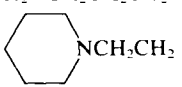
(259)

**1121a**, mp 114–115°C

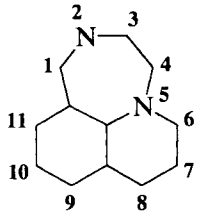
TABLE 143. 1,10-DISUBSTITUTED PYRIDO[1,2,3,-*ef*][1,5]BENZODIAZEPINE-2-ONE DERIVATIVES



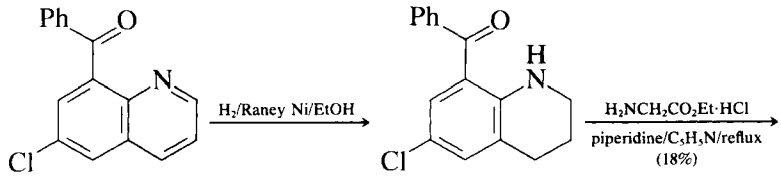

| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Other Data |
|---|---|---|---|---|
| H | H | Cl | 164–165 | |
| H | H | Me | 164–165 | |
| H | Me | H | 155–156 | |
| H | Et | H | 163–165 | |
| H | Et | Cl | 189–190 | |
| H | Et | Me | 169–170 | |
| H | Et | Me | 165–166 | |
| H | *n*-Pr | H | 133–134 | |
| H | *i*-Pr | H | 164–166 | |
| H | *i*-Pr | Cl | 214–215 | |
| H | *n*-Bu | H | 136–138 | |
| H | *n*-Bu | Cl | 154–155 | |
| H | *i*-Bu | H | 134–135 | |
| H | *n*-$C_5H_{11}$ | H | 94–95 | |
| H | *i*-$C_5H_{11}$ | H | 114–116 | |
| H | *n*-$C_6H_{13}$ | H | 103–104 | |
| H | *n*-$C_9H_{19}$ | H | 78–79 | |
| H | *n*-$C_{12}H_{25}$ | H | 83–85 | |
| H | $CH_2Ph$ | H | 213–215 | |

| | | | | |
|---|---|---|---|---|
| H | *p*-$ClC_6H_4CH_2$ | H | 242–244 | |
| H | 3,4-$Cl_2C_6H_3CH_2$ | H | 214–215 | |
| H |  | H | 180–182 | |
| H | Ph | H | 168–169 | 90% yield; isomeric lactam not isolated |
| H | *p*-$ClC_6H_4$ | H | 230–232 | |
| *i*-Pr | H | H | 114–115 | |
| Et | H | H | 93–94 | |
| Et | H | Cl | 109–110 | |
| Et | $CH_2Ph$ | H | 132–134 | |
| Et | Ph | H | 142–144 | |
| *i*-Pr | *p*-$ClC_6H_4CH_2$ | H | 124–125 | |
| $CH_2CH{=}CH_2$ | H | H | 102–103 | |
| COEt | H | H | 103–104 | |
| $(MeO)_2P(=O)CH_2$ | H | H | 194–196 | |
| $MeO_2C$ | H | H | 169–170 | |
| MeNHCO | H | H | 278–280 | |
| 3,4,5-$(MeO)_3C_6H_2$ | H | H | 138–139 | |
| $COCH_3$ | H | H | 112–113 | |
|  | H | H | 145–146 | |
| $Et_2NCH_2CH_2$ | H | H | 148–150 | 2HCl |
| $H_2NCH_2CH_2CH_2$ | Et | H | 163–165 | 2HCl |
|  | H | H | 154–155 | 2HCl |

## 46. Pyrido[3,2,1-*jk*][1,4]benzodiazepines

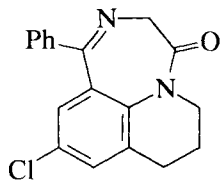



The goal of the first synthetic work on pyrido[3,2,1-*jk*][1,4]benzodiazepines (578) was the preparation of a tricyclic analog of diazepam. As shown in Eq. 260, 8-benzoyl-6-chloroquinoline (**1123**), prepared by a modified Skraup




**1123** **1124**

(260)

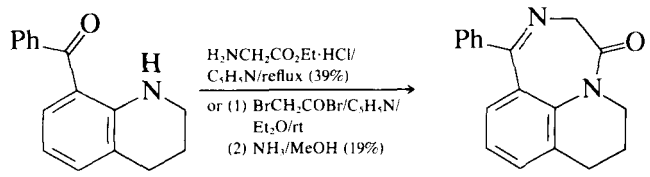



**1125**, mp 187–189°C (ir)

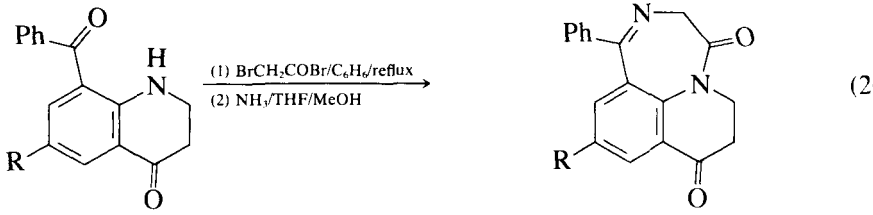
reaction, was reduced to the 1,2,3,4-tetrahydroquinoline **1124**, which was converted to the tricyclic product **1125** on reaction with glycine ethyl ester hydrochloride. The substance had significantly weaker biological activity than diazepam.

In a later study (391), the deschlorotetrahydroisoquinoline **1126** was converted to the tricyclic product **1127** on treatment with glycine ethyl ester hydrochloride or with bromoacetyl bromide followed by ammonia (Eq. 261). As in the previous study, compound **1127** had only weak diazepam-like activity. A later patent (579) described the preparation of both **1125** and **1127** by the bromoacetyl bromide procedure.

In an extension of this work (580) the two 4-ketotetrahydroquinolines **1128a** and **1128b** were converted to the tricyclic derivatives **1129a** and **1129b**, respectively (Eq. 262). Hydrogenation of these substances over platinum oxide selectively reduced the imine double bond to give **1130a** and **1130b**,




**1126** **1127**, mp 170.5–171.5°C (261)



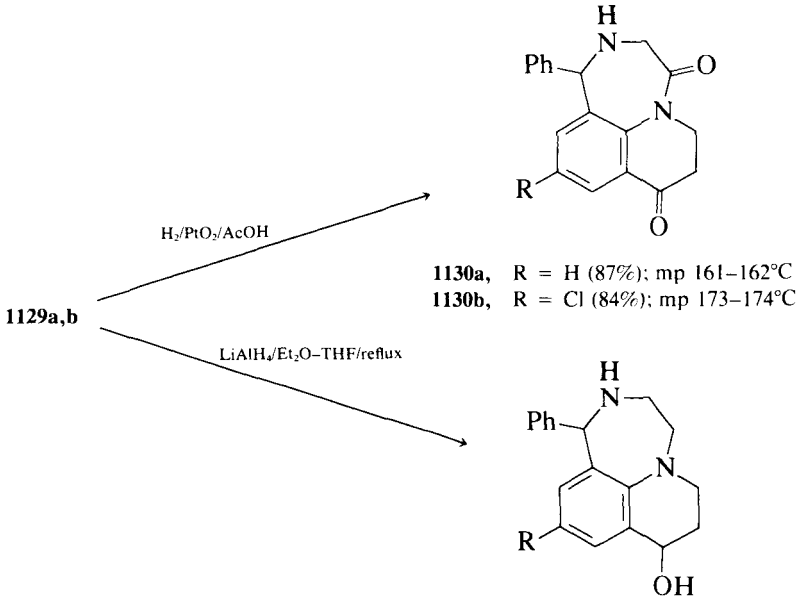

(262)

**1128a**, R = H
**1128b**, R = Cl

**1129a**, R = H (59%); mp 179–180°C (nmr)
**1129b**, R = Cl (35%); mp 187–188°C (nmr)

whereas lithium aluminum hydride yielded the lactam and ketone reduction products **1131a** and **1131b** (Eq. 263).

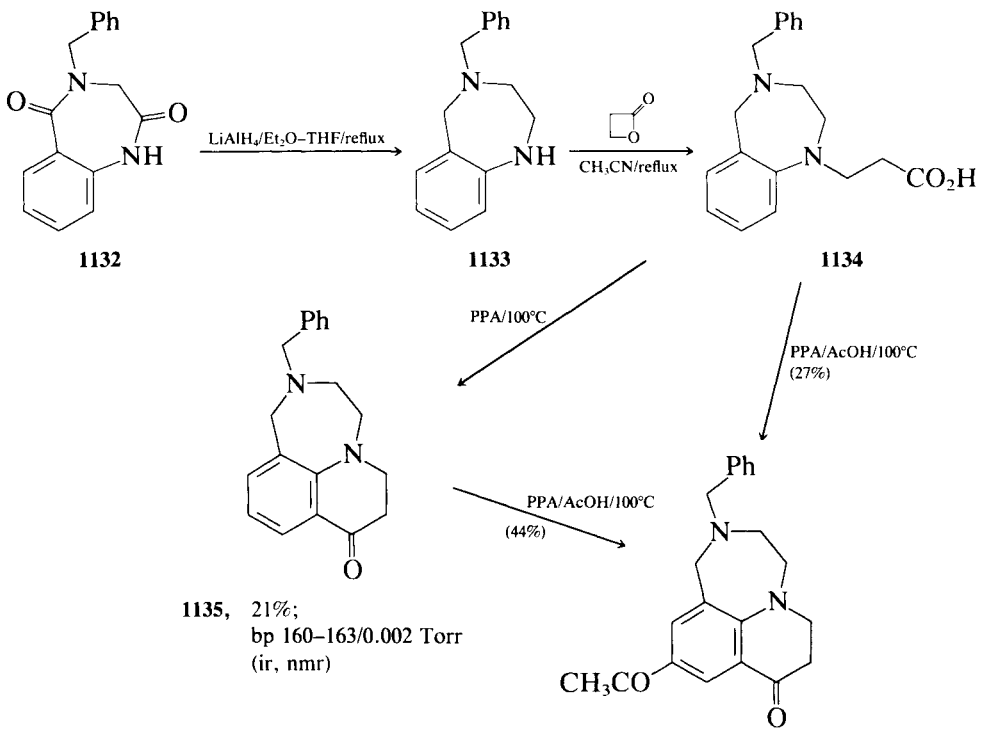
A second synthesis of the pyrido[3,2,1-*jk*][1,4]benzodiazepine system (489) is described in Fig. 86. Reduction of the dilactam **1132** with lithium aluminum




**1130a**, R = H (87%); mp 161–162°C
**1130b**, R = Cl (84%); mp 173–174°C

(263)

**1131a**, R = H (72%); mp 165–167°C
**1131b**, R = Cl (67%); mp 167–168°C



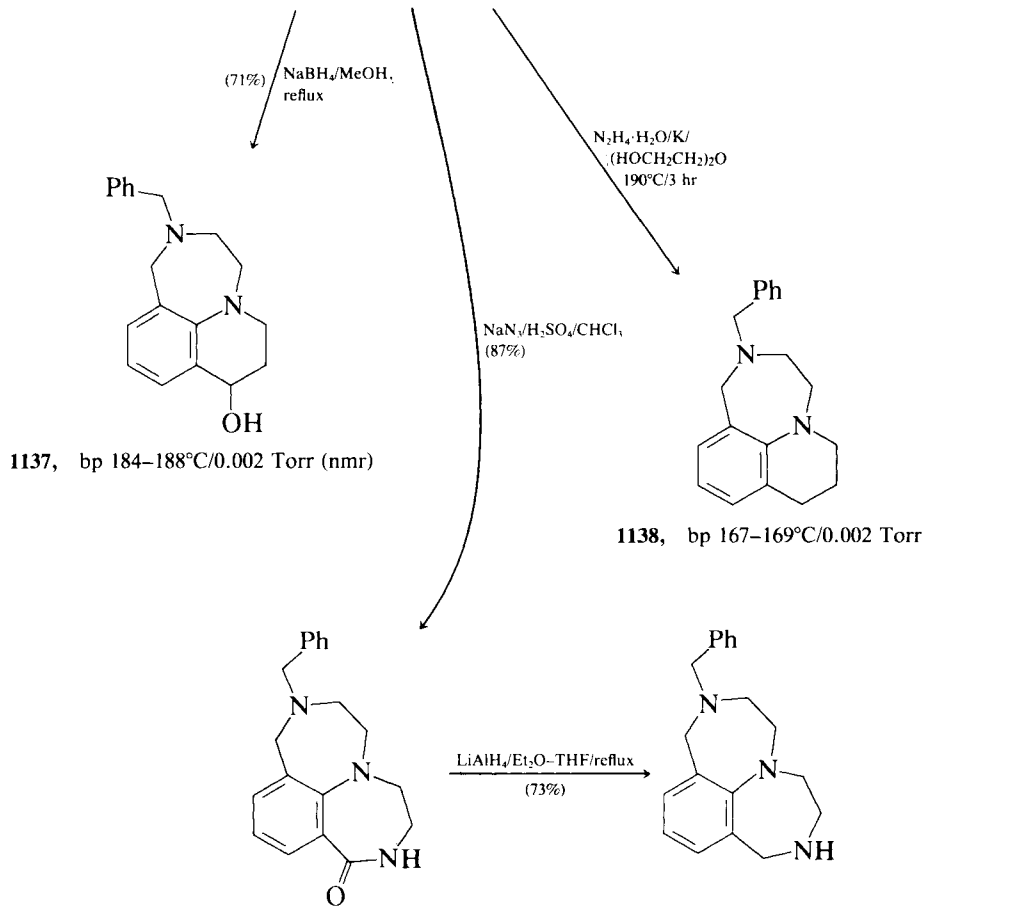

**1132**

**1133**

**1134**

**1135,** 21%;
bp 160–163/0.002 Torr
(ir, nmr)

**1136,** mp 124–125°C (nmr)




**1137,** bp 184–188°C/0.002 Torr (nmr)

**1138,** bp 167–169°C/0.002 Torr

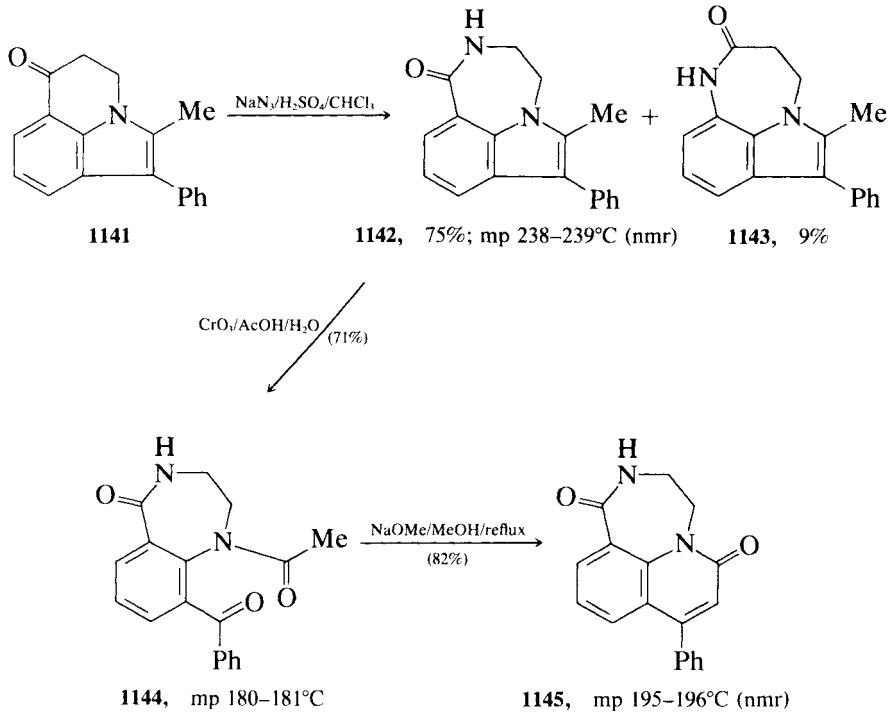
**1139,** mp 164–166°C

**1140,** bp 155–160°C/0.002 Torr (nmr)

**Figure 86**

hydride gave the diamine **1133**. This substance gave the acid **1134** on condensation with β-propiolactone. Cyclization to the desired tricyclic derivative **1135** was effected with PPA. When the cyclization was run with PPA in acetic acid, the acetyl derivative **1136** was also formed; the two products were separated by chromatography. Treatment of **1135** with PPA in acetic acid likewise gave the acetyl derivative **1136**. The tricyclic ketone **1135** was reduced with sodium borohydride to give the alcohol **1137**, whereas Wolff–Kishner reduction gave the tricyclic diamine **1138**. Schmidt reaction gave the lactam **1139**, the structure of which was confirmed by the nmr spectrum of the lithium aluminum hydride reduction product **1140.**

The tricyclic ketone **1141** was used as the starting material for another synthesis of a pyridobenzodiazepine derivative (403). As shown in Eq. 264,




**1141** **1142**, 75%; mp 238–239°C (nmr) **1143**, 9%

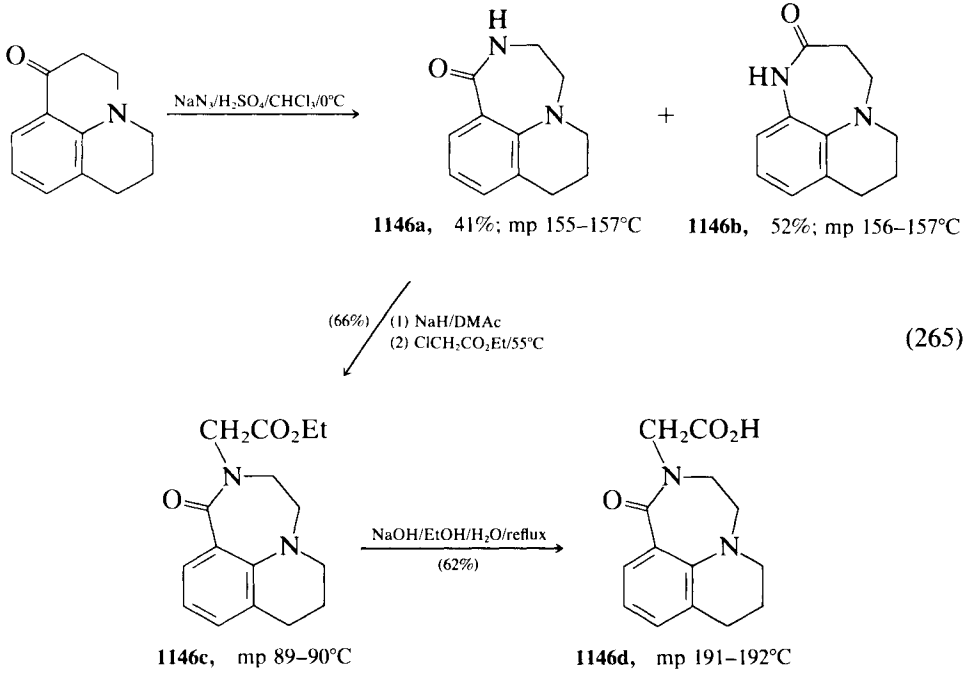
(264)

**1144**, mp 180–181°C **1145**, mp 195–196°C (nmr)

Schmidt reaction of **1141** gave the lactam **1142** in 75% yield, together with a small quantity of the isomer **1143**. Beckmann rearrangement gave **1142** and **1143** in yields of 10 and 5%, respectively. Chromic acid oxidation of **1142** gave the keto amide **1144,** which was cyclized with sodium methoxide in methanol to the dilactam **1145**.

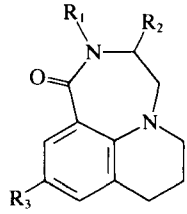
As described in the section on pyrido[1,2,3-*ef*][1,5]benzodiazepines (Section IX.45), Schmidt reaction of various 2,3,6,7-tetrahydro-1H,5H-benzo[*ij*]quinolizin-1-ones generally gave mixtures of two possible isomeric

lactams (577). In the simplest case (Eq. 265), a 93% yield of an almost equal mixture of the isomeric lactams **1146a** and **1146b** was obtained; the two substances were separated by chromatography. Alkylation of the lactam nitrogen in **1146a** was accomplished by treatment with sodium hydride in dimethylacetamide followed by addition of ethyl chloroacetate. Saponification of the resultant ester **1146c** yielded the acid **1146d**. Table 144 lists analogs prepared by this method.




(265)

TABLE 144. 3,4,7,8-TETRAHYDRO-6*H*-PYRIDO[3,2,1-*jk*]-[1,4]BENZODIAZEPIN-1(2*H*)-ONES



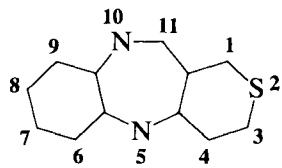
| $R_1$ | $R_2$ | $R_3$ | mp (°C) |
|---|---|---|---|
| H | H | Cl | 174–176 |
| H | H | Me | 175–176 |
| H | Me | H | 144–145 |

(*continued*)

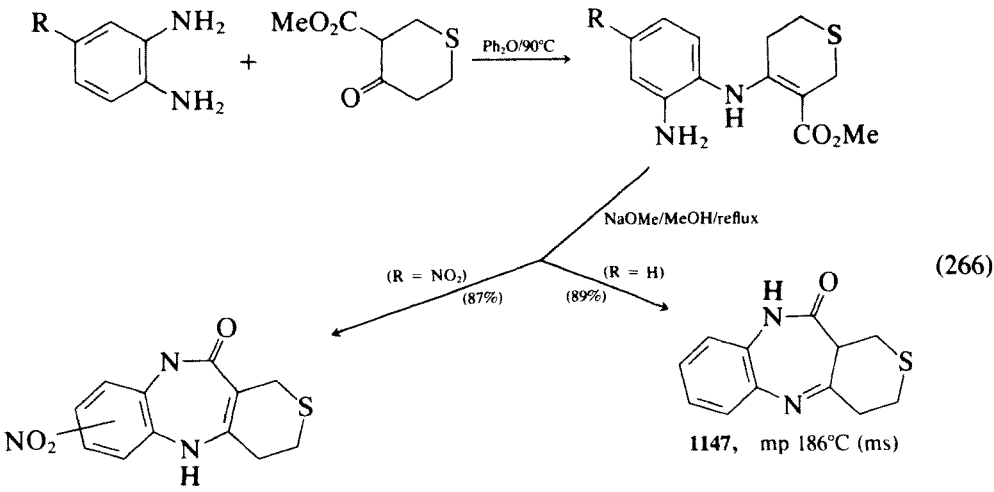
TABLE 144. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | mp (°C) |
|---|---|---|---|
| H | Et | H | 174–175 |
| H | Et | Cl | 198–200 |
| H | Et | MeO | 179–180 |
| H | Et | Me | 214–215 |
| H | *n*-Pr | H | 149–151 |
| H | *i*-Pr | H | 189–191 |
| H | *i*-Pr | Cl | 186–188 |
| H | *n*-Bu | H | 112–114 |
| H | *n*-Bu | Cl | 135–136 |
| H | *i*-Bu | H | 150–151 |
| H | $(CH_2)_4Me$ | H | 134–135 |
| H | $Me_2CHCH_2CH_2$ | H | 124–125 |
| H | $(CH_2)_5Me$ | H | 133–135 |
| H | $(CH_2)_8Me$ | H | 110–111 |
| H | $(CH_2)_{11}Me$ | H | 102–103 |
| H | $CH_2Ph$ | H | 149–150 |
| H | $CH_2C_6H_4Cl$-*p* | H | 213–215 |
| H | $CH_2C_6H_3Cl_2$-3,4 | H | 189–191 |
| H | H | H | 169–171 |
| Me | H | H | 111–113 |
| Et | Et | H | 76–78 |
| Et | $CH_2C_6H_4Cl$-*p* | H | 107–110 |
| $(MeO)_2\overset{O}{\overset{\|}{P}}CH_2$ | H | H | 156–157 |
| 3,4,5-$(MeO)_3C_6H_2CO$ | Et | H | 153–154 |
| 3,4,5-$(MeO)_3C_6H_2CO$ | *i*-Pr | H | 134–136 |
| 3,4,5-$(MeO)_3C_6H_2CO$ | *i*-Pr | H | 166–167 |
| $Me_2NCH_2CH_2$ | H | H | 176–178 (2HCl) |
| $Et_2NCH_2CH_2$ | H | H | 135–137 (2HCl) |

## 47. Thiopyrano[4,3-*b*][1,5]benzodiazepines (see Section XVI.21)



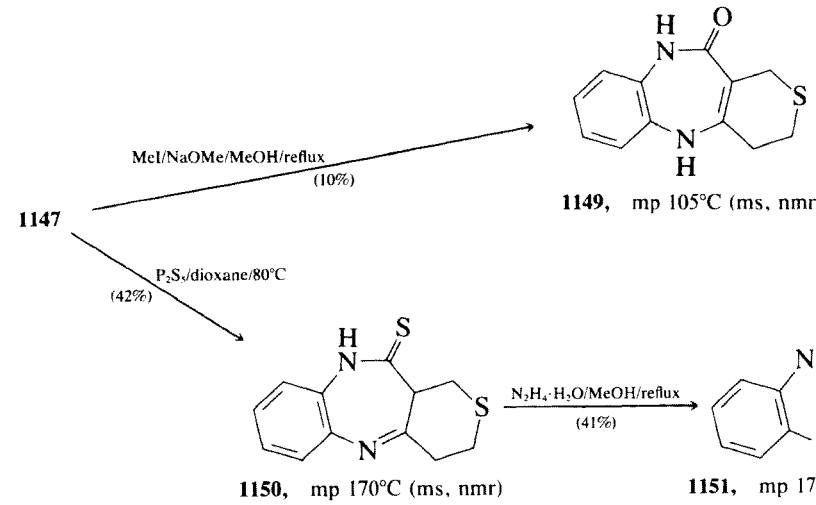

Condensation of 3-carbethoxythiopyran-4-one with *o*-phenylenediamine gave an adduct that was cyclized with sodium methoxide (581) to give the




(266)

**1148,** mp 250°C (ms, nmr)

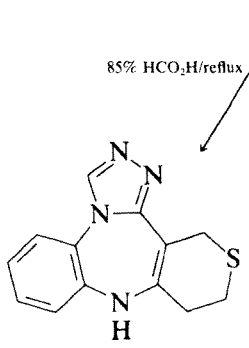
**1147,** mp 186°C (ms)




**1149,** mp 105°C (ms, nmr)

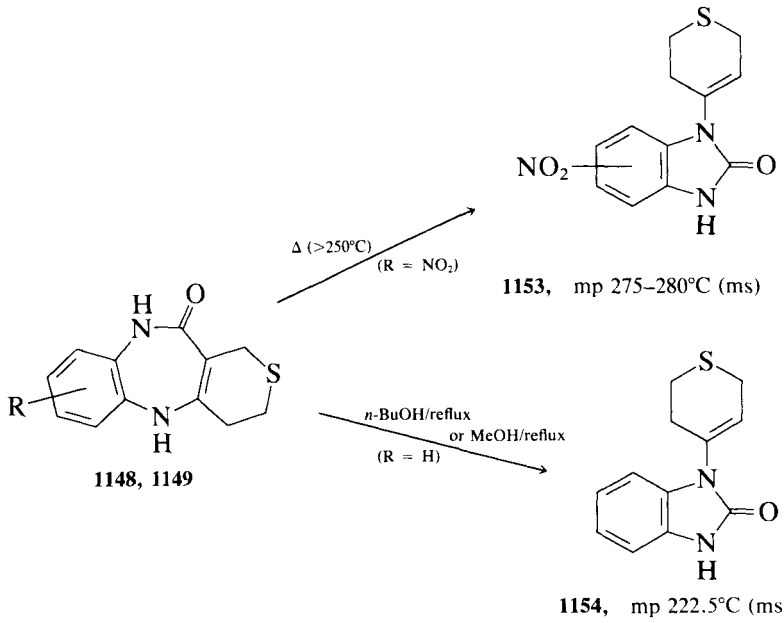
**1150,** mp 170°C (ms, nmr)

**1151,** mp 171.5°C (ms, nmr)




**1152,** mp 192°C (ms, nmr)

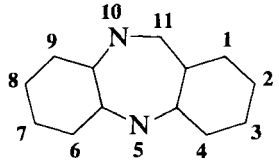
**Figure 87**




(267)

tricyclic lactam **1147** (Eq. 266). This procedure was repeated using 4-nitro-1,2-diaminobenzene as the starting material. The tricyclic product in this case was formulated as **1148,** with the position of the nitro group uncertain. Methylation of **1147** gave **1149**, in which the double bond was positioned as in **1148** (Fig. 87). Treatment of **1147** with phosphorus pentasulfide gave the thione **1150**, which was converted via the hydrazine **1151** to the tetracyclic triazole **1152.** Heating the tricyclic derivatives **1148** and **1149** gave the benzimidazole derivatives **1153** and **1154**, respectively, as shown in Eq. 267.

## 48. Diabenzo[*b*,*e*][1,4]diazepines (see Section XVI-22)




In 1924, as part of studies designed to lead to the elucidation of the structures of strychnine and brucine, Clemo and co-workers (582) described

the first synthesis of a dibenzo[*b,e*][1,4]diazepine derivative. Ullmann condensation of anthranilic acid and 2-chloronitrobenzene gave the nitro acid, which was reduced to the amino acid with ferrous sulfate in aqueous ammonia. Cyclization was accomplished by heating the amino acid at its melting point (210°C) or in refluxing xylene (Fig. 88). The tricyclic lactam **1155a** was readily hydrolyzed in refluxing methanolic potassium hydroxide, and could be acetylated to **1155b** with acetic anhydride or converted to the nitroso derivative **1155c** with sodium nitrite in aqueous acetic acid. Reduction of **1155c** with zinc dust and acetic acid in the presence of cyclohexanone gave the tetrahydrocarbazole **1156** (583).

The first mention of a biologically active 10,11-dihydrodibenzo[*b,e*]-[1,4]diazepin-11-one derivative was made in 1962 in a publication (584) describing the properties of compound **1157a**, a potent antihistamine. The following year a clinical study (585) and a chemical paper (9) appeared. In the latter, the synthesis of **1157a** and of a number of analogs was described. The synthetic pathway generally followed the earlier one (582), the main difference being that the amino acids were esterified prior to cyclization. Nitro compounds were reduced catalytically or, in the case of substances with substituents sensitive to hydrogenolysis, by treatment with alkaline or ammoniacal sodium dithionite. Alkylation of the lactam nitrogen in **1155d** was accomplished by forming the anion with sodium amide or potassium *tert*-butoxide and subsequently adding the appropriate alkyl chloride (Fig. 89). Hydrolysis of the lactam bond (e.g., in **1155f**) could be achieved by refluxing in 20% aqueous hydrochloric acid, but was accompanied by decarboxylation. Reduction of the lactam function in **1155e** with lithium aluminum hydride yielded the amine **1157a**. Substances prepared in this and related studies are listed in Tables 145–148. A patent (587) describes the preparation of **1157a** from an amino acid instead of an amino ester by refluxing in xylene or ethylene glycol or by treatment with dicyclohexylcarbodiimide in dioxane. Numerous analogs were prepared by these methods and are listed in Tables 146 and 147.

Also, published in 1963 was an account of the synthesis of compounds with dialkylaminoalkyl substituents at the 5-position (598). These substances were prepared from the tricyclic lactam originally obtained by Clemo and co-workers (582) by successive acylation with an $\omega$-chloroacyl chloride, treatment with an amine, and reduction with lithium aluminum hydride. This chemistry is exemplified by the stepwise conversion of **1155a** to **1155g–i** and **1157b**, as shown in Fig. 90. Additional compounds prepared by these methods are listed in Table 149. Compound **1157b** had antidepressant activity comparable to imipramine in various animal models, but was also toxic.

In later work (599), derivatives substituted at the 5-position were prepared either by alkylation of a 10-substituted tricyclic lactam or by alkylation of an intermediate *N*-(2-nitrophenyl)anthranilic acid ester. These approaches are illustrated by the synthesis of the $N^5$,$N^{10}$-disubstituted compound **1155n**

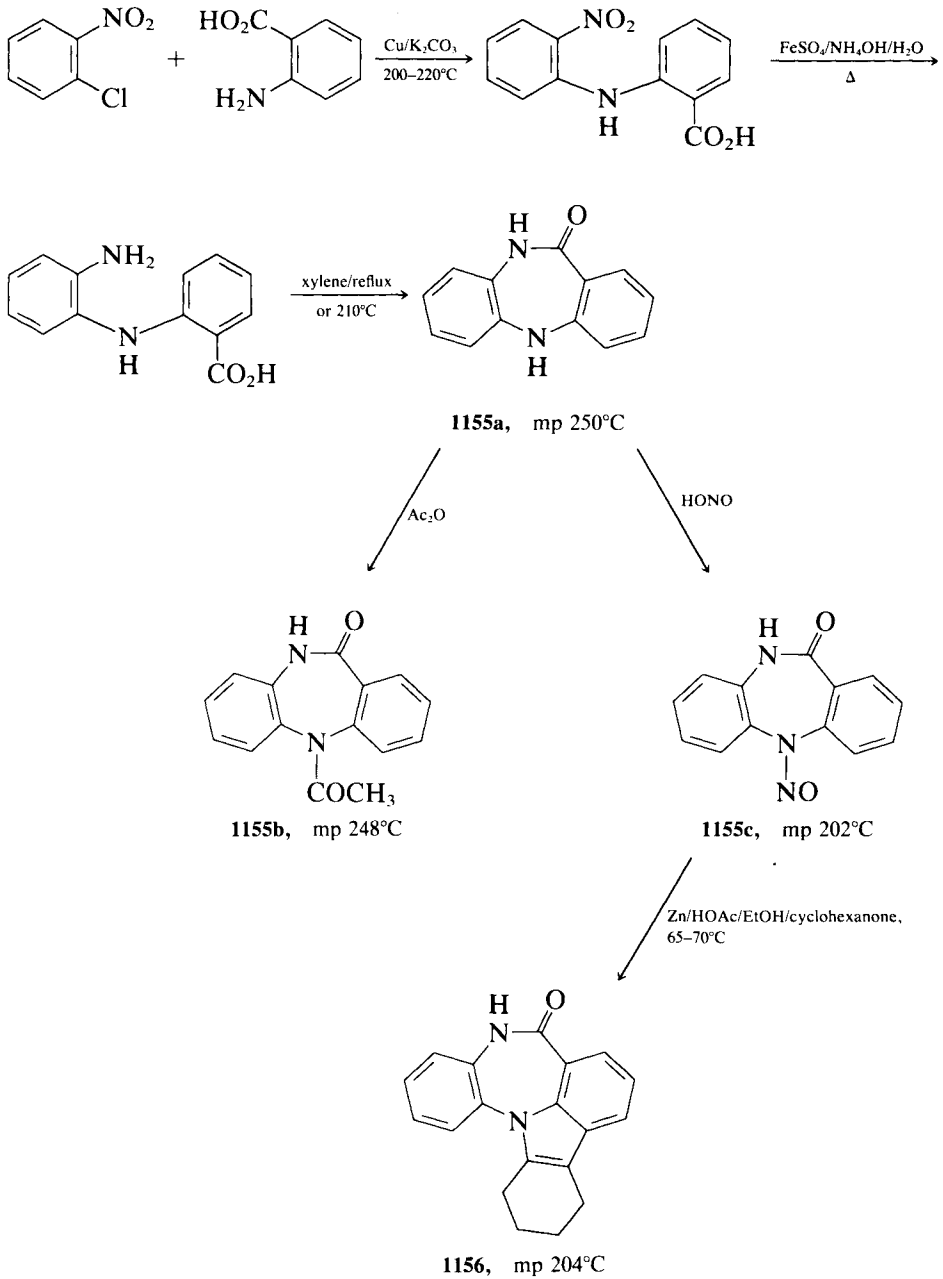
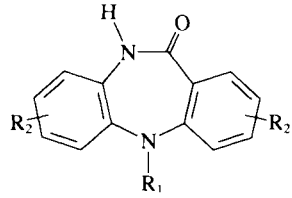

NO2
Cl
+
HO2C
H2N
Cu/K2CO3
200–220°C
NO2
N
H
CO2H
FeSO4/NH4OH/H2O
Δ
NH2
N
H
CO2H
xylene/reflux
or 210°C
H
O
N
N
H
1155a, mp 250°C
Ac2O
HONO
COCH3
1155b, mp 248°C
NO
1155c, mp 202°C
Zn/HOAc/EtOH/cyclohexanone,
65–70°C
1156, mp 204°C

**Figure 88**

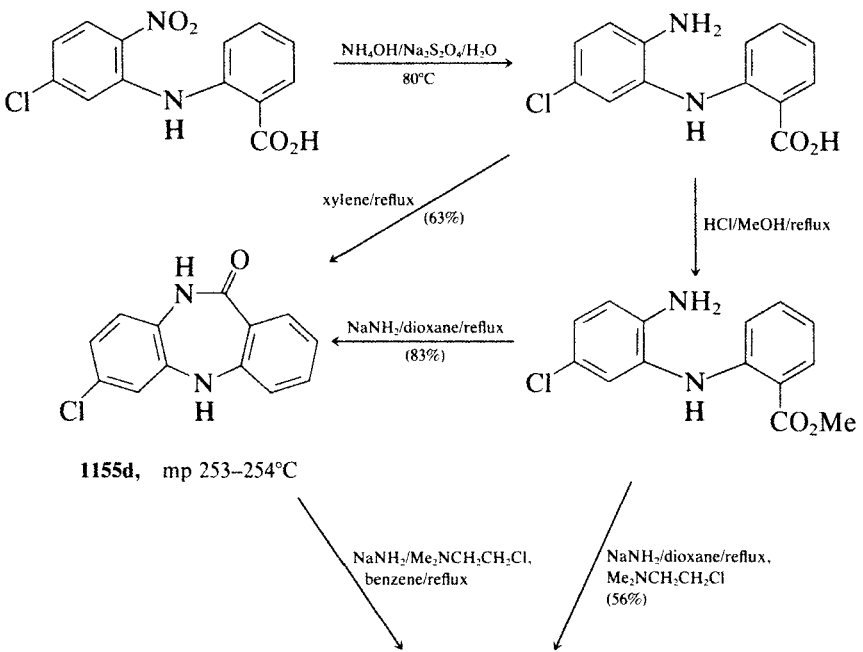
TABLE 145. DIBENZO [*b*,*e*] [1,4] DIAZEPIN-11-ONE DERIVATIVES



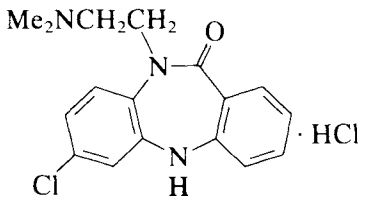
| $R_1$ | $R_2$ | mp (°C) | Refs. |
|---|---|---|---|
| H | 2-Cl | 259–260 | 9 |
| Me | 2-MeO | 200–212 | 9 |
| H | 3-Cl | 271 | 9 |
| H | 3-MeO | 232–233 | 9 |
| H | 6-Cl | 244–246 | 9 |
| H | 7-Cl | 253–254 | 9 |
| Me | 7-Cl | 226–227 | 9 |
| H | 7-MeO | 239–240 | 9 |
| H | 7-MeS | 211–212 | 9 |
| Me | 7-MeS | 225–226 | 9 |
| H | 8-Cl | 231–232 | 9 |
| Me | 8-Cl | 214–215 | 9 |
| H | 8-MeO | 174–176 | 9 |
| H | 8-$CF_3$ | 176–177 | 9 |
| Me | 8-$CF_3$ | 239–240 | 9 |
| H | 8-Me | 194–195 | 9 |
| Me | 8-Me | 228–229 | 9 |
| H | 2-MeO | 220–221 | 9 |
| H | 3-Me | 267–269 | 9 |
| Me | 8-MeO | 221–223 | 9 |
| H | 1-$CO_2H$ | 278 | 586 |
| H | 1-$CO_2H$, 8-$CF_3$ | 252 | 586 |
| H | 1, 8-$(CO_2H)_2$ | 315 | 586 |
| H | 1-$CO_2H$, 8-Cl | 280 | 586 |

from lactams **1155k** and **1155l** (Eq. 269) and of compound **1155i** by alkylation of an anthranilic ester (Eq. 268). Lactams could be reduced to amines with lithium aluminum hydride, as exemplified by the preparation of **1157b** from **1155i**. Additional substances prepared by these procedures are listed in Table 150. Also in 1963, Hanze and co-workers (602) described the preparation of an additional group of compounds using similar methods. Products obtained in this study and in related work are listed in Tables 151 and 152.

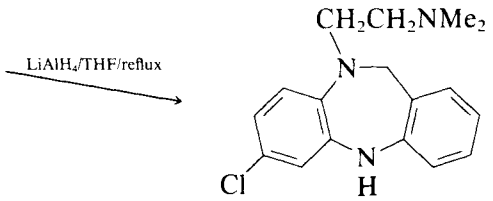
As shown in Eq. 270, lactam **1155i** and its demethylated metabolites (**1155o** and **1155p**) were also obtained (605, 606) from an amino ester in the dog and



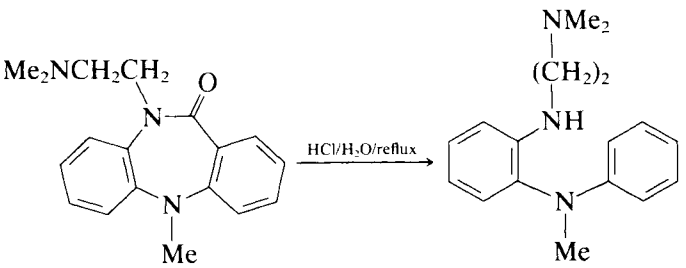

**1155d,** mp 253–254°C



**1155e,** 75%;
mp 225–233°C;
base, mp 165–166°C;
HBr, mp 229°C;
maleate, mp 146–148°C



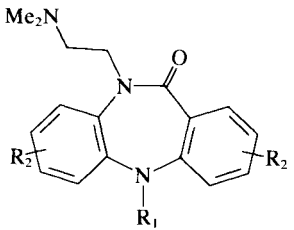
**1157a,** 75%; mp 87–89°C;
maleate, mp 86–88°C



**1155f**

**Figure 89**

TABLE 146. 10-DIMETHYLAMINOETHYLDIBENZO[*b*,*e*][1,4]DIAZEPIN-11-ONE DERIVATIVES

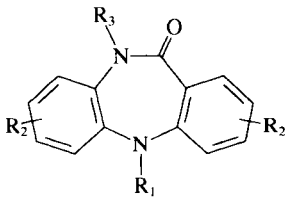



| $R_1$ | $R_2$ | Salt | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|
| H | H | | 112–114<br>210/0.05 | 82 | 9,587,588 |
| Me | H | | 116–117<br>185/0.01 | 85 | 9,587,588 |
| | | HCl | 234–240 | | |
| | | Pamoate | 168 | | 589 |
| H | 2-Cl | | 172–173 | 82 | 9,587,588 |
| Me | 2-MeO | | 201–202/0.04 | | |
| | | HCl | 207–210 | 91 | 9,587,588 |
| H | 3-Cl | | 159–160 | 83 | 9,587,588 |
| H | 3-MeO | | 141–143 | 81 | 9,588 |
| H | 6-Cl | | 122–123 | | 9 |
| Me | 7-Cl | | 179–180/0.05 | 99 | 9,587,588 |

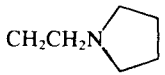
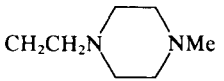
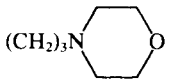
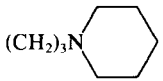
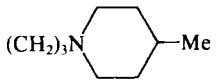
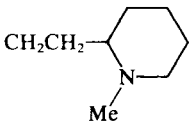
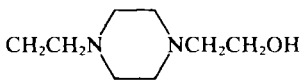
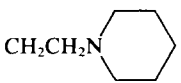
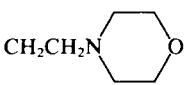
| | | | | | |
|---|---|---|---|---|---|
| | | HCl | 250–253 | | |
| H | 7-MeO | | 152–153 | | 9 |
| H | 7-MeS | | 126–129 | 60 | 9,587,588 |
| Me | 7-MeS | HCl | 205–207 | 81 | 9,588 |
| Me | 8-Cl | | 190/0.05 | | |
| | | HCl | 240–243 | 100 | 9,587,588 |
| H | 8-Cl | | 140–145 | 74 | 9,587,588 |
| H | 8-MeO | | 126–127 | 84 | 9,587,588 |
| H | 8-$CF_3$ | | 115–118 | 90 | 9,588 |
| Me | 8-$CF_3$ | HCl | 222–226 | 90 | 9,587,588 |
| H | 8-Me | | 137–138 | 80 | 9,587,588 |
| Me | 8-Me | | 193–195/0.02 | 90 | 9,587,588 |
| | | HCl | 220–222 | | |
| Me | 8-MeO | | 204–206/0.02 | | |
| | | HCl | 213–215 | 89 | 587,588 |
| H | 7-Me | | 159–161 | | 590 |
| Me | 7-Me | | 87–89 | | 590 |
| H | 7-$CF_3$ | | 134–136 | | 590 |
| | | Maleate | 130–133 | | |
| | | | 171–173 | | |
| | | Succinate | 185–187 | | |
| H | 7-Br | | 146–149 | | 590 |
| H | 3-MeO | | 141–143 | | 587 |
| H | 3-$CF_3$ | | 115–118 | | 587 |

[a]Dibenzepin: ir and uv spectra are given in Ref. 591, nmr data in Ref. 592.

TABLE 147. 10-AMINOALKYLDIBENZO[*b*,*e*][1,4]DIAZEPIN-11-ONE DERIVATIVES

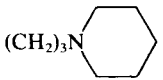
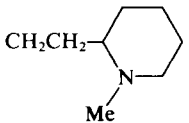
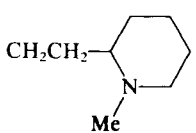


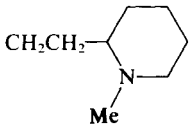
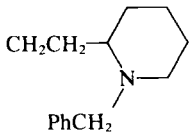
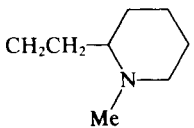
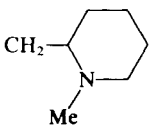
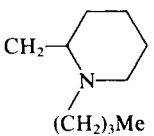
| $R_1$ | $R_2$ | $R_3$ | Salt | bp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| H | 7-Cl | $CH_2CH_2N$ | | 159–160 | 74 | 9,587,588 |
| H | 7-Cl | $CH_2CH_2N$ | | 187–189 | 66 | 9,587,588 |
| H | 7-Cl | $CH_2CH_2N$ O | | 220–222 | 50 | 9,587,588 |
| H | 7-Cl | $CH_2CHMeNMe_2$ | | 197–199 | 70 | 9,587,588 |
| H | 7-Cl | $(CH_2)_3NMe_2$ | | 137–139 | 68 | 9,587,588 |
| H | H | $(CH_2)_3NMe_2$ | HCl | 222–226 | 87 | 587,588 |
| Me | H | $(CH_2)_3NMe_2$ | | 75–78<br>205/0.05 | 75 | 587,588 |
| H | 8-Cl | $(CH_2)_3NMe_2$ | HCl | 249–251 | 100 | 587,588 |
| Me | 8-Cl | $(CH_2)_3NMe_2$ | | 192–193/0.01 | 85 | 587,588 |
| | | | HCl | 193–197 | | |
| Me | H | $CH_2CH_2NMe_2$ | Methosulfate | 180–185 | 82 | 588[a] |
| Me | H | $CH_2CH_2N$ | | 201–203/0.02 | 72 | 587,588 |
| | | | HCl | 140–153 | | |
| Me | H | $CH_2CH_2N$ O | | 211–213/0.007 | 58 | 587,588 |
| | | | HCl | 140–153 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Me | H |  | HCl | 206–207/0.005<br>100–105 | 68 | 587,588 |
| Me | H |  | 2HCl | 220/0.02<br>185–190 | 64 | 587,588 |
| Me | H | $CH_2CH_2NEt_2$ | | 186–187/0.01 | 88 | 587,588 |
| Me | H |  | | 115–120 | 54 | 587,588 |
| Me | H |  | | 94–96 | 83 | 587,588 |
| Me | H |  | 2HCl | 210–212/0.01<br>150–160 | 53 | 587,588 |
| Me | H |  | | 215–220/0.01 | 93 | 588 |
| Me | H |  | 2HCl | >60 | 53 | 587,588 |
| Me | H |  | | >60 | 61 | 587,588 |
| H | H |  | | 136–137 | 80 | 587,588 |
| H | H |  | | 116–118 | 56 | 587,588 |

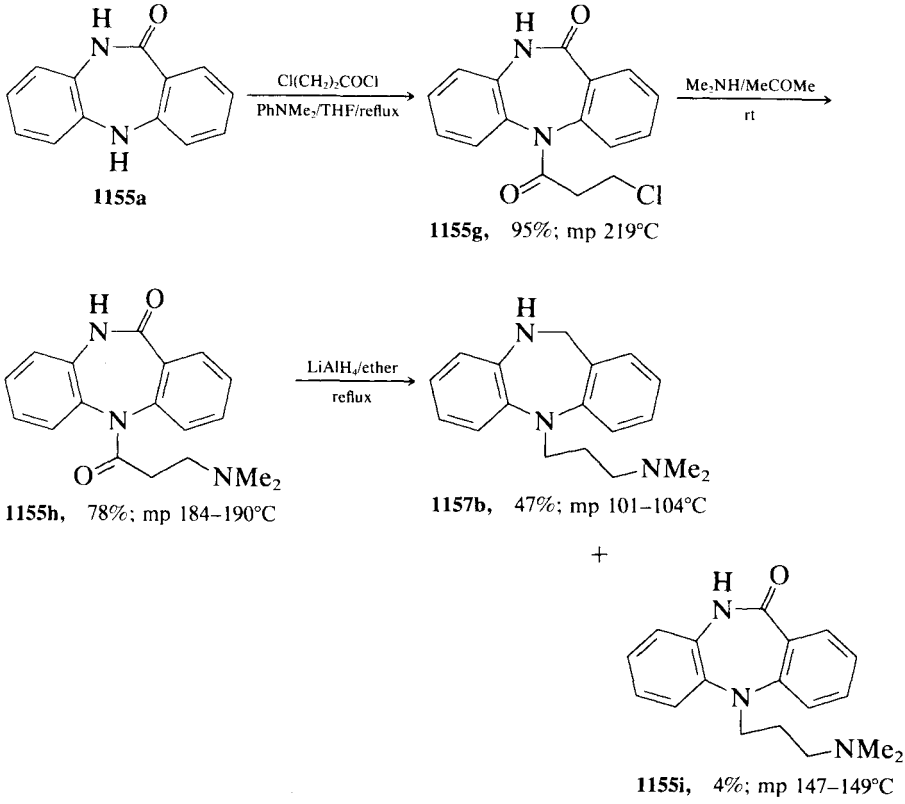
(*continued*)

TABLE 147. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | Salt | bp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| H | H |  | | 222–223/0.01 | 85 | 587,588 |
| H | H |  | | 134–136<br>225–226/0.03 | 74 | 588,593 |
| H | 8-MeO | $(CH_2)_3NMe_2$ | | 216/0.02 | 75 | 587,588 |
| | | | HCl | 184–186 | | |
| H | 8-Me | $(CH_2)_3NMe_2$ | | 108–110 | 82 | 587,588 |
| H | 3-Cl | $(CH_2)_3NMe_2$ | | 142–143 | 80 | 587,588 |
| Me | 8-Me | $(CH_2)_3NMe_2$ | | 78–80 | 91 | 587,588 |
| H | 7-Cl | $CH_2CH_2\overset{O}{\uparrow}NMe_2$ | | 181–182 | | 590[b] |
| H | 7-Cl | $CH_2CH_2NEt_2$ | | 194–196 | | 590 |
| | | | Maleate | 155–157 | | |
| | | | Succinate | 125–127 | | |
| H | 7-Cl | $CH_2CH_2NMeCH_2Ph$ | | 122–124 | | 590 |
| H | 7-Cl | $CH_2CH_2NHMe$ | | 140–141 | | 590[c] |
| | | | HBr | 234–236 | | |
| Me | H | $CH_2CHMeNMe_2$ | | 100–102 | 82 | 594 |
| | | | HCl | 204–209 | | |
| Me | H | $CHMeCH_2NMe_2$ | | 85–88<br>160/0.01 | 9 | 594 |
| | | | HCl | 210 | | |
| H | 7-Cl |  | | 178–181 | | 593 |
| | | | Fumarate | 216 | | |
| | | | HCl | 192–195 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Me | 7-Cl |  | Maleate | 135–137 | | 593 |
| H | H |  | | 140–141.5 | | 593 |
| H | 2,7-$Cl_2$ |  | Fumarate | 151–154 | | 593 |
| H | 7-Cl |  | Fumarate | 202–204<br>155 | | 593 |
| H | 7-Cl |  | Fumarate | 185–186<br>196–197.5 | | 593 |
| H | 8-$EtSO_2$ | $(CH_2)_3NMe_2$ | HCl | 230–232 | 54 | 595 |
| Me | 8-$EtSO_2$ | HCl | | 231–232 | 77 | 595,596 |

[a]Prepared from the tertiary amine.
[b]Prepared from the tertiary amine with $H_2O_2/H_2O$/EtOH under reflux.
[c]Prepared from the *N*-benzyl compound with $H_2$/Pd–C/EtOH.




**1155a**

**1155g**, 95%; mp 219°C

**1155h**, 78%; mp 184–190°C

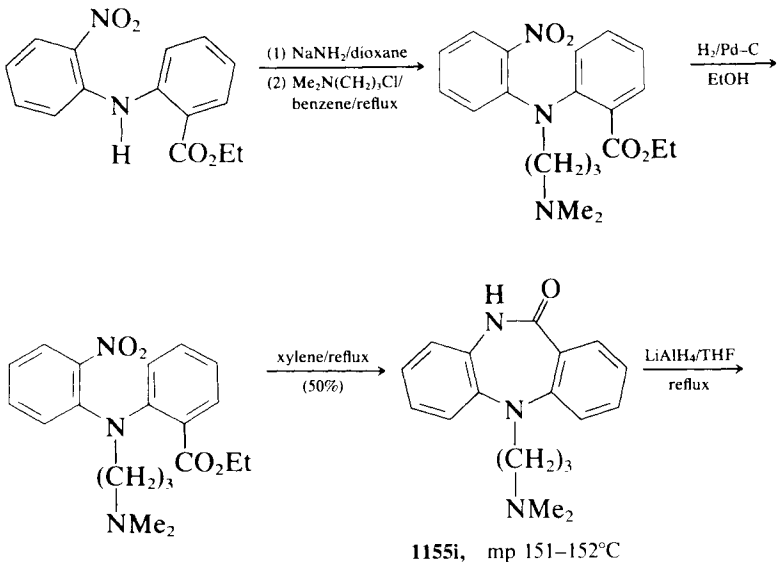
**1157b**, 47%; mp 101–104°C

**1155i**, 4%; mp 147–149°C

**Figure 90**

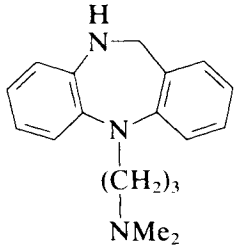
human. Detailed interpretation of the mass spectra of the metabolites was provided (606).

An important compound described by Hunziker and co-workers (9) was the $N^{10}$-substituted lactam **1158** (HF-1927, dibenzepin) which was synthesized by alkylation of **1159** and identified as an antidepressant. Publications reporting the animal pharmacology and clinical efficacy of **1158** appeared in 1964 (607). In later studies (608, 609) the preparation of the $^{14}C$-labeled drug was described, together with the synthesis of several potential demethylated metabolites by standard modifications of procedures previously described (Fig. 91). Treatment of **1158** with ethyl chloroformate gave the desired carbamate **1160**, which however, gave only a ring-opened *o*-phenylenediamine derivating (**1161**) on acid-catalyzed hydrolysis. The β-chloroethyl derivative **1162**, prepared via the alcohol **1163**, was converted to **1164a** by reaction with monomethylamine (609) but failed to give the corresponding primary amine with ammonia.



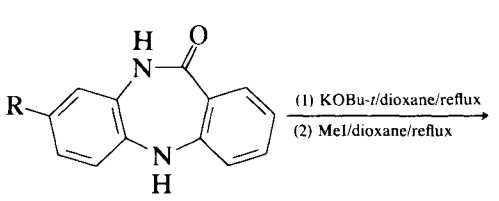

(268)

**1155i**, mp 151–152°C



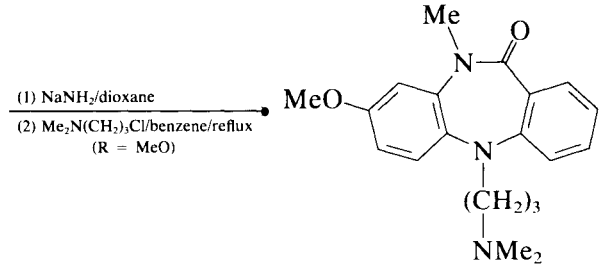

**1157b**, mp 102–104°C

A more successful approach to the synthesis of the monomethyl analogs **1164a** and **1164d** and the fully demethylated compounds **1164h** and **1164i** is shown in Fig. 92. Compounds **1164a** and **1164d** were generated by catalytic hydrogenolysis of the *N*-benzyl derivatives **1164b** and **1164c**, respectively. Formation of **1164d** was accompanied by some overreduction to the hexahydro compound **1164e**. The primary amines **1164h** and **1164i** were obtained by Raney nickel reduction of the acetonitriles **1164f** and **1164g**, respectively. Reactions that gave rise to the primary amine **1164h** also produced the tetracyclic amidine **1165.** The 8-hydroxy derivative **1166a** was prepared (608) by debenzylation of the 8-benzyloxy derivative **1166b** and alkylation of the resultant **1166c** (Eq. 271). Methylation of **1166a** then gave the 8-methoxy derivative **1166d** (588).



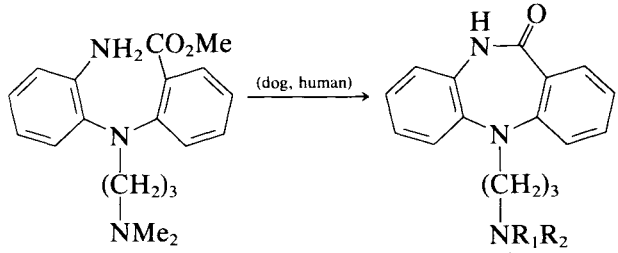

**1155j**, R = Me
**1155k**, R = MeO

**1155l**, R = Me; mp 166–168°C
**1155m**, R = MeO (72%); mp 165–166°C




(269)

**1155n**, 61%; mp 115–118°C




(270)

**1155i**, $R_1 = R_2 = Me$
**1155o**, $R_1 = R_2 = H$
**1155p**, $R_1 = Me$, $R_2 = H$

Compound **1158** was converted in man or the dog to the five demethylated metabolites shown in Table 153. The metabolites were identified by thin-layer chromatography as well as by infrared and mass spectral data (610,611).

Several papers (595,596,612) describe the preparation and biological properties of **1166f** (SM-307), which was claimed to be less toxic and more potent as an antidepressant agent than **1166a** (dibenzepine). The preparation of **1166h** and its nonmethylated analog **1166g** from **1166f** and **1166e** is described in Fig. 93, along with the synthesis of the related compounds **1166i–l.**

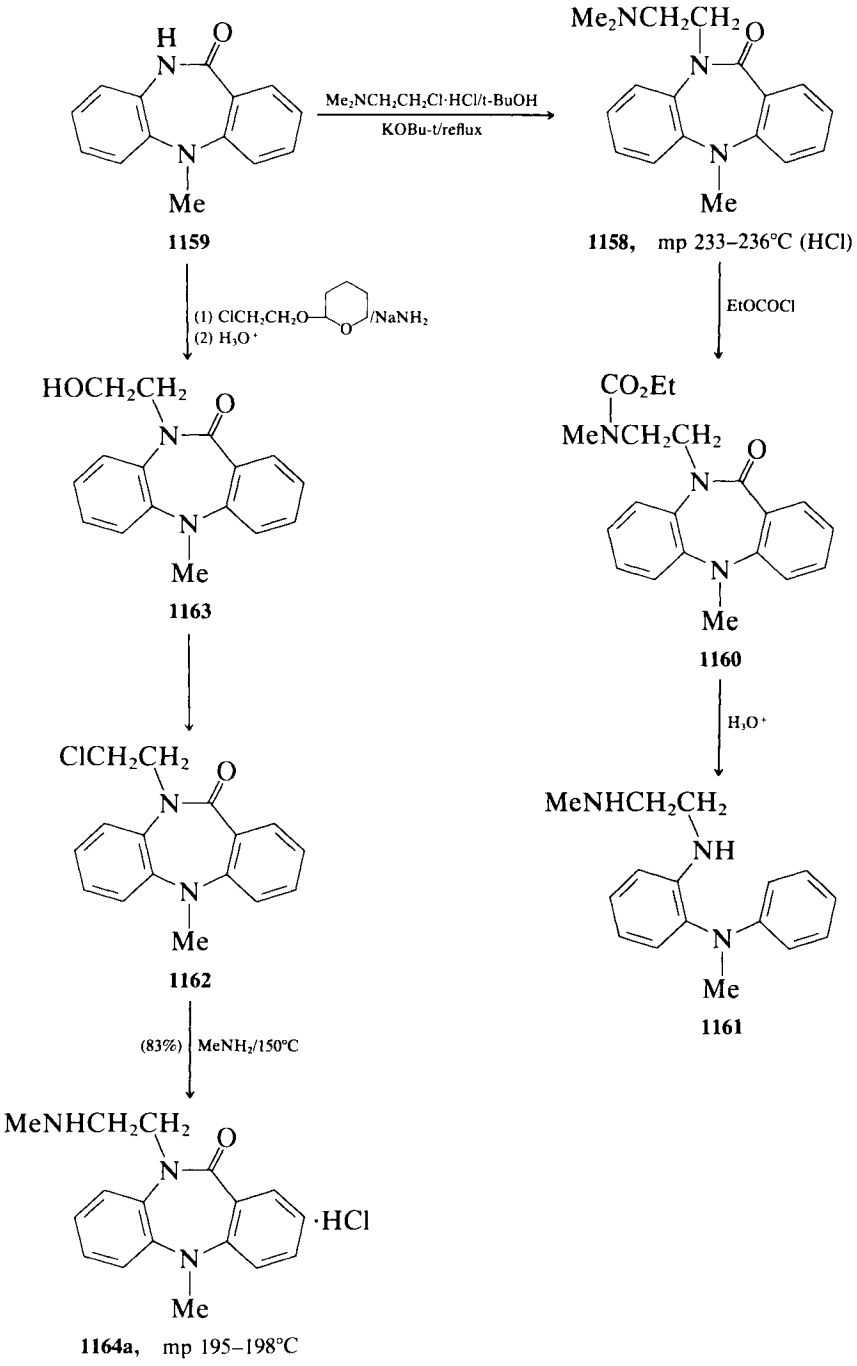
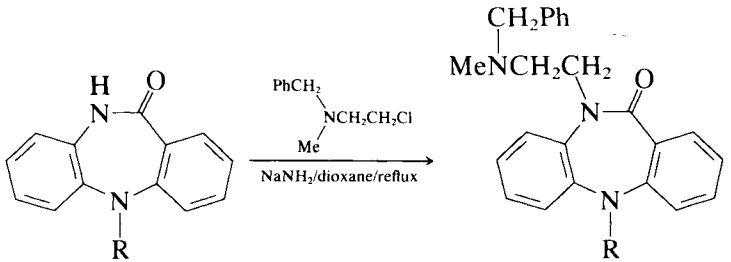

Me2NCH2CH2Cl·HCl/t-BuOH
KOBu-t/reflux
1159
1158, mp 233–236°C (HCl)
(1) ClCH2CH2O
(2) H3O+
/NaNH2
EtOCOCl
1163
1160
H3O+
1162
1161
(83%) MeNH2/150°C
·HCl
1164a, mp 195–198°C

**Figure 91**

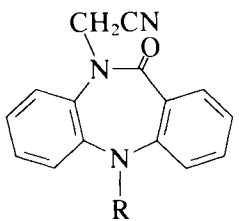



**1155a,** R = H
**1155q,** R = Me

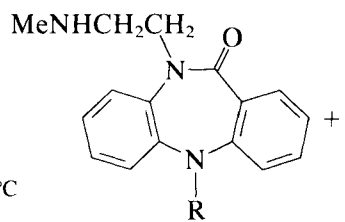
**1164b,** R = H (69%); mp 129–130°C
**1164c,** R = Me (86%); bp 240–242°C/0.05 mm

$ClCH_2CN/KI/KOBu\text{-}t/DMF/80°C$

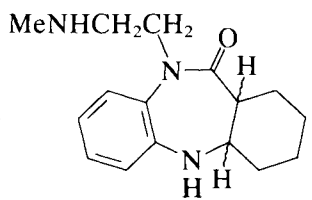
$H_2/Pd\text{-}C/EtOH$, 100 atm, 60°C




**1164f,** R = H (50%); mp 200–201°C
**1164g,** R = Me; mp 145–148°C



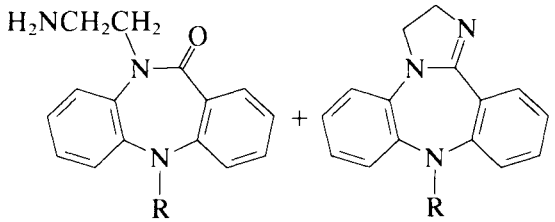

+



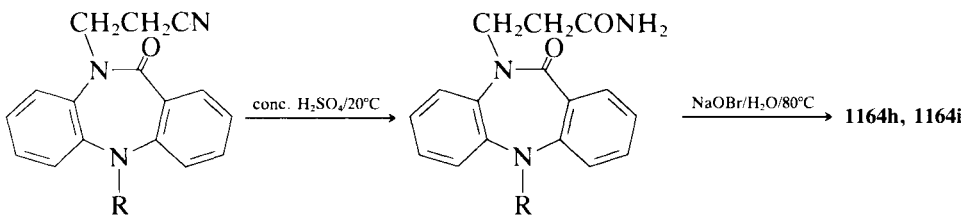

**1164d,** R = H; HCl, mp 214–215°C (202–208°C)
**1164a,** R = Me (48%); mp 233–236°C

**1164l,** mp 114–115°C; bp 168–175°C/0.05 mm

$H_2/Raney\ Ni/dioxane/NH_3$, 110 atm/rt

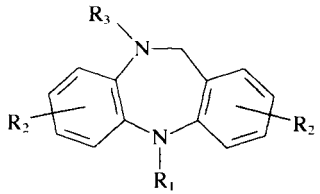


**1164h,** R = H; oxalate, mp 175–185°C
**1164i,** R = Me; bp 195–197°C/0.05 mm; HCl, mp >215°C
**1165,** R = Me; mp 134–136°C HCl, mp >310°C




**1164j,** R = H (82%); mp 177–178°C
**1164k,** R = Me (86%); mp 145–148°C

**Figure 92**



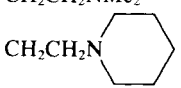
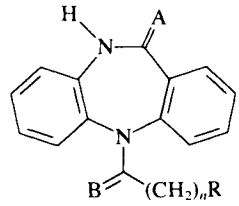
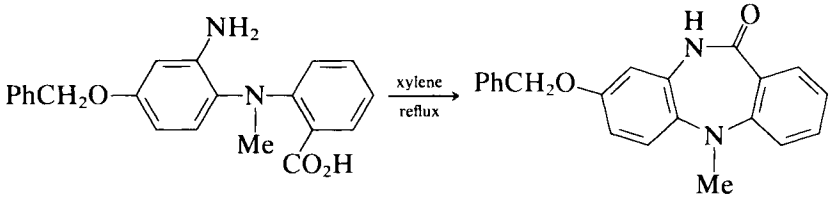

| $R_1$ | $R_2$ | $R_3$ | Salt | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| H | H | H | | 204–209 | | 9 |
| Me | H | H | | 118–120 | | 9 |
| H | 7-Cl | $CH_2CH_2NMe_2$ | | 86–88 | | 9,597 |
| | | | | 166–168/0.05 | 86 | |
| | | | Maleate | 100 | | |
| Me | H | $CH_2CH_2NMe_2$ | | 155–160/0.07 | 81 | 9 |
| | | | Maleate | 149–151 | | |
| Me | H | $(CH_2)_3NMe_2$ | | 162/0.05 | | |
| | | | Maleate | 145–148 | 76 | 597 |
| H | 8-Cl | $CH_2CH_2NMe_2$ | | 176/0.01 | 73 | 597 |
| H | 8-Cl | $(CH_2)_3NMe_2$ | | 185–187/0.05 | 77 | 597 |
| | | | HCl | 101–107 | | |
| H | H | $(CH_2)_3NMe_2$ | | 158–160/0.03 | 72 | 597 |
| H | 2-Cl | $CH_2CH_2NMe_2$ | | 175–177/0.01 | | 597 |
| H | 7-Cl |  | | 108–109 | | 597 |
| Me | 7-Cl | $CH_2CH_2NMe_2$ | | 170–171/0.05 | | 597 |
| Me | 7-MeS | $CH_2CH_2NMe_2$ | | 205–207/0.05 | | 597 |
| | | | Maleate | 134–137 | | |
| Me | 8-MeS | $CH_2CH_2NMe_2$ | | 151–158/0.05 | | 597 |
| | | | Maleate | 159–162 | | |
| H | 8-MeO | $CH_2CH_2NMe_2$ | | 180–181/0.05 | | 597 |
| Me | 8-MeO | $CH_2CH_2NMe_2$ | | 170–175/0.01 | | 597 |
| H | 8-$EtSO_2$ | $CH_2CH_2NMe_2$ | HCl | 202–207 | 27 | 595 |
| Me | 8-$EtSO_2$ | $CH_2CH_2NMe_2$ | HBr | 200–202 | | 595 |

TABLE 149. 5-SUBSTITUTED DIBENZO[*b*,*e*][1,4]DIAZEPINE DERIVATIVES

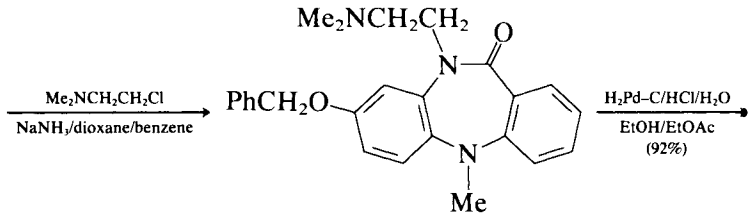


| A | B | *n* | R | mp (°C) | Yield (%) | Spectra |
|---|---|---|---|---|---|---|
| O | O | 1 | Cl | 239–241 | 68 | ir |
| O | O | 2 | $NEt_2$ | 128–129 | | |
| O | O | 1 | $NMe_2$ | 170–173 | | uv |
| O | O | 1 | $NEt_2$ | 145–146 | | |
| O | O | 2 | NHMe | 255–257[a] | 88 | |
| $H_2$ | $H_2$ | 2 | $NEt_2$ | 84 | 52 | |

[a]HCl salt.

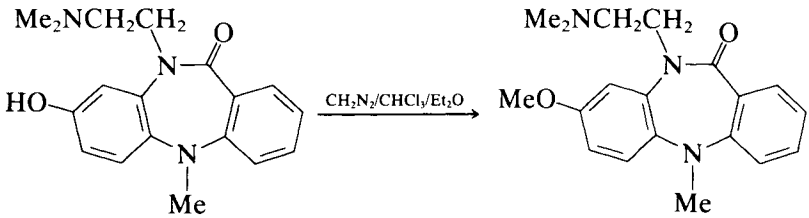


**1166b,** mp 163–167°C



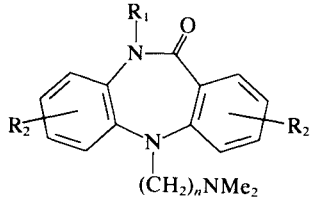
(271)

**1166c,** mp 105–108°C



**1166a,** HCl, mp 225–232°C **1166d**

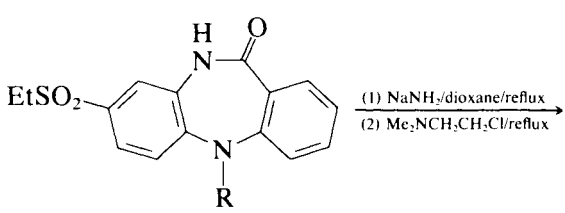
TABLE 150. 5-SUBSTITUTED DIBENZO[*b*,*e*][1,4]DIAZEPIN-11-ONE DERIVATIVES



| $R_1$ | $R_2$ | *n* | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|
| H | H | 2 | 194–196 | 53 | 599,600 |
| H | 3-Cl | 2 | 194–197 | 38 | 599,600 |
| H | 7-Cl | 2 | 202–204 | 54 | 599,600 |
| H | 7-MeO | 2 | 203–205 | | 599 |
| H | 7-MeS | 2 | 185–187 | | 599 |
| H | 8-Me | 2 | 165–167 | 40 | 599,600 |
| Me | 8-Me | 2 | 71–75<br>169–170/0.05 | 56 | 599,600 |
| H | 8-Cl | 2 | 186–187 | 44 | 599,600 |
| H | 8-$CF_3$ | 2 | 122–138<br>170–172 | 58 | 599,600 |
| H | 8-MeO | 2 | 157–159 | 56 | 599,600 |
| Me | 8-MeO | 2 | 115–118<br>187/0.05 | 62 | 599,600 |
| H | 7-Cl | 3 | 244–245 (HCl) | 56 | 599,600 |
| H | 8-Cl | 3 | 183–185 | 42 | 599,600 |
| $PhCH_2$ | H | 3 | 230/0.03 | 77 | 600 |
| Me | H | 2 | 186–188/0.03 | 81 | 600 |
| Me | H | 3 | 80–83<br>188–189/0.02 | 84 | 600 |
| $PhCH_2$ | H | 2 | 150–170 (HCl) | | 600 |
| Me | 8-Cl | 2 | 179/0.01 | 57 | 600 |
| H | 8-$CF_3$ | 2 | 170–172 | 58 | 601 |

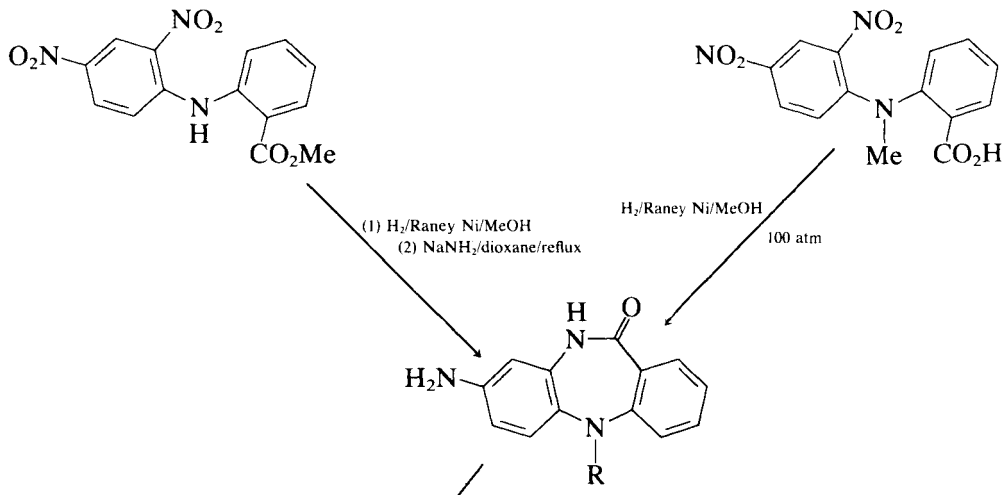
Bentley and Holliman (613) claimed that the diamino diacid **1167a** gave the dibenzodiazepinone **1168** on attempted recrystallization from nitrobenzene. Analogy was made to the cyclization of the monocarboxylic acid **1167b** studied by Jourdan (614). However, the latter author was under the impression that his product was in fact the phenazine **1169** rather than **1166i** (Eq. 272). There is insufficient information in the references cited to assess the validity of these claims.

Two reports (615,616) describe the synthesis of a group of urea derivatives of the dibenzo[*b*,*e*][1,4]diazepine ring system. Tricyclic lactam **1155q**, was prepared as described above (9) and reduced to the amine **1170a** with lithium aluminum hydride. Reaction of **1170a** with phosgene yielded the carbamyl chloride **1170b**, which on treatment with an amine gave the urea **1170c**. These reaction, as well as the lithium aluminum hydride reduction of amide **1155b**

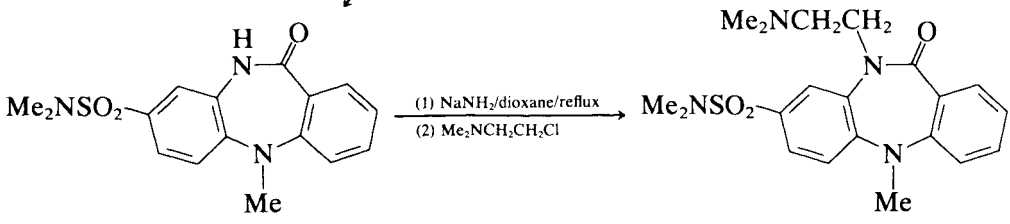



**1166e,** R = H; mp 141–143°C
**1166f,** R = Me; mp 256–257°C

**1166g,** R = H (69%); mp 244–245°C (HCl)
**1166h,** R = Me (78%); mp 133–136°C; HCl, mp 217–219°C




**1166i,** R = H (17%); mp 215–216°C
**1166j,** R = Me (18%); mp 233–235°C

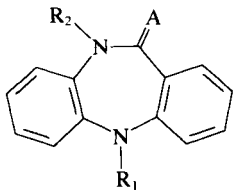



**1166k,** 30%; mp 266–269°C

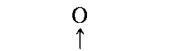
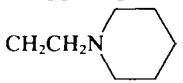
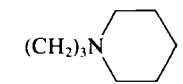
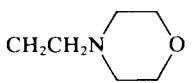
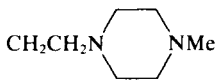
**1166l,** 38%; mp 192–195°C

**Figure 93**

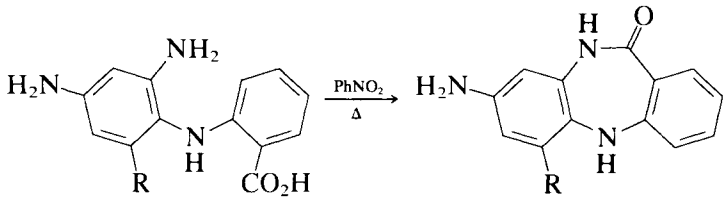
TABLE 151. 5- AND/OR 10-SUBSTITUTED DIBENZO[*b*,*e*][1,4]DIAZEPIN-11-ONE DERIVATIVES AND REDUCTION PRODUCTS




| $R_1$ | $R_2$ | A | Salt | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| H | $(CH_2)_2NEt_2$ | O | | 132–133 | 67 | 602,603 |
| H | $(CH_2)_3NMe_2$ | O | | 119–121 | 50 | 602,603 |
| | | | HCl | 226–227 | | 588 |
| H | $(CH_2)_3NEt_2$ | O | | 77–78 | | 602 |
| H | Me | O | | 207–208 | | 602 |
| H | $(CH_2)_2NEt_2$ | $H_2$ | 2HCl | 199.5–200.5 | 71 | 602,603 |
| H | $(CH_2)_3NMe_2$ | $H_2$ | | 160/0.05 | 82 | 602 |
| | | | 2HCl | 176–177 | | |
| $(CH_2)_2NEt_2$ | H | O | | 132–133.5 | 26 | 602,604 |
| $(CH_2)_3NMe_2$ | H | O | | 149–150 | 83 | 602 |
| $(CH_2)_3NEt_2$ | H | O | | 117–119 | | 602 |
| $(CH_2)_2NEt_2$ | H | $H_2$ | 2HCl | 221.5–223 | | 602 |
| $(CH_2)_3NMe_2$ | H | $H_2$ | | 100.5–102 | | 602 |
| $(CH_2)_3NEt_2$ | H | $H_2$ | | 81–83 | | 602 |

| | | | | | | |
|---|---|---|---|---|---|---|
|  | H | O | | 165 | | 602 |
|  | H | O | | 181.5–185.5 | | 602[a] |
| $(CH_2)_2NEt_2$ | Me | O | Methiodide | 219.5–221 | 85 | 602,604[a] |
| $(CH_2)_2NEt_2$ | $(CH_2)_3NMe_2$ | O | | 109–111.5 | | 602 |
| $(CH_2)_2NMe_2$ | Me | O | Methiodide | 155 | 41 | 600 |
| H | $PhCH_2$ | O | | 151–154 | 93 | 600 |
| $(CH_2)_2NMe_2$ | $PhCH_2$ | O | Methiodide | 120–123 | | 600 |
|  | H | O | | 184–186 | 75 | 600 |
|  | H | O | | 141–143 | 58 | 600 |
|  | H | O | | 218–219 | 66 | 600 |
|  | H | O | | 159–161 | 60 | 600 |

[a]Prepared from the tertiary amine.

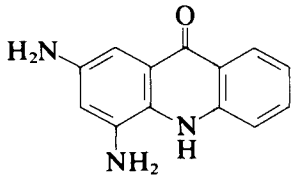


**1167a**, R = $CO_2H$
**1167b**, R = H

**1168**, R = $CO_2H$
**1166i**, R = H

(272)

or



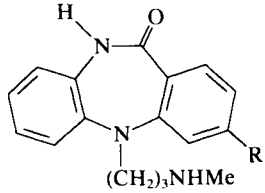
**1169**

and the acylation and subsequent lithium aluminum hydride reduction of amide **1155a**, are described in Fig. 94. Further examples are listed in Table 154. These substances are reported to have anti-inflammatory activity. A hydrazide was also prepared from **1170b** (617), as shown in Table 154.

Similar work is described in a Japanese patent (618), but in this case the urea function is attached to $N^5$ rather than to $N^{10}$. The preparation of $N^5$-ureido derivatives such as **1170h, 1170i,** and **1171c** was achieved by allowing the lactam **1155a** to react with phosgene or via the carbobenzyloxy derivatives **1171a** and **1171b** (Fig. 95).

A series of 10-aminoalkoxy derivatives has also been described (619,620,621). These substances were obtained by alkylation of *N*-hydroxy lactams (Fig.96). The *N*-hydroxy lactams **1172a** and **1172b** were obtained by

TABLE 152. 5-METHYLAMINOPROPYLDIBENZO[*b*,*e*][1,4]DIAZEPIN-11-ONE DERIVATIVES[a]



| R | mp (°C) | Yield (%) |
|---|---|---|
| H | 146.5–147.5 | 23 |
| Cl | 145.5–146.5 | |

[a]Ref. 604.

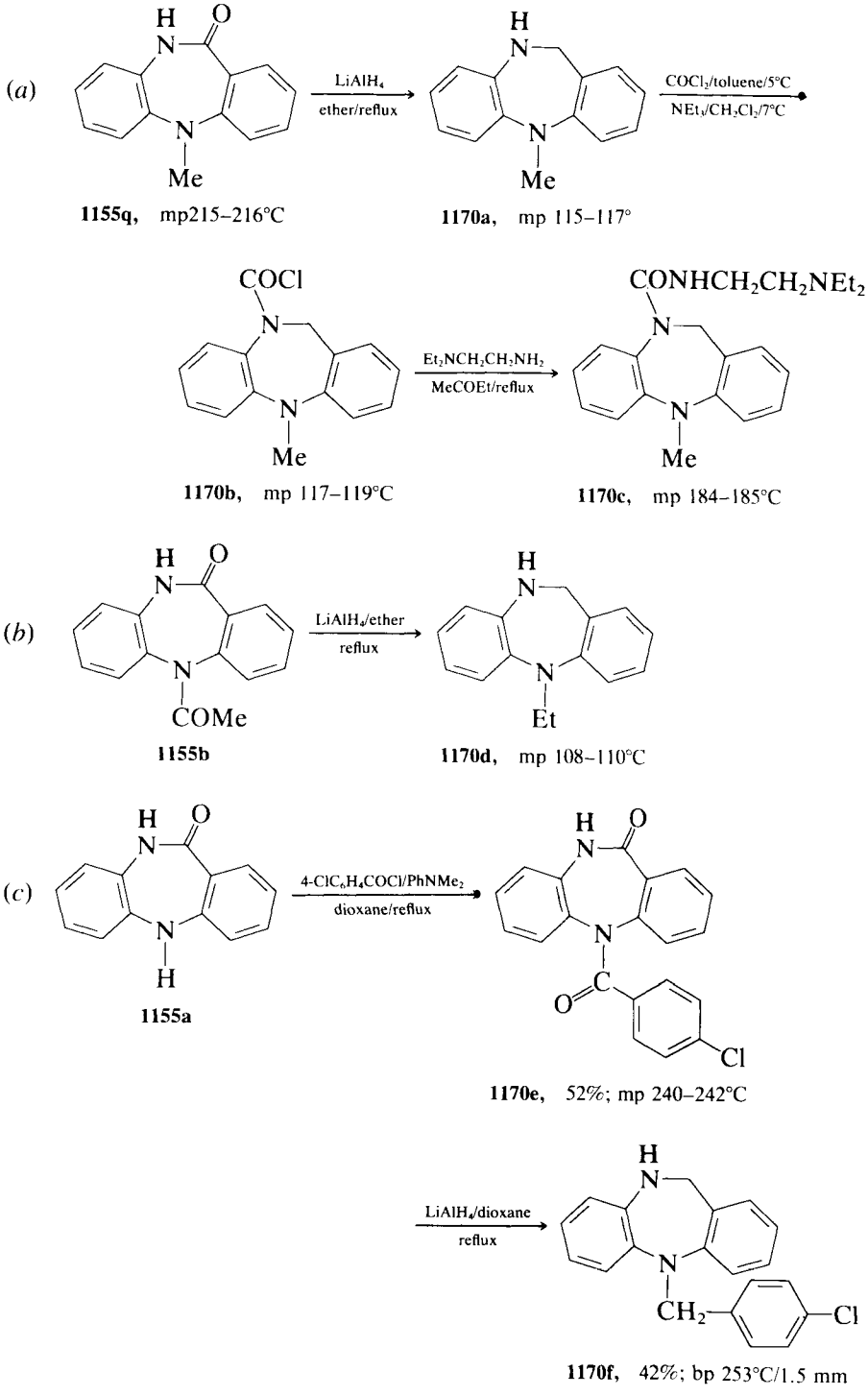
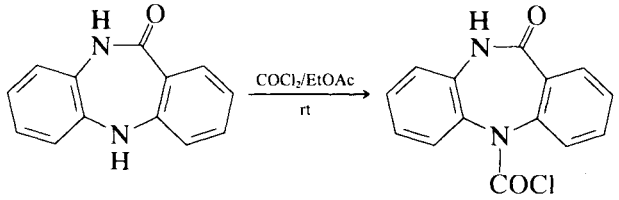

(a)
LiAlH4
ether/reflux
COCl2/toluene/5°C
NEt3/CH2Cl2/7°C
1155q, mp215–216°C
1170a, mp 115–117°
1170b, mp 117–119°C
Et2NCH2CH2NH2
MeCOEt/reflux
1170c, mp 184–185°C
(b)
LiAlH4/ether
reflux
1155b
1170d, mp 108–110°C
(c)
4-ClC6H4COCl/PhNMe2
dioxane/reflux
1155a
1170e, 52%; mp 240–242°C
LiAlH4/dioxane
reflux
1170f, 42%; bp 253°C/1.5 mm

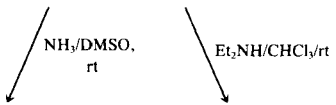
**Figure 94**

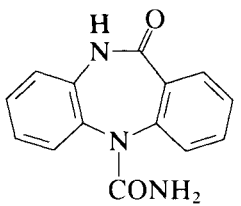
(*a*)



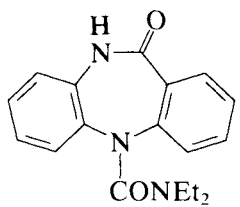

**1155a**

**1170g,** mp 253°C



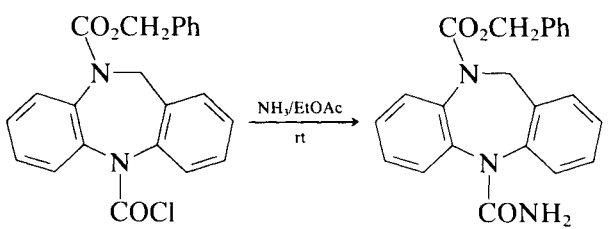



**1170h,** mp 330°C



**1170i,** mp 245–246°C

(*b*)




**1171a**

**1171b,** mp 184–186°C

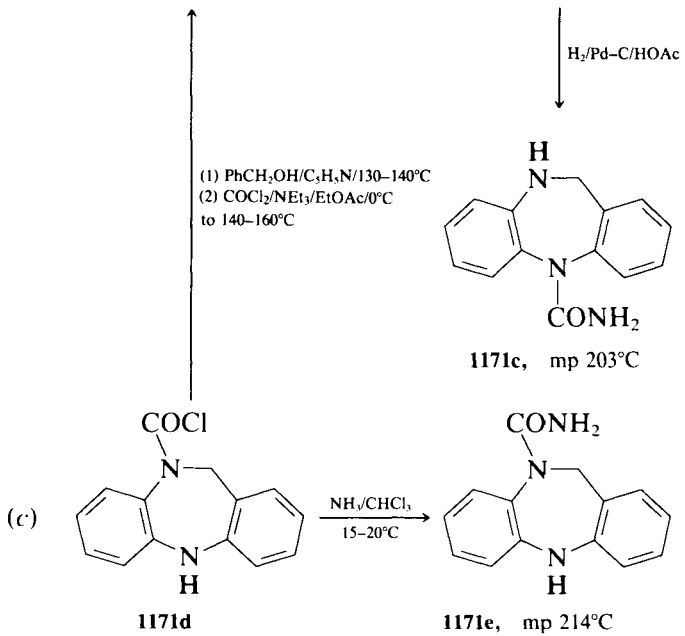
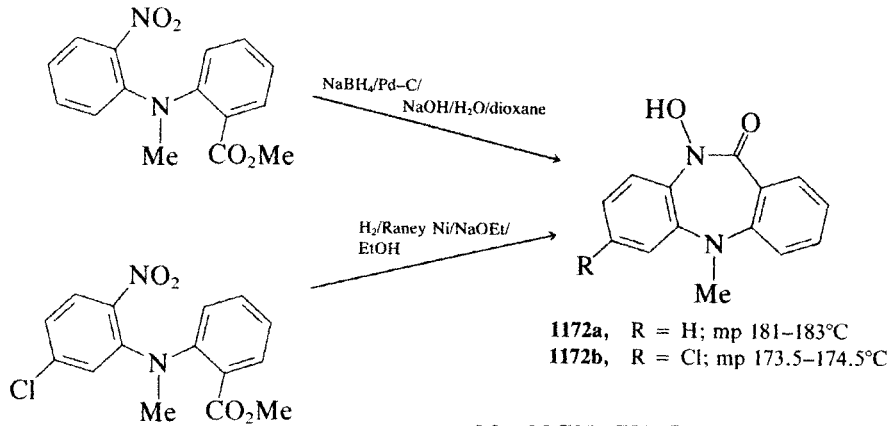
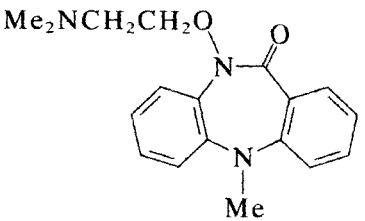

H2/Pd–C/HOAc
(1) PhCH2OH/C5H5N/130–140°C
(2) COCl2/NEt3/EtOAc/0°C
to 140–160°C
H
N
N
CONH2
1171c, mp 203°C
(c)
COCl
N
N
H
NH3/CHCl3
15–20°C
CONH2
N
N
H
1171d
1171e, mp 214°C

**Figure 95**

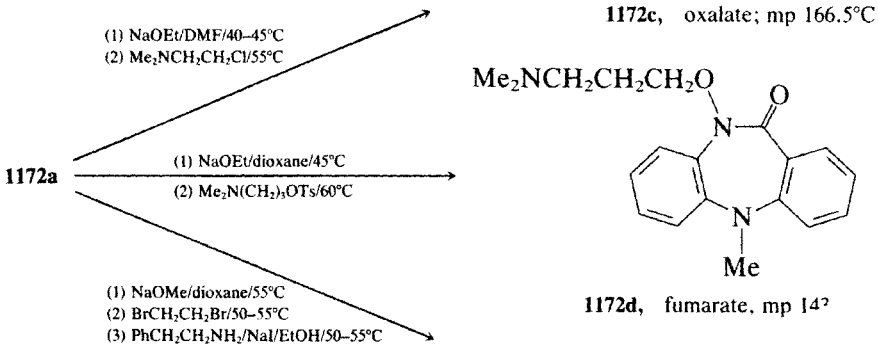



**1172a,** R = H; mp 181–183°C
**1172b,** R = Cl; mp 173.5–174.5°C

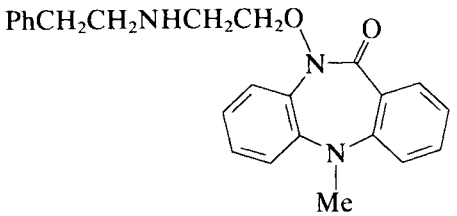



**1172c,** oxalate; mp 166.5°C

*(b)*

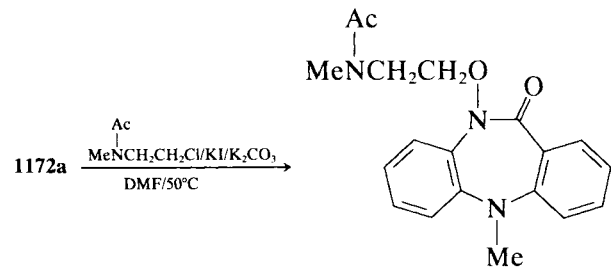



**1172d,** fumarate, mp 143

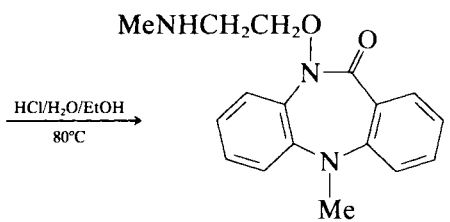


**1172e,** oxalate, mp 156–157°C

(*c*)



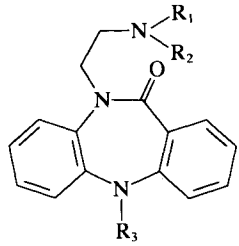
**1172f,** mp 93–95°C



**1172g,** mp 97–99°C;
fumarate, mp 127–129°C

**Figure 96**

TABLE 153. METABOLITES OF COMPOUND **1160**



| $R_1$ | $R_2$ | $R_3$ |
|---|---|---|
| H | Me | Me |
| Me | Me | H |
| H | Me | H |
| H | H | Me |
| H | H | H |

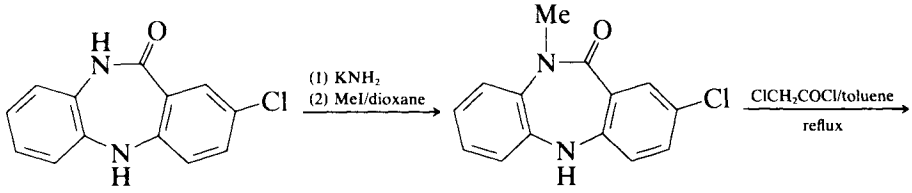
reductive cyclization of nitro esters under basic conditions. *O*-Alkylation could be achieved with various reagents to give products such as **1172c–g.** Further examples are listed in Table 155. Antidepressant and antihistaminic activities were claimed.

A large number of 5-aminoacetyl derivatives of tricyclic lactams were prepared and patented as antiulcer agents and gastric secretion inhibitors (559,622,623). For example, chloroacetylation of **1172i** followed by reaction of the product **1172j** with *N*-methylpiperazine yielded **1172k** (Eq. 273). Other compounds prepared by this approach are listed in Table 156.

*N*-Aminolactams such as **1172l** and **1172m** were prepared by amination with *O*-(2,4-dinitrophenyl)hydroxylamine under basic conditions (Eq. 274). These substances were claimed to be antipasmodic agents (624).

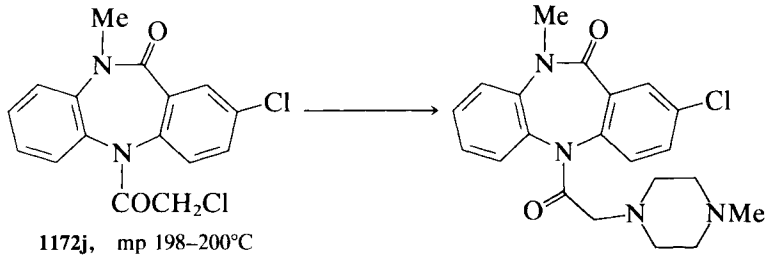
A less versatile synthesis of tricyclic lactams involves formation of the tricyclic ring system by nucleophilic aromatic substitution. As shown in Eq. 275, the cyclization of a sulfonamide with sodium hydride in refluxing dimethylformamide afforded the $N^5$-tosyl derivative **1172n.** Substrates lacking the nitro group could not be cyclized (625,626). In a related approach (Eq. 276) the dinitro compound **1173** could be prepared without recourse to sulfonamide activation (627). The mononitro analog **1174** was obtained by pyrolysis of an amino ester, as shown in Eq. 277 (626).

In an extension of this work (628) treatment of the nitro lactam **1174a** with phosphoryl chloride in dimethylformamide gave the benzimidazole **1175a** (Fig. 97). Other examples of this type of reaction include the transformations of **1155a** into **1175b**, of **1174b** into **1175c** and the $N^5$-formyl derivative **1176**, and of **1174a** into the benzimidazole **1175d**. The *N*-acetyl derivative **1177** was converted to the product lacking the nitro group (**1155b**) via catalytic hydrogenation, diazotization, and treatment with hypophosphorous acid.



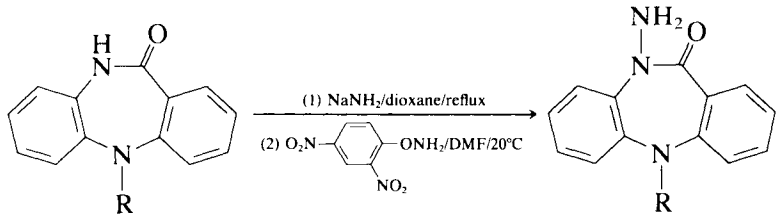

**1172h** **1172i**, mp 213–214°C

(273)



**1172j**, mp 198–200°C

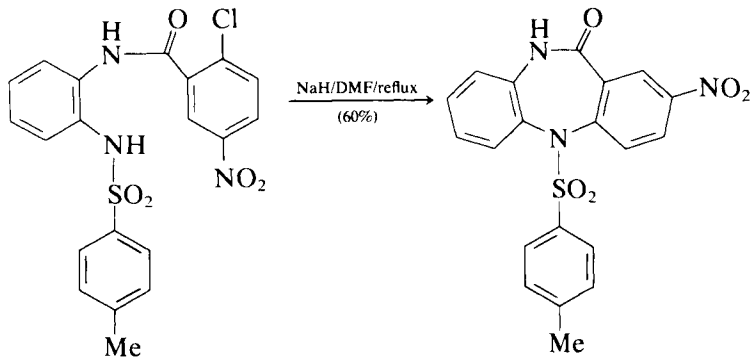
**1172k**, 90%; dihydrochloride, mp 246–248°C




(274)

**1155a**, R = H
**1155g**, R = Me

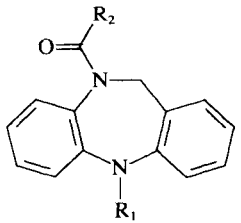
**1172l**, R = H; mp 206–207°C
**1172m**, R = Me; mp 176–179°C



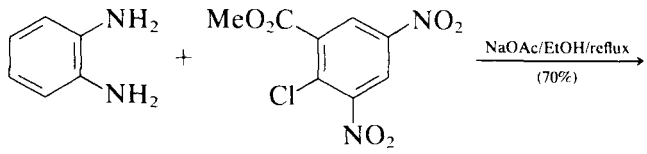

(275)

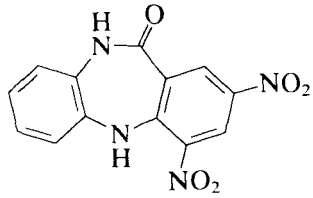
**1172n**, mp 252–255°C

TABLE 154. 5,11-DIHYDRO-10*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINE-10-CARBOXYLIC ACID DERIVATIVES



| $R_1$ | $R_2$ | mp (°C) | Refs. |
|---|---|---|---|
| H | Cl | 173–175 | 615,615 |
| Et | Cl | 162–164 | 615,616 |
| Me | $NHCH_2CH_2NEt_2$ | 184–185 (HCl) | 615,616 |
| H |  | 214–217 (HCl) | 615,616 |
| H | $NMeCH_2CH_2N(Me)CH_2Ph$ | 102–103 | 615,616 |
| 4-$ClC_6H_4CH_2$ | Cl | 157–159 | 616 |
| Et | $NHCH_2CH_2NEt_2$ | Oil | 616 |
| H | $NHCH_2CH_2NEt_2$ | 182–185 | 616 |
| 4-$ClC_6H_4CH_2$ | $NHCH_2CH_2NEt_2$ | 148–149 | 616 |
| Me | $N(CH_2C{\equiv}CH)CH_2CH_2NEt_2$ | 183–186 (HCl) | 616 |
| Me | $N(CH_2Ph)CH_2CH_2NEt_2$ | Oil | 616 |
| Me | $NHNH_2$ | 171–175 | 617 |



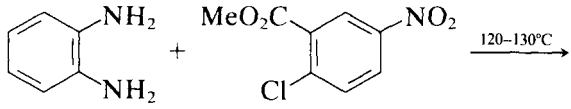



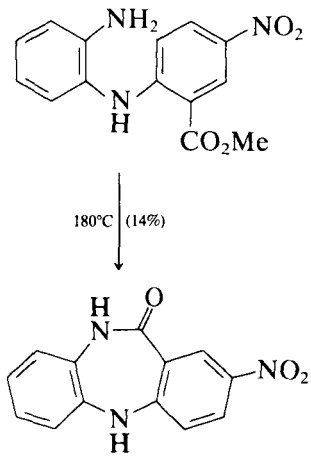

(276)

**1173**, mp 166–167°C

Nesmeyanov and co-workers (629) claimed the synthesis of the quaternary lactam **1178** by the method shown in Eq. 278. A photochemical synthesis of the tricyclic lactam **1179** is shown in Fig. 98. Irradiation of 1,2-diphenylindazolone (630) gave a 20% yield of a lactam whose structure was shown to be **1179** by an alternative nonphotochemical synthesis.

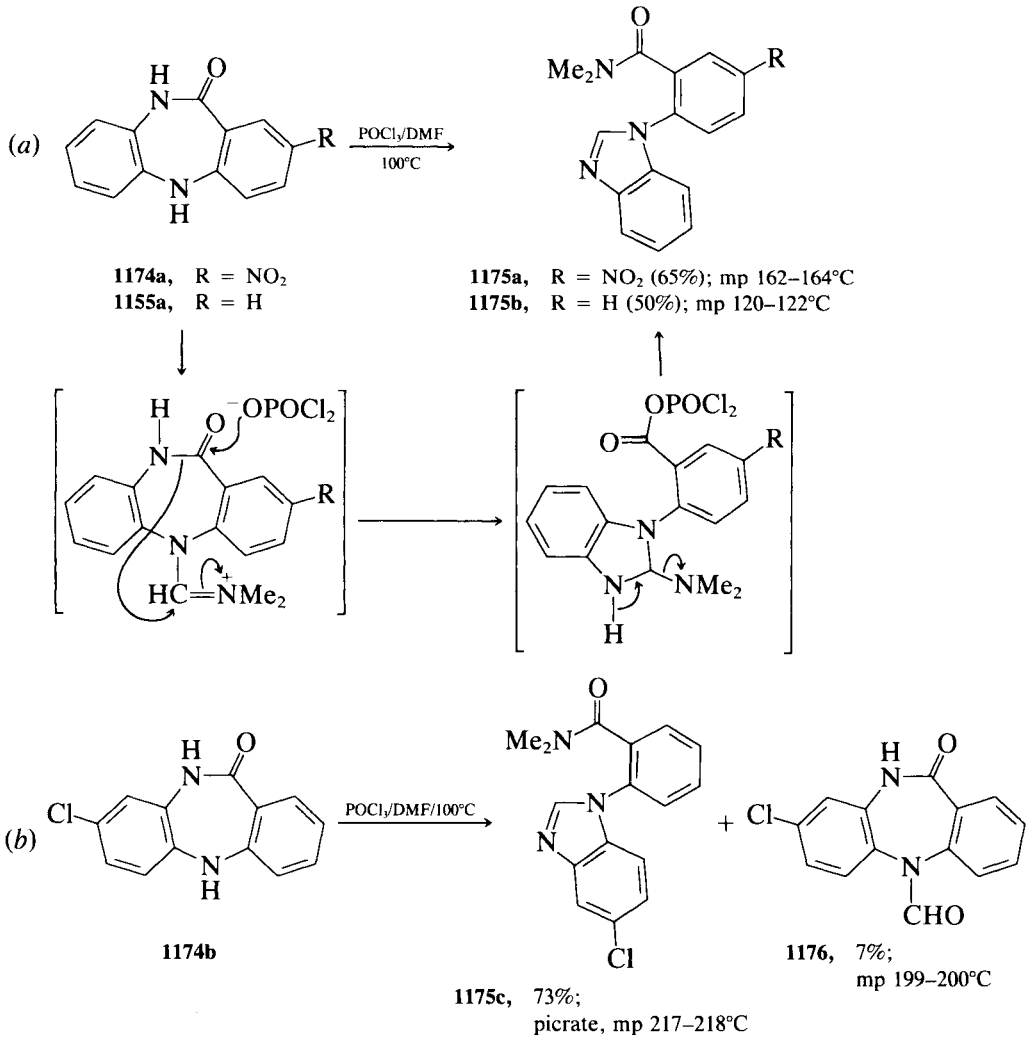
A second important group of dibenzo[*b*,*e*][1,4]diazepines is characterized




(277)

**1174**, mp >300°C


(a)
POCl3/DMF
100°C
1174a, R = NO2
1155a, R = H
1175a, R = NO2 (65%); mp 162–164°C
1175b, R = H (50%); mp 120–122°C
(b)
POCl3/DMF/100°C
1174b
1175c, 73%;
picrate, mp 217–218°C
1176, 7%;
mp 199–200°C

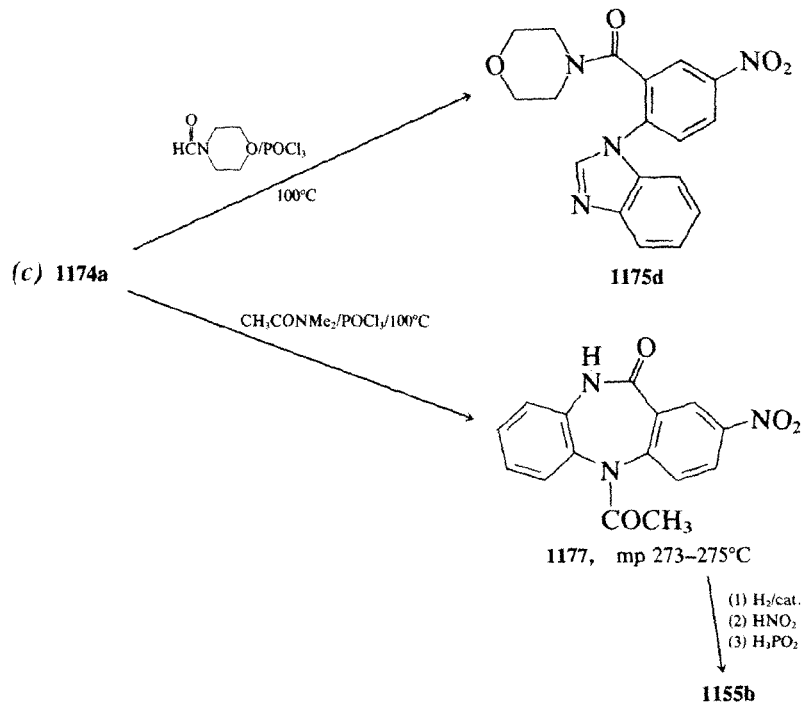
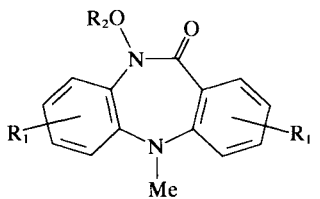
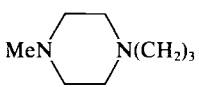
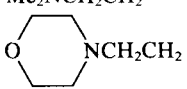
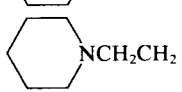

(c) 1174a
HCN
O/POCl3
100°C
1175d
CH3CONMe2/POCl3/100°C
1177, mp 273–275°C
(1) H2/cat.
(2) HNO2
(3) H3PO2
1155b

Figure 97

TABLE 155. 10-AMINOALKOXY- AND -HYDROXY-5-METHYLDIBENZO[*b*,*e*][1,4]DIAZEPIN-11-ONE DERIVATIVES



| $R_1$ | $R_2$ | Salt | mp (°C) | Refs. |
|---|---|---|---|---|
| 7-Cl | $Me_2NCH_2CH_2$ | | 115 | 619 |
| | | Fumarate | 160–161 | |
| H | $Me_2CHNHCH_2CH_2$ | | 87 | 619 |
| | | Oxalate | 167 | |
| H |  | | 102 | 619 |
| | | HCl | 208 | |
| 8-$CF_3$ | $Me_2NCH_2CH_2$ | Oxalate | 179 | 619 |
| H |  | | 130 | 619 |
| | | Maleate | 130.5–132 | |
| H |  | Oxalate | 156 | 619 |

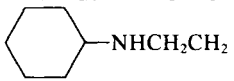
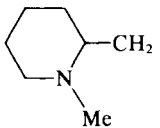
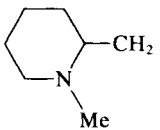
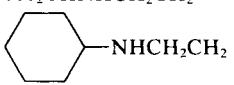
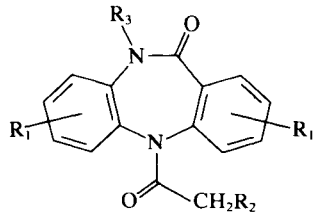
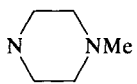
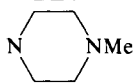
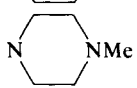
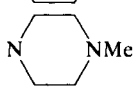
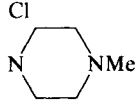
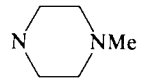
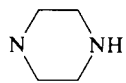
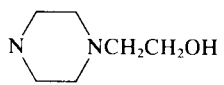
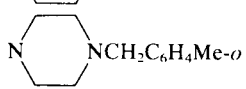
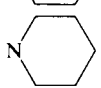
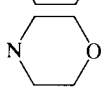
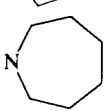
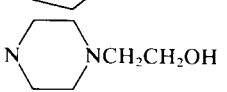
| | | | | |
|---|---|---|---|---|
| 2,7-$Cl_2$ | $Me_2NCH_2CH_2$ | | 126–127 | 619 |
| | | Fumarate | 172–173.5 | |
| 8-MeS | $Me_2NCH_2CH_2$ | | 95–97 | 619 |
| 8-$CF_3$ | H | | 170–173 | 621 |
| H | $Me(CH_2)_3NHCH_2CH_2$ | Oxalate | 127–129 | 619 |
| H |  | | 124–126 | 619 |
| | | Oxalate | 174–175 | |
| H |  | | 158–159 | 593 |
| 7-Cl |  | | 115–118 | 593 |
| H | $Me_2CHNHCH_2CH_2$ | Oxalate | 167 | 620 |
| H |  | Oxalate | 174–175 | 620 |
| H | $PhCH_2CH_2NHCH_2CH_2$ | Oxalate | 156–157 | 620 |
| 2,7-$Cl_2$ | H | | 209–211 | 621 |
| 7-Cl, 8-MeS | H | | 194 | 621 |
| H | H($N^5$-desmethyl) | | 203–205 | 621 |

TABLE 156. 5-AMINOMETHYL- AND 5-CHLOROMETHYLDIBENZO[*b*,*e*][1,4]DIAZEPIN-11-ONE DERIVATIVES

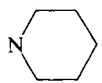
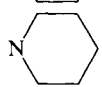
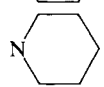
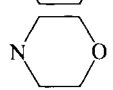
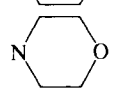
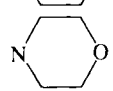
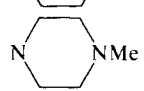


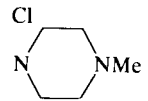
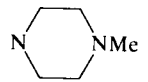
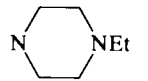
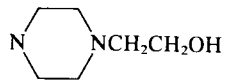
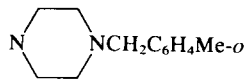
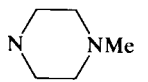
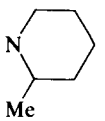
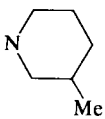
| $R_1$ | $R_2$ | $R_3$ | Salt | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| 2-Cl | Cl | H | | 218–219 | | 622 |
| 2-Cl |  | H | | 165–167 | 50 | 622 |
| H |  | H | 2HCl | 220 | 33 | 623 |
| 2-Cl |  | H | 2HCl | 225–228 | 78 | 623 |
| 3-Cl |  | H | HCl | 223–225 | 57 | 623 |
| 8-Cl |  | H | | 199–201 | 78 | 623 |
| 2-Cl | Cl | *n*-Bu | | 170 | | 623 |
| 2-Cl |  | *n*-Bu | 2HCl | 250 | 70 | 623 |

| | | | | | | |
|---|---|---|---|---|---|---|
| H |  | Me | Difumarate | 166–168 | 75 | 622,623 |
| H |  | H | 2HCl | 218–220 | 35 | 623 |
| H |  | H | 2HCl | 245–247 | 70 | 623[a] |
| H |  | H | 2HCl | 213–215 | 25 | 623 |
| H |  | H | 2HCl | 222–223 | 25 | 623 |
| H |  | H | | 198–199 | 65 | 623 |
| H |  | H | | 188–189 | 80 | 623 |
| H |  | H | | 100–105 | 30 | 623 |
| H |  | H | Fumarate | 222–224 | 45 | 623 |
| 2-Cl |  | *n*-Bu | 2HCl | 245 | 65 | 623 |

(*continued*)

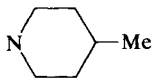
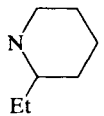
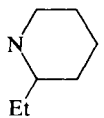
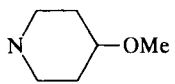
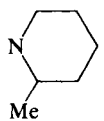
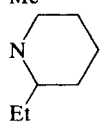
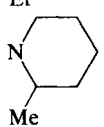
TABLE 156. (*Continued*)

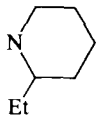
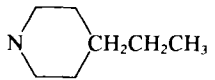
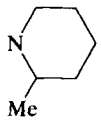
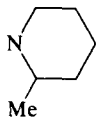
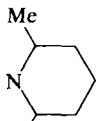
| $R_1$ | $R_2$ | $R_3$ | Salt | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| H |  | Me | | 135–137 | 54 | 623 |
| 2-Cl | Cl | H | | 218–219 | | 623 |
| 2-Cl |  | H | | 165–167 | 50 | 623 |
| 2-Cl |  | Me | HCl | 261–263 | 59 | 623 |
| H |  | Me | HCl | 253–255 | 65 | 623 |
| 2-Cl |  | H | | 189–190 | 71 | 623 |
| 2-Cl |  | Me | HCl | 263–268 | 88 | 623 |
| H |  | Me | HCl | 160–165 | 83 | 623 |
| 2-Cl |  | H | | 226–228 | 71 | 623 |
| 2-Cl |  | Me | | 147–149 | 50 | 623 |
| 2-Cl |  | Et | 2HCl | 238–240 | 77 | 623 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2-Cl |  | Et | | 155–157 | | 623 |
| 2-Cl | | Pr | | 66–69 | 62 | 623 |
| 3-Cl |  | Me | | 122–123 | 85 | 623 |
| 3-Cl |  | Me | | 171–173 | | 623 |
| H |  | H | 2HCl | 289–290 | 41 | 623 |
| H |  | Me | | 80–82 | 41 | 623 |
| H |  | Me | Fumarate | 198–201 | 83 | 623 |
| 2-Cl |  | H | 2HCl | >270 | 80 | 623 |
| H |  | Et | Difumarate | 126–128 | 52 | 623 |
| H |  | H | | 188–189 | 45 | 623 |
| H |  | H | HCl | 112–114<br>210–213 | 35 | 623 |

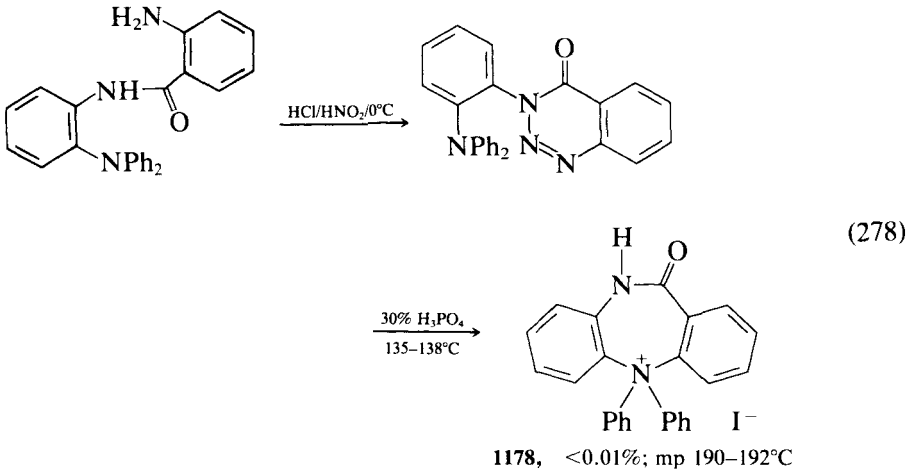
(*continued*)

TABLE 156. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | Salt | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| H |  | H | | 202–203 | 55 | 623 |
| H |  | H | | 168–170 | 32 | 623 |
| H |  | Me | HCl | 174 | 65 | 623 |
| H |  | H | | 166–167 | 45 | 623 |
| 2-Cl |  | H | | 189–191 | 65 | 623 |
| 2-Cl |  | H | | 181–184 | 56 | 623 |
| 2-Cl |  | Me | | 112–114 | 80 | 623 |

| | | | | | | |
|---|---|---|---|---|---|---|
| H |  | Et | HCl | 178–181 | 55 | 623 |
| H |  | H | HCl | 210–215 | 40 | 623 |
| H |  | Et | | 106–108 | | 623 |
| | | | Fumarate | 135 | 50 | |
| 8-Cl |  | H | | 243–245 | 65 | 623 |
| H |  | H | HCl | 221–223 | 35 | 623 |
| H | $N(CH_2CH{=}CH_2)_2$ | H | | 143–145 | 63 | 559 |
| | | | Fumarate | 131–133 | | 559 |
| H | $N(CH_2CH{=}CH_2)_2$ | Me | | 92–93 | 55 | 559 |
| H | $N(CH_2CH{=}CH_2)_2$ | Et | HCl | 145 | 28 | 559 |
| H | Cl | Et | | 174–175 | | 559 |
| 2-Cl | $N(CH_2CH{=}CH_2)_2$ | H | | 134–136 | 65 | 559 |
| | | | Fumarate | 158–161 | | 559 |
| 2-Cl | $N(CH_2CH{=}CH_2)_2$ | Me | | 101–103 | 64 | 559 |
| 8-Cl | $N(CH_2CH{=}CH_2)_2$ | H | | 143–145 | 48 | 559 |
| 3-Cl | $N(CH_2CH{=}CH_2)_2$ | H | | 160–161 | 50 | 559 |

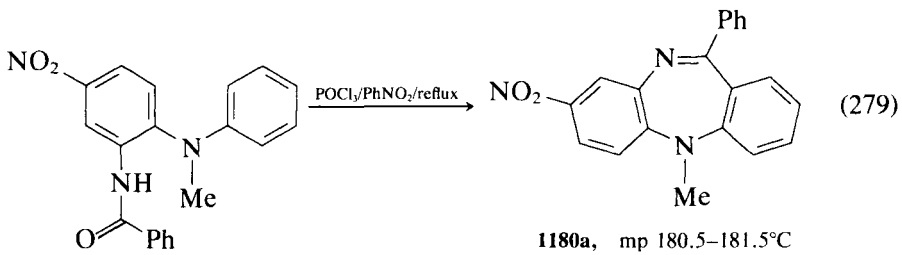
[a]Obtained by debenzylation of the corresponding *N*-benzyl compound.




(278)

**1178**, <0.01%; mp 190–192°C

by the presence of a 10,11-imine function. A patent (631) described the first synthesis of such derivatives by cyclization of an *N*-phenyl-*N'*-acyl-*o*-phenylenediamine. The preparation of the 8-nitro derivative **1180a** (Eq. 279) illustrates this approach. Other compounds prepared by this general procedure are listed in Table 157.




(279)

**1180a**, mp 180.5–181.5°C

Numerous other dibenzo[*b*,*e*][1,4]diazepine derivatives (599,632) were prepared by polyphosphoric acid cyclization, as illustrated in Fig. 99 by the synthesis of the 5-dimethylaminoethyl derivative **1180b**. Further examples are listed in Table 158. Reduction of the imines led to the corresponding amines, as illustrated by the conversion of **1180c** to **1180d**. Other reduced products obtained in this fashion are given in Table 159, and the corresponding *N*-acylated derivatives are listed in Table 160. Saturated amines could be reoxidized to imines with mercuric acetate, as exemplified by the formation of **1180f** from **1180e** (Fig. 99). Imines with a 5-methyl substituent, such as **1180g** and **1180h**, were also prepared (633). These and the corresponding 10,11-dihydro derivatives **1181a** and **1181b** are shown in Fig. 100.

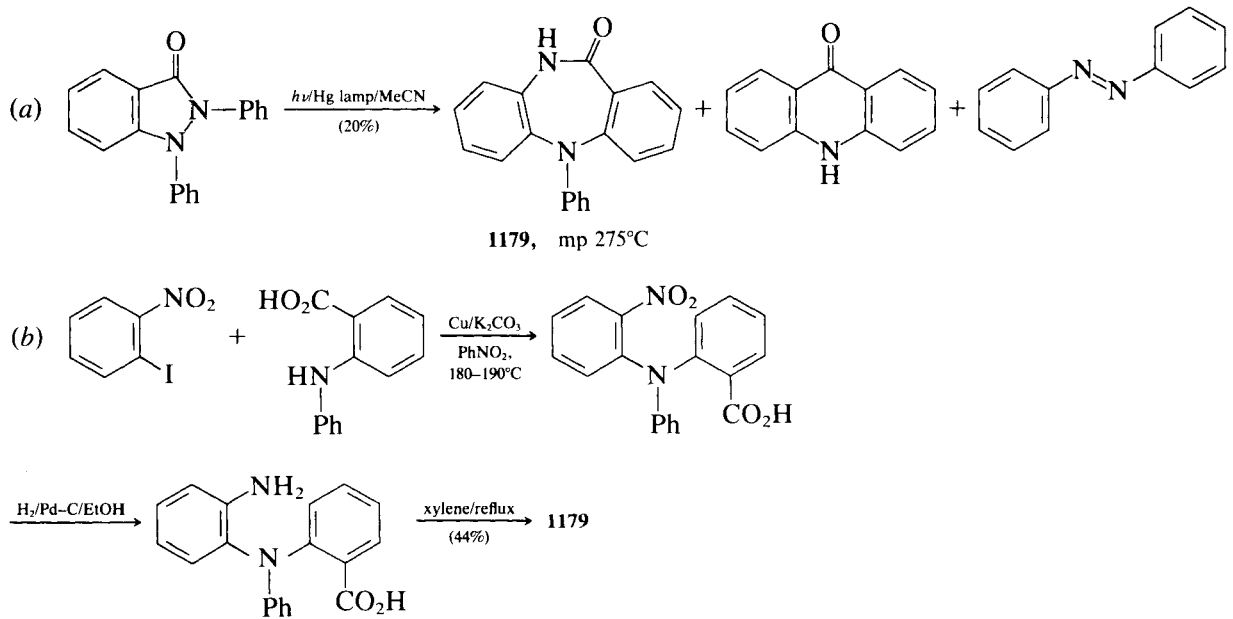
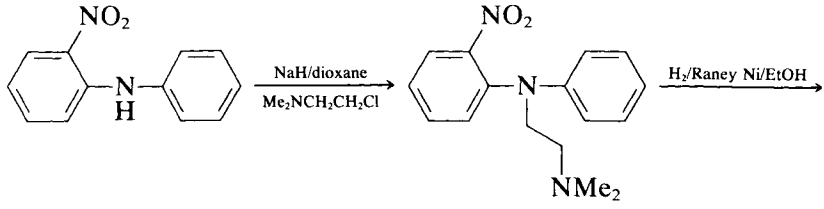
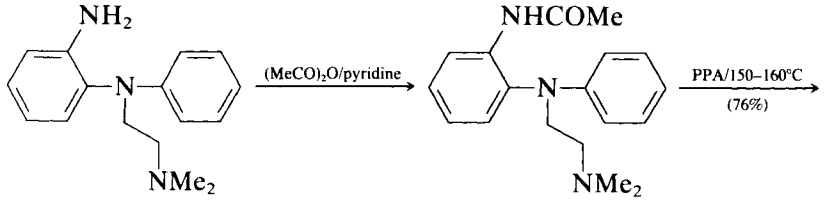
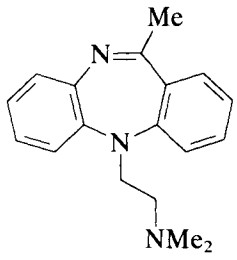

(a)
hν/Hg lamp/MeCN
(20%)
1179, mp 275°C
(b)
Cu/K2CO3
PhNO2,
180–190°C
H2/Pd–C/EtOH
xylene/reflux
(44%)
1179

**Figure 98**

(*a*)

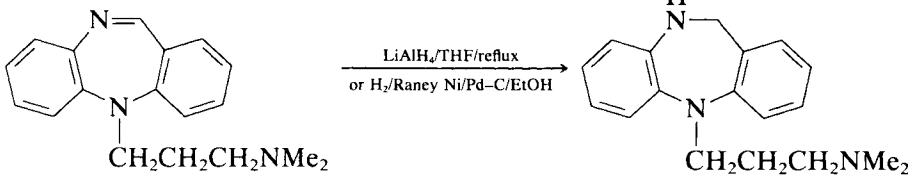



**1180b,** mp 113–115°C

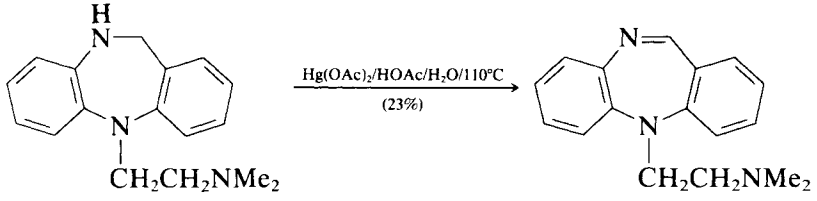
(*b*)




**1180c**

**1180d,** mp 102–104°C

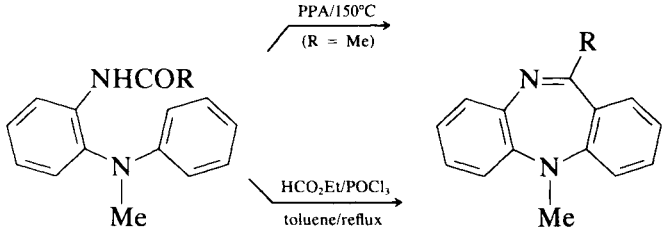
(*c*)




**1180e**

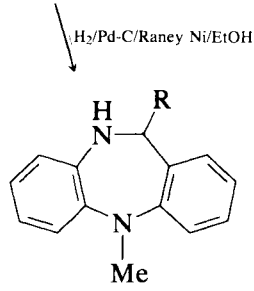
**1180f,** mp 98°C

**Figure 99**




**1180g,** R = Me (85%); mp 96–97°C, bp 138–142°C/0.01 Torr; p$K_a$(water) = 4.63

**1180h,** R = H (40%); mp 90–93°C, bp 140–145°C/0.01 Torr; p$K_a$(water) = 4.03

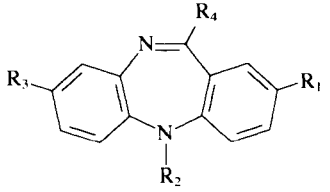



**1181a,** R = Me; mp 129–130°C; p$K_a$ (water) = 4.83

**1181b,** R = H; mp 118–120°C; p$K_a$ (water) = 4.56

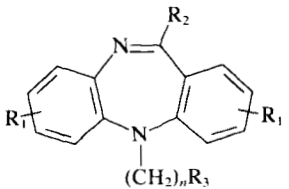
**Figure 100**

TABLE 157. 5-SUBSTITUTED 5*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES

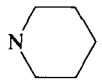
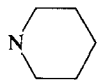
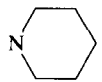
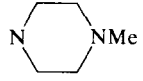
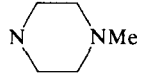
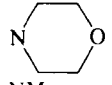



| $R_1$ | $R_2$ | $R_3$ | $R^4$ | mp (°C) |
|---|---|---|---|---|
| H | Me | $NO_2$ | 4-$NO_2C_6H_4$ | 256–258 |
| $NO_2$ | Me | $NO_2$ | Ph | 258–260 |
| Br | Me | Br | Ph | 171–172 |
| MeO | Me | $NO_2$ | Ph | 190–190.5 |
| MeO | Me | $NO_2$ | Me | 216.5–217 |
| MeO | Me | $NO_2$ | H | 172–173 |
| H | Me | H | Ph | 137–138 |
| H | Ph | H | Ph | 157.5–158 |

TABLE 158. 5-AMINALKYL-5*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES

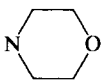
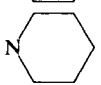
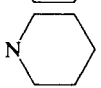
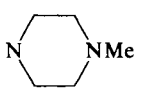
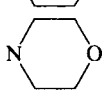
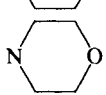
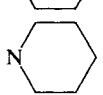



| $R_1$ | $R_2$ | $R_3$ | $n$ | Salt | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|---|
| H | H | $NMe_2$ | 2 | | 98 | 89 | 559,631 |
| H | *i*-Pr | $NMe_2$ | 2 | | 72–74 | 66 | 599,631 |
| | | | | | 150–155/0.1 | | |
| 1-MeO | Me | $NMe_2$ | 2 | | 104–105 | | 599 |
| 2-MeO | Me | $NMe_2$ | 2 | | 103–104 | 55 | 599,631 |
| 3-MeO | Me | $NMe_2$ | 2 | | 100–101 | 81 | 599,631 |
| 4-MeO | Me | $NMe_2$ | 2 | | 94–97 | 69 | 599,631 |
| 4-MeS | Me | $NMe_2$ | 2 | | 78–81 | 71 | 599,631 |
| | | | | | 170–172/0.5 | | |
| 7-Cl | Me | $NMe_2$ | 2 | | 97–98 | 61 | 599,631 |
| 7-MeO | Me | $NMe_2$ | 2 | | 101–103 | 49 | 599,631 |
| 8-Me | Me | $NMe_2$ | 2 | | 153–154/0.05 | 92 | 599,631 |
| | | | | Maleate | 151–154 | | |
| H | H | $NMe_2$ | 3 | | 162/0.01 | 65 | 599,631 |
| H | Me | $NMe_2$ | 3 | | 164/0.01 | 83 | 599,631 |
| 2-MeO | Me | $NMe_2$ | 3 | Maleate | 138–139 | 47 | 599,631 |
| 3-MeO | Me | $NMe_2$ | 3 | Maleate | 160–164 | 78 | 599,631 |
| 4-MeO | Me | $NMe_2$ | 3 | | 90–91 | 79 | 599,631 |
| 7-Cl | H | $NMe_2$ | 2 | | 91–93 | 64 | 599 |
| 7-Cl | H | $NMe_2$ | 3 | Maleate | 155–156 | 61 | 599,632 |
| 7-Cl | Me | $NMe_2$ | 3 | Maleate | 182–186 | 84 | 599,632 |
| 7-MeO | Me | $NMe_2$ | 3 | Maleate | 152–155 | 31 | 599,632 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| H | *i*-Pr | $NMe_2$ | 3 | | 163–165/0.03 | 47 | 632 |
| H | Me | $NEt_2$ | 2 | | 77–79 | 79 | 632 |
| H | Me | $NEt_2$ | 3 | | 180–183/0.03 | 90 | 632 |
| H | Me |  | 2 | | 144–145 | 90 | 632 |
| H | Me |  | 3 | | 185–189/0.008 | 82 | 632 |
| H | Et |  | 3 | | 140–142 | 85 | 632 |
| H | Me |  | 3 | | 126–127 | 76 | 632 |
| H | Et |  | 3 | | 139–140 | 95 | 632 |
| H | Me |  | 2 | | 136 | 75 | 632 |
| H | Me |  | 3 | | 166–168 | 71 | 632 |
| H | Me |  | 3 | | 90–92 | 85 | 632 |
| 8-MeO | Me | $NMe_2$ | 2 | | 162–163/0.01 | 50 | 632 |
| 8-MeO | Me | $NMe_2$ | 3 | | 173–174/0.01 | 51 | 632 |
| 8-Cl | H | $NMe_2$ | 2 | | 171–173/0.02 | 66 | 632 |
| 8-Cl | Me | $NMe_2$ | 3 | | 174–175/0.06 | 70 | 632 |
| H | H | $NMe_2$ | 3 | Methiodide | 234–235 | 85 | 632[a] |
| H | H | $NMe_2$ | 3 | Methobromide | 235–237 | | 632[a] |

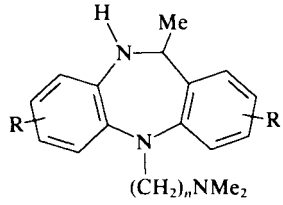
(*continued*)

TABLE 158. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | $n$ | Salt | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|---|
| H | Me |  | 2 | Methosulfate | 152–153 | 90 | 632[a] |
| H | Me |  | 3 | Methosulfate | 161–162 | 89 | 632 |
| H | Me |  | 3 | Methiodide | 206–208 | 89 | 632 |
| H | Me |  | 3 | Methobromide | 204–206 | | 632 |
| H | Ph | $NMe_2$ | 3 | Methosulfate | 219–224 | 89 | 632 |
| 7-Cl | Me |  | 2 | | 101–103 | 72 | 632 |
| 7-Cl | Me |  | 2 | | 64–67 | 69 | 632 |
| 7-Cl | Me |  | 3 | | 128–130 | 74 | 632 |
| H | H |  (1′-Me) | 2 | | 118–121 | 90 | 632 |

[a]Prepared from the tertiary amine.

TABLE 159. 5,11-DIHYDRO-5-DIMETHYLAMINOALKYL-11-METHYL-10*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES

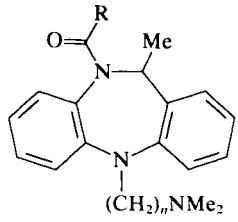



| R | *n* | mp (°C) |
|---|---|---|
| H | 2 | 75–76 |
| 2-MeO | 2 | 73–76 |
| 4-MeO | 2 | 101–103 |
| 7-Cl | 2 | 107–109 |
| H | 3 | 86–88 |
| 7-Cl | 3 | 74–78 |

A number of 10-alkyl derivatives were prepared from **1181a** and are listed in Table 161. Additional substances were described in a British patent (634); these are listed in Table 162. Derivatives with an aminoalkyl substituent at the 11-position (635) are listed in Tables 163 and 164.

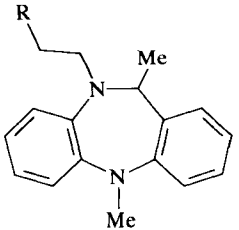
Amidine derivatives of the tricyclic lactams are also known (636–641). These substances were prepared by various approaches (Fig. 101): the formation of **1182a** from a urea, **1182b** from an amino amide, **1182b** and **1182c**, from thioethers **1182d** and **1182e**, and **1182f** from lactam **1182g** via the corresponding imino chloride. Thioether **1182d** was obtained by *S*-methylation of thiolactam **1182h**. $N^5$-Substituted thiolactams such as **1182i** could be pre-

TABLE 160. 5,11-DIHYDRO-10-ACYL-5-DIMETHYLAMINOETHYL-11-METHYL-10*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES




| R | *n* | mp (°C) |
|---|---|---|
| Me | 2 | 126–128 |
| Ph | 2 | 97–98 |
| Me | 3 | 81–82 |

TABLE 161. 5,11-DIHYDRO-10-AMINOALKYL-5,11-DIMETHYL-10*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES



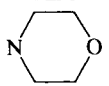
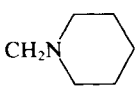
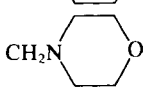
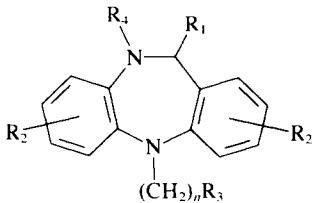
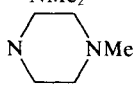
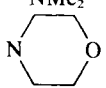
| R | Salt | mp (°C) or bp (°C/torr) | Yield (%) | Refs. |
|---|---|---|---|---|
| $NMe_2$ | | 145–150/0.01 | 80 | 597,633 |
| | D-Tartrate | 125–127 | | |
|  | | 170–175/0.02 | 76 | 597,633 |
| | Maleate | 151–154 | | |
|  | | 180–185/0.01 | 21 | 597,633 |
| $CH_2NMe_2$ | | 150–155/0.08 | 84 | 597,633 |
| | Maleate | 121–122 | | |
|  | | 170–175/0.01 | 74 | 597,633 |
| | Maleate | 157–159 | | |
|  | | 180–185/0.01 | 41 | 597,633 |

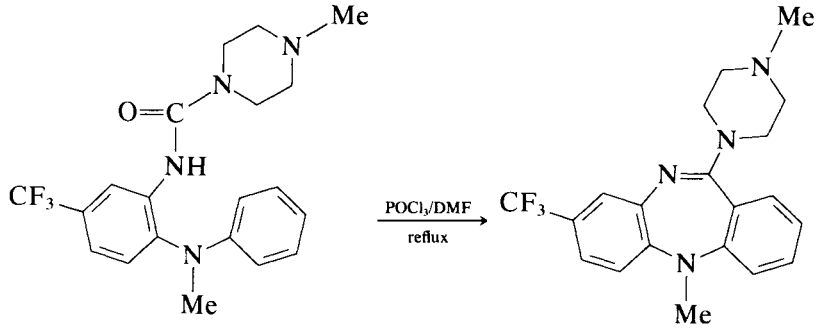
TABLE 162. 5,11-DIHYDRO-5-AMINOALKYL-10*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES



| $R_1$ | $R_2$ | $R_3$ | $R_4$ | *n* | mp (°C) or bp (°C/torr) | Yield | Refs. |
|---|---|---|---|---|---|---|---|
| Me | H | $NMe_2$ | H | 2 | 204–208[a] | 82 | 634[b] |
| Me | H | $NMe_2$ | H | 3 | 203–204[a] | | 634[b] |
| Ph | H | $NMe_2$ | H | 2 | 159–160 | 75 | 634 |
| Ph | H | $NMe_2$ | H | 2 | 214–218[a] | 83 | 634[b] |
| Ph | H | $NMe_2$ | H | 3 | 125–128<br>210/ 0.01 | 60 | 634 |
| Ph | H | $NMe_2$ | H | 3 | 217–219[a] | 75 | 634[b] |
| Me | 8-Me | $NMe_2$ | H | 2 | 164–165/0.05 | 68 | 634 |
| Me | H |  | H | 2 | 81–83 | 80 | 634 |
| Me | 4-MeO | $NMe_2$ | H | 2 | 101–103 | 85 | 634 |
| Me | 2-MeO | $NMe_2$ | H | 2 | 74–76 | 73 | 634 |
| Me | H |  | H | 3 | 84–86 | 80 | 634 |
| Me | H |  | H | 2 | 80–83 (117–119) | 71 | 634 |
| H | H | $NMe_2$ | Me | 2 | 165–167/0.02 | 60 | 634 |
| H | H | $NMe_2$ | Me | 2 | 177–182[a] | | 634[b] |
| H | H | $NMe_2$ | $CH_2Ph$ | 2 | 45–47<br>212–214/0.08 | 63 | 634 |
| H | H | $NMe_2$ | $CH_2Ph$ | 2 | 138–143[a] | | 634[b] |

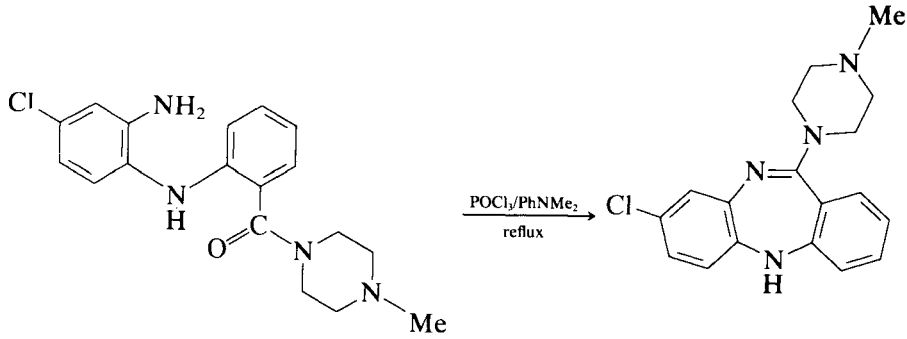
[a]Methosulfate. [b]Prepared from the tertiary amine.

(*a*)



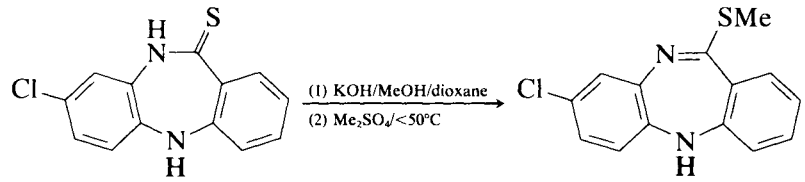

**1182a,** mp 184–185°C

(*b*)



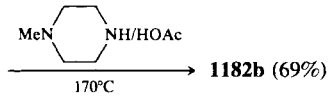

**1182b,** 41%; mp 182–184°C

(*c*)




**1182h**

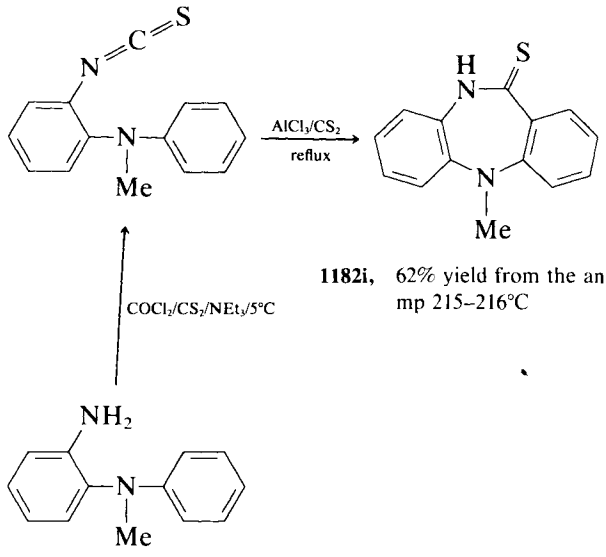
**1182d,** 81%; mp 116–121°C




**1182b** (69%)

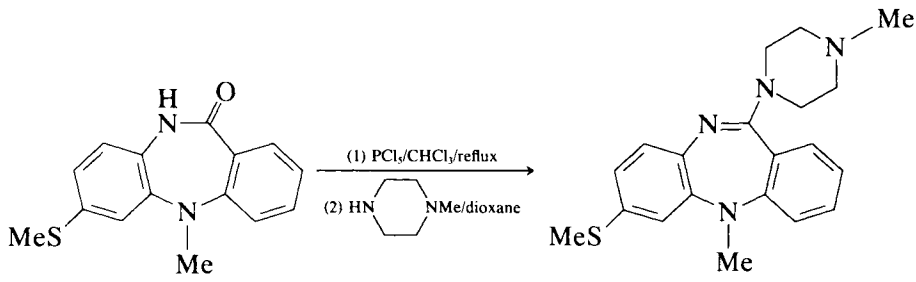
**Figure 101**

(*d*)




**1182i,** 62% yield from the aniline; mp 215–216°C

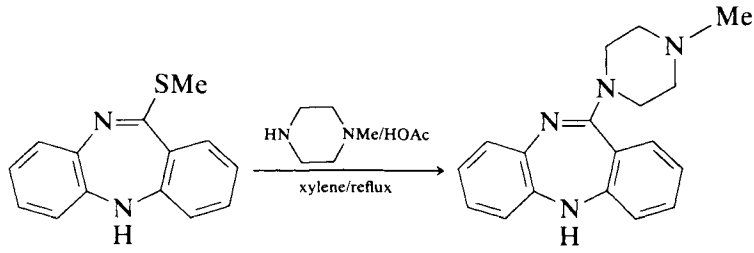
(*e*)




**1182g**

**1182f,** 52%; mp 171–173°C

(*f*)

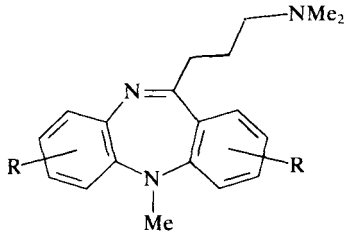



**1182e**

**1182c,** 87%; mp 184–185°C

**Figure 101** (***continued***)

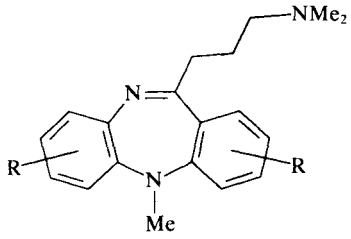
TABLE 163. 11-DIMETHYLAMINOPROPYL-5-METHYL-5*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES[a]




| R | Salt | mp (°C) or bp (°C/torr) |
|---|---|---|
| H | | 66–68 |
| | | 172–174/0.02 |
| 2-Cl | | 171–174/0.05 |
| | Oxalate | 188–191 |
| 7-Cl | | 68–70 |
| 8-Cl | | 188–191/0.05 |
| | Oxalate | 175–181 |

[a]Ref. 635.

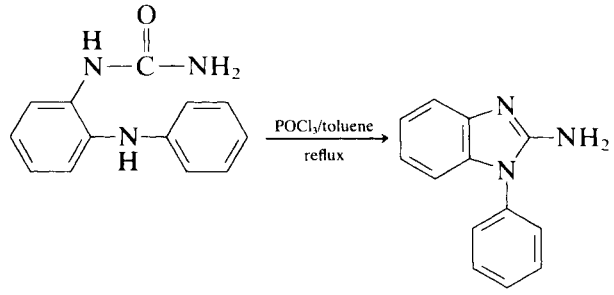
TABLE 164. 5,11-DIHYDRO-11-DIMETHYLAMINOPROPYL-5-METHYL-10*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES[a]



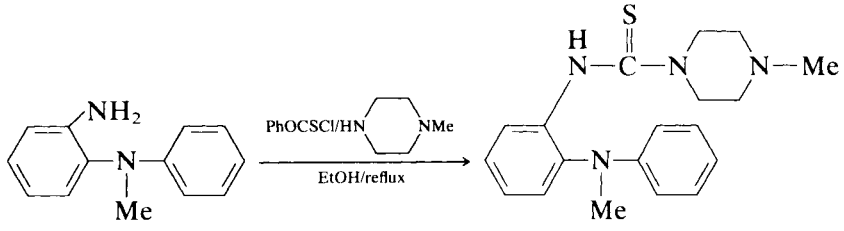

| R | Salt | mp (°C) or bp (°C/torr) |
|---|---|---|
| 2-Cl | | 177–180/0.05 |
| | Oxalate | 99–106 |
| H | | 164–167/0.02 |
| | Maleate | 125–131 |
| 7-Cl | | 182–186/0.05 |
| | Maleate | 121–125 |
| 8-Cl | | 70–73 |
| | | 190–193/0.05 |

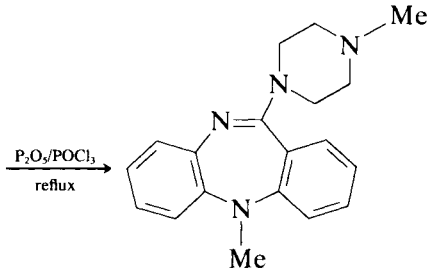
[a]Ref. 635.

pared by cyclization of isothiocyanates (Fig. 101). Compounds lacking a substituent on $N^5$ could not be prepared by cyclization of ureas; as indicated by the example shown in Eq. 280, this approach resulted in the formation of 2-aminobenzimidazoles (640). A patent (642) described the preparation of the tricyclic amidine **1182j** by cyclization of a thiourea (Eq. 281).




(280)



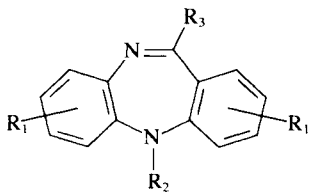



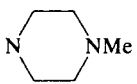
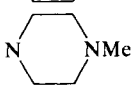
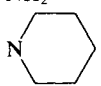
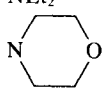

(281)

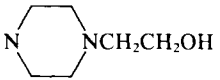
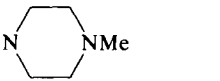
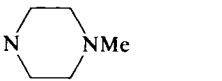
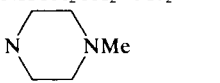
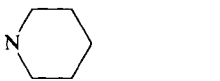
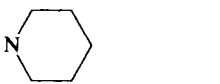
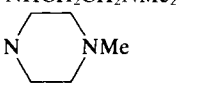
**1182j,** mp 119–120°C

The substances shown in Fig. 101 and Table 165 were studied as neuroleptic agents. The 2-chloro derivative **1183a** (Eq. 282) was identified initially as being a compound of particular interest (638). However, a most important development was the subsequent discovery that the isomeric 8-chloro compound **1183b** (HF-1854, clozapine) is a clinically effective neuroleptic agent of a new pharmacologic type (654,655,656). Most importantly, **1183b** did not cause catalepsy in rats (654) and, when evaluated clinically, was devoid of

TABLE 165. 11-AMINO-5*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES

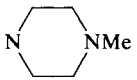
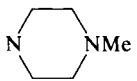
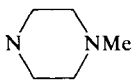
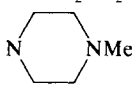
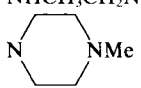
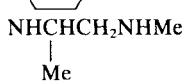
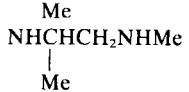
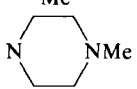
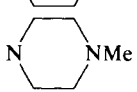


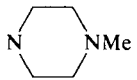
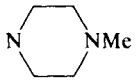
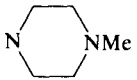
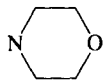
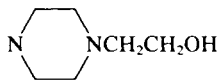
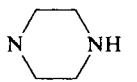
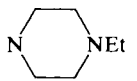
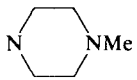
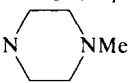
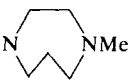
| $R_1$ | $R_2$ | $R_3$ | Salt | m (°C) or bp (°C/torr) | Yield (%) | Method[a] | Refs. |
|---|---|---|---|---|---|---|---|
| 8-Cl | Me |  | | 164–165 | 66 | A, C | |
| H | H |  | | 129–131 | 39<br>61 | A<br>B | 637<br>643 |
| 7-Cl | H |  | | 179–181 | 85 | B | 637,640 |
| H | Me | $NH_2$ | | 167–168 | 61 | B, C, E | 637,643 |
| H | Me |  | | 162–163 | 57<br>64 | C<br>B | 637<br>643 |
| H | Me | $NHCH_2CH_2NMe_2$ | | 167–170 | 59 | B, C, E | 637,640,643 |
| H | H | $NHCH_2CH_2NMe_2$ | | 143–144 | 35<br>76 | C, E<br>B | 637,640,643 |
| H | H | $NEt_2$ | HCl | 230–240 | 42 | B | 637,643 |
| H | H |  | | 201–203 | 85 | B | 637,643 |
| H | H | $NHCH_2CH_2NEt_2$ | | 205–210/0.01 | 81 | B, C | 637,643,644 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| H | H | $NH(CH_2)_3NMe_2$ | | 148–150 | 86 | B, C | 637,643,644 |
| H | H | $NHCHMe(CH_2)_3NMe_2$ | | 204–208/0.05 | 83 | B, C | 637,643,644 |
| H | H |  | | 182–184 | 66 | B | 637,643 |
| H | Me | $NH(CH_2)_3NMe_2$ | | 73–75 | 68 | B, C | 637,643,644 |
| H | Me |  | | 124–125 | 73<br>80 | B<br>A<br>I | 637,643<br>640<br>641 |
| 2-MeO | H | $NHCH_2CH_2NMe_2$ | 2HCl | >160 | 87 | B, C | 637,643,644 |
| 2-MeO | H |  | 2HCl | 210 | 78 | B | 637,643 |
| 7-Cl | Me | $NHCH_2CH_2NMe_2$ | | 155–156 | 63 | B, C | 637,643,644 |
| 7-Cl | Me |  | | 201–203 | 51 | B | 637,640,643 |
| 8-Cl | H |  | | 148–151 | 27 | B | 637,643 |
| 8-Cl | H | $NHCH_2CH_2NMe_2$ | | 156–158 | 83 | B | 637,640,643 |
| H | H | $NHCH(Me)(CH_2)_3NEt_2$ | 2HCl | 244–246 | 65 | B, C | 637,643,644 |
| 7-Cl | H |  | | 157–159 | 83 | B | 637,643 |
| 7-Cl | H | $NHCH_2CH_2NMe_2$ | | 157–159 | 60 | B | 637,643 |
| 8-MeO | Me |  | | 139 | 50 | B | 637,640,643 |

(*continued*)

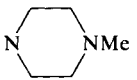
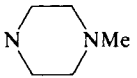
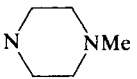
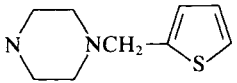
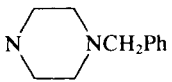
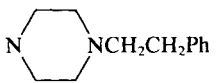
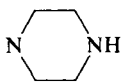
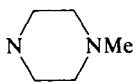
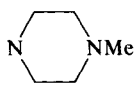
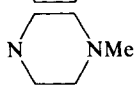
TABLE 165. (*Continued*)

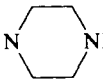
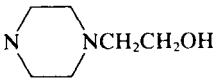
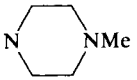
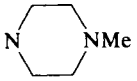
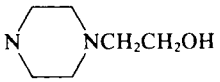
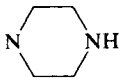
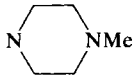
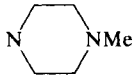
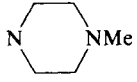
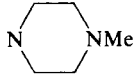
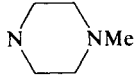
| $R_1$ | $R_2$ | $R_3$ | Salt | m (°C) or bp (°C/torr) | Yield (%) | Method[a] | Refs. |
|---|---|---|---|---|---|---|---|
| 3-Me | H |  | | 168–170 | 65 | B | 637,643 |
| 8-Me | H |  | | 188–190 | 72 | B | 637,643,644 |
| 8-Me | Me |  | | 171–173 | 62 | B | 637,640,643 |
| 8-Me | H | $NHCH_2CH_2NMe_2$ | | 175–177 | 52 | B, C | 637,643,644 |
| 3-Cl | H |  | | 169–171 | 60 | B | 637,640,643 |
| 3-Cl | H | $NHCH_3CH_2NMe_2$ | | 136–137 | 55 | B | 637,643 |
| 3-MeO | H |  | | 212–214 | 76 | B | 637,643 |
| H | H |  | | 168–169/0.01 | 69 | B, C | 637,643,644 |
| 8-Cl | H |  | | 103–106 | 81 | A, B | 637,643 |
| 8-$CF_3$ | H |  | | 193–194 | 75 | A, B | 637,640,643 |
| 4-MeS | Me |  | | 140 | 62 | A, B | 637,643 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2-Cl | H |  | | 203–205 | 88 | A, B | 637,640,643 |
| 8-$CF_3$ | Me |  | | 184–185 | | | 637,640 |
| 7-MeS | H |  | | 120 (146–150) | | | 637 |
| 8-Cl | H |  | | 169–170 | | | 637 |
| 8-Cl | H |  | | 241–244 | | | 637,640 |
| 8-Cl | H |  | | 105–116 | 70 | B | 637,640,643 |
| 8-Cl | H |  | | 162–163 | 55<br>78 | F<br>B | 640<br>640 |
| 7-MeO | H |  | | 227–228 | | | 640 |
| H | Me | $NHC_6H_4Cl$-*p* | | 108–111 | | C | 644 |
| H | Me |  | Dimethiodide | 198–200 | 57 | D | 639 |
| 8-Cl | H |  | | 105–106 | | | 640 |

(*continued*)

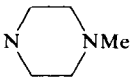
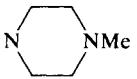
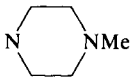
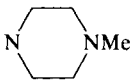
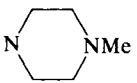
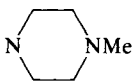
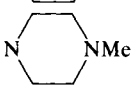
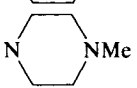
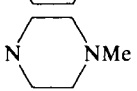
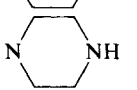
TABLE 165. *(Continued)*

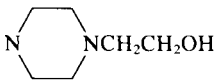
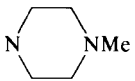
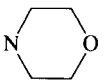
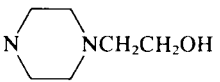
| $R_1$ | $R_2$ | $R_3$ | Salt | m (°C) or bp (°C/torr) | Yield (%) | Method[a] | Refs. |
|---|---|---|---|---|---|---|---|
| 8-Cl | H |  | | 181–183 | 82<br>90 | A, B, E<br>I | 640,643<br>641 |
| 8-MeO | H |  | | 183–184 | 85 | B | 640 |
| 2-$CF_3O$ | Me |  | | 146–148 | 68 | C | 645 |
| H | Me |  | 2HCl | 230–233 | | A, G | 646,647 |
| H | Me |  | 2HCl | 226–227 | | A, G | 646,647 |
| H | Me |  | Fumarate | 209–210 | | A, G | 646,647 |
| 2-$MeSO_2$ | H |  | 2HBr | 233–248 | | H | 648 |
| 2-$MeSO_2$ | H |  | 2HBr | 225–230 | | E, B, H | 648,649 |
| 7-MeS | Me |  | | 171–173 | 52 | A | 650 |
| 2,8-$Cl_2$ | H |  | | 192–195 | | F, B, I | 651 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2,8-$Cl_2$ | H |  | Maleate | 216–219 | B | 651 |
| 2,8-$Cl_2$ | H |  | | 178–180 | B | 651 |
| 7,8-$OCH_2O$ | H |  | | 195–197 | | 651 |
| 7,8-$OCH_2CH_2O$ | H |  | | 215–216 | | 651 |
| 7,8-$OCH_2O$ | Me |  | | 161–164 | | 651 |
| 7,8-$OCH_2O$ | Me |  | | 154–157 | | 651 |
| 8-Cl, 2-Me | H |  | | 187–189 | | 651 |
| 3,7-$Cl_2$ | H |  | | 207–209 | | 651 |
| 2,7-$Cl_2$ | H |  | | 178–180 | | 651 |
| 3,8-$Cl_2$ | H |  | | 203–205 | | 651 |
| 2-$Me_2NSO_2$, 8-Cl | H |  | | 198–200 | | 651 |

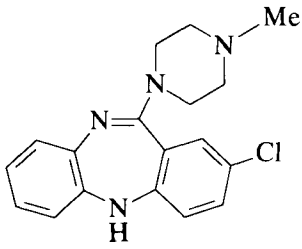
*(continued)*

TABLE 165. *(Continued)*

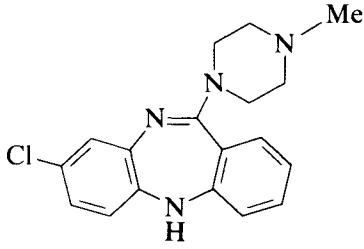
| $R_1$ | $R_2$ | $R_3$ | Salt | m (°C) or bp (°C/torr) | Yield (%) | Method[a] | Refs. |
|---|---|---|---|---|---|---|---|
| 8-Br, 2-Cl | H |  | | 198–200 | | | 651 |
| 2-Cl, 8-Me | H |  | | 236–237 | | | 651 |
| 2-Cl, 8-MeO | H |  | | 178–179 | | | 651 |
| 2-Cl, 8-Ets | H |  | | 182–184 | | | 651 |
| 7,8-$OCH_2CH_2O$ | Me |  | | 275–276 | | | 651 |
| 7,8-$(MeO)_2$ | Me |  | | 171–172 | | | 651 |
| 2,4-$Cl_2$ | H |  | | 115–117 | | | 651 |
| 2,8-$Cl_2$ | Me |  | | 163–167 | | | 651 |
| 7,8-$Cl_2$ | H |  | | 154 | | | 651 |
| 7,8-$Cl_2$ | H |  | | 214–216 | | | 651 |

| | | | | | |
|---|---|---|---|---|---|
| 7,8-$Cl_2$ | H |  | | 219–222 | 651 |
| 8-$EtSO_2$ | Me |  | 2HCl | 102–105 | 652,653 |
| 8-$EtSO_2$ | Me |  | | 125–127 | 652,653 |
| 8-$EtSO_2$ | Me |  | | 172–173 | 652,653 |
| 8-$EtSO_2$ | Me | NHEt | | 172–173 | 653 |

[a]Method A: Preparation via the imino chloride. Method B: Preparation via the imino thioether. Method C: Preparation by cyclization of the urea. Method D: MeBr/MeOH, 100°C. Method E: Cyclization of the amino amide. Method F: Treatment of the NH compound with an alkyl halide. Method G: (a) NaH/dioxane on the NH compound, (b) RBr. Method H: Permanganate oxidation of the thioether. Method I: Treatment of the lactam with $TiCl_4$/amine in refluxing anisole/toluene.



**1183a**

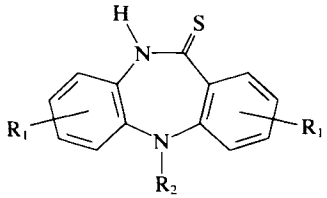


**1183b**

(282)

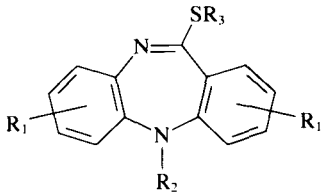
extrapyramidal effects (Parkinson-like syndrome) (655,656). Extensive metabolism was noted in man. The principal metabolites were the product of demethylation of the piperazine ring, the *N*-oxide resulting from oxidation of the methylated nitrogen, and some phenolic derivatives (657). Detailed X-ray crystallographic studies on clozapine and analogs have been published (658,659). Animal test data on analogs of **1183b** were provided (654). A list of these analogs is given in Table 165, and the corresponding thiolactam and thioimino ether intermediates are given in Tables 166 and 167, respectively. Imino ether and thioether derivatives with a basic group in the side chain were prepared by standard methods and were claimed to exhibit antihistamine activity (660,661). These substances are listed in Table 168.

TABLE 166. DIBENZO[*b*,*e*][1,4]DIAZEPINE-11-THIONE DERIVATIVES



| $R_1$ | $R_2$ | mp (°C) |
|---|---|---|
| H | Me | 215–216 |
| 2-Cl | H | 247–256 |
| 3-Cl | H | 236–242 |
| 7-Cl | H | 273–274 |
| 7-Cl | Me | 233–238 |
| 8-Me | H | 232–237 |
| 8-Me | Me | 248–252 |
| 8-Cl | H | 253–262 |
| 8-Cl | Me | 240 (dec.) |
| 8-MeO | H | 244–256 |
| 8-MeO | Me | 228–234 |
| 8-$CF_3$ | H | 231–235 |
| 8-$CF_3$ | Me | 200–202 |

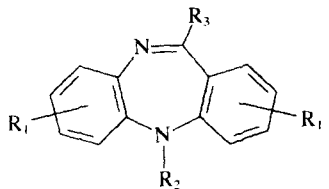
TABLE 167. 11-ALKYLTHIO-5*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES



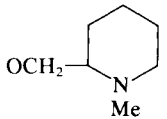
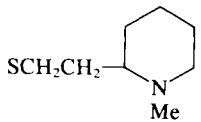
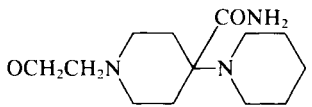
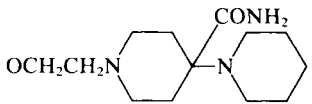
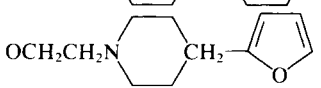

| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) | Method[a] | Spectra | Refs. |
|---|---|---|---|---|---|---|---|
| H | H | Me | 177–180 | | | | 640 |
| H | H | $CH_2CN$ | 118–124 | | A | | 640 |
| H | Me | Me | 125–126 | | | | 640 |
| H | Me | $CH_2CN$ | 145–150 | 96 | A | uv | 640 |
| 2-Cl | H | Me | 144–147 | | | | 640 |
| 3-Cl | H | Me | 187–188 | | | | 640 |
| 7-Cl | H | Me | 156–158 | | | | 640 |
| 7-Cl | H | $CH_2C_6H_4NO_2$-*p* | 182–183 | 89 | B | uv | 640 |
| 7-Cl | Me | Me | 137–138 | | | | 640 |
| 8-Me | H | Me | 98–106 | | | | 640 |
| 8-Me | Me | Me | 111–113 | | | | 640 |
| 8-Cl | H | Me | 116–121 | | | | 640 |
| 8-Cl | H | $CH_2C_6H_4NO_2$-*p* | 82–85 | | | | 640 |
| 8-Cl | Me | Me | 132–133 | | | | 640 |
| 8-MeO | H | Me | 126–128 | | | | 640 |
| 8-MeO | Me | Me | 118–119 | | | | 640 |
| 8-$CF_3$ | H | Me | 220–232 | | | | 640 |
| 8-$CF_3$ | Me | Me | 186–187 | | | | 640 |
| 8-$EtSO_2$ | Me | Me | 148–149 | | | | 652 |
| 8-$EtSO_2$ | Me | $CH_2C_6H_4NO_2$-*p* | 128–132 | | | | 652 |

[a]Method A: Reaction of the thiolactam with *t*-BuOK/*t*-BuOH/$ClCH_2CN$, 100°C. Method B: Reaction of the thiolactam with *t*-BuOK/*t*-BuOH/4-$NO_2C_6H_4CH_2Cl$, 60°C.

TABLE 168. 11-AMINOALKOXY- AND 11-AMINOALKYLTHIO-5*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES

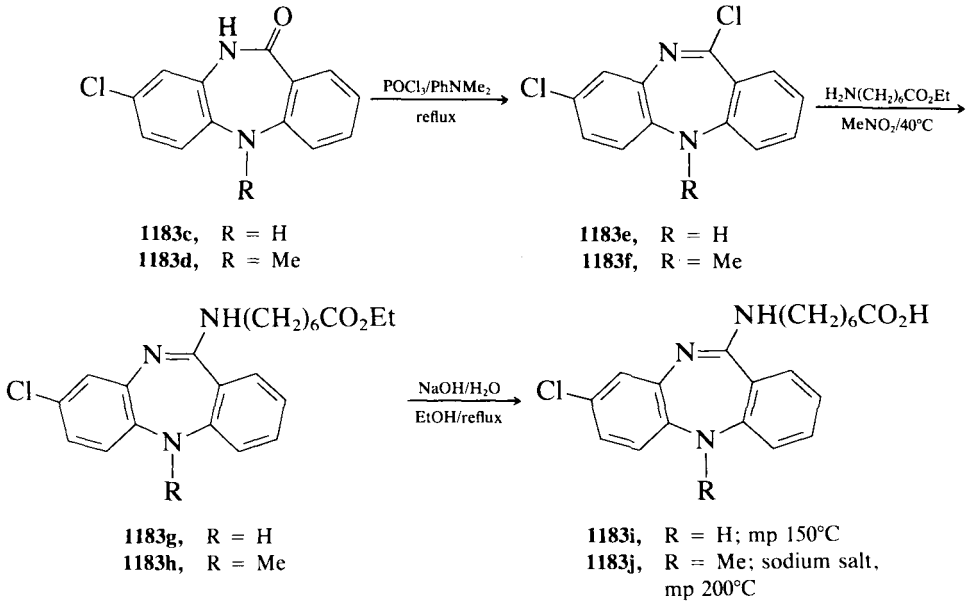



| $R_1$ | $R_2$ | $R_3$ | Salt | mp (°C) | Refs. |
|---|---|---|---|---|---|
| H | Me | $OCH_2CH_2NMe_2$ | | 81–85 | 660 |
| | | | Fumarate | 142–144 | 660 |
| H | Me | $OCH_2CH_2NHMe$ | Oxalate | 177–178 | 660 |
| H | H | $SCH_2CH_2NMe_2$ | | 148–151 | 660 |
| H | Me | $SCH_2CH_2NMe_2$ | | 73–75.5 | 660 |
| | | | Oxalate | 203–204 | 660 |
| 2-Cl | Me | $SCH_2CH_2NMe_2$ | Oxalate | 189–190 | 660 |
| 8-Cl | Me | $SCH_2CH_2NMe_2$ | | 150–153 | 660 |
| 7-Cl | H | $OCH_2CH_2NMe_2$ | Oxalate | 201–201.5 | 660 |
| 2-Cl | Me | $OCH_2CH_2NMe_2$ | Fumarate | 158–160 | 660 |
| 8-Cl | Me | $OCH_2CH_2NMe_2$ | Oxalate | 176–178 | 660 |
| 7-Cl | Me | $OCH_2CH_2NMe_2$ | HCl | 168–170 | 660 |

| | | | | | |
|---|---|---|---|---|---|
| H | Me | $O(CH_2)_3NMe_2$ | Fumarate | 170–173 | 660 |
| H | Me |  | Oxalate | 159–162 | 660 |
| 7-Cl | H |  | | 149–153 | 660 |
| H | Me |  | | 152–153 | 661 |
| 2-Me | Me |  | 2HCl | 230 | 661 |
| H | Me |  | Dimaleate | 160–162 | 661 |
| 8-$EtSO_2$ | Me | $SCH_2CH_2NEt_2$ | Dimaleate | 134–135 | 652 |

The preparation of derivatives with a carboxylic acid function in the sidechain (662) is shown in Eq. 283. Lactams **1183c** and **1183d** were converted to the corresponding imino chlorides **1183e** and **1183f,** and the latter were aminated to the esters **1183g** and **1183h**, respectively. Saponification of the esters yielded the acids **1183i** and **1183j**.

The methodology described above has been extended to provide routes to derivatives in which a fourth heterocyclic ring is fused to the dibenzo[*b,e*][1,4]diazepine system. Thus, as shown in Fig. 102, reaction of the thiolactam **1184** with acetylhydrazide gave the tetracyclic triazole **1185a** (663). Similarly, condensation of **1184** with hydrazine yielded the hydrazide **1185b,** which was then subjected to acylation and cyclization in acetic acid to the tetracyclic product **1185c**. Triazinone derivatives were prepared from thiolactams by reaction with ethyl carbazate (664); an example is the synthesis of compound **1185d**.




**1183c,** R = H
**1183d,** R = Me

**1183e,** R = H
**1183f,** R = Me

(283)

**1183g,** R = H
**1183h,** R = Me

**1183i,** R = H; mp 150°C
**1183j,** R = Me; sodium salt, mp 200°C

Imidazole derivatives were also accessible from thiolactam or thioimino ether intermediates (665, 666). This approach is illustrated by the synthesis of the imidazole **1187a** via ring closure of the dimethylacetal **1186** and of the methylimidazole **1187b** from thioether **1188** by reaction with propargylamine with acid-catalyzed cyclization (Fig. 103). Dimethylacetal **1186** could be obtained from either the thiolactam **1184** or the thioether **1188** on treatment with aminoacetaldehyde dimethylacetal.

Also in the category of fused tetracyclic derivatives, the tetrazole **1189**

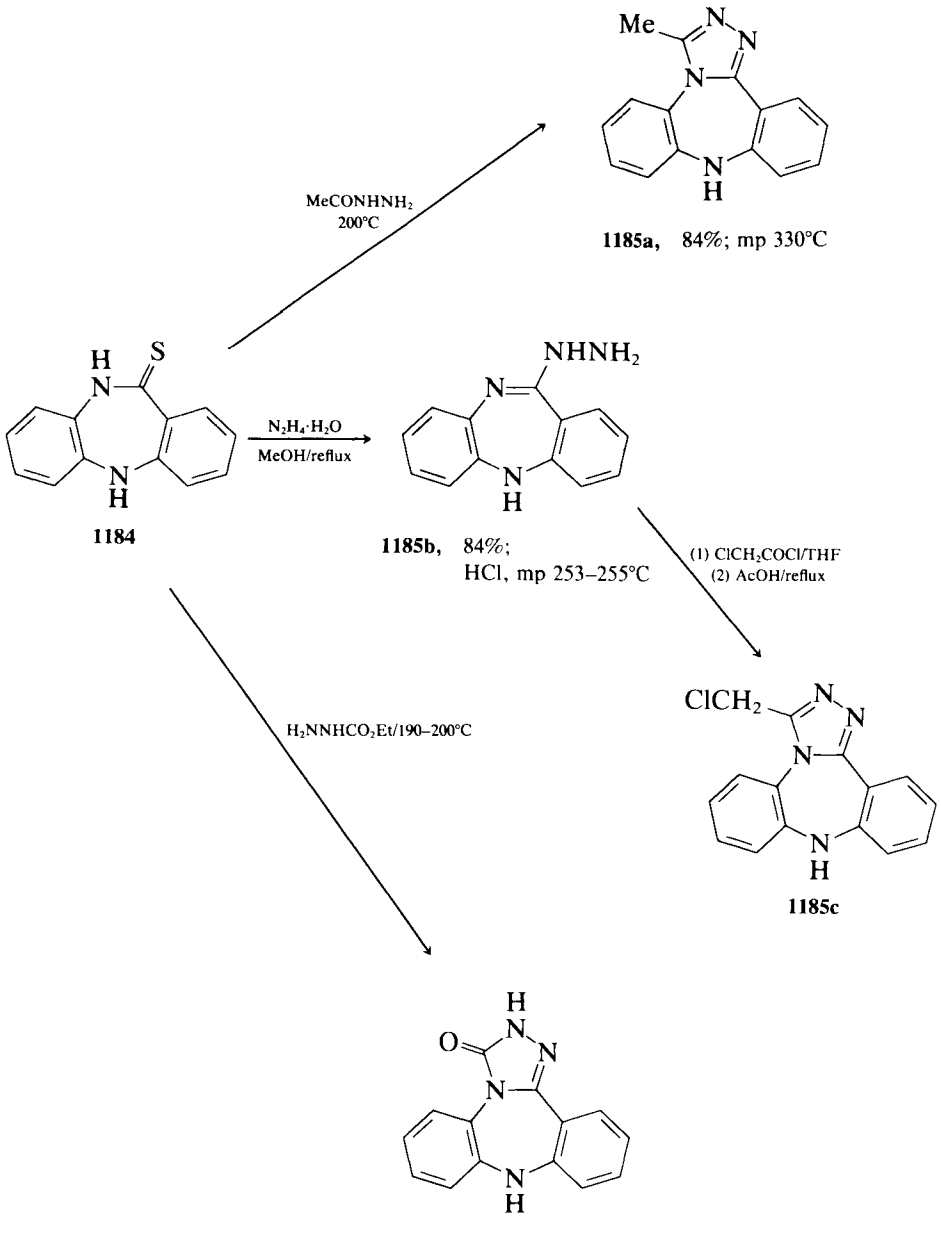

Me
MeCONHNH2
200°C
1185a, 84%; mp 330°C
NHNH2
N2H4·H2O
MeOH/reflux
1184
1185b, 84%;
HCl, mp 253–255°C
(1) ClCH2COCl/THF
(2) AcOH/reflux
ClCH2
1185c
H2NNHCO2Et/190–200°C
1185d, 66%; mp 263–264.5°C

**Figure 102**

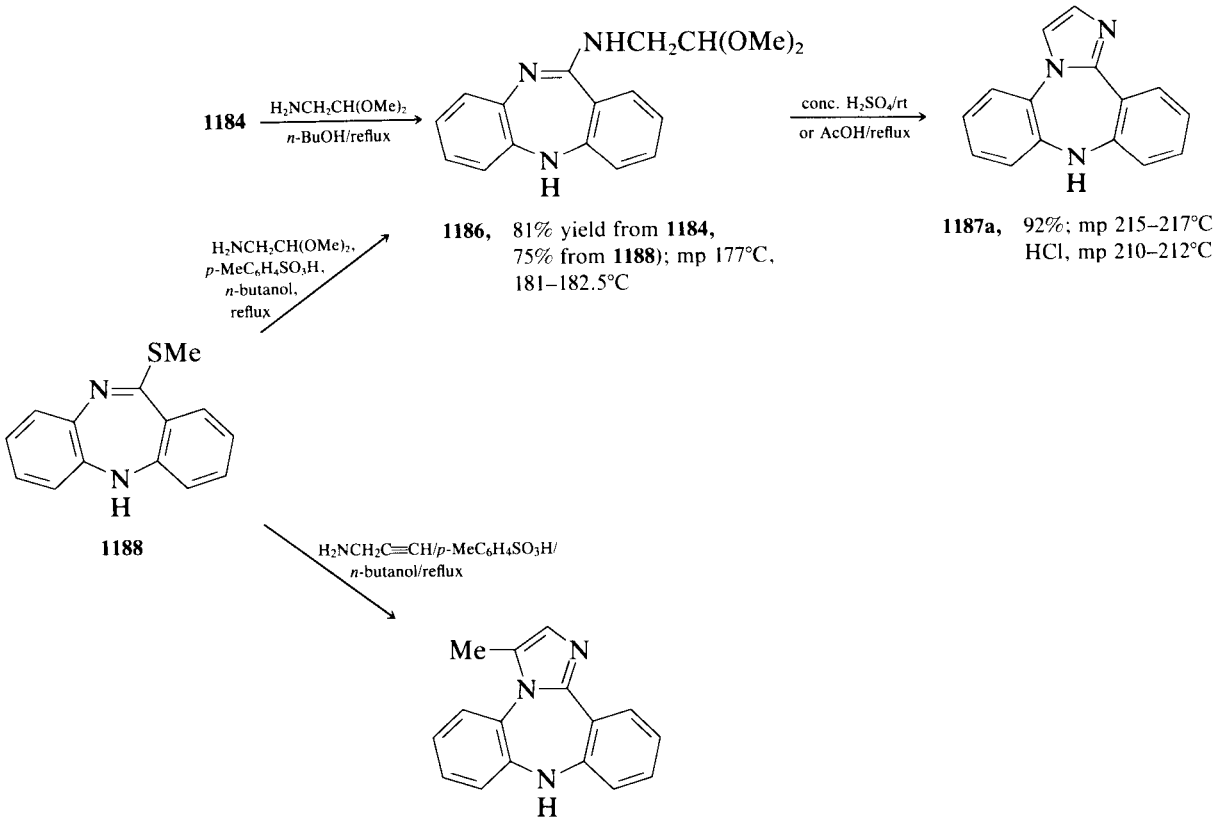
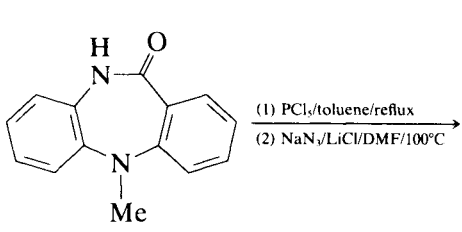
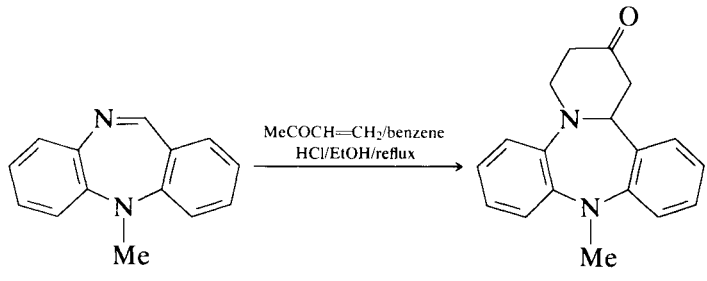

1184
H2NCH2CH(OMe)2
n-BuOH/reflux
NHCH2CH(OMe)2
N
N
H
1186, 81% yield from 1184, 75% from 1188); mp 177°C, 181–182.5°C
conc. H2SO4/rt
or AcOH/reflux
N
N
H
1187a, 92%; mp 215–217°C HCl, mp 210–212°C
H2NCH2CH(OMe)2, p-MeC6H4SO3H, n-butanol, reflux
SMe
N
N
H
1188
H2NCH2C≡CH/p-MeC6H4SO3H/ n-butanol/reflux
Me
N
N
N
H
1187b, 71%; HCl, mp 252–256°C

**Figure 103**

was prepared (667) by reaction of the imino chloride derived from lactam **1159** with sodium azide/lithium chloride in dimethylformamide at 100°C (Eq 284). Reaction of the imine **1180h** with methyl vinyl ketone under acidic conditions (668) gave the tetracyclic piperidone **1190** shown in Eq. 285.



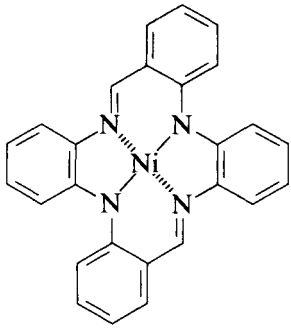

**1159** **1189**, 71%; mp 149–150°C (284)



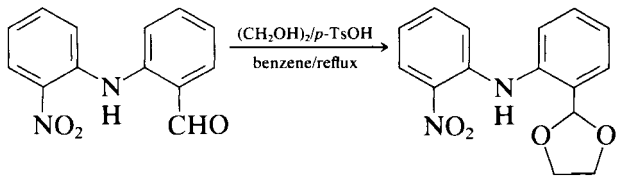

**1180h** **1190**, mp 176–178°C (285)

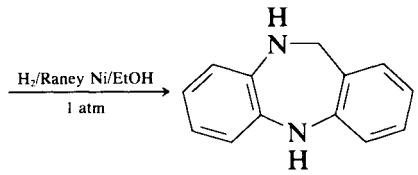
Certain dibenzo[*b*,*e*][1,4]diazepines have been prepared from *N*-2-nitrophenylanthranilaldehyde and derivatives thereof. In the first such study (669) the stated goal was the preparation of the macrocyclic nickel(II) complex **1191** by dimerization of the amino aldehyde in the presence of nickel(II) ions. In an attempt to prepare the amino aldehyde, the acetal shown in Fig. 104 was hydrogenated, but cyclization to the dibenzo [*b*, *e*] [1, 4] diazepine **1192** occurred. Hydrogenation of the nitro aldehyde in the presence of cupric benzenesulfonate gave only the benzenesulfonate salt of **1192**. A similar reaction occurred in the presence of nickel benzenesulfonate. Finally, hydrogenation of amidine derivatives of the nitro aldehyde also gave **1192** (Eq. 286).

In a study involving reduction of related nitro ketones (670), hydrogenation in ethyl acetate was found to produce tricyclic imines, as illustrated in Eq. 287 by the formation of **1193**. Further examples are listed in Table 169. Yields were 50–70%, except for the products containing a nitro group, which were obtained in yields of less than 10%. The starting materials were obtained by reaction of an *o*-amino ketone with a 2-nitrofluorobenzene.

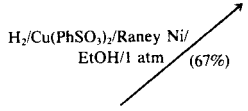


**1191**




**1192,** mp 208.5–210°C;
benzenesulfonate, mp 219–220°C



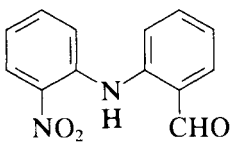
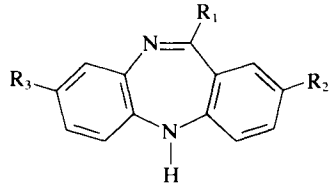



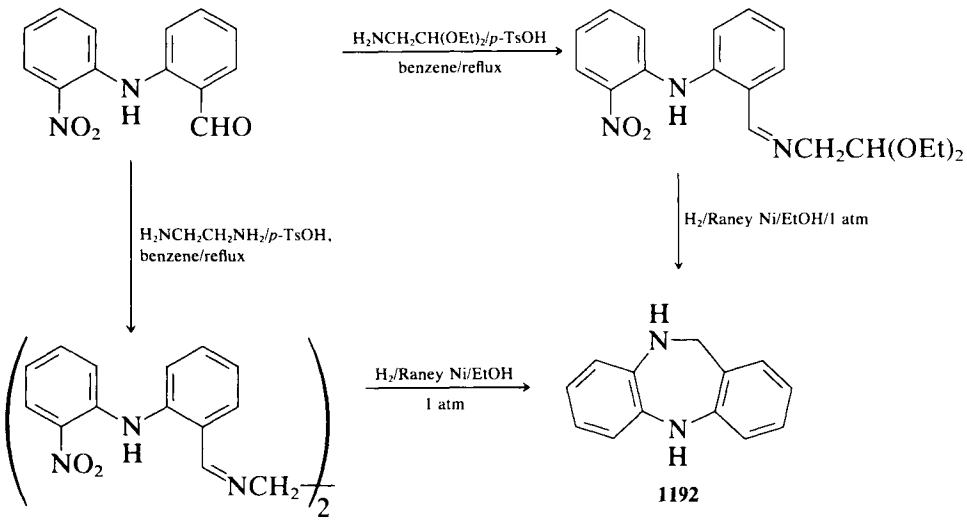

**Figure 104**

Reaction of *N*, *N*-diphenylbenzimidazoline with hydrogen chloride in benzene (672) gave the dibenzo[*b*,*e*][1,4]diazepine derivative **1194**, presumably by the pathway indicated in Eq. 288. When the *N*-methylacridinium salts shown in Eq. 289 were treated with hydroxylamine-*o*-sulfonic acid in methanolic ammonia, dibenzo[*b*,*e*][1,4]diazepine derivatives **1180g, 1180h,** and **1195** were produced (673). The mechanism proposed for this reaction is indicated.

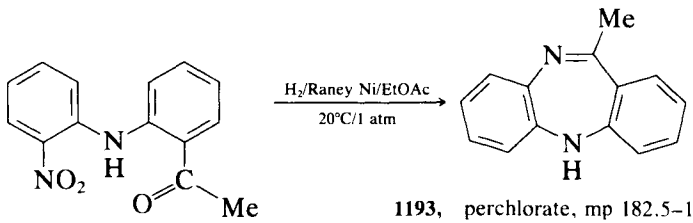
TABLE 169. 11-SUBSTITUTED 5*H*-DIBENZO[*b*,*e*][1,4]DIAZEPINES



| $R_1$ | $R_2$ | $R_3$ | Salt | mp (°C) | Refs. |
|---|---|---|---|---|---|
| Ph | H | H | | 154.5 | 670 |
| 4-$MeC_6H_4$ | H | H | | 180.5–181.5 | 670 |
| 4-$MeOC_6H_4$ | H | H | | 122–124 | 670 |
| Ph | Me | H | | 228–229 | 670 |
| Ph | Cl | H | | 203–204 | 670 |
| Me | H | $NO_2$ | $HClO_4$ | 115–130 | 670 |
| Ph | H | $NO_2$ | $HClO_4$ | 155–165 | 670 |
| 4-$MeC_6H_4$ | H | $NO_2$ | $HClO_4$ | 160–280 | 670 |
| Ph | H | $NO_2$ | $HClO_4$ | 180–220 | 670 |
| Ph | Br | H | | 196–198.5 | 671 |

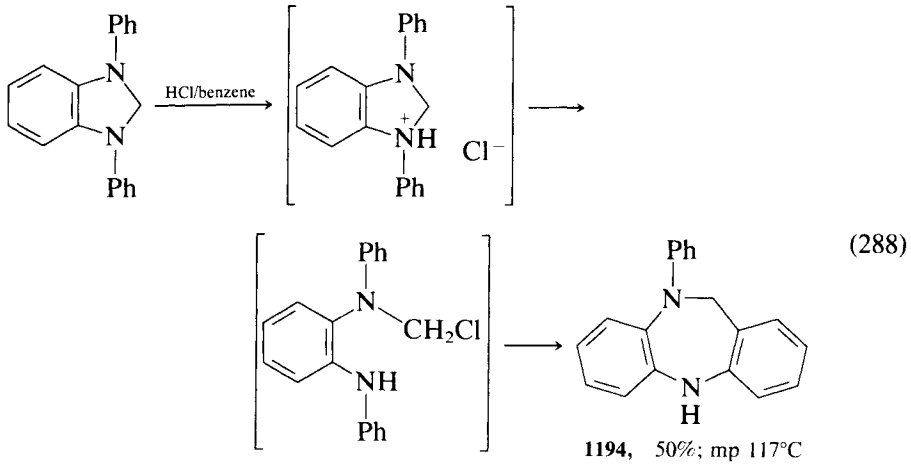



(286)




(287)

**1193**, perchlorate, mp 182.5–186.5°C




**1194**, 50%; mp 117°C (288)

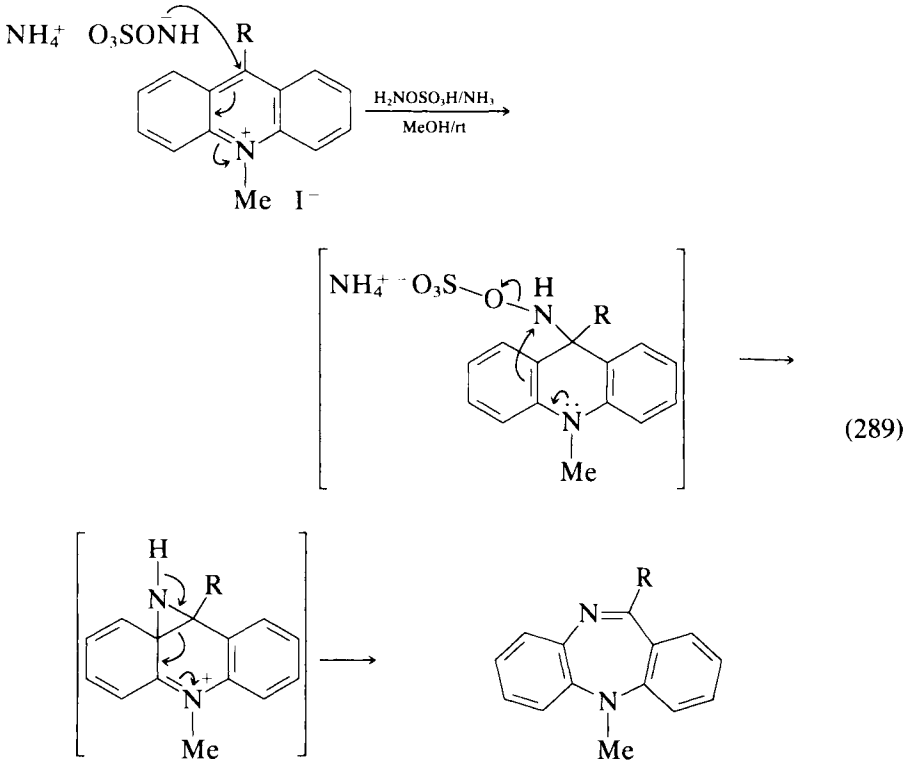
*S*-Ethylation of the benzodiazepine derivative **1196** and subsequent reaction of the thioether **1197** with dimethyl acetylenedicarboxylate gave an adduct assigned structure **1198**. It was suggested (674) that after normal addition of the diester to the enamine, ethanethiol was eliminated, allowing addition of a second molecule of diester (Fig. 105).

A number of studies were undertaken with the specific goal of preparing tetracyclic derivatives of the dibenzo[*b*,*e*][1,4]dizaepine ring system. In the first of these, reaction of *N*-phenyl-*o*-phenylenediamine with chloroacetyl chloride followed by cyclization with polyphosphate ester gave the chloromethylimine **1199** (Fig. 106), which was converted to **1200** by reaction with methylamine. The saturated ethylenediamine **1201** was obtained from **1200** by sodium borohydride or lithium aluminum hydride reduction. Condensation of **1201** with diethyl oxalate gave the diketopiperazine **1202a**, which was reduced to **1202b** with diborane (675). Compound **1202b** is an aza analog of the antidepressant mianserin.

In a related study (676), the ethylenediamine derivative **1201** was condensed with formaldehyde to obtain the imidazolidine **1202c** (Eq. 290). Similar cyclizations of the propylenediamines **1203a** and **1203b** to the piperazines **1203c** and **1203d** were also reported (677, 678).

Reaction of an *o*-phenylenediamine with a suitably substituted cyclohexanone has proved to be a versatile approach for the synthesis of dibenzo-[*b*,*e*] [1,4] diazepine derivatives in which one six-membered ring is alicyclic. However, an obvious disadvantage of this method is that if unsymmetric diamines are used, either a mixture of products or a product of uncertain structure results.

As shown in Eq. 291, condensation of *o*-phenylenediamine with ethyl cyclohexanone-2-carboxylate followed by pyrolysis of the resulting imine (679) gave the tricyclic lactam **1204**. Similarly, the tricyclic imine **1205** was

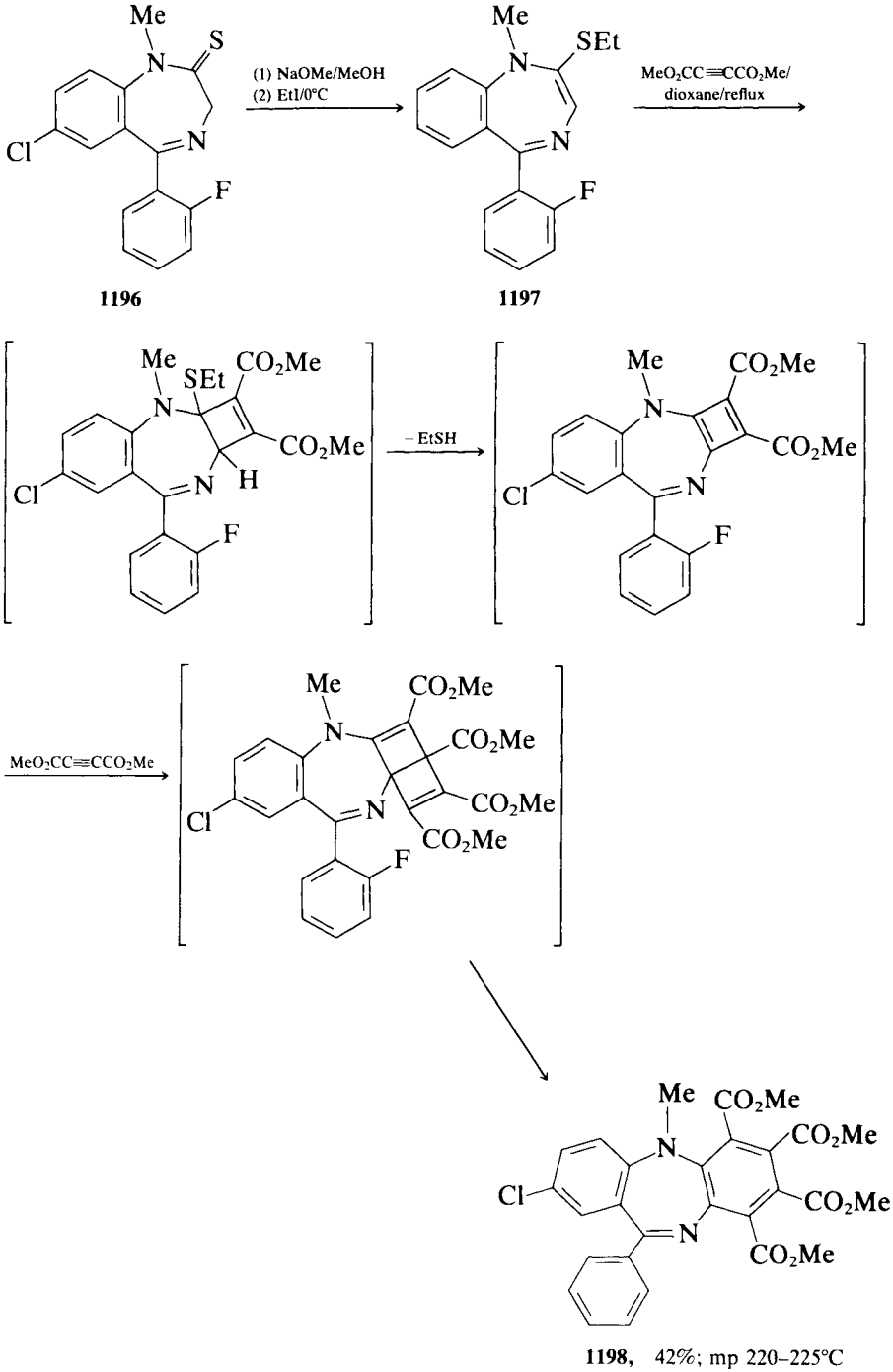



(289)

**1180h**, R = H (72%); mp 96°C
**1180g**, R = Me (17%); picrate, mp 203–204°C
**1195**, R = Ph (19%); mp 142°C

obtained when equimolar amounts of *o*-phenylenediamine and 2-formylcyclohexanone were allowed to react under acidic conditions (426). When the relative amount of 2-formylcyclohexanone was doubled, the bis adduct **1206** was obtained; this gave a low yield of **1205** on treatment with 70% perchloric acid in ethanol (Eq. 292). Treatment of *o*-phenylenediamine with 2-chloromethylenecyclohexanone gave a tricyclic product that was formulated (428) as **1207** (Eq. 293).

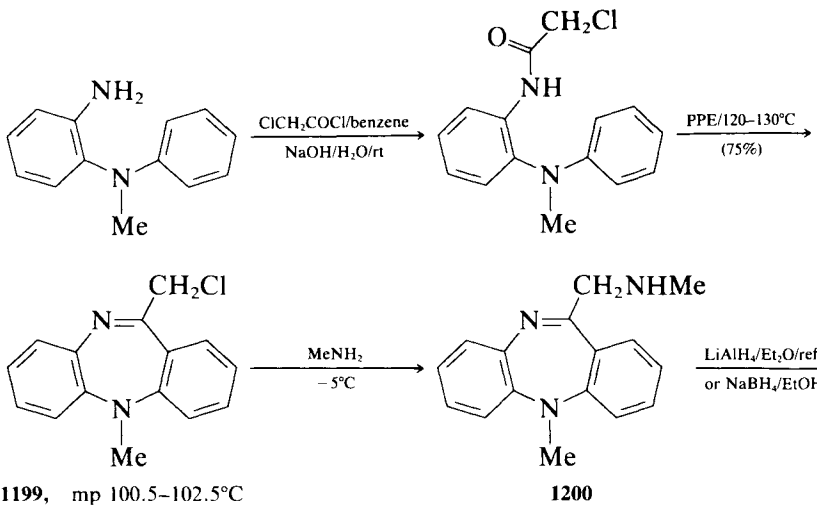
Reaction of *o*-phenylenediamines with 2-piperidinomethylcyclohexanone gave the 4,5-imines **1208a–c** (Eq. 294). The imine function in **1208c** was reduced with sodium borohydride to yield the amine **1208d** (680). When 1-acetylcyclohexene was employed (681), the 10, 11-imine **1208e** was produced (Eq. 295). No assignment of stereochemistry was provided. A similar reaction with 1-formyl-2-chlorocyclohexene (23) gave the $\alpha$, $\beta$-unsaturated imine **1209a** (Eq. 296). The corresponding 11-methyl compound **1209b** was obtained under similar reaction conditions using 2-acetyl-2-chlorocyclohexene as the starting material (427). Analogous reaction products (**1210a** and **1210b**) with 1-aryl substituents (682) are described in Eq. 297. Reaction



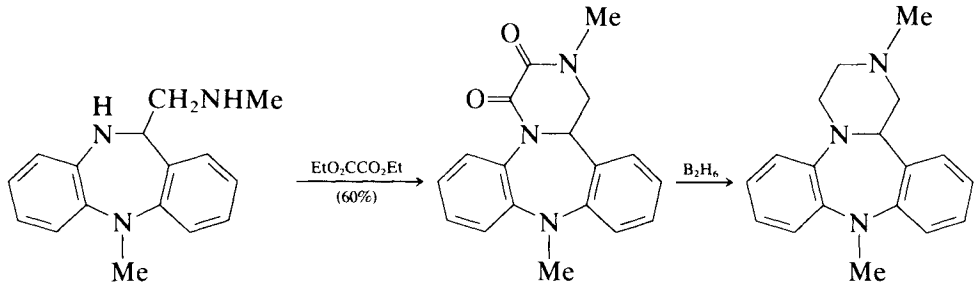

**1196** **1197**

**1198,** 42%; mp 220–225°C

**Figure 105**



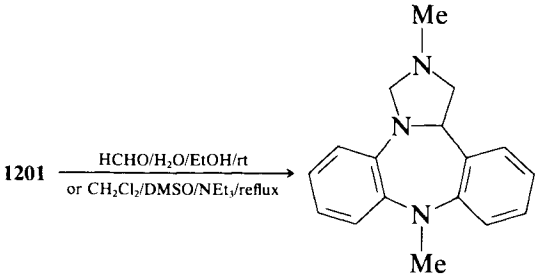

**1199,** mp 100.5–102.5°C **1200**



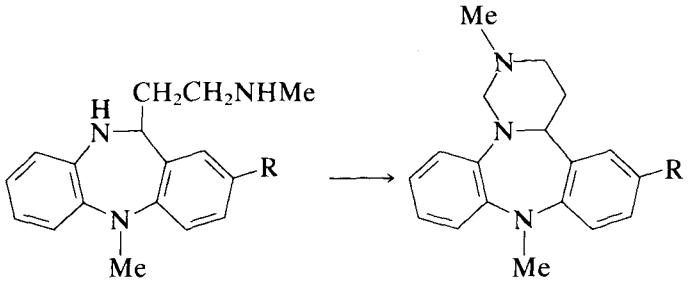

**1201** **1202a,** mp 170–180°C **1202b**

**Figure 106**

of *o*-phenylenediamine with 2-anilinomethylene-1,3-cyclohexanones gave transaminated intermediates which could be cyclized under acidic conditions (683, 684) to the products **1211a–d** (Fig. 107). These salts could be converted



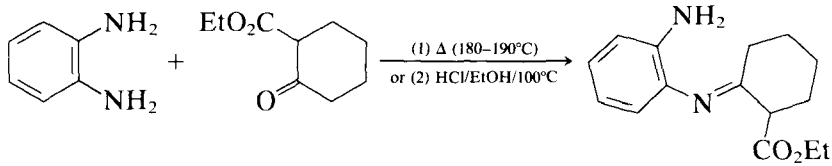

**1202c,** mp 100–102°C (290a)



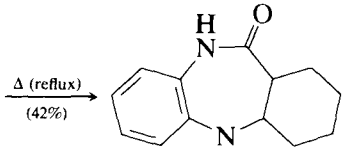
**1203a**, R = OMe
**1203b**, R = H

**1203c**, R = OMe; picrate, mp 103–108°C; fumarate, mp 210–215°C; methiodide, mp 204–207°C
**1203d**, R = H; methiodide, mp 212–215°C

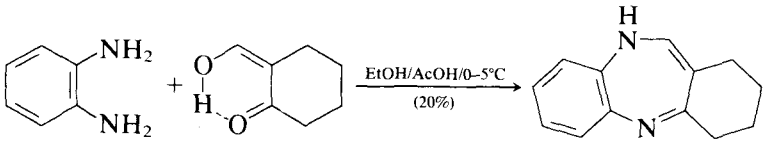
(290b)



(291)

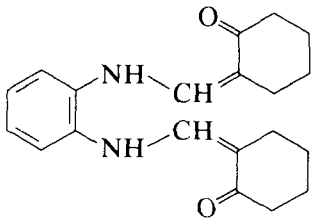


**1204**, mp 182–183°C



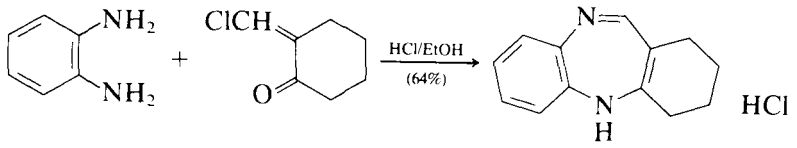
(molar ratio 1:1)

**1205** (perchlorate)



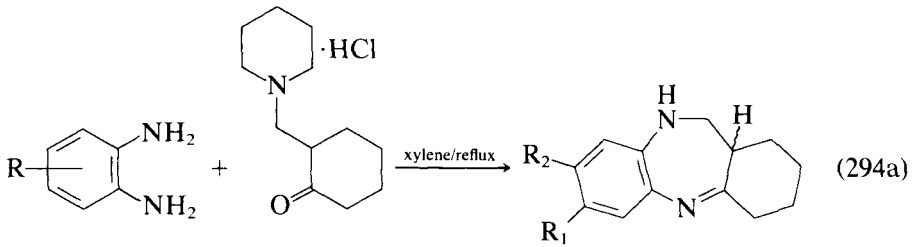
(292)

**1206**



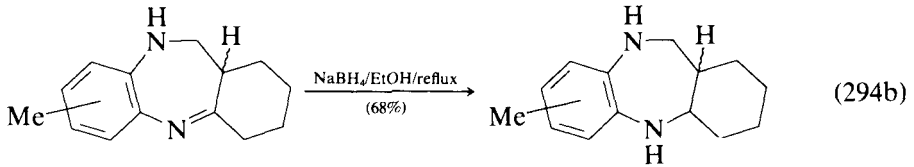
(293)

**1207,** mp 174–175°C;
perchlorate, mp 181–182°C



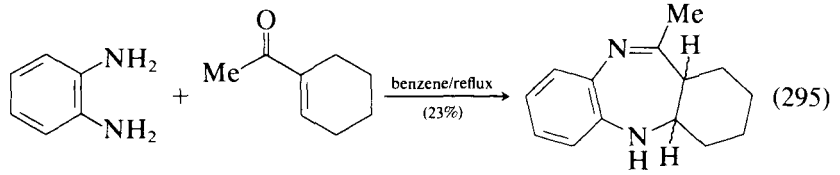
(294a)

**1208a,** $R_1 = R_2$ = Me (68%); mp 53–54°C
**1208b,** $R_1 = R_2$ = H (69%); mp 40–44°C
**1208c,** $R_1$ or $R_2$ = Me (75%); bp 175°C/0.015 Torr
HCl, mp 222–225°C



(294b)

**1208c** **1208d,** bp 160°C/0.1 Torr

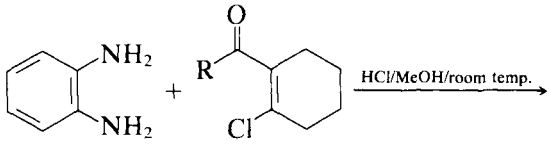


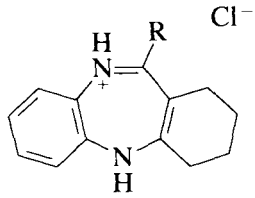
(295)

**1208e,** bp 160°C/2 Torr;
$n_D^{20}$ = 1.5933;
HBr, mp 210°C

to the respective free bases, which were isolated as enols (**1212a, 1212b**) or ketones (**1213a–c** or **1214a–c**), depending on the conditions employed for isolation.

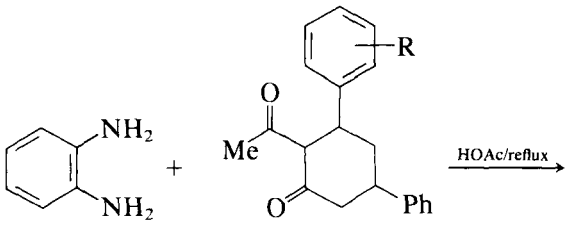
Condensation of the 11-methyl salt **1211b** with an aromatic aldehyde could be effected under acid conditions (685) to give the styryl derivative **1215**, as



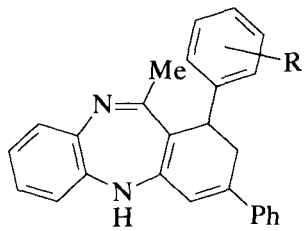




(296)

**1209a**, R = H (64%); mp 174–175°C; perchlorate, mp 181–182°C
**1209b**, R = Me (53%); mp 194–196°C



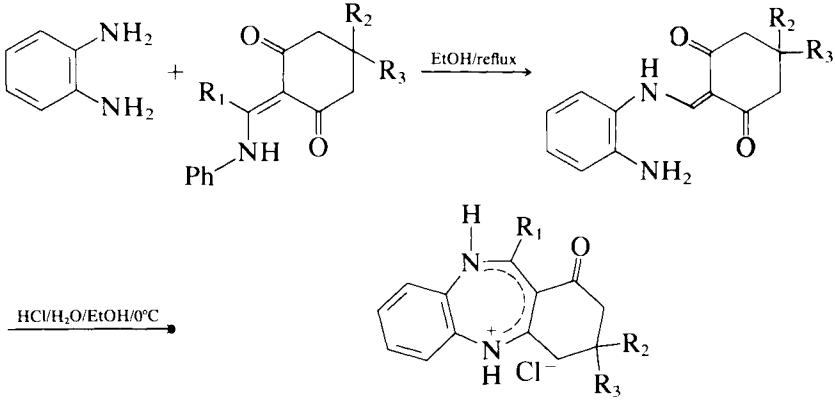

(297)



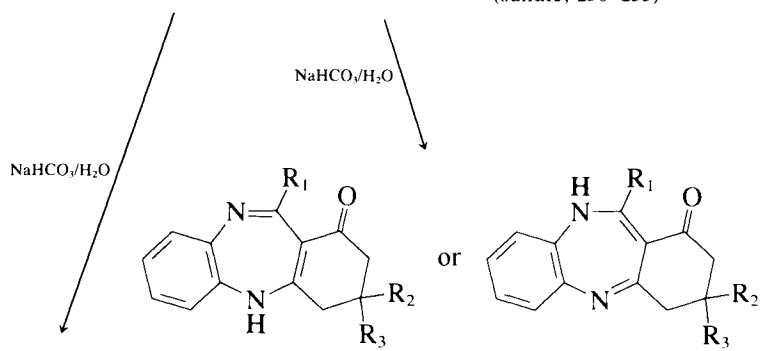

**1210a**, R = H (43%); mp 122°C
**1210b**, R = 3,4-methylenedioxy (46%); mp 116°C

shown in Fig. 108. Similar condensations of the free bases **1214d–f** with dimethylformamide dimethyl acetal yielded the enamines **1216a–c**, respectively. The adducts were condensed with primary amines to give the tetracyclic fused pyridines **1217a–c** (686).

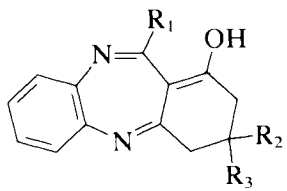
Acid-catalyzed hydrolysis of one of these tricyclic products was studied (687). Hydrolysis of **1213a** with hydrochloric or phosphoric acid gave a benzimidazole derivative and acetone, presumably via the intermediates




| | $R_1$ | $R_2$ | $R_3$ | Yield (%) | mp (°C) |
|---|---|---|---|---|---|
| **1211a** | H | H | H | 48 | 223–224 |
| **1211b** | H | Me | Me | 60 | 219 |
| **1211c** | H | Ph | H | 45 | 224–225 |
| **1211d** | Me | Me | Me | 83 | 263–265 (sulfate, 250–253) |

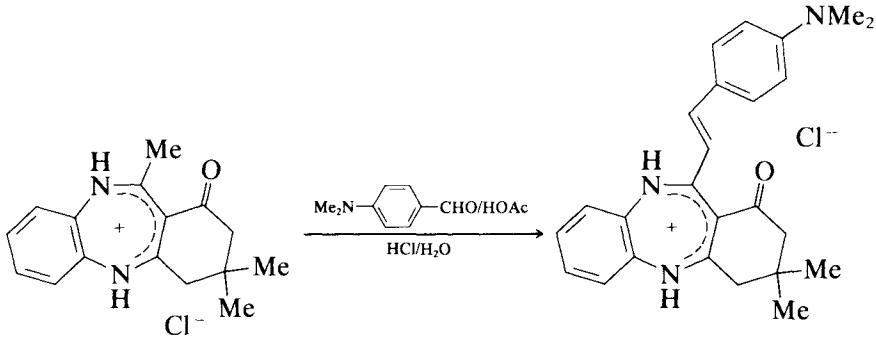



**1213a/1214a,** $R_1 = R_2 = R_3$ = Me; mp 119–120°C
**1213b/1214b,** $R_1 = R_2 = R_3$ = H; mp 218–221°C
**1213c/1214c,** $R_1$ = H, $R_2 = R_3$ = Me; mp 225–227°C



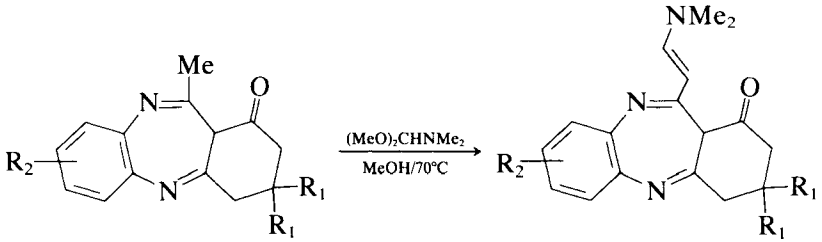
**1212a,** $R_1 = R_2 = R_3$ = Me; mp 193–199°C
**1212b,** $R_1$ = H, $R_2 = R_3$ = Me; mp 110–115°C

**Figure 107**



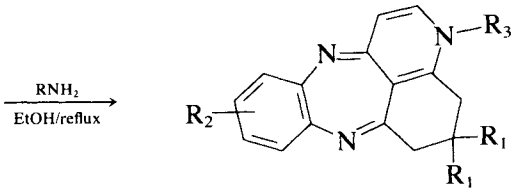

**1211b**

**1215,** 87%; mp 241–242°C; free base, mp 228°C




**1214d,** $R_1 = R_2 = H$; mp 244°C
**1214e,** $R_1$ = Me, $R_2$ = H; mp 265°C
**1214f,** $R_1$ = Me, $R_2$ = 7- or 8-Cl; mp 256°C

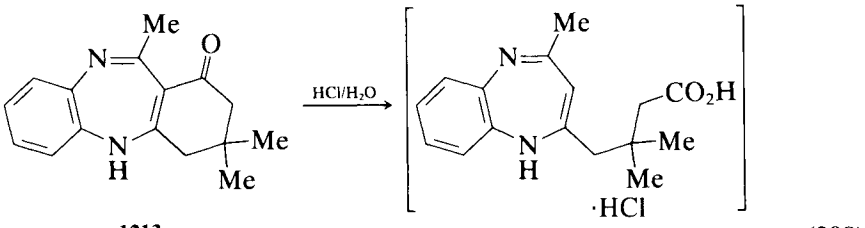
**1216a,** $R_1 = R_2 = H$ (79%); mp 244°C
**1216b,** $R_1$ = Me, $R_2$ = H (80%); mp 265°C
**1216c,** $R_1$ = Me, $R_2$ = 7- or 8-Cl (75%); mp 249°C




**1217a,** $R_3$ = 4-$MeOC_6H_4$, $R_1 = R_2 = H$ (82%); mp 300°C
**1217b,** $R_3 = H$, $R_1$ = Me, $R_2 = H$ (77%); mp 214°C
**1217c,** $R_3$ = 4-$MeOC_6H_4$, $R_1$ = Me, $R_2$ = 7- or 8-Cl (80%); mp 279°C

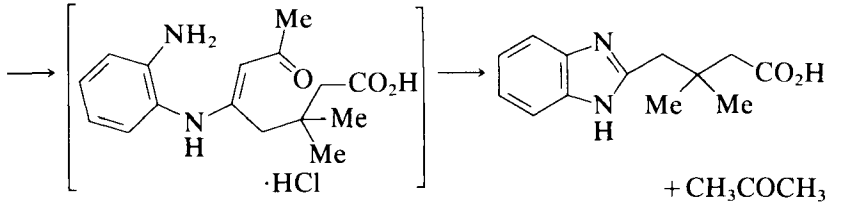
**Figure 108**

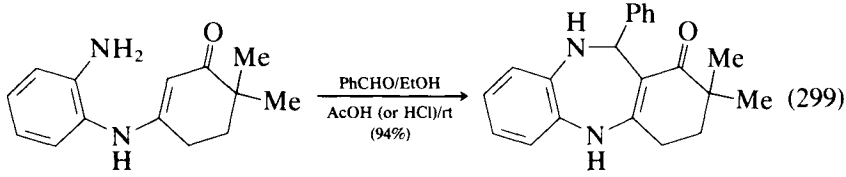
shown in Eq. 298. In a more versatile synthesis (688), the adduct of *o*-phenylenediamine and dimedone was treated with benzaldehyde in the presence of hydrogen chloride or acetic acid as a catalyst. Cyclization to **1218** by a Mannich-type process occurred (Eq. 299). Additional examples (689) are given in Table 170.




**1213a**

(298)

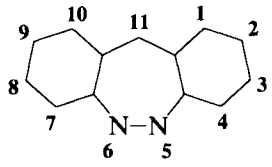



(299)

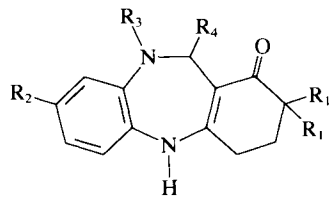
**1218,** mp 258.5–259.5°C

## 49. Dibenzo[*c*,*f*][1,2]diazepines (see Section XVI)




The earliest synthesis of the dibenzo[*c*,*f*][1,2]diazepine ring system was achieved by Duval (690) in 1905 when he treated the dinitro compound **1219** (X = $NH_2$, Y = $H_2$) with zinc and obtained the azoxy derivative **1220** (X = $NH_2$, Y = $H_2$). Various reagents could be used to further reduce **1220**

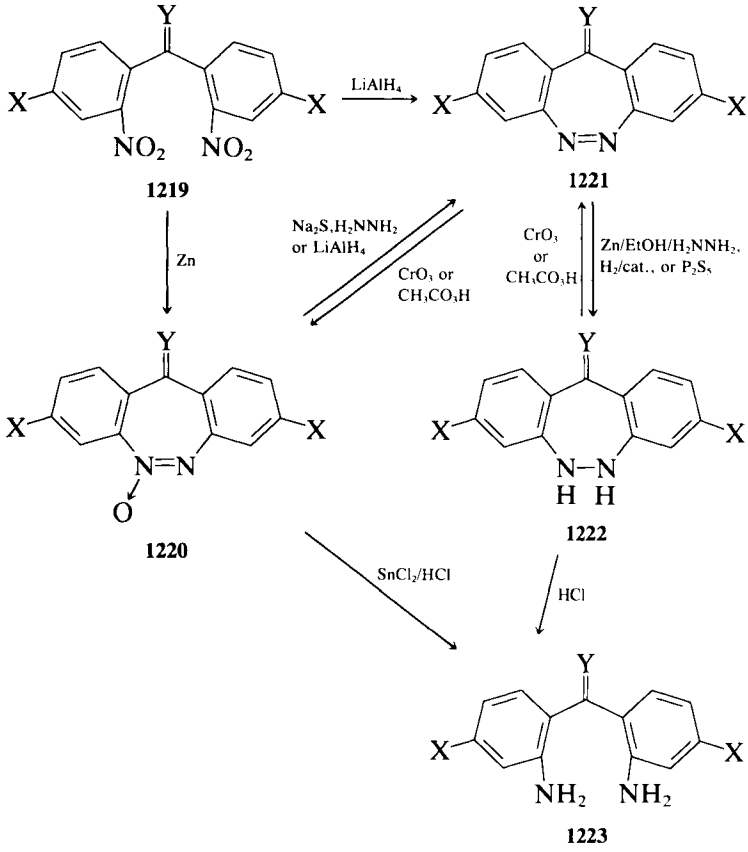
TABLE 170. 2,3,4,5,10,11-HEXAHYDRO-1*H*-DIBENZO[*b*,*e*][1,4]DIAZEPIN-1-ONES



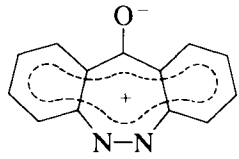
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) |
|---|---|---|---|---|
| Me | H | H | H | 225–227 |
| Me | H | H | Me | 242–244 |
| H | H | H | Et | 181–182 |
| Me | H | H | Et | 243–246 |
| Me | H | H | 4-$ClC_6H_4$ | 241–242 |
| Me | H | H | 4-$NO_2C_6H_4$ | 270 |
| Me | H | H | 2-$C_5H_5N$ | 261–263 |
| Me | Cl | H | Ph | 242–242.5 |
| Me | Cl | H | H | 208–209 |
| Me | Cl | H | Me | 235.5–236.5 |
| Me | Cl | H | Et | 224–225 |
| Me | Cl | H | 4-$ClC_6H_4$ | 264–265.5 |
| Me | Cl | H | 4-$NO_2C_6H_4$ | 269–270 |
| Me | Cl | H | 2-$C_5H_5N$ | 268–269 |
| Me | Cl | $CH_3CO$ | 4-$ClC_6H_4$ | 271–272 |

to **1221**, including sodium sulfide (691,692,693), hydrazine (691,692,693), and lithium aluminum hydride (691) (Fig. 109). Attempted reduction of **1220** with stannous chloride in hydrochloric acid gave the ring-cleaved product **1223** (690,694). Later workers found that **1219** could be converted directly to **1221** with lithium aluminum hydride (692,695,696). Compound **1219** (X = Cl, Y = O) was also transformed directly to **1221** (X = Cl, Y = $H_2$) with lithium aluminum hydride (692). Direct ring closure of **1219** to **1221** (X = H, Y = O) was accomplished in 82% yield with glucose and 40% sodium hydroxide (697). Further reduction of **1221** to **1222** could be performed with zinc in ethanol (695,696,698), hydrazine (691,692), hydrogen (693,699), or phosphorus pentasulfide (700). The dihydro derivatives **1222** were unstable and disproportionated readily to **1221** and **1223** in concentrated hydrochloric acid (693,694). Reduction of the azo group of **1221** to give the diamino derivative **1223** was effected with hydrogen (691,693,697), sodium sulfide (693), or hydrazine under Wolff–Kishner conditions (693). Oxidative conversions **1221** to **1220** and of **1222** to **1221** could be carried out with chromium trioxide or peracetic acid (693,701). The dibenzo[*c*,*f*][1,2]diazepines prepared under these conditions are listed in Table 171.

The 11-oxo derivatives **1221** (Y = O) were prepared directly from **1219** (Y = O) and also by chromium trioxide oxidation of **1221** (Y = $H_2$) (693,701).




**1219** **1221** **1220** **1222** **1223**

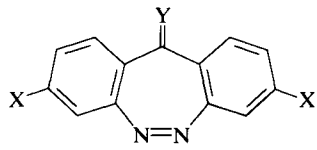


**1224**

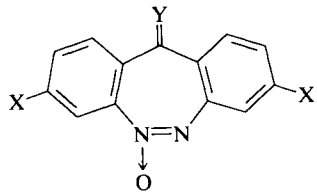
**Figure 109**

Excess oxidizing agent led to formation of azoxy ketone **1220** (Y = O). The carbonyl compound **1221** (Y = O) was somewhat unreactive, probably because of conjugation with the azo group. Polarographic studies on **1221** (X = H, Y = O) indicated that structure **1224** was an important contributor to the resonance hybrid, but ultraviolet and infrared spectra were inconclusive (697). Although hydrazine did not form an adduct, under forcing conditions oximes and semicarbazones of **1221** (Y = O) could be prepared (693,701). Grignard additions were not successful, but acetylides did add to yield car-

TABLE 171. DIBENZO[*c*,*f*][1,2]DIAZEPINES



| X | Y | mp (°C) | Refs. |
|---|---|---|---|
| $NH_2$ | $H_2$ | 233 | 690,702 |
| $NMe_2$ | $H_2$ | 213 | 700,702 |
| $CO_2Et$ | $H_2$ | 233 | 700,702 |
| H | $H_2$ | 112.5 | 691,692,695,700,701,703 |
| F | $H_2$ | 184–185 | 692,693 |
| Cl | $H_2$ | 204–205 | 692,693,704 |
| Br | $H_2$ | 215–216 | 692,693,704 |
| I | $H_2$ | 244.5 | 692,693 |
| H | O | 198–199 | 692,697,699,705 |
| F | O | 234–235 | 692 |
| Cl | O | 232–238 | 692,693,701 |
| Br | O | 166–168 | 692,693 |
| Cl | H, OH | 176–178 | 701 |
| F | H, OH | 152–154 | 701 |
| Br | H, OH | 178–180 | 701 |



| | | | |
|---|---|---|---|
| $NH_2$ | $H_2$ | 272 | 690,691,706 |
| H | $H_2$ | 134.5–135.5 | 691,701,703 |
| F | $H_2$ | 178–180 | 692,693 |
| Cl | $H_2$ | 289 | 692,693,703 |
| Br | $H_2$ | 219–220 | 692,693,703 |
| I | $H_2$ | 226–227 | 692,693 |
| $NO_2$ | $H_2$ | 212–214 | 707 |
| H | O | 204 | 705 |
| Cl | O | 253–254 | 692,701 |
| Br | O | 266–269 | 693,701 |
| Cl | H, OH | 189–196 | 701 |
| H | $H_2$ | 105–105.5 | 691,695 |
| F | $H_2$ | 137–138 | 692 |
| Cl | $H_2$ | 145–146 | 692,693 |
| H | O | | 699 |
| Cl | O | 245–246 | 693,701 |
| Br | O | 241–243 | 693 |
| Cl | H, OH | | 693 |

binols as well as minor amounts of acridine (699). With disodium diacetylide, the diadduct **1225** was formed (699) (Fig. 110). The acetylene adduct **1226** underwent a Meyer–Schuster rearrangement to give **1227** (699).

With phosphonate ylides, the 11-oxo derivatives **1228** gave the unsaturated adducts **1229**. Reduction of **1228** with aluminum isopropoxide led to **1230**, as shown in Eq. 300 (693,701). These reactions could also be carried out with the analogous azoxy compounds **1220** (Y = O). The carbonyl adducts of **1220** (Y = O) and **1221** (Y = O) are listed in Table 172.

As shown in Eq. 301, nitration of **1228** (X = H) in fuming nitric acid led to the azoxy adducts **1231** and **1232**, probably via the azoxy intermediate **1233** (705). The nitro compound **1220** (X = $NO_2$, Y = $H_2$) was produced from the corresponding diazonium salt (**1220**; X = $N_2{\bullet}BF_4$, Y = $H_2$) by using sodium nitrite (707). In contrast, treatment of **1234a** with potassium nitrate in concentrated sulfuric acid led to the ring-contracted cinnoline **1235**, as shown in Eq. 302 (693,708). A similarly rearranged product was observed

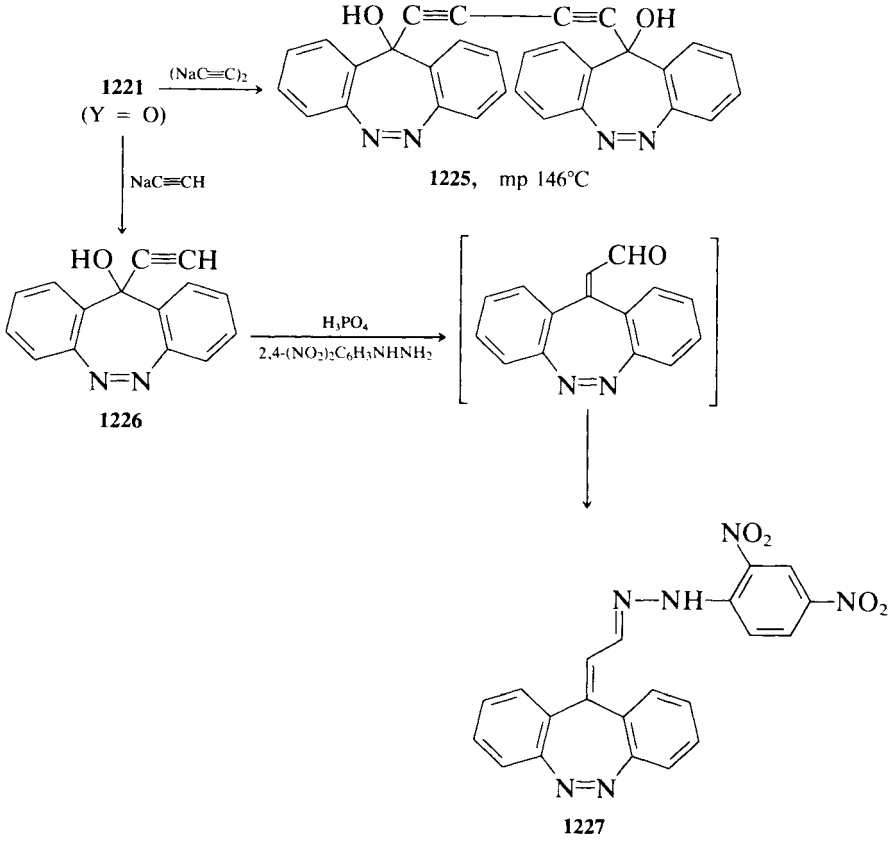
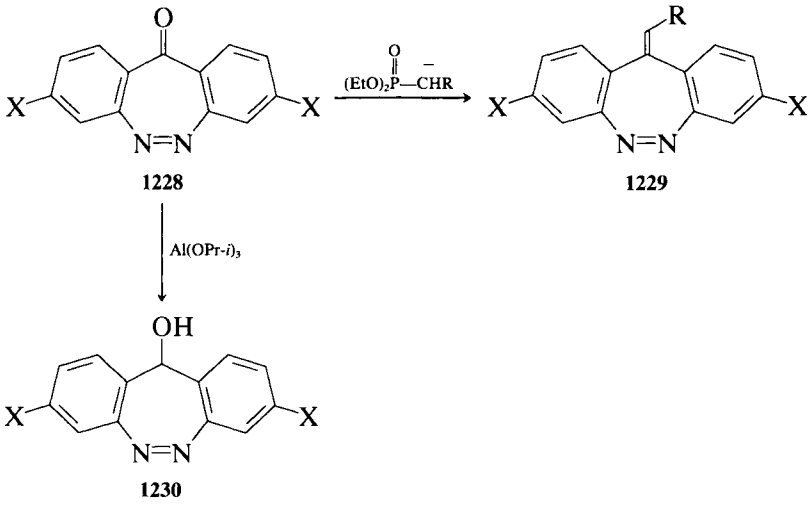
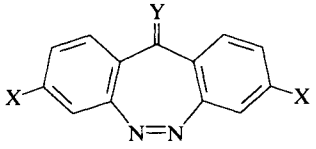



**Figure 110**

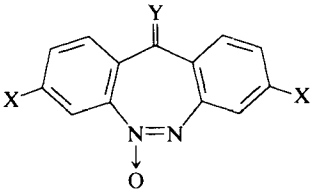



(300)

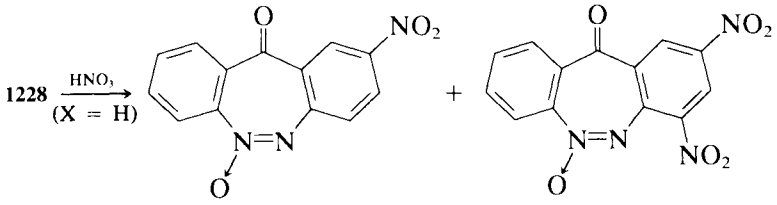
TABLE 172. 11*H*-DIBENZO[*c*,*f*][1,2]DIAZEPIN-11-ONE DERIVATIVES AND ADDITION PRODUCTS




| X | Y | mp, °C | Refs. |
|---|---|---|---|
| Cl | NOH | 263–265 | 701 |
| Cl | $NNHCONH_2$ | 248–149 | 701 |
| H | OH, C≡CH | 200 | 699 |
| H | OH, $C{\equiv}CCH_2NMe_2$ | 179–180 | 699 |
| H | OH, C≡CPh | 226–228 | 699 |
| H | $CHCHNNHC_6H_3(NO_2)$-2,4 | 272 | 699 |
| Cl | $CHCO_2Et$ | 113–115 | 693,701 |
| Cl | CHCN | 210–212 | 693,701 |
| Cl | CHCOPh | 70–74 | 693,701 |
| Cl | $CHCONEt_2$ | 109–112 | 693,701 |
| Cl | $CHCH_2NEt_2$ | | 693 |

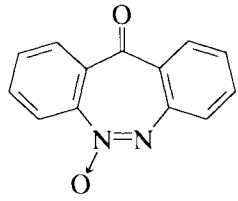



| | | | |
|---|---|---|---|
| Cl | NOH | 272–275 | 693,701 |
| Cl | $NNHCONH_2$ | 233–235 | 693,701 |
| Cl | $CHCO_2Et$ | 145–155 | 701 |

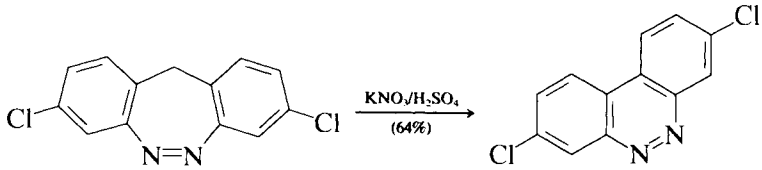



**1231**, 28%; mp 217°C **1232**, 28%; mp 266°C

(301)




**1233**, mp 204°

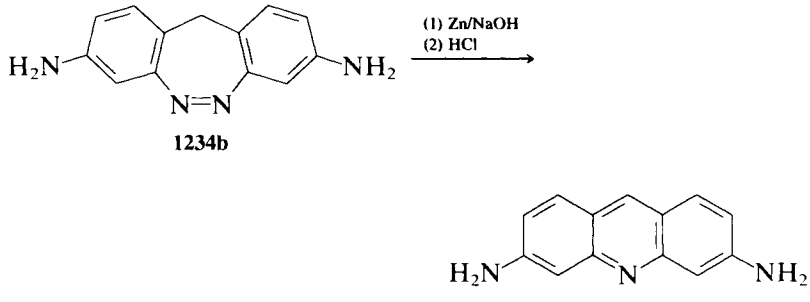



**1234a** **1235**

(302)

in several attempted additions of stabilized phosphonate anions to **1228** (X = Cl) (709). Ring contraction of **1234b** to an acridine **1236** occurred (Eq. 303) with zinc under alkaline conditions followed by the addition of hydrochloric acid (694).

The 5,6-azo functionality has also been the target of chemical studies (Eq. 304). Metal complexes formed on mixing **1237** (X = H, Cl) with transition

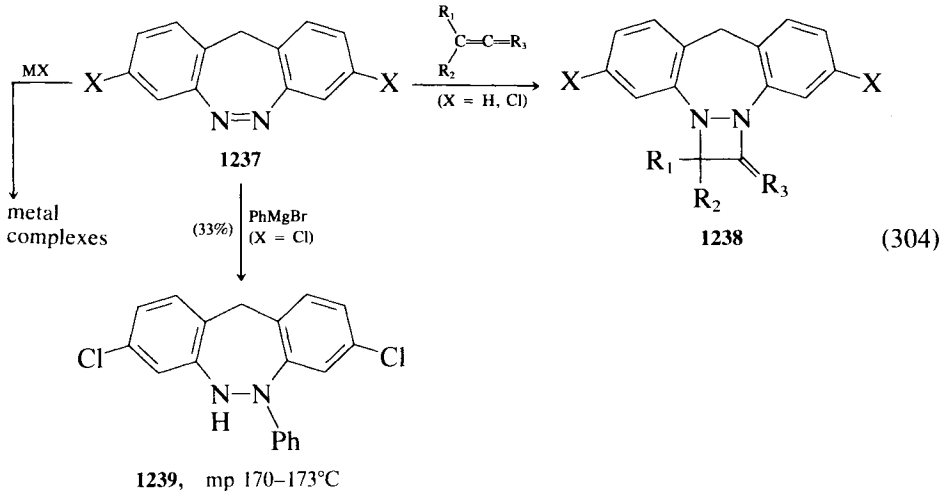



**1234b**

(303)

**1236**

metal salts. The adducts are listed in Table 173 (693,710,711). The salts varied in stability. The copper complex hydrolyzed in water overnight, whereas the silver complex was stable in refluxing dilute hydrochloric acid.



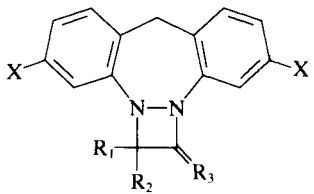

(304)

Azo compound **1237** (X = H, Cl) formed adducts **1238** with ketenes and ketenimines (693,699,701,712). These derivatives are summarized in Table 174. Phenylmagnesium bromide addition to **1237** afforded **1239** (Eq. 304) in 33% yield (693,701). The unstable 5,6-dihydrodiazepine derivatives **1222** formed the stable products **1240** (699), **1241** (698), and **1242** (692,693) with malonic acid derivatives (Eq. 305).

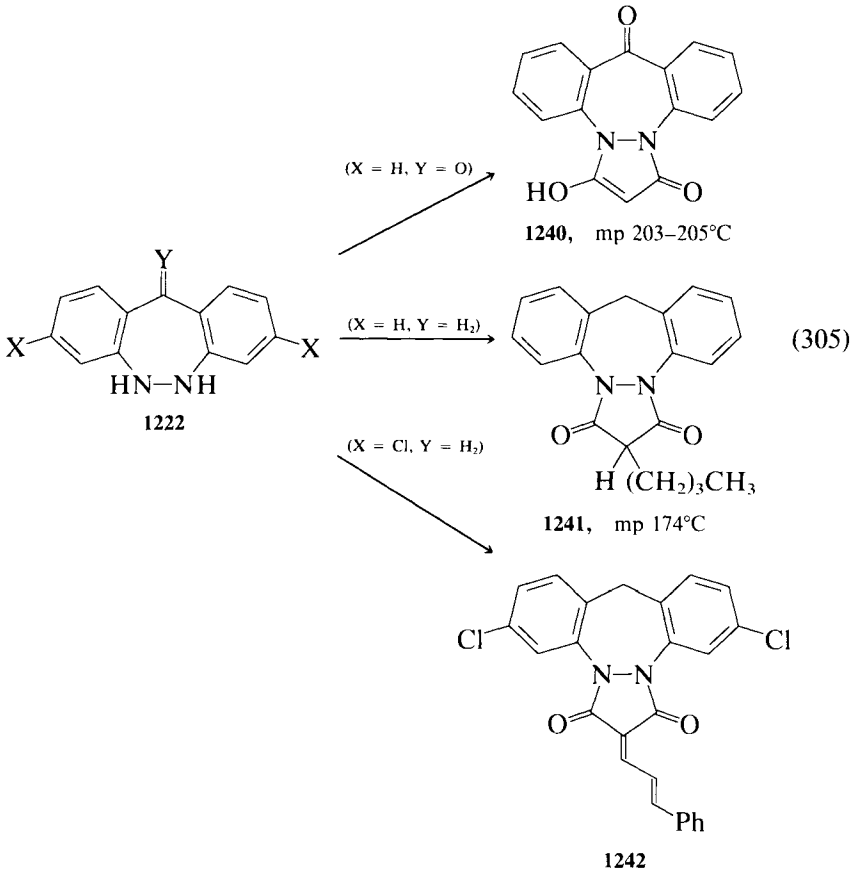
TABLE 173. METAL COMPLEXES OF 3-CHLORO-11*H*-DIBENZO[*c*,*f*][1,2]DIAZEPINES

| Salt | mp (°C) | Diazepine to Metal Ratio |
|---|---|---|
| CuCl | >360 | 1:1 |
| $H_2PtCl_6$ | >360 | 2:1 |
| $H_2PtCl_6$ | >360 | 1:1 |
| $AgNO_3$ | 245–247 | 1:1 |
| $PdCl_2$ | 274–276 | 2:1 |
| $HAuCl_4 \cdot 3H_2O$ | >360 | 1:1 |

TABLE 174. KETENE ADDUCTS OF DIBENZO[*c*,*f*][1,2]DIAZEPINES



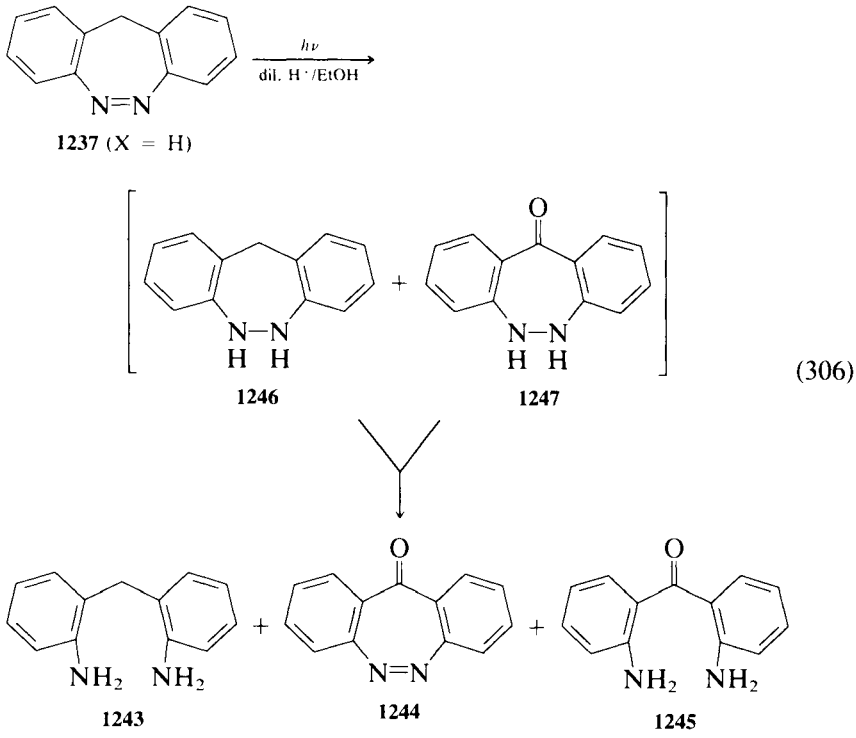

| X | $R_1$ | $R_2$ | $R_3$ | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|---|---|
| H | H | H | O | 10 | 150–154 | 699 |
| H | Me | Me | O | 30 | 138–140 | 699 |
| H | Me | Me | $NC_6H_4Me$-*p* | 40 | 219–220 | 699 |
| H | Ph | Ph | O | 80 | 214–215 | 699 |
| H | Ph | Ph | $NC_6H_4Me$-*p* | 75 | 231–233 | 699,712 |
| Cl | Et | *n*-Bu | O | 30 | 93–94 | 693,701 |
| H | Et | *n*-Bu | O | 37 | 87–89 | 693,701 |




(305)

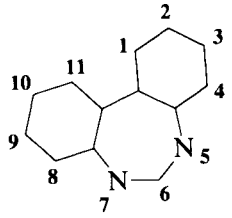
The photochemistry of this ring system was also studied. In sunlight, **1237** (X = H) in 1% ethanolic sulfuric acid gave products **1243, 1244,** and **1245** as well as the starting material (Eq. 306). The results are compatible with the intermediate formation of a 1:1 mixture of **1246** and **1247**, which disproportionate to the four observed products (704).

Photolysis of **1219** (Y = $H_2$) in isopropanol (Fig. 111) led to azoxy derivatives **1220** (Y = O), which could be reduced to the azo compounds **1221** with magnesium in ethanol. Photolytic by-products included **1248, 1249,** and **1250** (703). In contrast, in dilute sulfuric acid **1219** underwent photorearrangement to yield primarily the 2,1-benzisoxazoles **1251** in 45–50% yield, with **1220** as minor products (713). The mass spectral fragmentation of derivatives of this ring system (714,715), as well as their fluorescence properties (716,717), have been analyzed.

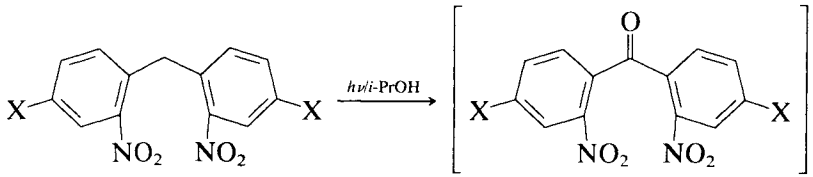



(306)

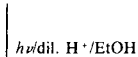
## 50. Dibenzo[*d*,*f*][1,3]diazepines (see Section XVI.24)

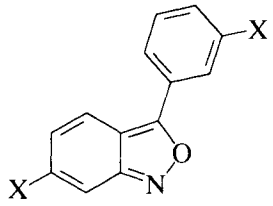



Derivatives of the dibenzo[*d*,*f*][1,3]diazepine ring system are generally prepared from a 2,2′-diaminobiphenyl species. Thus 2,2′-diaminobiphenyl (**1252**) can be condensed with urea at 200°C (718) to yield the tricyclic 6-oxo derivative **1253** (Fig. 112). Alternative syntheses of **1253** include rearrangement of the diacylazide **1254** in wet benzene (719,720), reaction of **1252** with phosgene (721), decomposition of diazide **1255** with diiron nonacarbonyl (722), and thermolysis of **1256** via isocyanate **1257** (723). Although the urea function was stable to lithium aluminum hydride (724), it did undergo *N*-

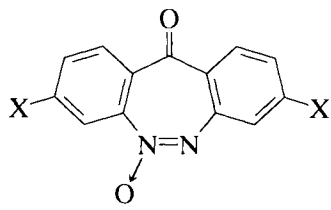



**1219** (Y = $H_2$)



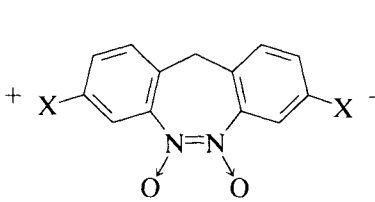




**1251**

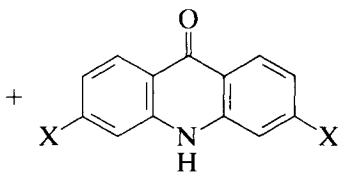



**1220** (Y = O)

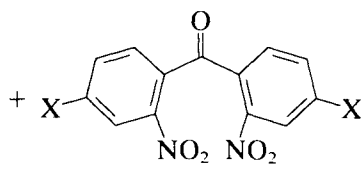
| X | Yield (%) |
|---|---|
| H | 45 |
| Cl | 38 |
| Br | 35 |




**1248**




**1249**




**1250**

**Figure 111**

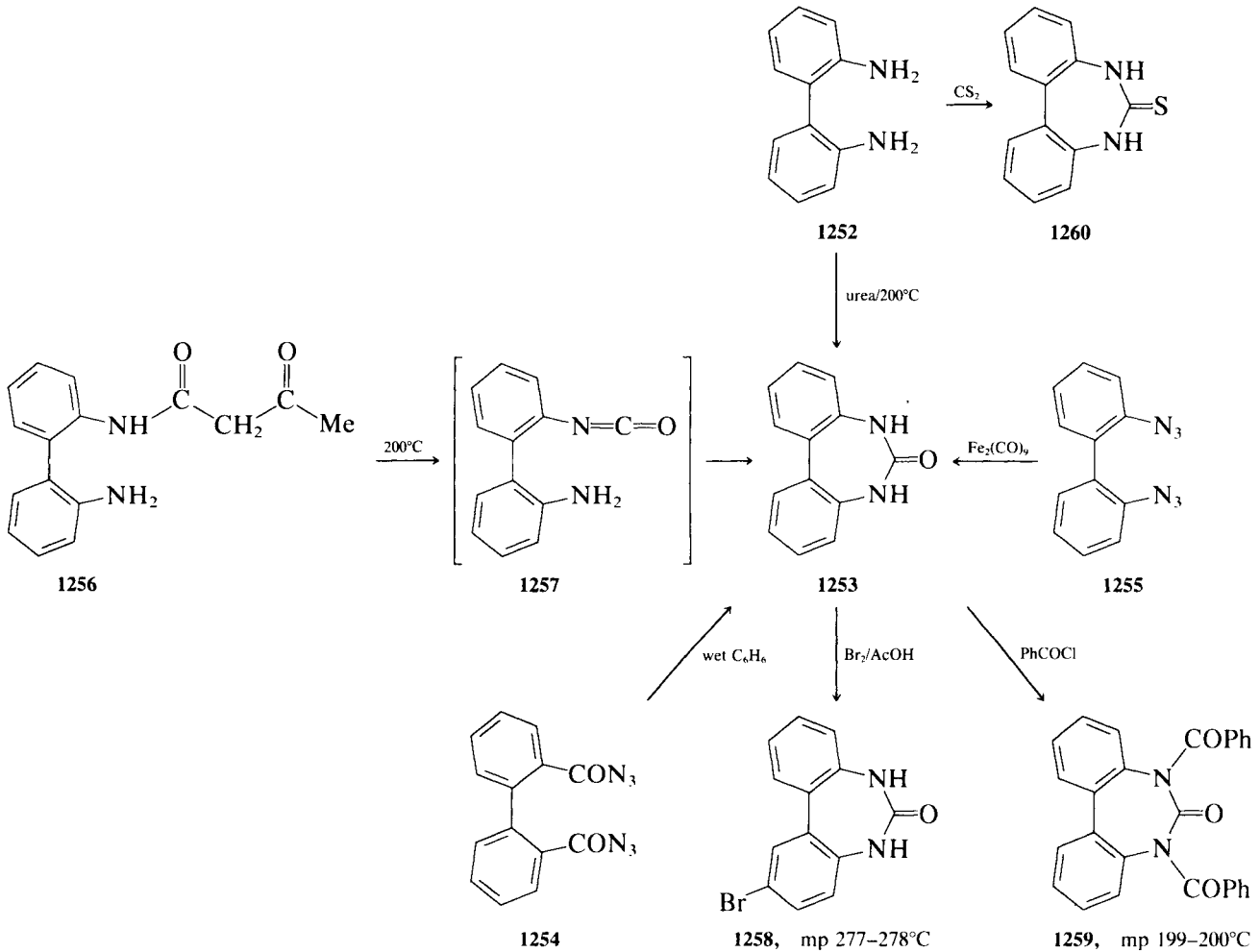

NH2
NH2
CS2
NH
S
NH
1252
1260
urea/200°C
O
O
NH
C
CH2
C
Me
NH2
200°C
N=C=O
NH2
NH
O
NH
Fe2(CO)9
N3
N3
1256
1257
1253
1255
wet C6H6
Br2/AcOH
PhCOCl
CON3
CON3
NH
O
NH
Br
COPh
N
O
N
COPh
1254
1258, mp 277–278°C
1259, mp 199–200°C

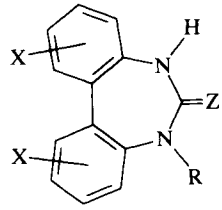
**Figure 112**

alkylation (725). Bromination of **1253** gave **1258** (723), and treatment of **1253** with benzoyl chloride generated **1259** (721). The thioxodiazepine **1260** was prepared from **1252** by addition of carbon disulfide (719). Compounds of this class are summarized in Table 175 (718–732).

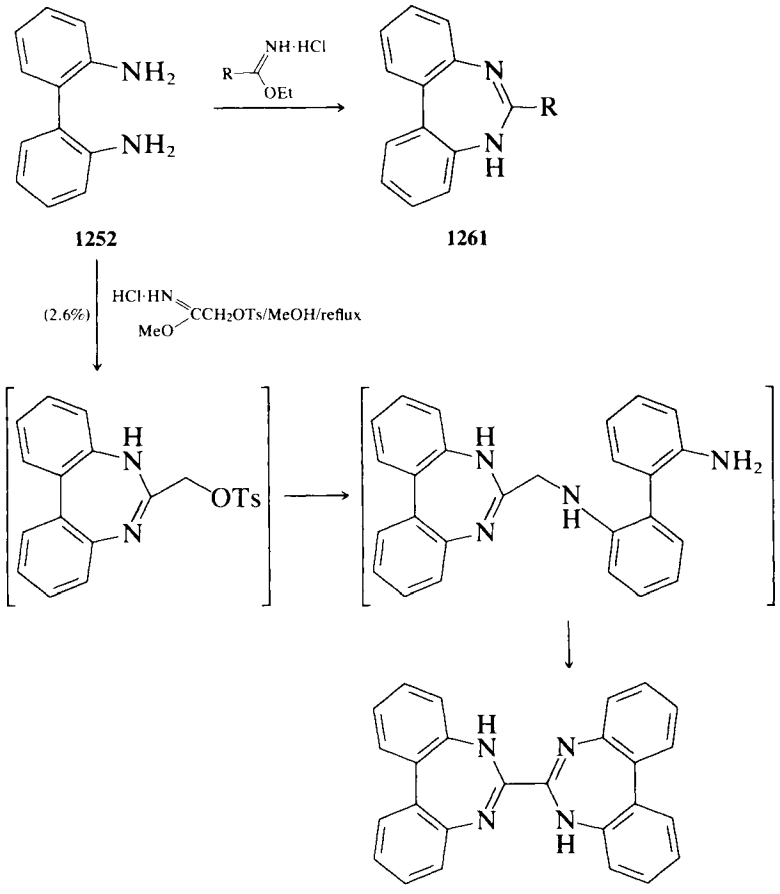
Several routes for the preparation of amidine derivatives of this ring system have been developed. The most common approach is outlined in Fig. 113. Condensation of **1252** with imino ethers afforded the amidines **1261** in reasonable yields (723,733–737). An amidine dimer (**1262**) was obtained in 2.6% yield via a tosylate intermediate (735). The amidines **1261** prepared by the imino ether method are listed in Table 176.

Another approach to the generation of amidines **1261** is illustrated by the examples in Eqs. 307–310. Monoacetamide **1263**, on treatment with phosphoryl chloride, cyclized to **1264** (732). Although monoamides were generally used, diamides also could be cyclized, as shown in the preparation of **1265** (732,738). When the cyclization was conducted with dibenzamide **1266**, some phenanthridine **1267** was obtained in addition to amidine **1268** (738). Reaction of the Schiff base **1269** with phosphoryl chloride led to *in situ* generation of

TABLE 175. 5,7-DIHYDRO-6*H*-DIBENZO[*d*,*f*][1,3]DIAZEPIN-6-ONE AND DERIVATIVES




| X | Z | R | mp (°C) | Refs. |
|---|---|---|---|---|
| H | O | H | 311–313 | 718–722,726,727 |
| H | S | H | 242–243 | 728,729 |
| 1,11-$Me_2$ | O | H | 350 | 730,731 |
| 3,9-$Ph_2$ | O | H | 390–392 | 724 |
| 3,9-$Me_2$ | O | H | 337–338 | 725 |
| 3,9-$Cl_2$ | O | H | 342–343 | 725 |
| 2,10-$Cl_2$ | O | H | 333 | 725 |
| H | O | $CH_2CH_2NMe_2$ | 124–128 | 725 |
| H | O | $(CH_2)_3NMe_2$ | 116–119 | 725 |
| H | O | $(CH_2)_3NEt_2$ | 77–78 | 725 |
| H | O | $(CH_2)_3NMeCH_2Ph$ | 119–120 | 725 |
| H | O | $(CH_2)_3NHMe$ | 214–215 | 725 |
| 3,9-$Me_2$ | O | $(CH_2)_3NHMe$ | 147 | 725 |
| 1,11-$Me_2$ | O | $(CH_2)_3NHMe$ | 131–133 | 725,732 |
| 3,9-$Cl_2$ | O | $(CH_2)_3NHMe$ | 196–197 | 725 |
| 2,10-$Cl_2$ | O | $(CH_2)_3NHMe$ | 177–178 | 725 |



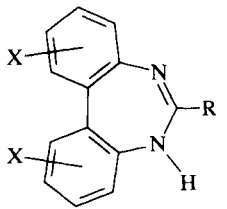

**1262**, mp 285–286°C

**Figure 113**

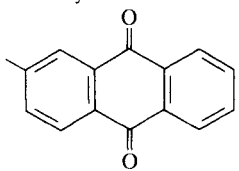
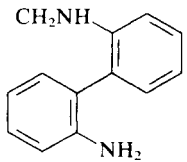
the aminocinnamamide **1270**, which formed amidine **1271**. Compound **1270** could be isolated and converted to **1271** in a separate step (739). Amidines obtained by cyclization of amides are listed in Table 177. Other reagents used to prepare **1261** include nitriles and orthoesters (727,741,742,743). Substances prepared in this manner are listed in Table 178.

As shown in Fig. 114, when **1252** was allowed to react with triethyl orthoformate, the 6-ethoxydiazepine **1272** was isolated but was rapidly converted to the amidine **1273** by ethanol elimination (727). The only other reported dihydroamidine was obtained by addition of chloral to **1252**. The product **1274** was also *N*-nitrosated to yield **1275** (744). Although several attempts to alkylate **1261** led to ring-fission products (732,741), it was found that treatment of **1264** with sodium amide in ammonia followed by addition

TABLE 176. 6-SUBSTITUTED 5*H*-DIBENZO[*d*,*f*][1,3]DIAZEPINES



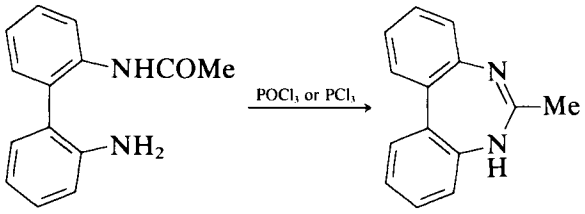

| X | R | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|
| H | Me | 59 | 227 | 723,733 |
| H | Ph | 73 | 165 | 723,733,736,737 |
| H | $CH_2NO_2$ | 85 | 257 | 733 |
| H | $CH_2CN$ | 65 | 205–210 | 733 |
| H | $CH_2CO_2Et$ | 76 | 140–142 | 733 |
| H | $CH_2CO_2Me$ | 69 | 169–177 | 733 |
| H | *p*-$MeC_6H_4SO_2NHCH_2$ | 35 | 145–150 | 733 |
| H | *p*-$NO_2C_6H_4$ | 80 | 187–190 | 733,734,736,737 |
| H | 3-Pyridyl | 38 | 200–200.5 | 733 |
| H | 2-Furyl | 54 | 156 | 733,737 |
| H | 2-Naphthyl | 60 | 176–178 | 733 |
| H | CHOHPh | 40 | 96–101 | 734 |
| H | COPh | 22 | 132–134 | 734 |
| H | *p*-$ClC_6H_4CHOH$ | 33 | 109 | 734 |
| H | *p*-$ClC_6H_4CO$ | 26 | 155–156 | 734 |
| H | 4-OH, 3-$MeOC_6H_3CHOH$ | 17 | 149 | 734 |
| H | 4-OH, 3-$MeOC_6H_3CO$ | 9 | 200–203 | 734 |
| H | *p*-$NO_2C_6H_4CO$ | 36 | 198–200 | 734 |
| H | *o*-$NO_2C_6H_4CO$ | 32 | 198–200 | 734 |
| H | *p*-$MeOC_6H_4CO$ | 27 | 155–156 | 734 |
| H | 2-OH, 3-$MeOC_6H_4CO$ | 23 | 145 | 734 |

| | | | | |
|---|---|---|---|---|
| H | $p$-$NO_2C_6H_4CH_2$ | 62 | 181–183 | 734 |
| H | $CH_2CONH_2$ | 31 | 231–233 | 734 |
| H | $CH_2CO_2Ph$ | 5 | 126–127 | 734 |
| H | CHCHPh | 17 | 148–151 | 734 |
| H | $p$-$MeC_6H_4$ | 18 | 135–136 | 734,736,737 |
| H | $p$-$ClC_6H_4$ | 51 | 157–158 | 734 |
| H | $m$-$NO_2C_6H_4$ | 47 | 191–194 | 734,736,737 |
| H | $p$-$MeOC_6H_4$ | 73 | 192 | 734,736,737 |
| H | 3,4-$(OCH_2O)C_6H_3$ | 50 | 211–213 | 734 |
| H | 2-Quinolinyl | 50 | 158–159 | 734 |
| H | 2-Thienyl | 72 | 164 | 734,737 |
| H | 3-Indolyl | 65 | 258 | 734 |
| H |  | 75 | 245–246 | 734 |
| H | $CH_2OTs$ | | | 735 |
| H |  | | | 735 |
| H | $m$-$MeOC_6H_4$ | | 177 | 736,737 |
| H | $p$-$FC_6H_4$ | | 186 | 736 |
| H | $m$-$FC_6H_4$ | | 162 | 736,737 |
| H | $p$-$BrC_6H_4$ | | 163 | 736,737 |
| H | $m$-$BrC_6H_4$ | | 174 | 736,737 |
| 3,9-$Cl_2$ | Ph | | 231 | 736 |
| 3,9-$Cl_2$ | $m$-$MeOC_6H_4$ | | 207 | 736 |

(*continued*)

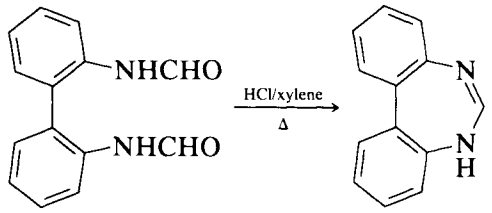
TABLE 176. (*Continued*)

| X | R | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|
| 3,9-$Cl_2$ | *p*-$MeC_6H_4$ | | 189 | 736 |
| 3,9-$Cl_2$ | *m*-$FC_6H_4$ | | 216 | 736 |
| 3,9-$Cl_2$ | *p*-$BrC_6H_4$ | | 228 | 736 |
| 3,9-$Cl_2$ | *m*-$BrC_6H_4$ | | 210 | 736 |
| 3,9-$Cl_2$ | *m*-$NO_2C_6H_4$ | | 212 | 736 |
| 2,10-$Cl_2$ | Ph | | 231 | 737 |
| 2,10-$Cl_2$ | *m*-$NO_2C_6H_4$ | | 212 | 737 |
| 2,10-$Cl_2$ | *p*-$MeC_6H_4$ | | 189 | 737 |
| 2,10-$Cl_2$ | *m*-$FC_6H_4$ | | 216 | 737 |
| 2,10-$Cl_2$ | *p*-$BrC_6H_4$ | | 228 | 737 |
| 3,9-$Br_2$ | Ph | | 234 | 737 |
| 3,9-$Br_2$ | *p*-$NO_2C_6H_4$ | | 264 | 737 |
| 3,9-$Br_2$ | *m*-$NO_2C_6H_4$ | | 214 | 737 |
| 3,9-$Br_2$ | *p*-$MeC_6H_4$ | | 212 | 737 |
| 3,9-$(CO_2Me)_2$ | Ph | | 230–232 | 731 |
| 3,9-$(NO_2)_2$ | Ph | | | 731 |



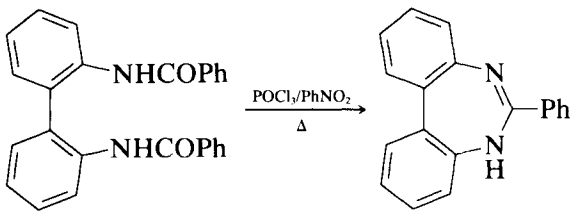

(307)

**1263** **1264**



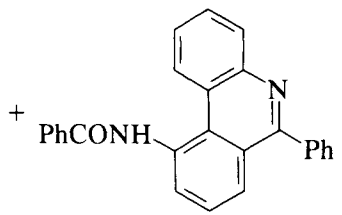

(308)

**1265**




**1266** **1268**

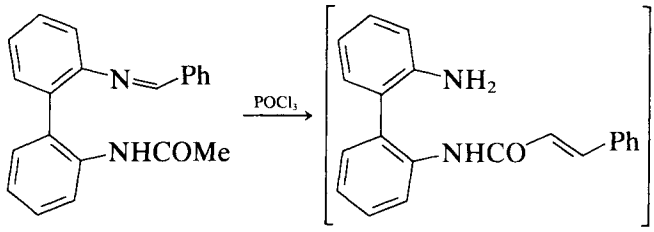
(309)



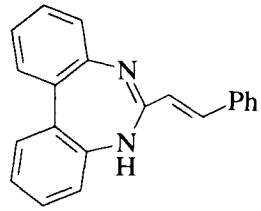

**1267**

of methyl iodide led to the *N*-methyl adduct **1276**, which could be quaternized with methyl sulfate to yield **1277** (743), as shown in Eq. 311. The cyclobutenediylium-2,4-diolate adduct **1278** was obtained from **1264** (745).

Guanidine derivatives of this ring system were produced as outlined in Fig. 115 (729,746). Condensation of **1252** with *S*-methylisothiourea sulfate (method A) led to **1279**, reaction of **1252** with carbodiimides produced **1280** (method B), and generation of the methylthio intermediate **1281** from **1260**

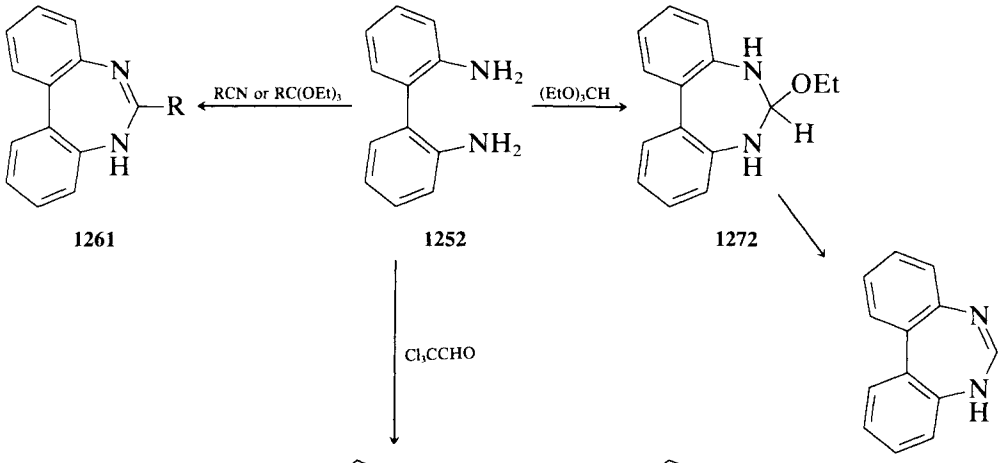



**1269** **1270**




**1271**

(310)

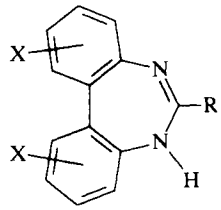



**1261** **1252** **1272** **1273**

**1274,** mp 111°C **1275,** mp 133°C

**Figure 114**

TABLE 177. 5*H*-DIBENZO[*d*,*f*][1,3]DIAZEPINES

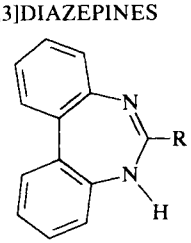


| X | R | mp (°C) | Refs. |
|---|---|---|---|
| H | Me | 228 | 732 |
| H | Ph | 165–166 | 732,739,741 |
| H | H | 245–246 | 732 |
| 1,11-$Me_2$ | Ph | 208 | 732 |
| 3,9-$(NO_2)_2$ | Ph | 348–350 | 741 |
| H | *o*-$HO_3SC_6H_4$ | 402–403 | 727,740 |
| H | CHCHPh | 148–151 | 739 |

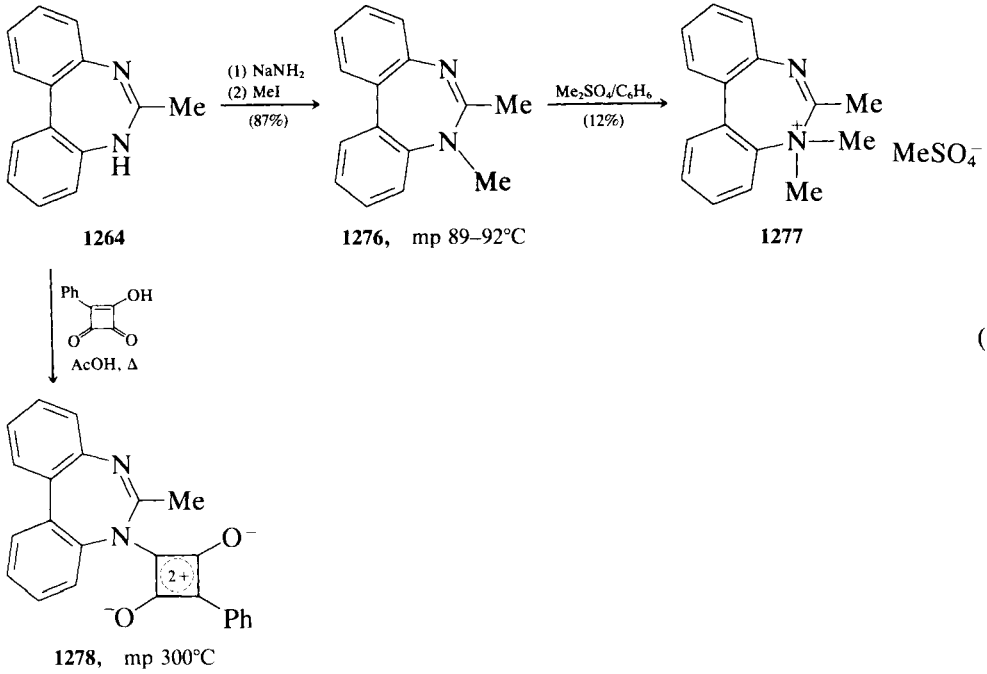
and subsequent amination afforded **1280** (method C). Compounds obtained via these routes are listed in Table 179.

Reduction of 2,2′-dinitrobiphenyl (**1282**) either chemically (747) or electrolytically (748,749) afforded 2,2′dihydroxyaminobiphenyl (**1283**), which could be trapped with aldehydes or ketones to give the diazepines **1284** (Fig. 116). Products prepared by this approach are listed in Table 180. When oxygen

TABLE 178. 5*H*-DIBENZO[*d*,*f*][1,3]DIAZEPINES



| R | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|
| Ph | | 160–164 | 727,741,743 |
| *p*-$NO_2C_6H_4$ | | 186–187 | 741 |
| *n*-$C_9H_{19}$ | 45 | 73–75 | 742,743 |
| H | 31 | 244–247 | 743 |
| Me | 70 | 168 | 727,743 |
| Et | 34 | 160–161 | 727,743 |
| EtO | 23 | 135 | 727 |
| H | 93 | 235 (picrate) | 727 |




**1264** **1276,** mp 89–92°C **1277**

(311)

**1278,** mp 300°C

was not excluded during the reduction, the cinnoline *N*-oxide **1285** was formed (749). The only chemistry reported for these dihydroxydiazepines was acetylation to **1286** (749). When formaldehyde was used to trap the reduction product **1283,** *N*-hydroxyamidine **1287** was isolated (749). Electrolysis of the mononitrobiphenyl **1288** afforded thione **1289** by intramolecular trapping (Eq. 312) (750).

Metal complexes of 6-arylamidines **1290** were obtained on reaction with titanium tetrachloride or stannic chloride (751), as shown in Eq. 313. Complexes obtained by this route are listed in Table 181.

Substitution at the 1- and 11-positions of this ring system results in rigid conformations and allows the preparation of optically active compounds (730,731,732). Starting from resolved 2,2′diamino-6,6′-dimethylbiphenyl, the corresponding diazepines **1291** and **1292** were obtained in optically active form.

A number of additional studies on members of this ring system were carried out. Mass spectra of several 5,7-dihydroxy derivatives of structure **1284** were analyzed (748,752), ionization constants for a series of amidines of structure **1261** were determined and correlated with Hammett $\sigma$-constants (736,753), and calculations on the electronic structure of the ring system were performed (737,754,755).

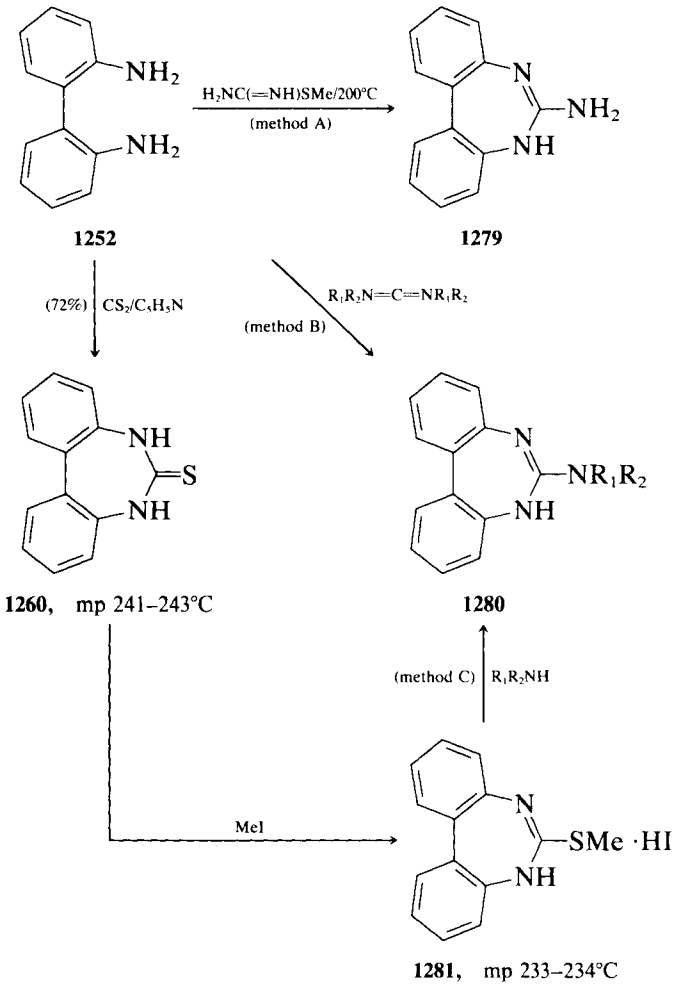
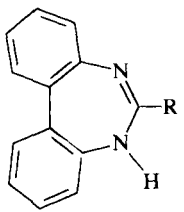
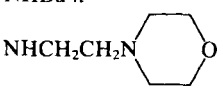
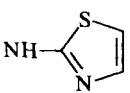
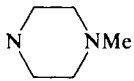
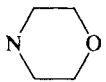
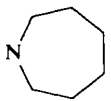

NH2
NH2
H2NC(=NH)SMe/200°C
(method A)
N
NH2
NH
1252
1279
(72%)
CS2/C5H5N
R1R2N=C=NR1R2
(method B)
NH
S
NH
N
NR1R2
NH
1260, mp 241–243°C
1280
(method C)
R1R2NH
MeI
N
SMe ·HI
NH
1281, mp 233–234°C

**Figure 115**

TABLE 179. 6-AMINO-5*H*-DIBENZO[*d*,*f*][1,3]DIAZEPINES AND INTERMEDIATE METHYLTHIO COMPOUNDS

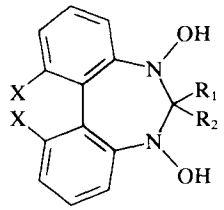


| R | Method[a] | Yield (%) | Salt | mp (°C) | Refs. |
|---|---|---|---|---|---|
| $NH_2$ | A | 36 | | 208–209 | 729,746 |
| $NHC_6H_{11}$ | B | 41 | | 231–232 | 729,746 |
| NHPr-*i* | B | 52 | | 228–229 | 729,746 |
| NHMe | C | 90 | | 243–245 | 729,746 |
| NHEt | C | 58 | | 213–215 | 729,746 |
| NHBu-*n* | C | 48 | HCl | 239–241 | 729,746 |
|  | C | 70 | 2HCl | 277–278 | 729,746 |
|  | C | 89 | | 204–205 | 729,746 |
| NHOH | C | 90 | HCl | 225–226 | 729,746 |
| $NHCH_2CO_2Et$ | C | 41 | HCl | 193–194 | 729,746 |

| | | | | | |
|---|---|---|---|---|---|
| NHPh | C | 96 | | 255–256 | 729,746 |
| $NMe_2$ | C | 54 | HCl | >310 | 729,746 |
| $NEt_2$ | C | 56 | HCl | >310 | 729,746 |
|  | C | 67 | | 144–145 | 729,746 |
|  | C | 44 | | >310 | 729 |
|  | C | 87 | | >310 | 729 |
|  | C | 74 | | >310 | 729,746 |
|  | C | 53 | | 69–80[b] | 729,746 |
| $NMeCH_2CH_2NMe_2$ | C | 76 | HCl | 250–251 | 729,746 |
| $NMeCH_2CH_2NEt_2$ | C | 81 | 2HCl | 246–247 | 729,746 |
| $NEtCH_2CH_2NEt_2$ | C | 68 | 2HCl | 159–161 | 729,746 |
| MeS | | | | 165–166 | 729,746 |

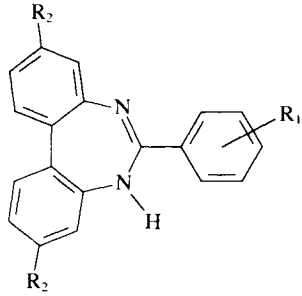
[a]See Fig. 115.
[b]EtOH solvate.

TABLE 180. 6-SUBSTITUTED 5,7-DIHYDROXY-5*H*-DIBENZO[*d*,*f*][1,3]DIAZEPINES




| X | $R_1$ | $R_2$ | mp (°C) | Refs. |
|---|---|---|---|---|
| H | H | Me | 168–170 | 747,749 |
| H | H | Et | 139–142 | 747,749 |
| H | H | *n*-$C_3H_7$ | 120–122 | 749 |
| H | H | *n*-$C_4H_9$ | 110–112 | 749 |
| H | Me | Me | 231–232 | 749 |
| H | Me | Et | 188–189 | 749 |
| H | Me | *n*-$C_3H_7$ | 200–203 | 749 |
| H | $CD_3$ | $CD_3$ | 227–230 | 749 |
| H | $(CH_2)_4$ | | 202–204 | 749 |
| H | $(CH_2)_5$ | | 175–178 | 749 |
| H | H | 4-Pyridyl | 215–217 | 749 |
| H | H | 5-Methyl-2-thiazolyl | 185–186 | 749 |
| Me | H | Me | 145–147 | 749 |
| Me | Me | Me | 187–189 | 749 |

TABLE 181. 6-ARYL-5*H*-DIBENZO[*d*,*f*][1,3]DIAZEPINES




| $R_1$ | $R_2$ | Salt |
|---|---|---|
| H | H | $TiCl_4$, $SnCl_4$ |
| *p*-Me | H | $TiCl_4$ |
| *p*-$NO_2$ | H | $TiCl_4$, $SnCl_4$ |
| *m*-$NO_2$ | H | $TiCl_4$, $SnCl_4$ |
| *p*-F | H | $TiCl_4$, $SnCl_4$ |
| *p*-MeO | H | $TiCl_4$ |
| H | Cl | $TiCl_4$ |
| *p*-Me | Cl | $SnCl_4$ |

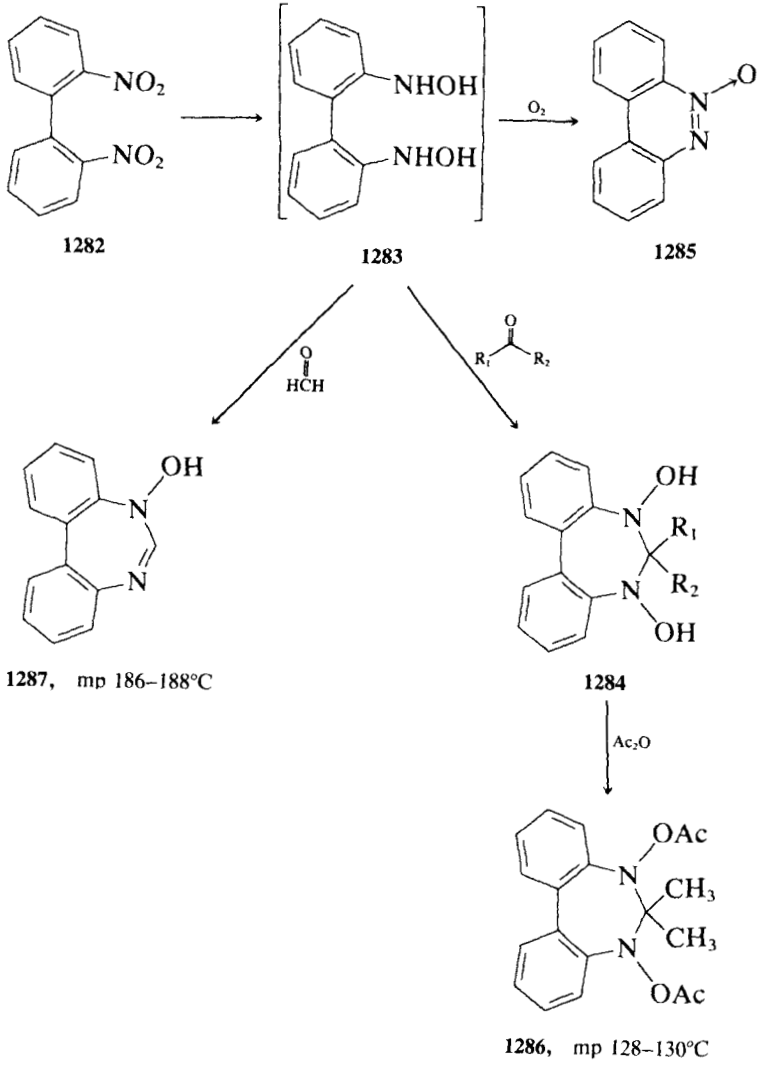
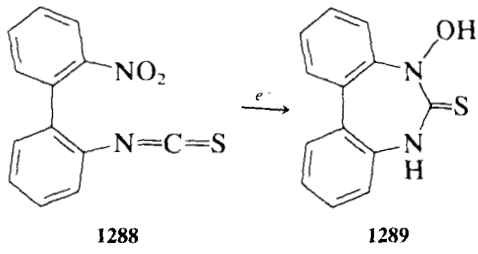
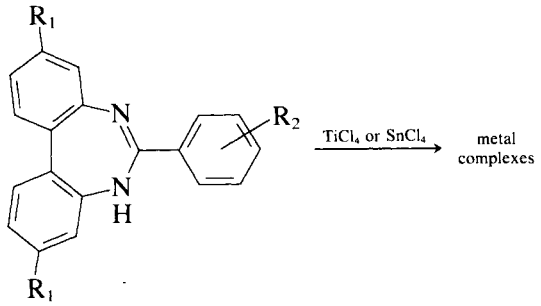



**Figure 116**

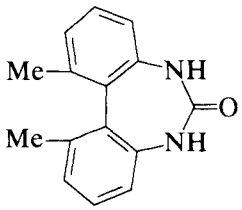



(312)

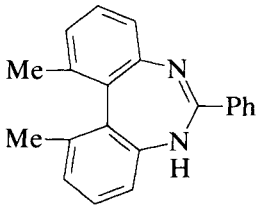



(313)

1290




1291

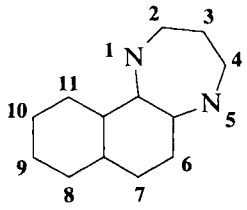



1292

| | $[\alpha]_D$ | mp (°C) |
|---|---|---|
| R-(−) | −67.2 | 332 |
| S-(+) | +75.7 | 350 |

| | $[\alpha]_D$ | mp (°C) |
|---|---|---|
| R-(−) | −1010 | 244–245 |
| S-(+) | +1000 | 242–244 |

## 51. Naphtho[1,2-*b*][1,4]diazepines




The definitive study on the reaction of 1,2-diaminonaphthalene with ethyl acetoacetate and crotonic acid was published by Israel and Zoll in 1972 (756). These reactions led to the formation of derivatives of the naphtho[1,2-*b*][1,4]diazepine ring system. Earlier, similar studies had led to erroneous or vague conclusions (757,758,759).

Israel and Zoll reported that the reaction of 1,2-diaminonaphthalene and ethyl acetoacetate in refluxing xylene (Fig. 117) gave the isopropenylimidazolone **1293** and the naphthodiazepine **1294**. Structure **1293** was confirmed by unambiguous synthesis of the corresponding dihydro derivative. It was realized that the imidazolone product arose by thermal rearrangement of the

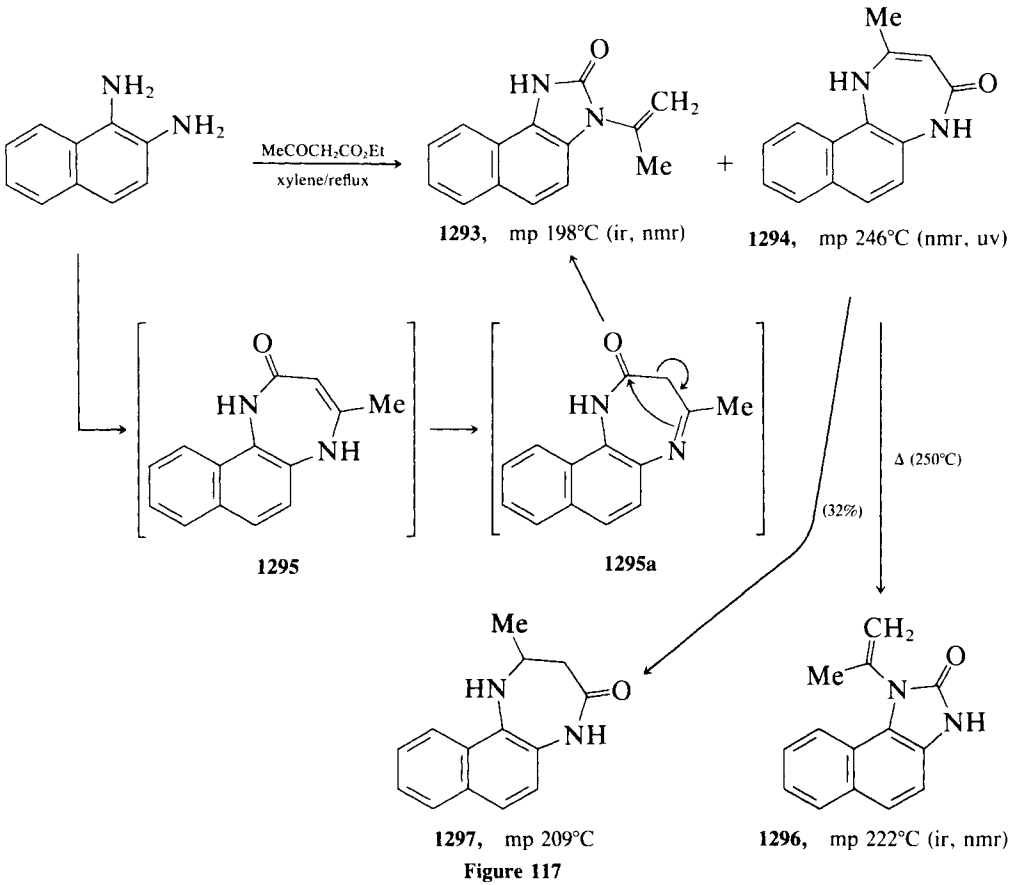
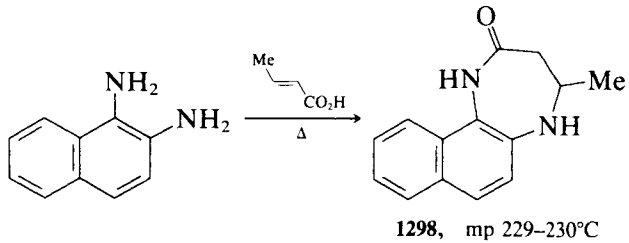



**Figure 117**

transitory diazepine intermetidate **1295**. However, thermolysis of **1294** did not give rise to **1293**; instead, the isomeric isopropenylimidazolone derivative **1296** was formed (but only at 250°C). No trace of **1295** would be found in the original reaction mixture. Fusion of 1,2-diaminonaphthalene with crotonic acid (Eq. 314) gave a product that was different from the lactam (**1297**) obtained by hydrogenation of **1294.** Thus the crotonic acid/1,2-naphthalenediamine product was assigned structure **1298**.

Products from the reactions described above had previously been assigned incorrect structures (757). Other reactions described in this earlier study




(314)

**1298**, mp 229–230°C

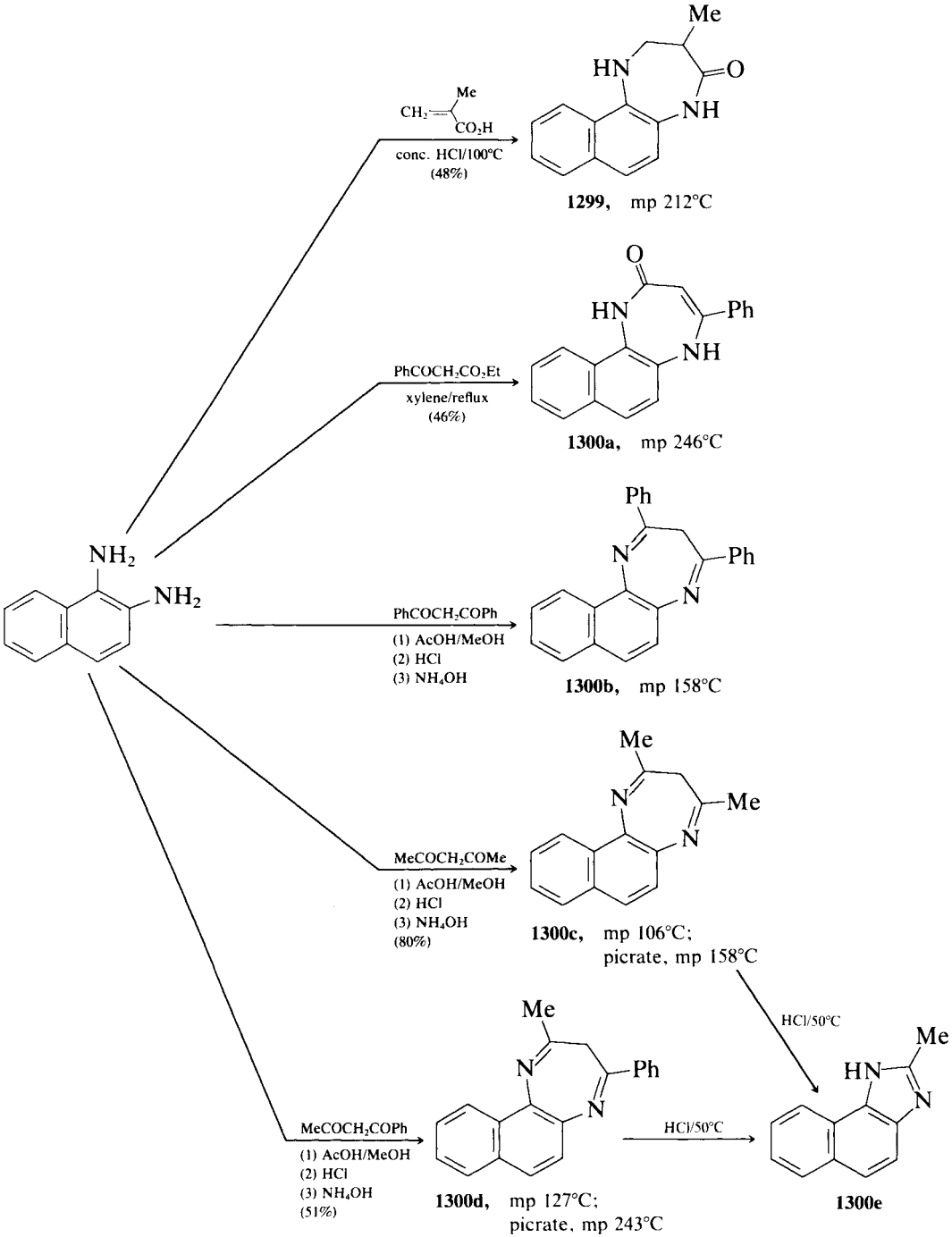
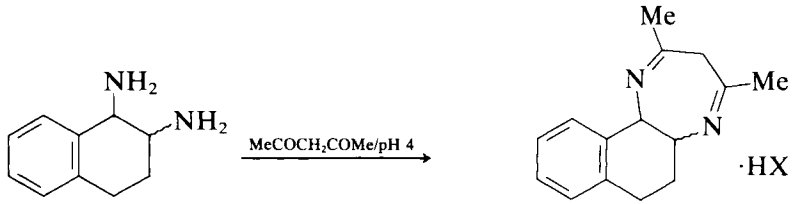

Me
HN
O
NH
CH2=C(Me)CO2H
conc. HCl/100°C
(48%)
1299, mp 212°C
O
HN
Ph
NH
PhCOCH2CO2Et
xylene/reflux
(46%)
1300a, mp 246°C
NH2
NH2
Ph
N
Ph
N
PhCOCH2COPh
(1) AcOH/MeOH
(2) HCl
(3) NH4OH
1300b, mp 158°C
Me
N
Me
N
MeCOCH2COMe
(1) AcOH/MeOH
(2) HCl
(3) NH4OH
(80%)
1300c, mp 106°C;
picrate, mp 158°C
HCl/50°C
Me
N
Ph
N
MeCOCH2COPh
(1) AcOH/MeOH
(2) HCl
(3) NH4OH
(51%)
HCl/50°C
Me
HN
N
1300d, mp 127°C;
picrate, mp 243°C
1300e

**Figure 118**

(757) are listed in Fig. 118. The identity of the products **1299** and **1300a**, obtained by reaction of 1,2-naphthalenediamine with methacrylic acid and ethyl benzoylacetate, respectively, are open to question. Reaction of the diamine with β-ketones was also studied, but the structures **1300b–d** assigned to the products were not proved. Compounds **1300c** and **1300d** were thermally unstable, and both gave the same imidazole derivatives (**1300e**) at 50°C (Fig. 118). In a later study of the condensation reaction with acetylacetone (24), the 1,2-diaminonaphthalene was prepared *in situ*, and the final product was isolated as a perchlorate salt. Corresponding derivatives were prepared by allowing the isomeric 1,2,3,4-tetrahydro-1,2-diaminonaphthalenes to react with 2,4-pentanedione at pH 4 (Eq. 315). Ultraviolet spectra of the two salts (*cis*-**1300f** and *trans*-**1300f**) indicated that both kinds of ring fusion could accommodate the chromophore without distortion (443).

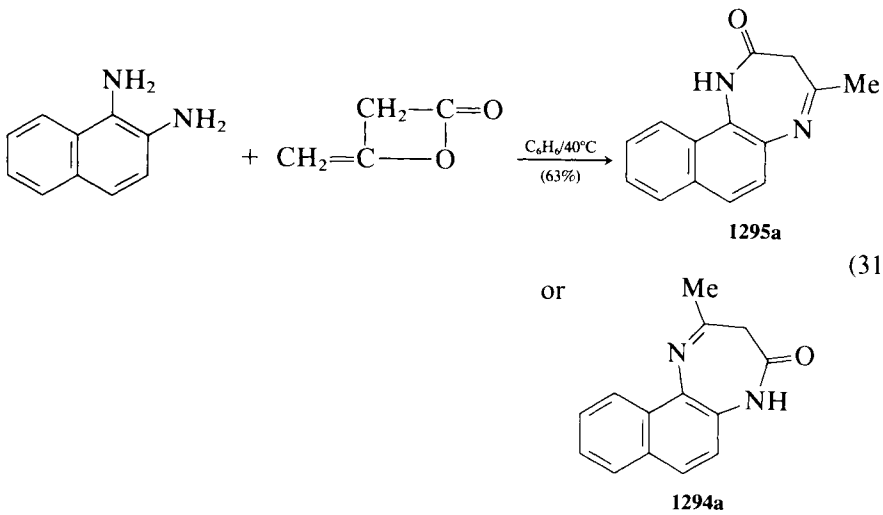



(315)

*cis*-**1300f**, X = $ClO_4$ (54%); mp 154–157°C (uv, nmr)

*trans*-**1300f**, X = Cl (63%); mp >300°C (uv, nmr)

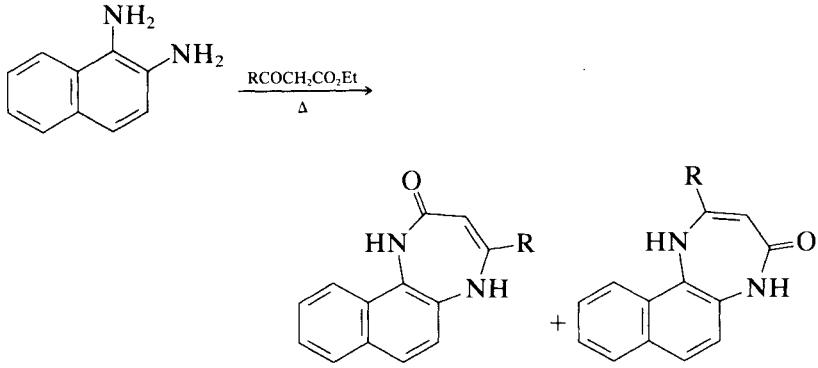
Ried and Torinus (758) reported that the reaction of 1,2-naphthalenediamine with diketene yielded a product melting at 227°C, but the structure of this compound was left uncertain (Eq. 316). In a later study Barchet and Merz (759) reinvestigated the reaction of 1,2-naphthalenediamine with ethyl




(316)

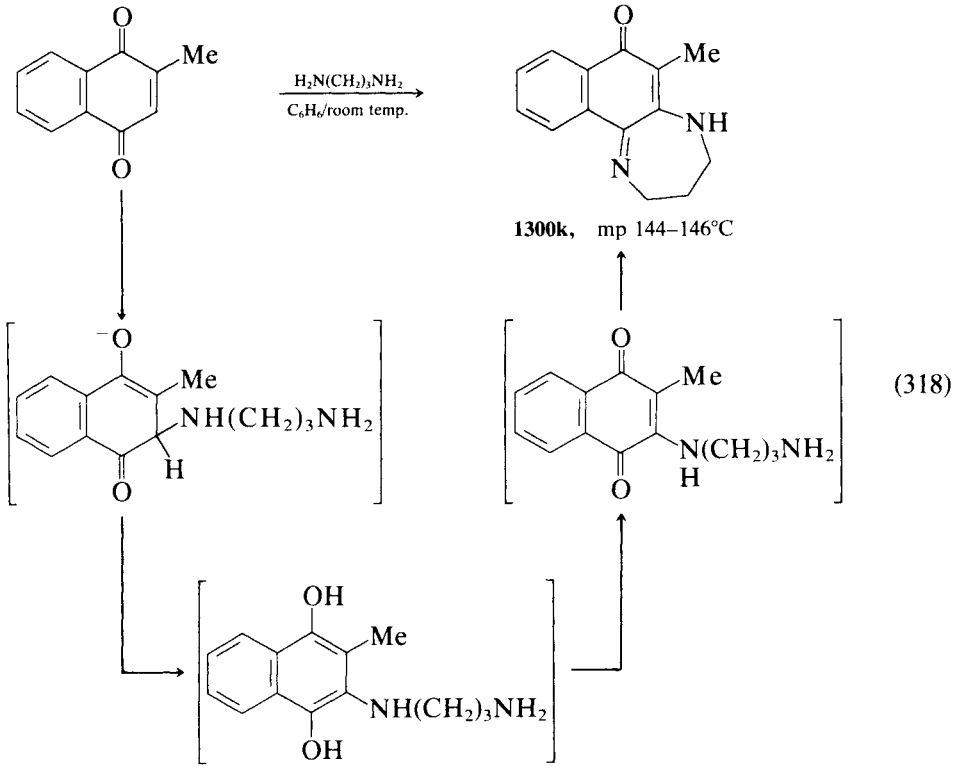
benzoylacetate and obtained a mixture of the products **1300g** and **1300h**, as shown in Eq. 317. A mixture of compounds **1300i** and **1300j** was formed when ethyl nicotinoylacetate was used.

Reaction of 2-methylnaphthoquinone with 1,3-diaminopropane gave the tricyclic derivative **1300k** (Eq. 318). The reaction was run in the presence




(317)

**1300g/1300h,** R = Ph; mp 189–232°C (uv, ir)
**1300i/1300j,** R = 3-pyridyl; mp 209–230°C (uv, ir)

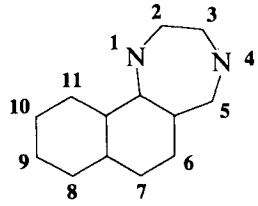



(318)

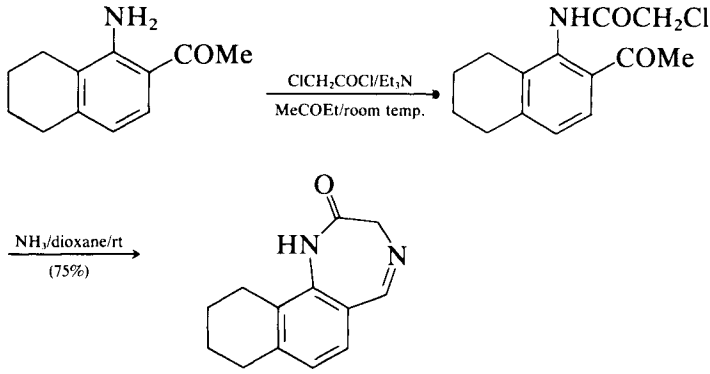
of air. The intermediate aminohydroquinone presumably underwent oxidation to a quinone followed by cyclization (760).

No general correlation was found between the proton chemical shifts and the $\pi$-electron densities at the adjacent carbon atom of a number of diazepinium perchlorates (761).

## 52. Naphtho[1,2-*e*][1,4]diazepines



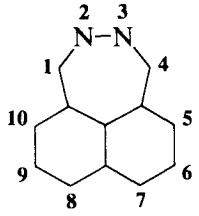

The only known naphtho[1,2-*e*][1,4]diazepine (762) is the lactam **13001**, which was prepared as shown in Eq. 319.




(319)

**13001**, mp 206–208°C (ir, nmr)

## 53. Naphtho[1,8-*de*][1,2]diazepines (see Section XVI.25)



In 1925 Bistrzycki and Risi (763) reported that treatment of the anhydride **1301** with hydrazine hydrate in refluxing ethanol (Fig. 119) gave the cyclic hydrazide **1302**, which could be distinguished from the isomeric *N*-aminoimide obtained earlier (764), since it failed to react with a second mole of anhydride and did not form a benzylidene derivative. Acetylation gave the diacetyl derivative **1303**. Subsequently, the 8-nitro derivative **1304** was also prepared (765). Polish workers (766) reported that treatment of **1302** with 2,4-dinitrochlorobenzene gave the *N*-aryl derivative **1305**, which rearranged

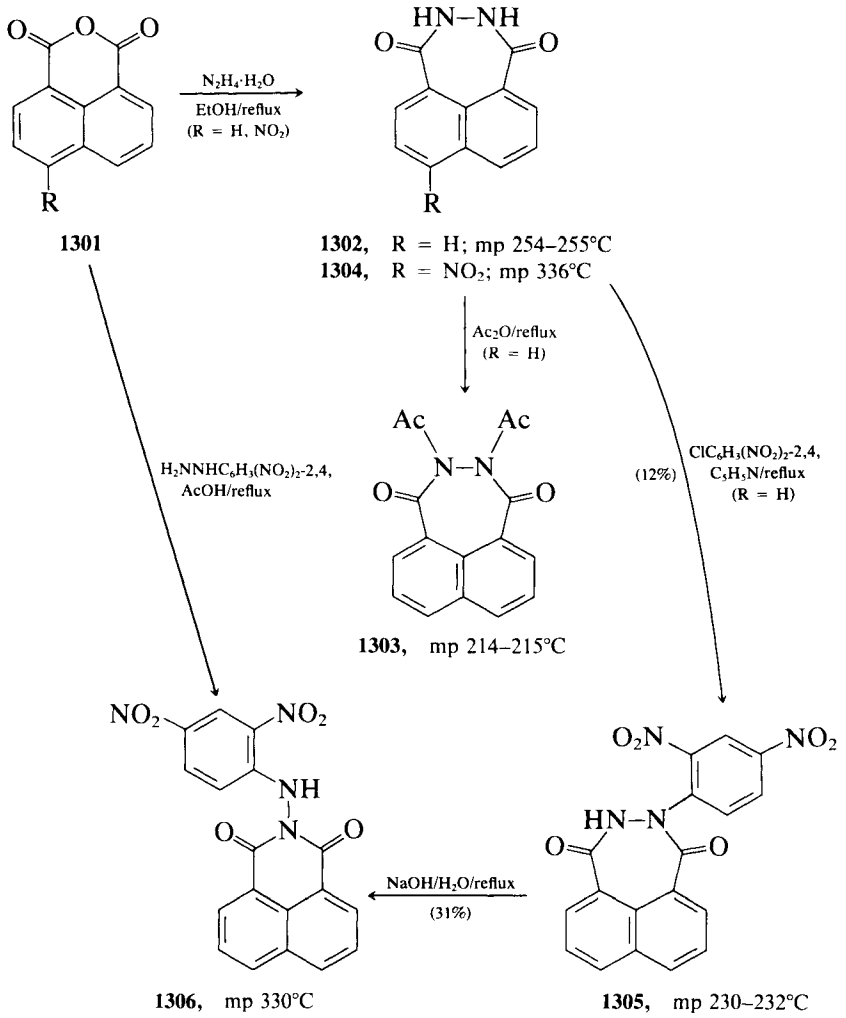



**Figure 119**

under basic conditions to the anilinoimide **1306**. Compound **1306** could also be obtained from the anhydride **1301** with 2,4-dinitrophenylhydrazine.

Reaction of the dibromide **1307** with the dipotassium salt of *tert*-butyl hydrazodiformate gave the naphtho[1,8-*de*][1,2]diazepine derivative **1308** (Fig. 120) (767). The dicarbamate was hydrolyzed to the cyclic hydrazine **1309,** which was in turn oxidized either to the azo compound **1310** or the hydrazone **1311**. Benzoylation of **1309** yielded the bis(benzamide) **1312**.

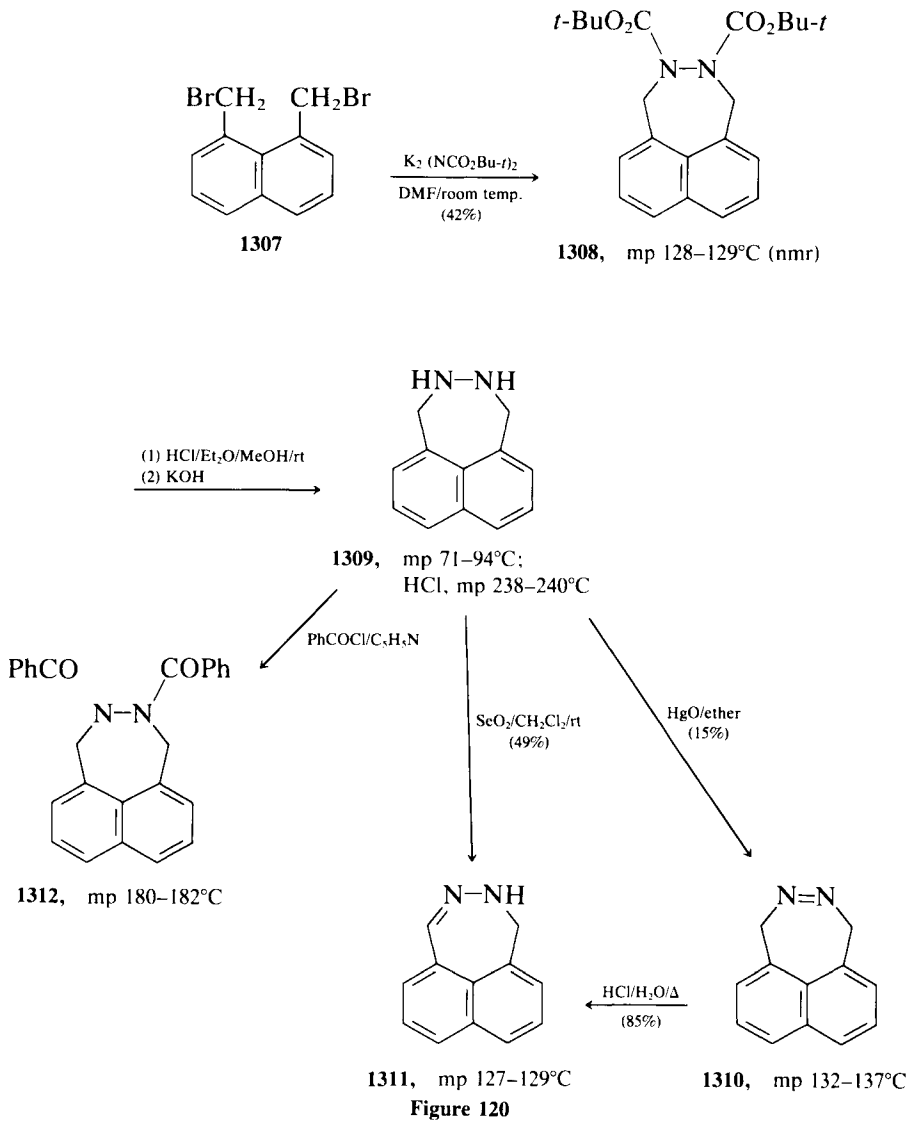
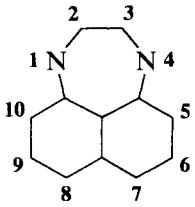
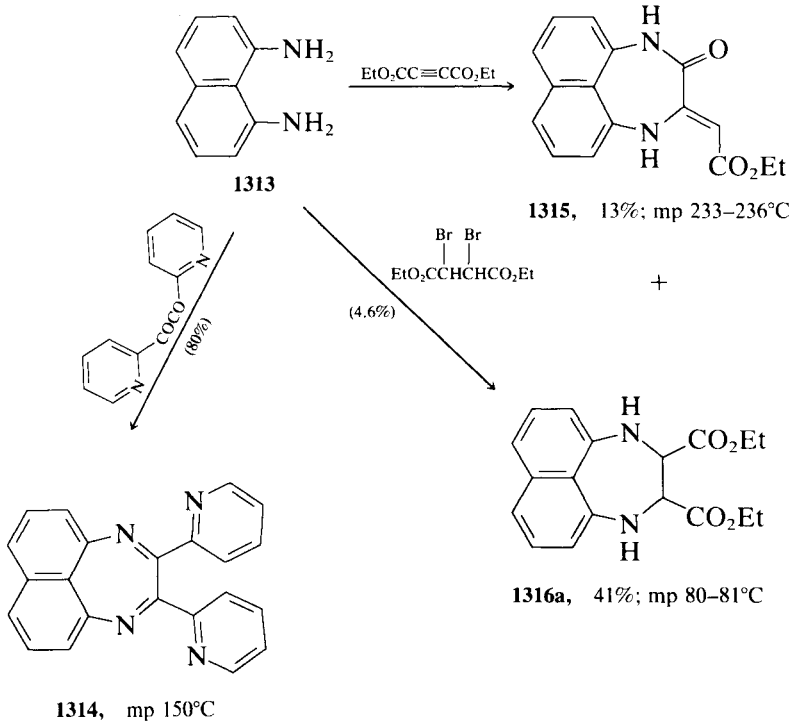



**Figure 120**

## 54. Naphtho[1,8-*ef*][1,4]diazepines



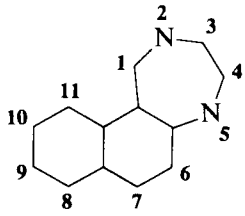

Naphtho[1,8-*ef*][1,4]diazepines have been prepared from 1,8-diaminonaphthalene (**1313**) as shown in Eq. 320. Condensation of **1313** with 2,2′-



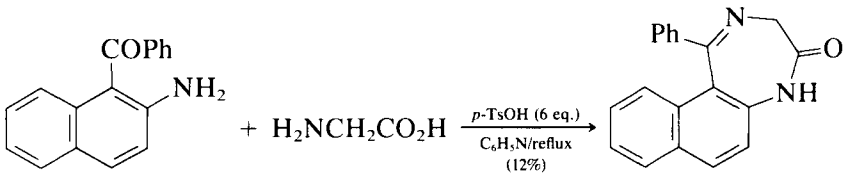

(320)

pyridil gave **1314** in 80% yield (768). With diethyl acetylenedicarboxylate, **1313** yielded the tricyclic diazepines **1315** and **1316a**. Product **1316a** could also be prepared in low yield from diethyl 2,3-dibromosuccinate (769). These compounds were evaluated for their metal-chelating properties.

## 55. Naphtho[2,1-*e*][1,4]diazepines



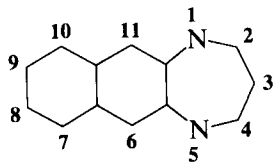

Condensation of 2-amino-1-naphthophenone with glycine under the conditions specified in Eq. 321 gave the naphtho[2,1-*e*][1,4]diazepine derivative **1316b** (770), which is the sole known member of this ring system to date.



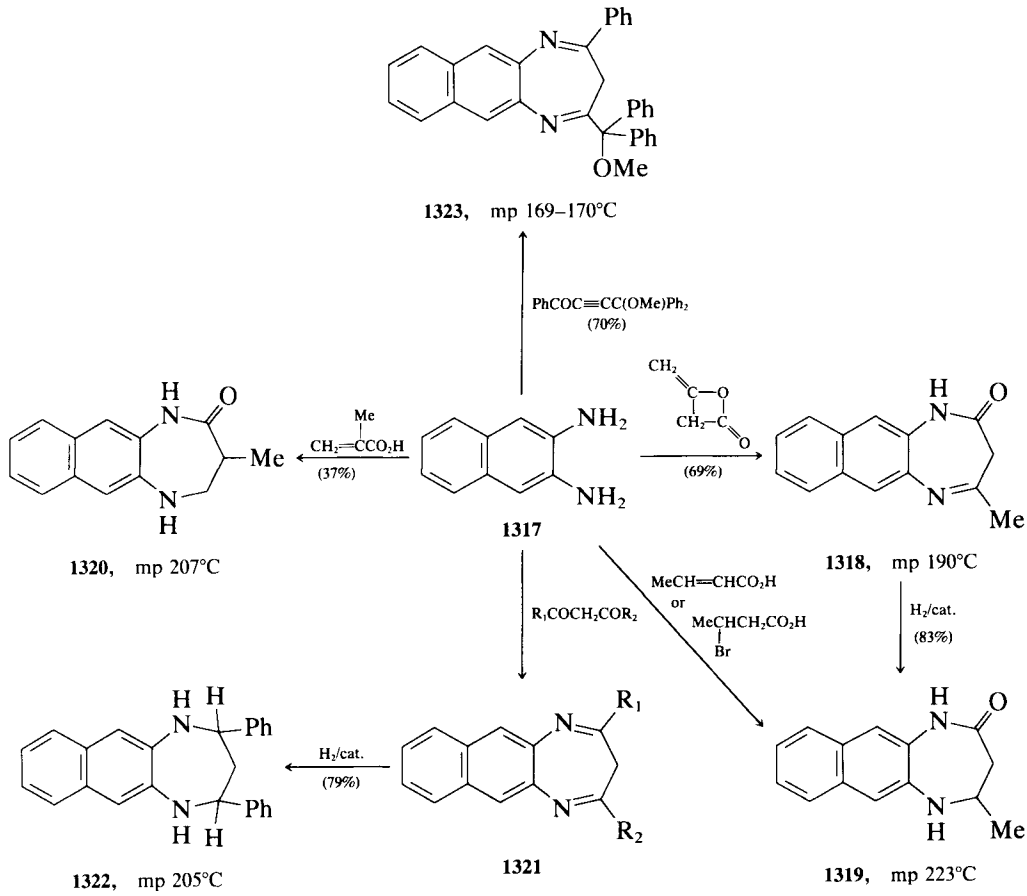

(321)

**1316b**, mp 156–159°C

## 56. Naphtho[2,3-*b*][1,4]diazepines (see Section XVI.26)




Naphtho[2,3-*b*][1,4]diazepines were prepared from 2,3-diaminonaphthalene (**1317**) using chemistry developed for *o*-phenylenediamine. Thus, as shown in Fig 121, condensation of **1317** with diketene afforded the tricyclic diazepinone **1318**, which could be hydrogenated to **1319** in 83% yield. Compound **1319** could also be obtained directly from **1317** by reaction with crotonic acid (37% yield) or 3-bromobutyric acid (62% yield) (758). Similarly, reaction of **1317** with methacrylic acid at 180°C generated diazepine **1320** in 37% yield (758). The use of 1,3-diketones for condensations with **1317** usually produced unstable iminium salts or 2-substituted benzimidazoles, but in several cases an isolable diazepine product (**1321**) was obtained (24,758). Hydrogenation of **1321** ($R_1$ = $R_2$ = Ph) yielded the stable diazepine **1322** (758). Treatment

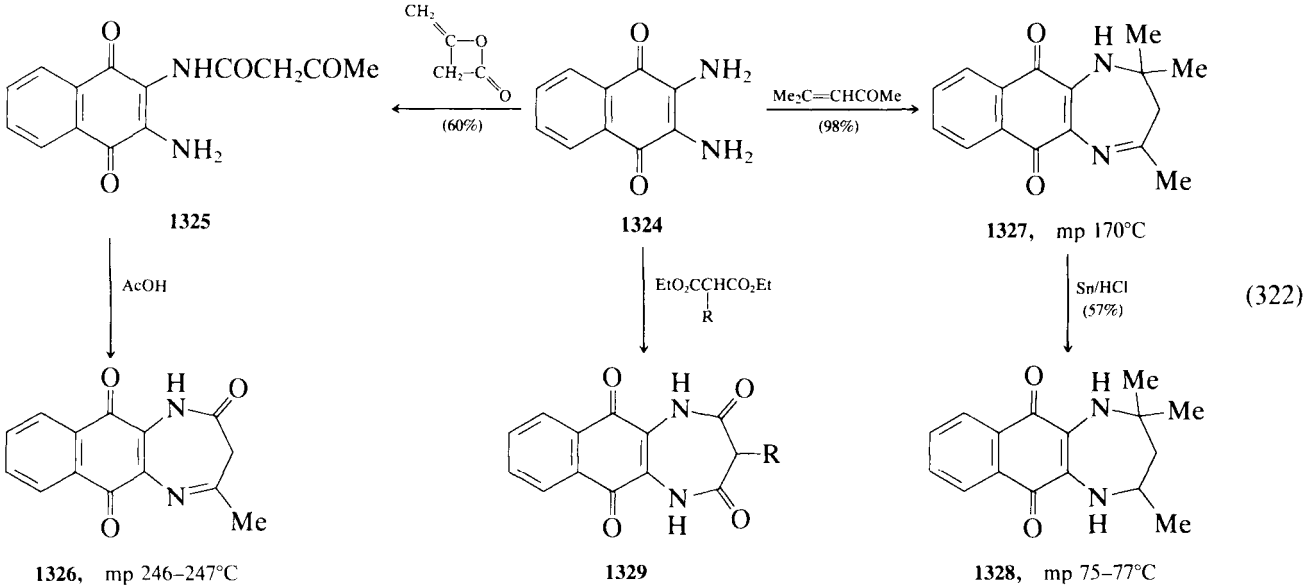



| $R_1$ | $R_2$ | Yield (%) | mp (°C) | Refs. |
|---|---|---|---|---|
| Ph | Me | 81 | 102 | 758 |
| Ph | Ph | 87 | 170 | 758 |
| Me | Me | 79 | 256–260 (HCl) | 24 |

**Figure 121**

of **1317** with an acetylenic ketone led to **1323** (771). MO calculations for this ring system were performed and compared with long-wavelength transitions (761).

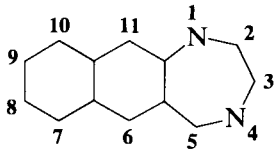
Analogous chemistry carried out with 2,3-diamino-1,4-naphthoquinone (**1324**) is outlined in Eq. 322. Condensation with diketene led to the diazepine **1326** via amide **1325** (772). Reaction of **1324** with mesityl oxide afforded **1327**, which could be reduced with tin in hydrochloric acid to **1328** (773). Condensation of **1324** with substituted malonate esters at 150–170°C generated the diazepinediones **1329** (774).



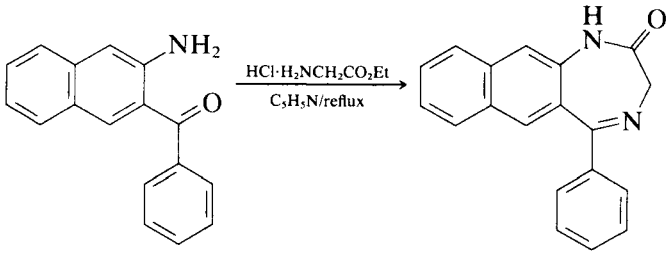

(322)

| R | mp (°C) | Yield (%) |
|---|---|---|
| H | 126–127 | 90 |
| *n*-Pr | 154–155 | 84 |
| *n*-Bu | 136 | 80 |
| $CH_2Ph$ | 121 | 72 |

## 57. Naphtho[2,3-*e*][1,4]diazepines

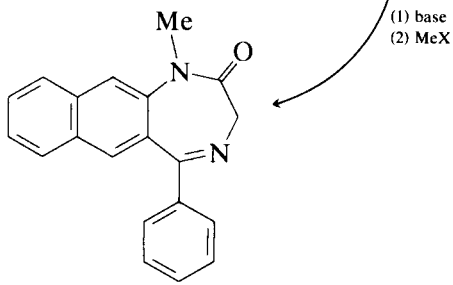



Reaction of the amino ketone **1330** with ethyl glycinate gave the naphthodiazepine derivative **1331a**, as shown in Eq. 323. The *N*-methyl derivative **1331b** was prepared from **1331a** by an unspecified procedure (775). A similar approach was used (762) to prepare the tetrahydronaphthalene derivative **1331c** (Eq. 324).

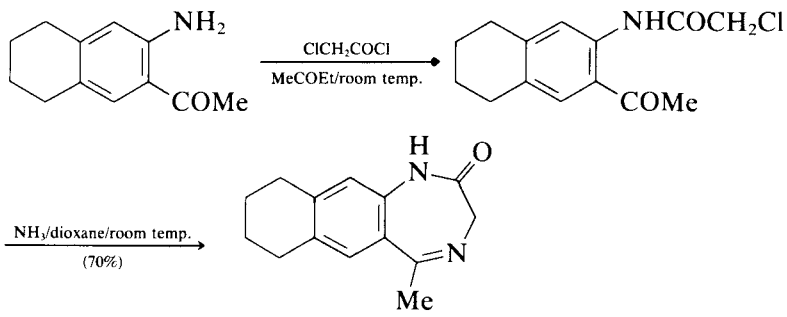



**1330** **1331a**, mp 276–278°C

(323)




**1331b**, mp 153–155°C

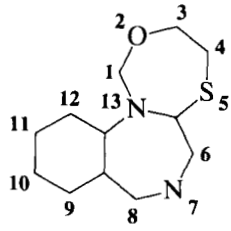



(324)

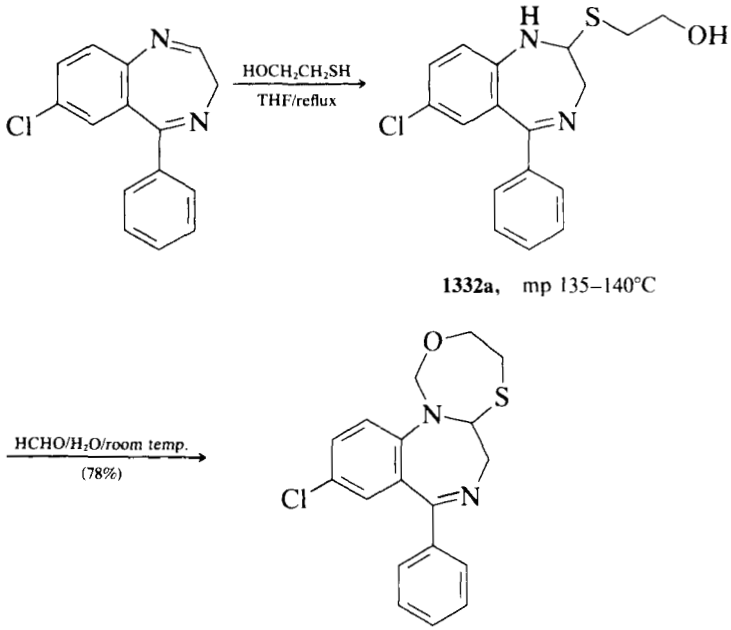
**1331c**, mp 230–232°C (ir, nmr)

# X. 6,7,7-SYSTEMS

## 1. [1,5,3]Oxathiazepino[3,4-*a*][1,4]benzodiazepines




As part of a study (90) of the reactions of 7-chloro-5-phenyl-3*H*-[1,4] benzodiazepine, nucleophiles were found to add readily to the unhindered imine function. Reaction with mercaptoethanol gave the adduct **1332a,** which was converted to the tricyclic oxathiazepine derivative **1332b** on treatment with formaldehyde (Eq. 325).

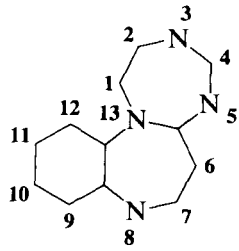



**1332a,** mp 135–140°C

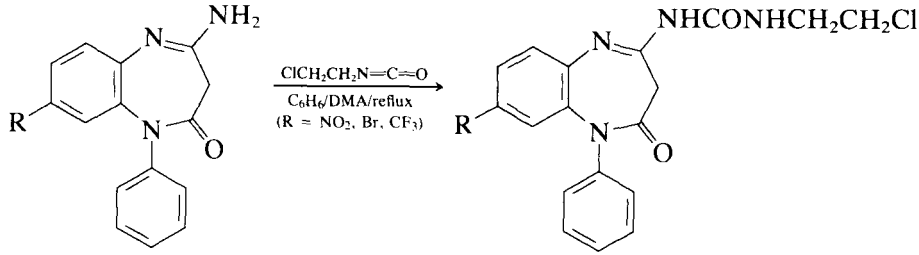
**1332b,** mp 160–164°C (ir, nmr, ms)

(325)

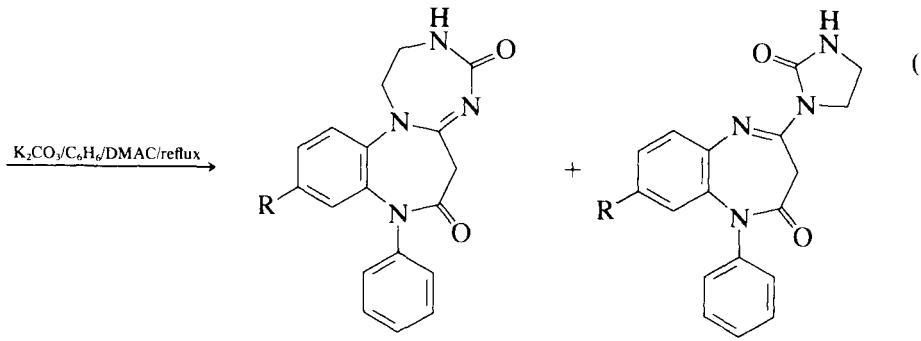
## 2. [1,3,5]Triazepino[1,2-*a*][1,5]benzodiazepines



Reaction of the amidines **1333** with chloroethyl isocyanate gave the ureas **1334,** which could be cyclized under basic conditions to give mixtures of the fused triazepine derivatives **1335a–c** and the corresponding imidazolidinones **1336**, as shown in Eq. 326. The isomeric products could be differentiated on the basis of their nmr spectra (776). The conformationally rigid nature of the diazepine ring in compounds **1335a–c** resulted in signals for the $CH_2$ protons that were much sharper than the corresponding signals in the spectra of the imidazolidinones.




**1333** **1334**

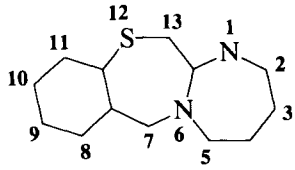



(326)

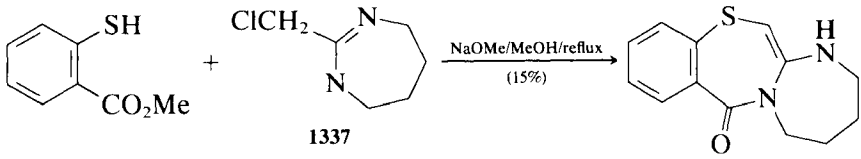
**1335a,** R = $NO_2$; mp 268–270°C
**1335b,** R = Br; mp 200–203°C
**1335c,** R = $CF_3$; mp 208–210°C

**1336**

### 3. [1,3]Diazepino[2,1-*c*][1,4]benzothiazepines



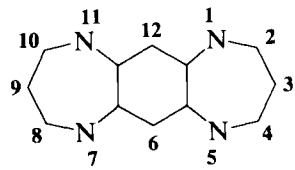

As shown in Eq. 327, reaction of methyl thiosalicylate with the chloromethylamidine **1337** gave the thiazepine derivative **1338** (777).




(327)

**1338**, mp 246°C

### 4. Benzo[1,2-*b*:4,5-*b*']bis[1,4]diazepines




In the single study on benzo[1,2-*b*;4,5-*b*']bis[1,4]diazepine derivatives reported to date (778), 1,2,4,5-tetraaminobenzene was first condensed with ethyl acetoacetate (Fig. 122) to give an open-chain product whose structure was apparent from the presence of two nonequivalent aromatic protons in the nmr spectrum. Cyclization of this intermediate with sodium ethoxide in ethanol gave the tricyclic derivative **1339**. The position of the double bonds in **1339** was determined on the basis of nmr studies. Acid hydrolysis of **1339** gave a bisimidazole. Condensation of 1,2,4,5-tetraaminobenzene tetrahydrochloride with acetylacetone in aqueous pyridine gave the tricyclic derivative **1340** in a single step.

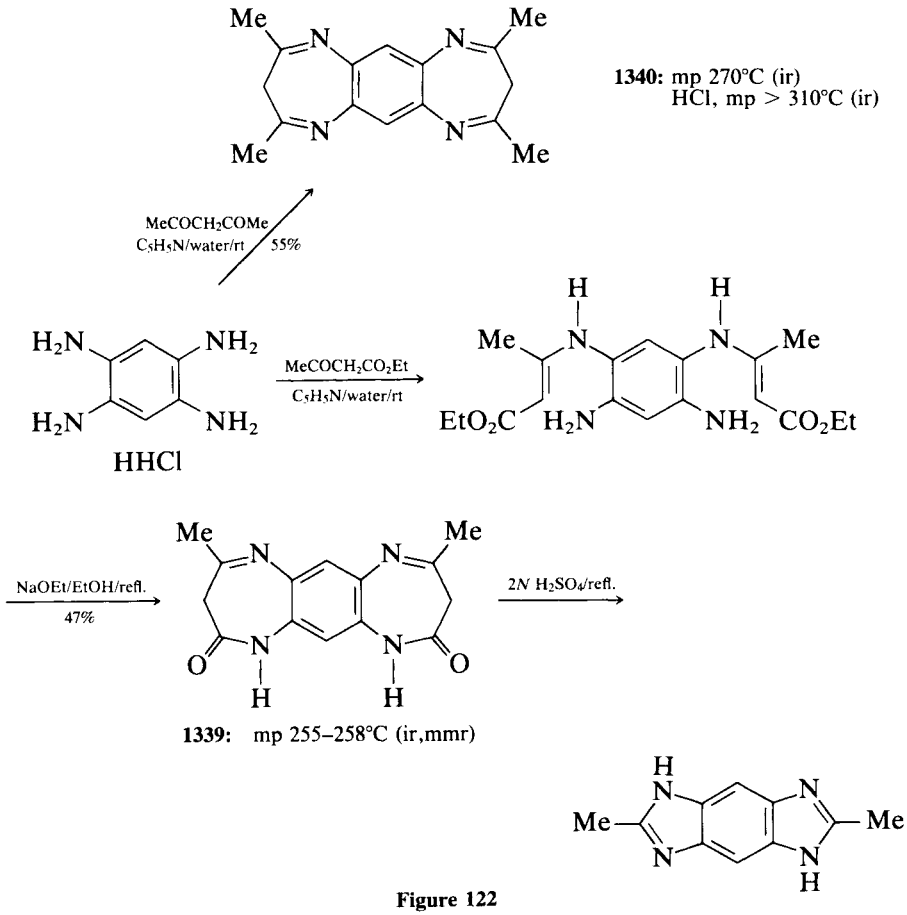
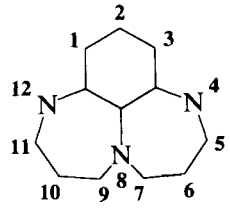
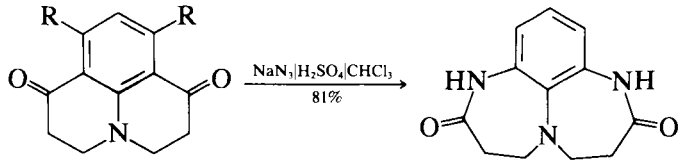



Figure 122

## 5. [1,4]Diazepino[1,2,3,-*ef*][1,5]benzodiazepines




When 1,6-dioxojulolidine (**1341**) was subjected to a Schmidt reaction (779), dilactam **1342** was the presumed product. No reaction was observed with the dimethyl compound **1343** (Eq. 328).

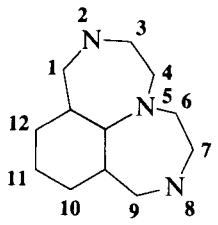


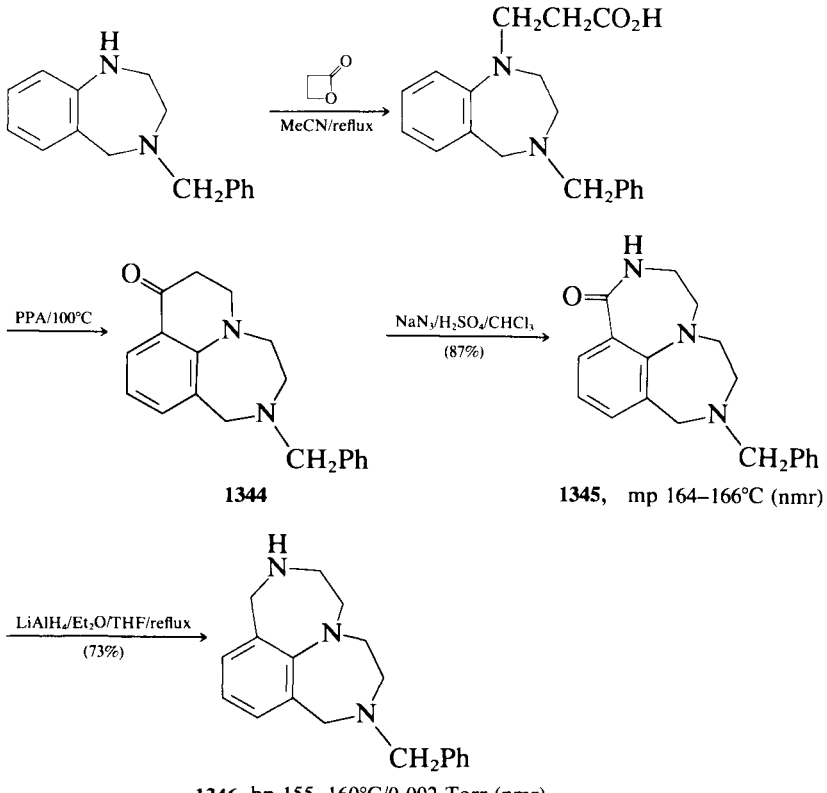

(328)

**1341;** R = H
**1343;** R = Me

**1342:** mp 356°C

## 6. [1,4]Diazepino[6,7,1-*jk*][1,4]benzodiazepines




**1344**

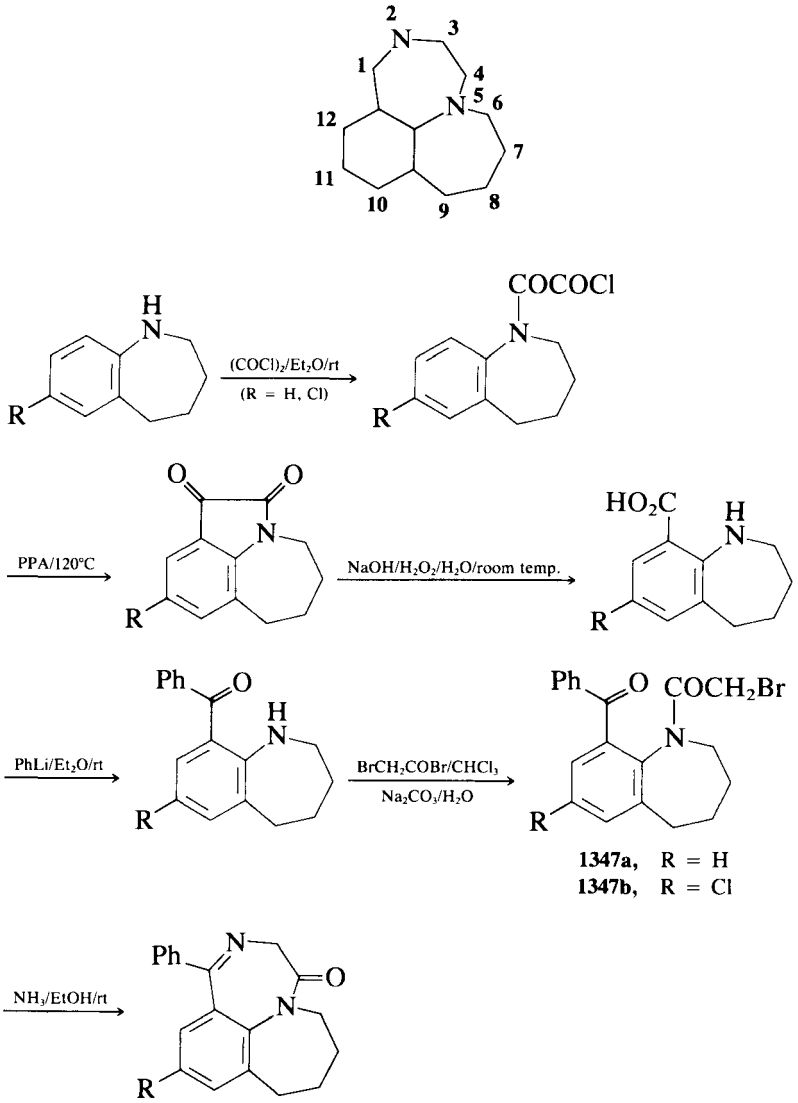
**1345,** mp 164–166°C (nmr)

**1346,** bp 155–160°C/0.002 Torr (nmr)

**Figure 123**

Ring enlargement of the pyridobenzodiazepinone derivative **1344** via a Schmidt reaction (Fig. 123) gave the lactam **1345**, whose structure was determined from the nmr spectrum of the lithium aluminum hydride reduction product **1346** (489).

## 7. Azepino[3,2,1-*jk*][1,4]benzodiazepines



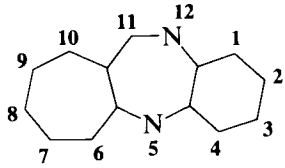

**1347a**, R = H
**1347b**, R = Cl

**1348a**, R = H (47%); mp 208–209°C
**1348b**, R = Cl (63%); mp 165–166°C

**Figure 124**

Two examples of azepino[3,2,1-*jk*][1,4]benzodiazepines have been prepared (780) via standard reactions in benzodiazepine chemistry (Fig. 124). The key step in the formation of the tricyclic products **1348a** and **1348b** was the reaction of the bromoketones **1347a** and **1347b** with ammonia.

## 8. Benzo[*b*]cyclohepta[*e*][1,4]diazepines (see Section XVII.4)




As shown in Fig 125, condensation of 2-hydroxymethylenecycloheptan-tricyclic diazepinium salt **1349**, which was readily hydrolyzed in warm water. one with *o*-phenylenediamine in the presence of perchloric acid gave the

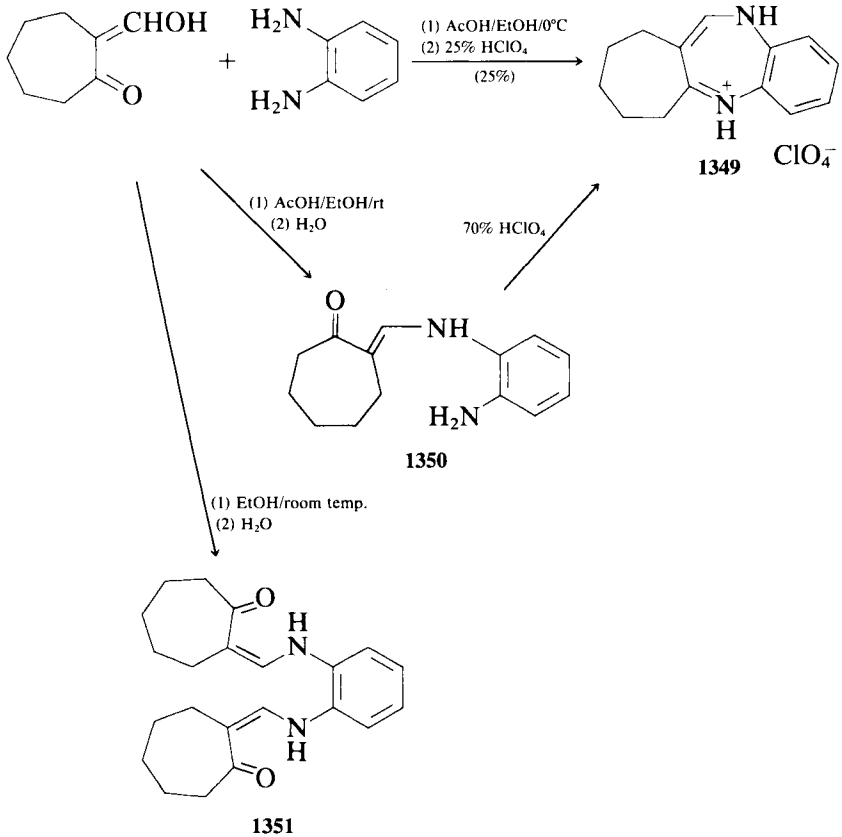
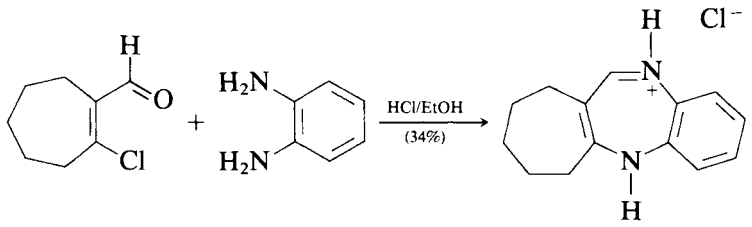


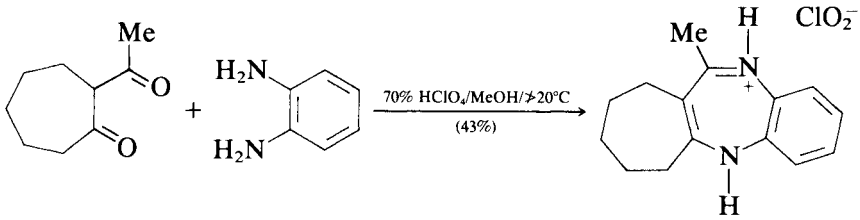

**Figure 125**

When acetic acid was used as catalyst, the monocondensation product **1350** could be isolated (426). Under neutral conditions, only the bisadduct **1351** was formed. A similar reaction could be effected with the β-chlorovinylaldehyde (428) and 2-acetylcycloheptanone (427), as shown in Eq. 329, but the products were formulated as **1352a** and **1352b**, respectively, as opposed to the double bond positional isomer **1349**.




(329a)

**1352a,** mp 164–165°C (uv)




(329b)

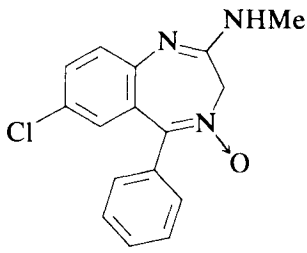
**1352b,** mp 172–173°C (uv)

# ADDENDUM

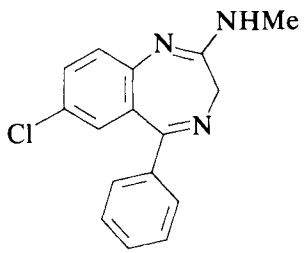
## XI. 3,6,7-SYSTEMS

### 1. Oxazirino[2,3-*d*][1,4]benzodiazepines (see Section II.)

Irradiation of chlordiazepoxide (**11**) in the presence of glutathione led to the formation of the deoxygenated compound **1353** as well as an unidentified glutathione conjugate (781). These substances, together with **11**, were also found when the oxaziridine **12** (the primary photoproduct in the absence of glutathione) was treated with glutathione at room temperature in the dark (Eq. 330).

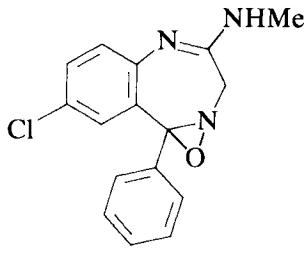


11



1353

+ conjugate (330a)

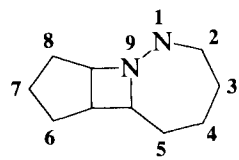


12

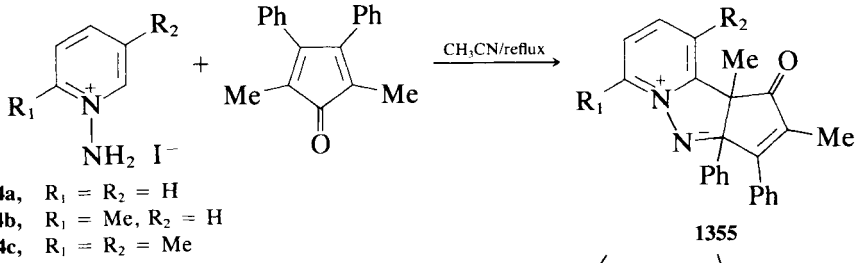
glutathione → 11 + 1353 + conjugate (330b)

## XII. 4,5,7-SYSTEMS

### 1. Cyclopent[3,4]azeto[1,2-*b*][1,2]diazepines

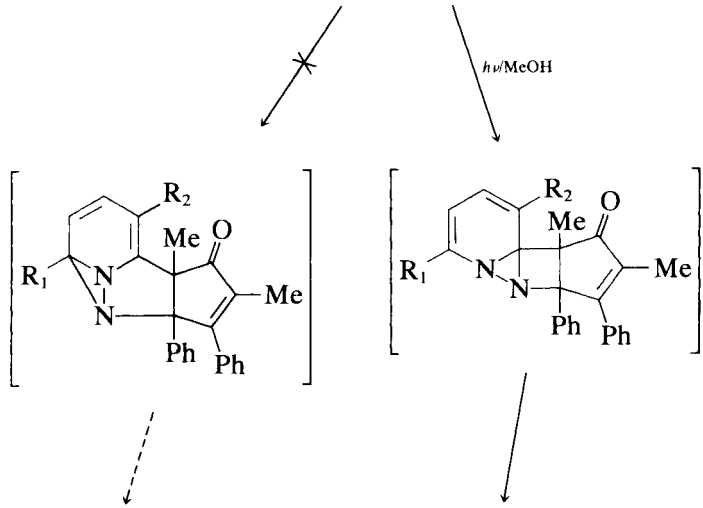


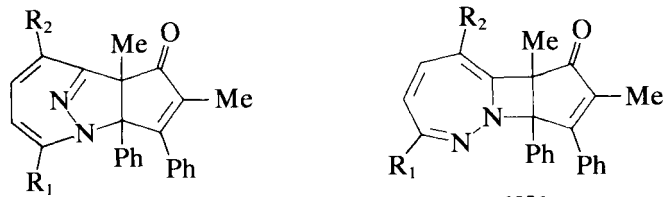
Reaction of the *N*-aminopyridinium iodides **1354** with 2,5-dimethyl-3,4-diphenylcyclopentadienone gave the adducts **1355** (782) which, on irradiation using a high-pressure mercury lamp, gave rearrangement products. On the basis of nmr spectra, these were formulated as **1356** as opposed to the alternative **1357** (783). The nmr evidence is suggestive of **1356**, but **1357** can probably be excluded because of the bridgehead double bond (Fig. 126). Heating **1356a** in chloroform solution in a sealed tube gave **1355** ($R_1 = R_2 = H$) in 80% yield. Reaction of **1356a** with an additional mole of 2,5-dimethyl-3,4-diphenylcyclopentadienone gave the adduct **1356d**.




**1354a,** $R_1 = R_2 = H$
**1354b,** $R_1 = Me$, $R_2 = H$
**1354c,** $R_1 = R_2 = Me$

**1355**

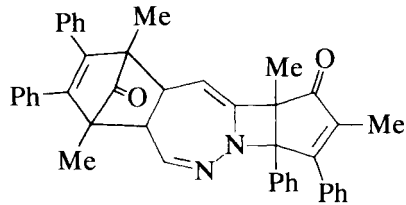



**1357**

**1356**

**1356a,** $R_1 = R_2 = H$; mp 103—107°C; 62% (uv, ir, nmr)
**1356b,** $R_1 = Me$, $R_2 = H$; mp 201–205°C (18%)
**1356c,** $R_1 = R_2 = Me$; Oil (10%)



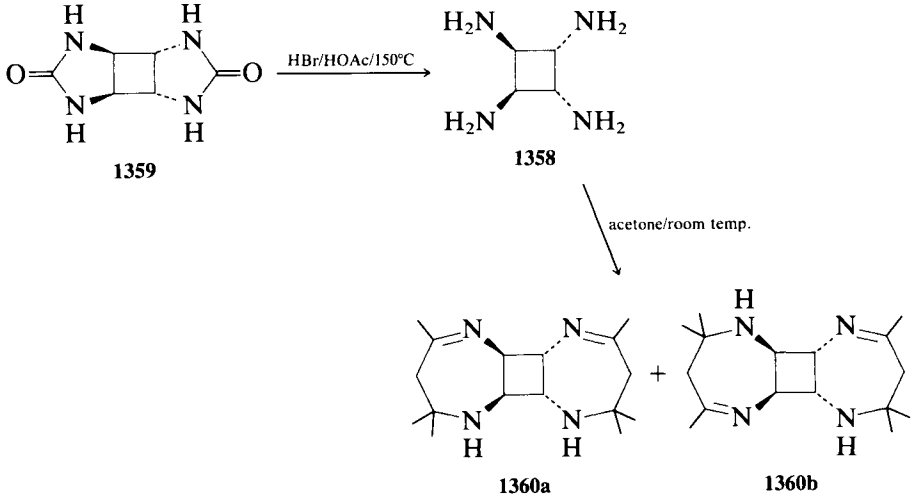

**1356d,** mp 193–194°C (40% from **1356a**)

**Figure 126**

# XIII. 4,7,7-SYSTEMS

## 1. Cyclobuta[1,2-*b*:3,4-*b'*]bis[1,4]diazepines (see Section IV.1)

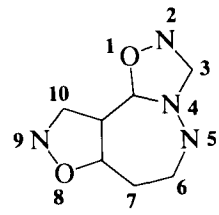
The tetraaminocyclobutane **1358**, obtained by treatment of the urea derivative **1359** with hydrogen bromide in acetic acid (784), gave a mixture of the two tricyclic derivatives **1360a** and **1360b** on reaction with acetone (Eq. 331). The two isomers, which were not separated, were characterized by nmr (785).




**1359** **1358** **1360a** **1360b** (331)

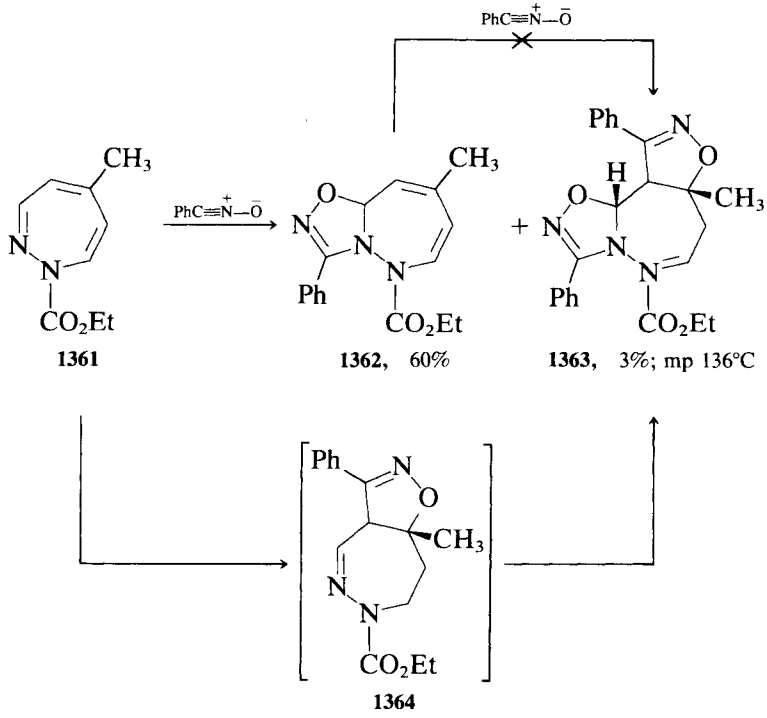
# XIV. 5,5,7-SYSTEMS

## 1. Isoxasolo[4,5-*d*][1,2,4]oxadiazolo[4,3,-*b*][1,2]diazepines



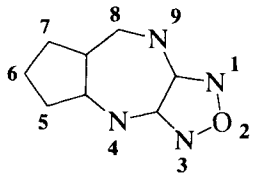
1,3-Dipolar cycloaddition of benzonitrile oxide to 1-ethoxycarbonyl-5-methyl-1,2-diazepine (**1361**) produced the 1:1 adduct **1362** as well as minor

amounts of the bisadduct **1363** (Eq. 332). Since reaction of **1362** with excess benzonitrile oxide did not lead to **1363**, its formation was proposed to proceed via the monoadduct **1364**, which was not observe (786).

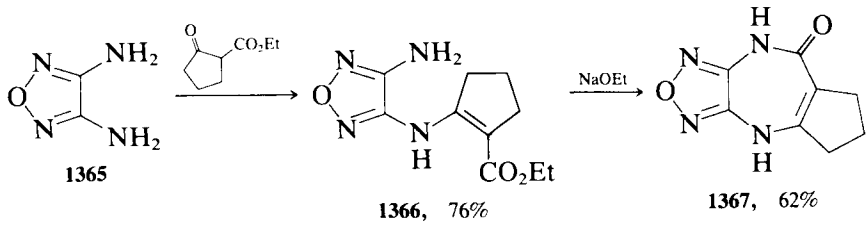



(332)

## 2. Cyclopent[*e*][1,2,5]oxadiazolo[3,4-*b*][1,4]diazepines

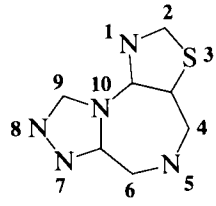


Condensation of 3,4-diaminofurazan (**1365**) with 2-carbethoxycyclopentanone in refluxing acetic acid gave the enamide **1366** (Eq. 333), which was cyclized to **1367** with sodium ethoxide in ethanol (787).




1365 1366, 76% 1367, 62% (333)

### 3. Triazolo[5,4-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepines



Reaction of the 1,3-oxathiolium cation **1368** with cyanamide gave thiazole **1369**, as shown in Fig. 127. Amidation of **1369** with carbobenzyloxyglycyl chloride generated **1370**. Deprotection of **1370** followed by cyclization using 1,4-diazabicyclooctane (DABCO) yielded diazepinone **1372**. Annelation of the triazole ring onto **1372** was carried out in the usual manner to give the product **1375** (788).

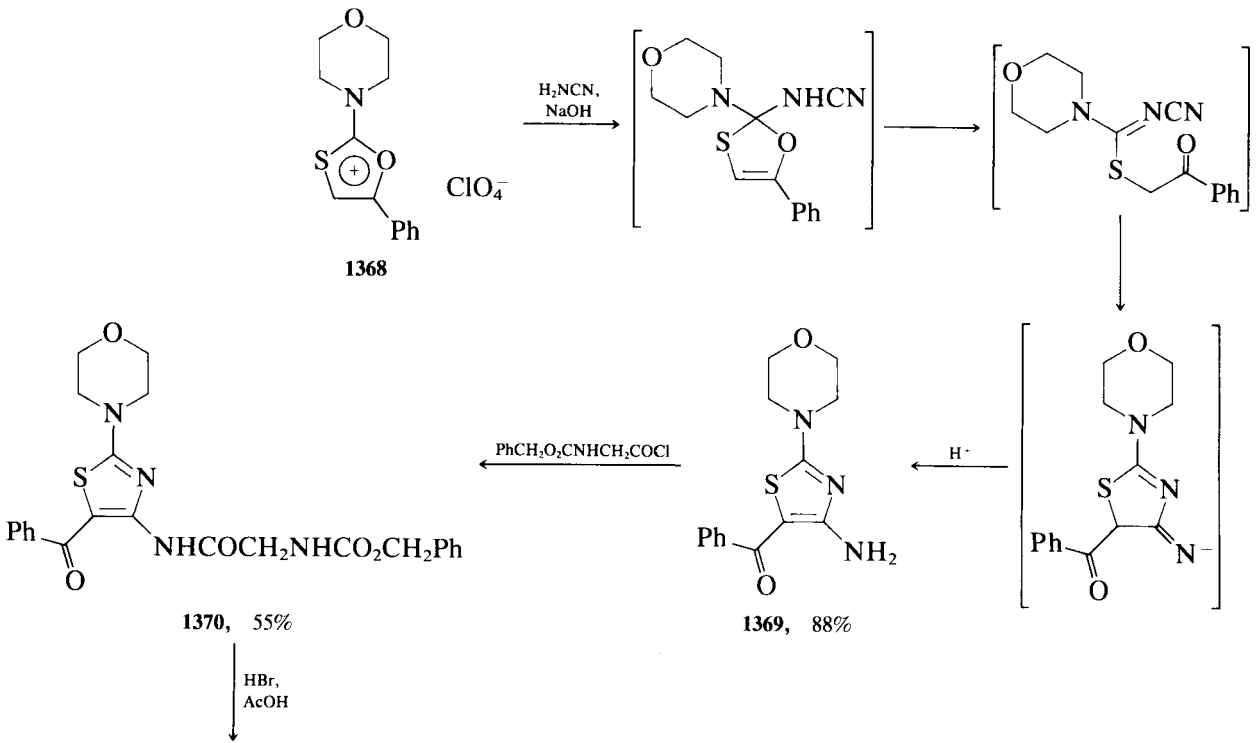
### 4. Thieno[3,2-*f*][1,2,4]triazolo[1,5-*a*][1,4]diazepines (see Section V.4)

Several patents that describe work related to Fig. 3 and compounds listed in Table 6 have appeared (789,790).

### 5. Thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepines (see Section V.5)

A number of patents that describe additional thieno[3,2-*f*][1,2,4]triazolo-[4,3*a*][1,4]diazepines of general structure **61** have appeared. These include 9-alkyl- (791,792), 2-iodo- (793,794) 9-methylthiomethyl (795), 9-dimethylamino- (796), and 9-piperazinyl derivatives of this ring system (797,798). The methods used were the same as outlined in Fig. 4 and Eq. 15. A series of 9-oxo compounds of the general structure **62** were obtained by hydrolysis of the corresponding 9-alkoxy derivatives (799). These syntheses were further amplified in several publications (790,800–803).

An alternate synthesis of this ring system has also been reported (804). Mercaptoacetaldehyde **1376** was condensed with 2-cyano-*N*-(cyanomethyl)acetamide to give the aminothiophene **1377** (Fig. 128). Cyclization of


1368
$ClO_4^-$
$H_2NCN$, NaOH
NHCN
NCN
Ph
$PhCH_2O_2CNHCH_2COCl$
$H^+$
$NH_2$
$NHCOCH_2NHCO_2CH_2Ph$
1369, 88%
1370, 55%
HBr, AcOH

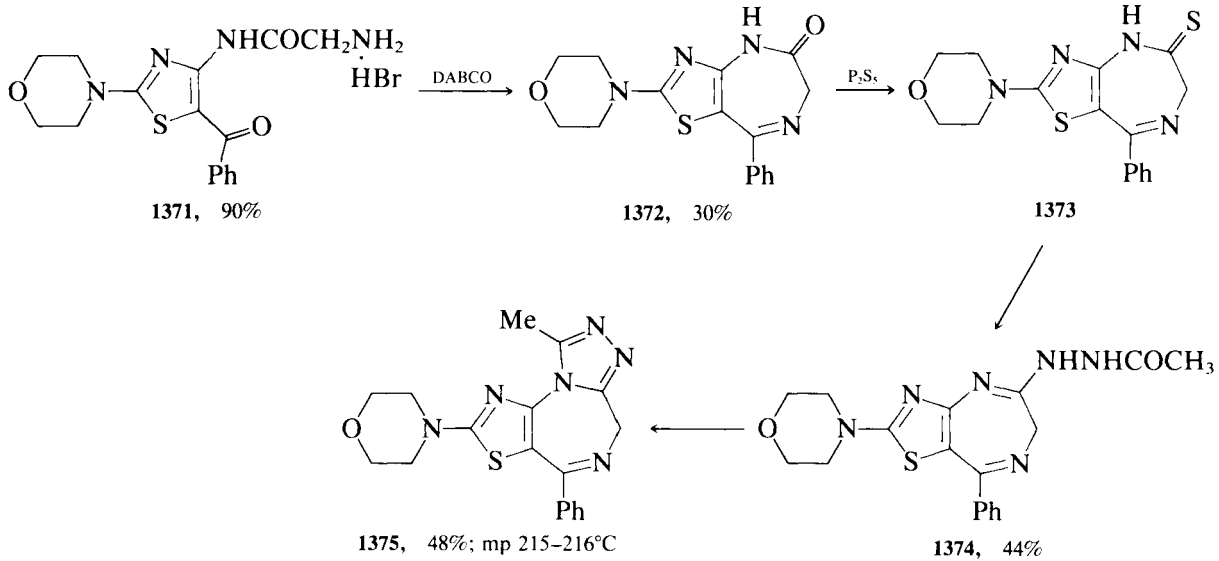

NHCOCH2NH2
HBr
DABCO
P2S5
Ph
1371, 90%
1372, 30%
1373
NHNHCOCH3
Me
1374, 44%
1375, 48%; mp 215–216°C

Figure 127

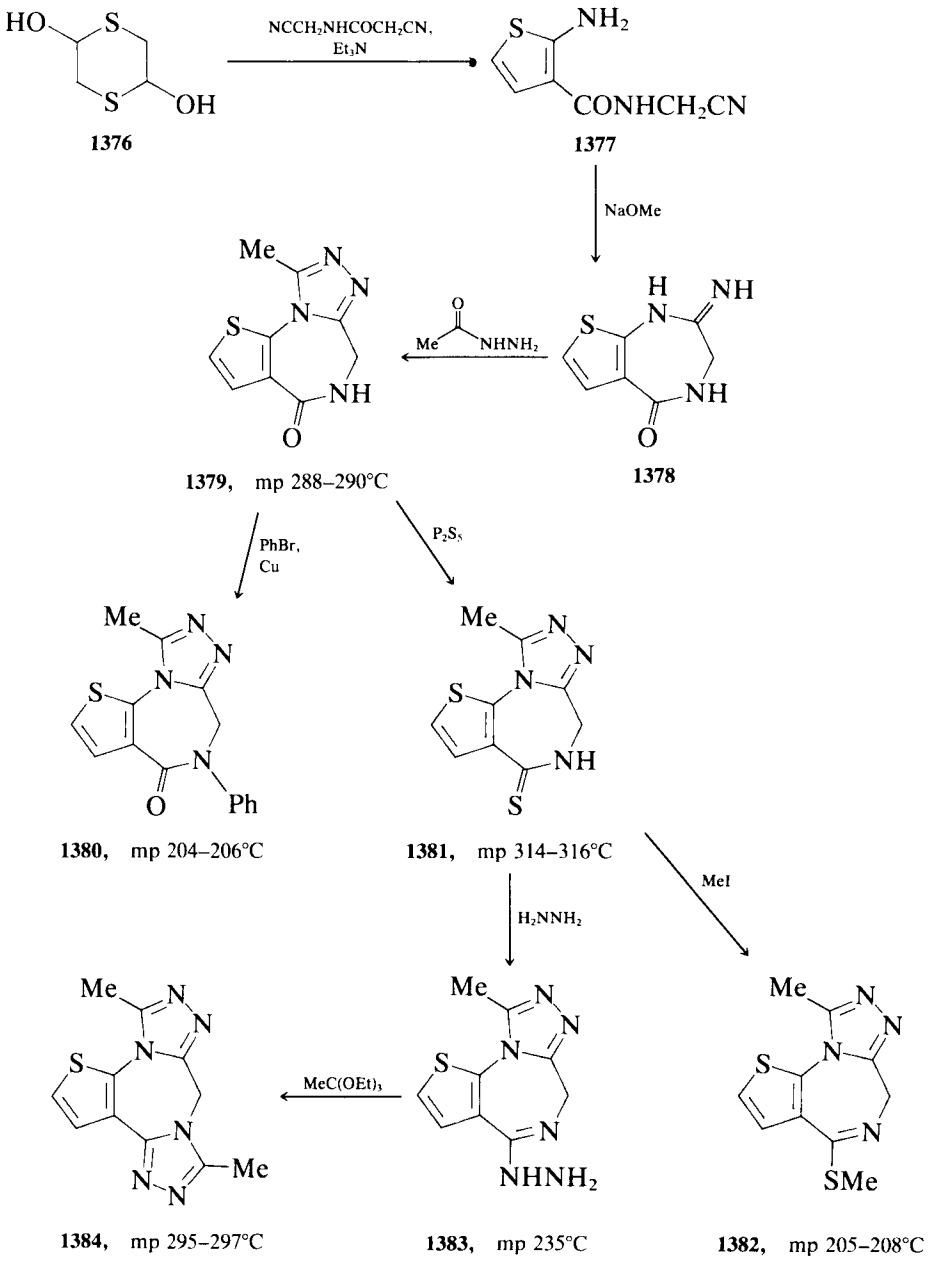
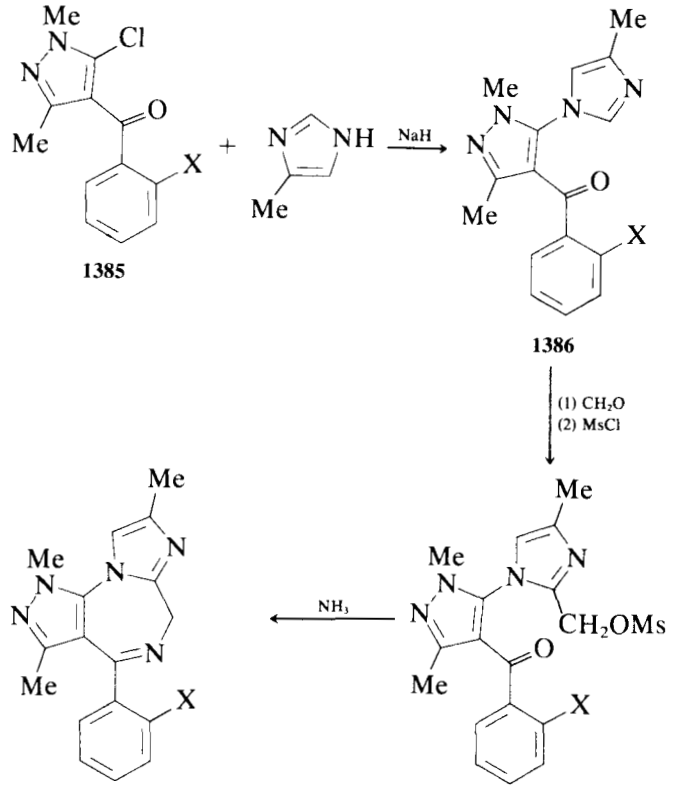

HO
S
S
OH
1376
NCCH2NHCOCH2CN,
Et3N
NH2
S
CONHCH2CN
1377
NaOMe
Me
N
N
N
S
NH
O
1379, mp 288–290°C
O
Me
NHNH2
H
NH
N
S
NH
O
1378
PhBr,
Cu
P2S5
Ph
1380, mp 204–206°C
S
1381, mp 314–316°C
H2NNH2
MeI
MeC(OEt)3
NHNH2
1384, mp 295–297°C
1383, mp 235°C
SMe
1382, mp 205–208°C

**Figure 128**

**1377** with sodium methoxide produced amidine **1378**, which was converted to triazole **1379** with acetylhydrazide. Attempted addition of phenylmagnesium bromide or phenyllithium to **1379** failed. However, reaction of **1379** with bromobenzene in the presence of copper powder produced **1380**. Conversion of **1379** to thione **1381**, followed by methylation, gave **1382**. Addition of hydrazine to **1381** produced **1383**, which could be cyclized to the bistriazole **1384**.

### 6. Imidazo[1,2-*a*]pyrazolo[4,3-*f*][1,4]diazepines (see Section V.10)

An alternate synthesis of compounds related to **106** has appeared (805). Addition of 4-methylimidazole to pyrazole **1385** gave **1386** (Eq. 334). Condensation of **1386** with formaldehyde followed by mesylation generated **1387**, and cyclization of **1387** with ammonia led to diazepines **1388** (805).




(334)

**1385**

**1386**

**1387**

**1388a**, X = Cl; mp 150–153°C
**1388b**, X = F; mp 153–154°C

### 7. Imidazo[1,5-*a*]pyrazolo[4,3-*f*][1,4]diazepines (see Section V.11)

A Belgian patent (806) and Fryer et al. (807) essentially describe the previously disclosed synthesis of **110**.

### 8. Imidazo[1,2-*a*]thieno[3,2-*f*][1,4]diazepines (see Section V.12)

A patent has appeared describing the synthesis of **114** ($R_1$ = H, $R_2$ = Cl, X = *o*-Cl; mp 128–129°C) by the route outlined in Eq. 25 (808).

### 9. Imidazo[1,5-*a*]thieno[2,3-*f*][1,4]diazepines (see Section V.13)

Two papers (807,809) describe the previously reported synthesis of **121**.

### 10. Imidazo[1,5-*a*]thieno[3,2-*f*][1,4]diazepines (see Section V.14)

Two papers (806,807) describe the previously reported syntheses of compounds **122** and **125a–e.**

### 11. Pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepines (see Section V.16)

An alternate synthesis of the pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepine ring system that produces a variety of derivatives was developed starting with 3-cyano-2-(*N*-pyrrolo)thiophene. Intermediate **1389** was condensed with aldehydes to give the imines **1390,** which were cyclized in ethanolic hydrochloric acid to **1391** (Fig. 129). The tricyclic product **1391** was then dehydrogenated to **1392** with palladium on carbon. Analogs of this type are listed in Table 182 (810,811). Treatment of **1389** with phosgene produced the isocyanate **1393,** which was cyclized to lactam **1394** with zinc chloride. Addition of amines to **1393** generated the ureas **1395,** which were cyclized to compounds **1396** with phosphorus oxychloride (812),

Intermediate **1397** underwent Vilsmeier formylation to give **1398**, which was deprotected with hydrazine to yield imine **1399** (Fig. 130). Hydrogenation of **1399** afforded **1400**, which could also be prepared directly from **1401** by hydrogenation. Acylated derivatives (**1402**) of amine **1400** are listed in Table 183 (813). Intermediate **1401** was converted in alcoholic sodium hydroxide to the alkoxy derivatives **1403**. These products are listed in Table 184 (814). Similarly, reaction of **1401** with methyl ketones in the presence of basic hydrogen peroxide generated ketones **1404a–c** (815).

Compound **1403** (R = Me) was oxidized with potassium permanganate to give **1405** (Eq. 335), which was hydrolyzed to the imide **1406**. Lithium aluminum hydride reduction of **1403** (R = Me) afforded **1407,** while catalytic hydrogenation yielded **1408** (815).

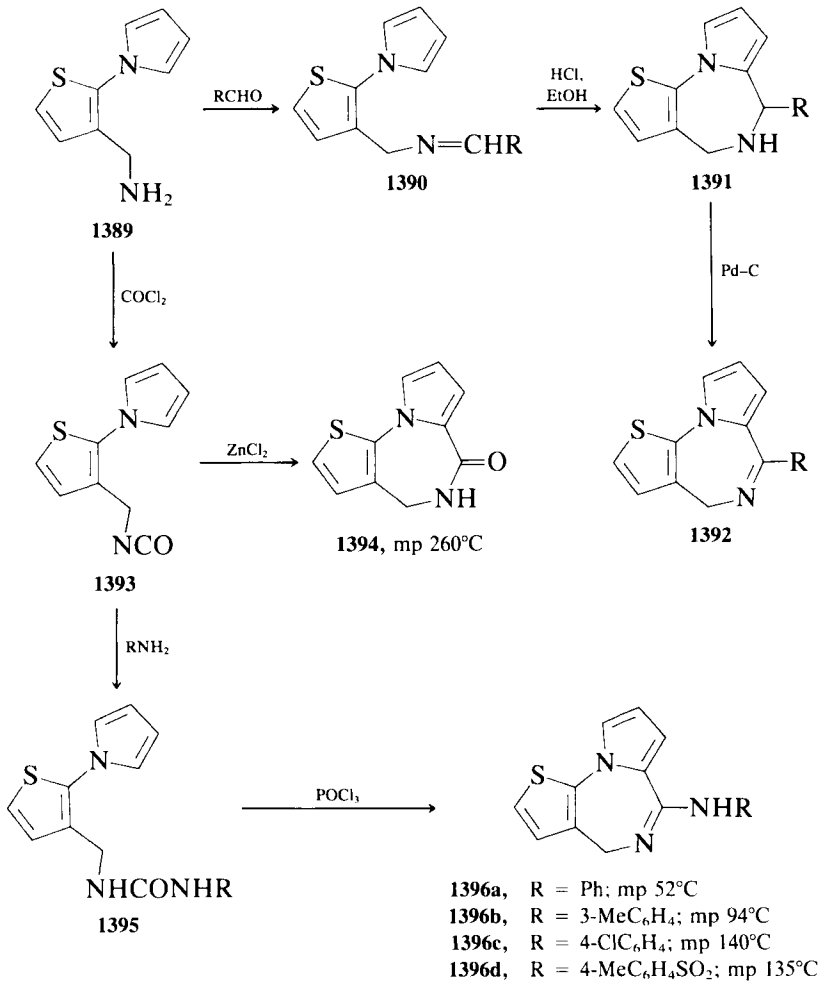
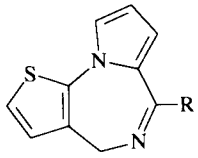



**Figure 129**

TABLE 182. 6-SUBSTITUTED PYRROLO[1,2-*a*]THIENO[3,2,-*f*][1,4]DIAZEPINES



| R | mp (°C) or bp (°C/torr) | Refs. |
|---|---|---|
| Ph | 94 | 810 |
| 4-$CH_3C_6H_4$ | 102 | 810 |
| 4-$FC_6H_4$ | 106 | 810 |
| 4-$ClC_6H_4$ | 110 | 810 |

(*continued*)

TABLE 182. (*Continued*)

| R | mp (°C) or bp (°C/torr) | Refs. |
|---|---|---|
|  | 200/0.1 | 810 |
| H | 205/0.1 | 811 |
| $CH_3$ | 210/0.1 | 811 |
| $C_2H_5$ | 200/0.1 | 811 |
|  | 120 | 811 |

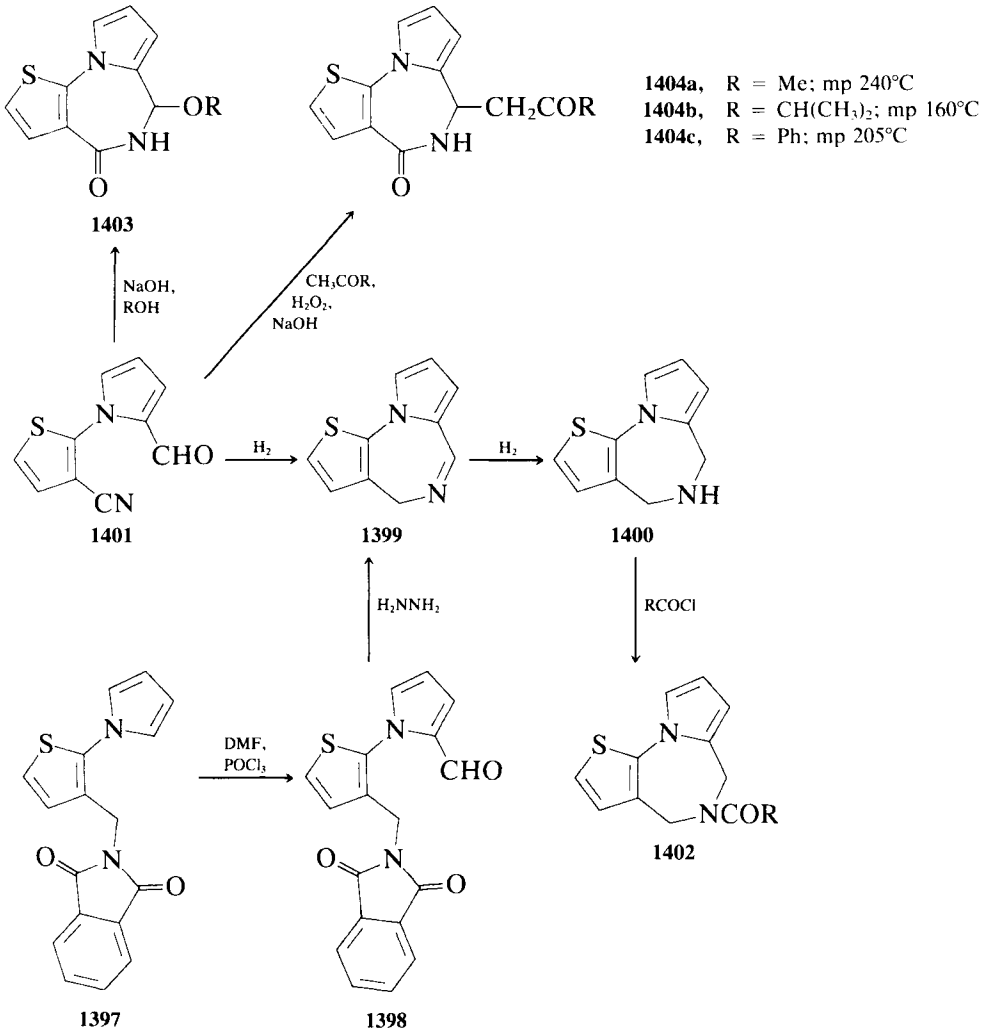
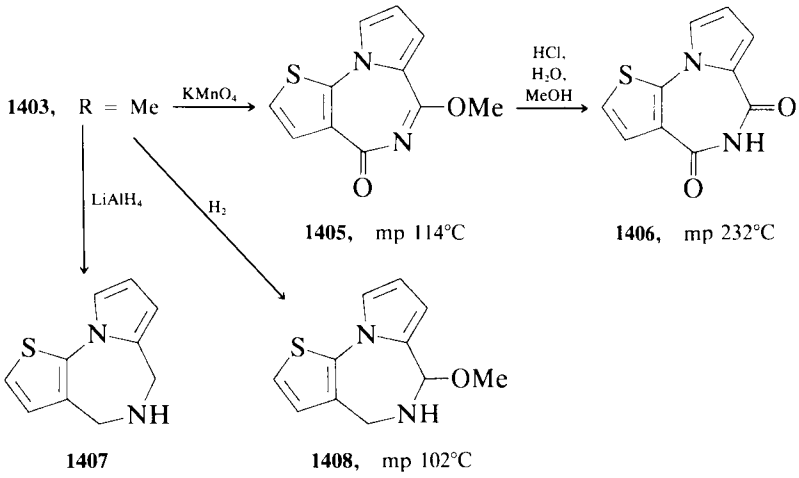
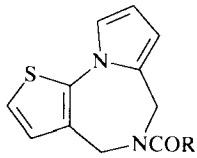



**Figure 130**



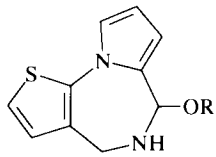

(335)

TABLE 183. 5-ACYLPYRROLO[1,2-*a*]THIENO[3,2-*f*][1,4]DIAZEPINES




| R | mp (°C) | bp (°C/torr) |
|---|---|---|
| Me | 82 | |
| $CH(CH_3)_2$ | | 220/0.1 |
| Ph | 82 | |
| $4\text{-}CH_3C_6H_4$ | 60 | |
| $4\text{-}ClC_6H_4$ | 120 | |
| $4\text{-}NO_2C_6H_4$ | 159 | |
| $NEt_2$ | | 200/0.1 |
| $NPh_2$ | 136 | |

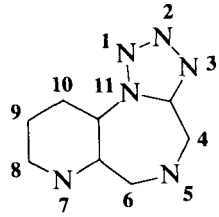
TABLE 184. 7-ALKOXYPYRROLO[1,2-*a*]THIENO[3,2-*f*][1,4]DIAZEPINES



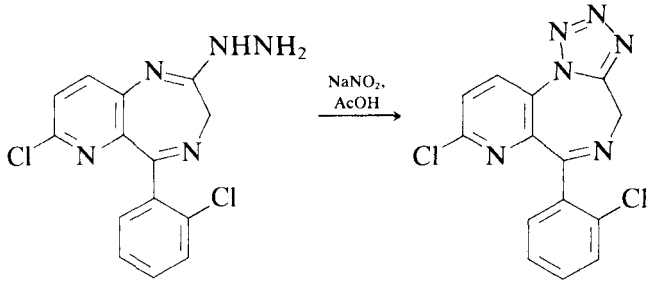

| R | mp (°C) |
|---|---|
| Me | 158 |
| Et | 140 |
| $n\text{-}C_3H_7$ | 115 |
| $(CH_2)_2OEt$ | 138 |
| $(CH_2)_3OC_4H_9\text{-}n$ | 81 |
| $CH_2CH{=}CH_2$ | 116 |

# XV. 5,6,7-SYSTEMS

## 1. Pyrido[2,3-*f*][tetrazolo][1,5-*a*][1,4]diazepines



Using the chemistry developed for the synthesis of the corresponding benzodiazepine system, pyridodiazepine **1409** was transformed into tetrazolopyridodiazepine **1410** (Eq. 336) with sodium nitrite in acetic acid (816).

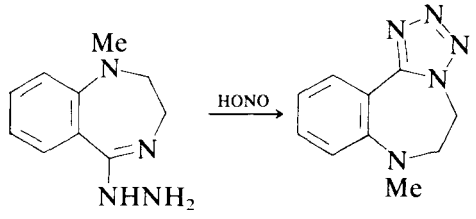


(336)

**1409** **1410**, mp 200–202°C

## 2. Tetrazolo[1,5,-*d*][1,4]benzodiazepines (see Section VI.3)

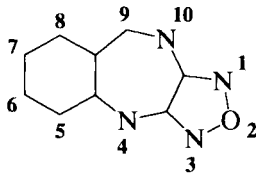
An alternate synthesis of the tetrazolo[1,5-*d*][1,4]benzodiazepine ring system, in which the tetrazole ring is fused onto a benzodiazepine derivative, is outlined in Eq. 337. Reaction of **1411**, available from the corresponding lactam, with nitrous acid afforded the tetrazole **1412** in 86% yield (817).



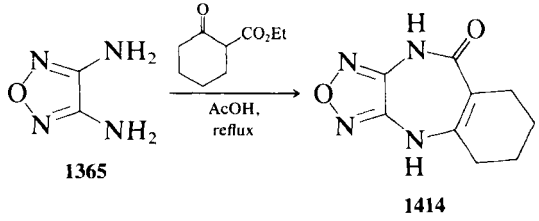
(337)

**1411** **1412**, mp 130°C

### 3. [1,2,5]Oxadiazolo[3,4-*b*][1,4]benzodiazepines

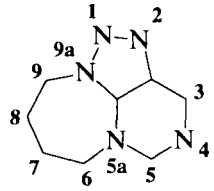


Reaction of the 3,4-diaminofurazan **1365** (Eq. 338) with 2-carbethoxycyclohexanone in refluxing acetic acid yielded the diazepinone **1414** in 33% yield (787).

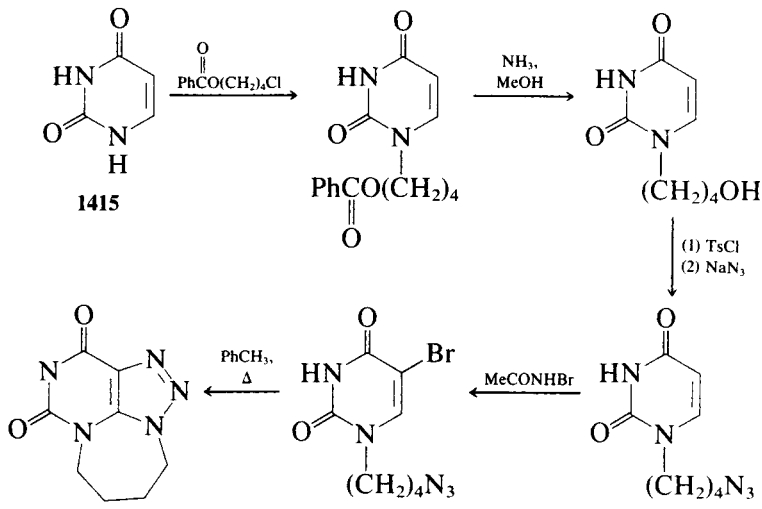


**1365** **1414** (338)

### 4. 1,2,4,5a,9a-Pentaazabenz[*cd*]azulenes



The 1,2,4,5a,9a-pentaazabenz[*cd*]azulene ring system was prepared as part of a model study designed to investigate intramolecular thermal reactions between the base and the 5′-functionalized sugar moiety of nucleosides. Thus, uracil (**1415**) was alkylated and converted to the triazole **1416** (Eq. 339) in 49% yield (818).

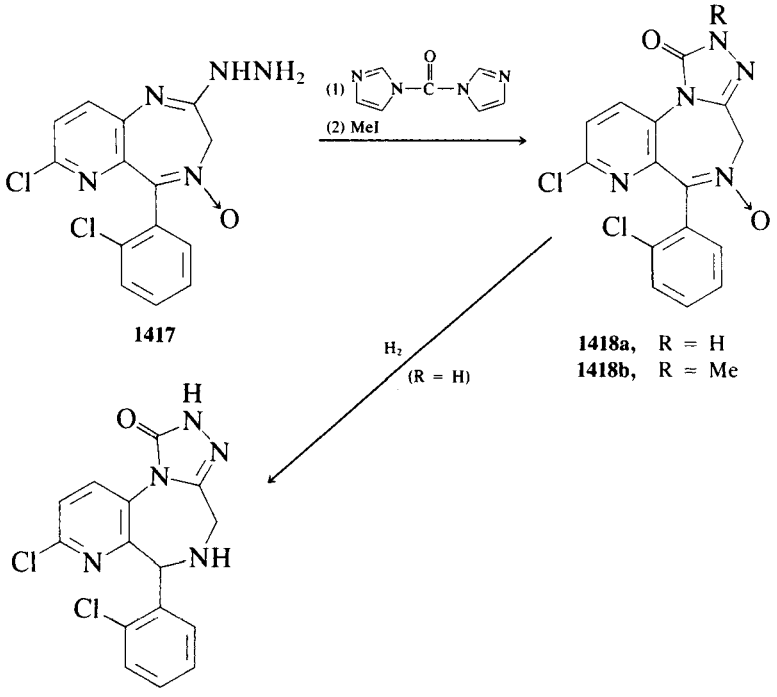



1415

1416, mp >300°C (339)

## 5. Pyrido[2,3-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepines (see Section VI.8)

The work described in Eq. 40 have been expanded to include numerous additional examples, which are listed in Table 185. A series of 1-oxo deriv-

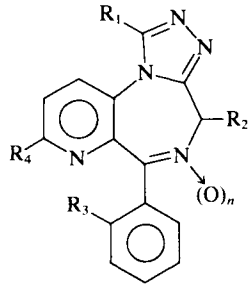



1417

1418a, R = H
1418b, R = Me (340)

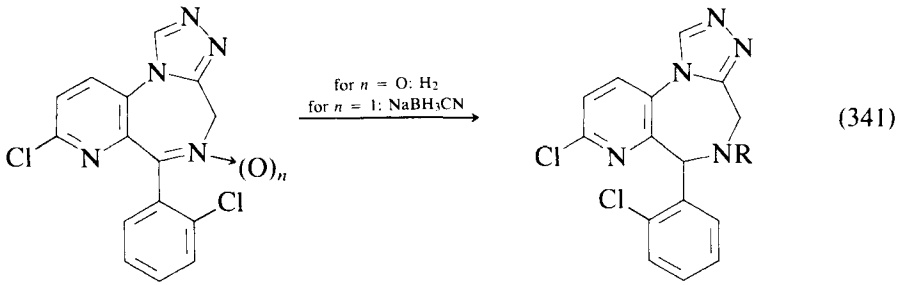
1419, mp 180–182°C

TABLE 185. PYRIDO[2,3-*f*][1,2,4]TRIAZOLO[4,3-*a*][1,4]DIAZEPINES



| *n* | $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) |
|---|---|---|---|---|---|
| 1 | H | H | Cl | Cl | 242–244 |
| 1 | H | H | H | Cl | 244–246 |
| 0 | H | H | Cl | Cl | 247–248 |
| 0 | H | H | H | Br | 224–226 |
| 0 | OEt | H | Cl | Cl | 202–204 |
| 0 | $OCH_2Br$ | H | Cl | Cl | 235–240 |
| 0 | SH | H | Cl | Cl | 250–252 |
| 1 | H | H | H | SMe | 244–246 |
| 0 | SMe | H | Cl | Cl | 230–232 |
| 0 | H | OMe | Cl | Cl | 240–243 |
| 0 | H | OH | Cl | Cl | 310 |
| 0 | H | OH | F | Cl | 290 |
| 0 | H | H | Cl | $NMe_2$ | 240–242 |
| 0 | H | H | F | Cl | 198–200 |
| 0 | H | H | H | Cl | 180–182 |
| 0 | H | H | H | SMe | 190–192 |
| 0 | H | OAc | Cl | Cl | 230–235 |
| 0 | H | OAc | F | Cl | 210–212 |

atives was also prepared, as illustrated for the conversion of **1417** (Eq. 340) to **1418a** and then to **1418b**; these are listed to Table 186. In addition, the 5,6-dihydro analogs **1419**, **1421a**, and **1421b** (Eq. 341) were prepared (816).

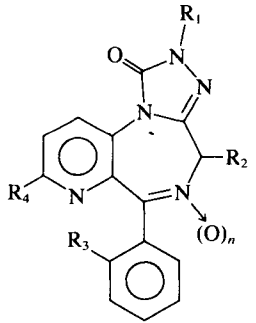



(341)

**1420a**, $n$ = 0
**1420b**, $n$ = 1

**1421a**, R = H; mp 206–208°C
**1421b**, R = OH; mp 230–232°C

TABLE 186. 1-OXOPYRIDO[2,3-*f*][1,2,4]TRIAZOLO[4,3-*a*][1,4]DIAZEPINES

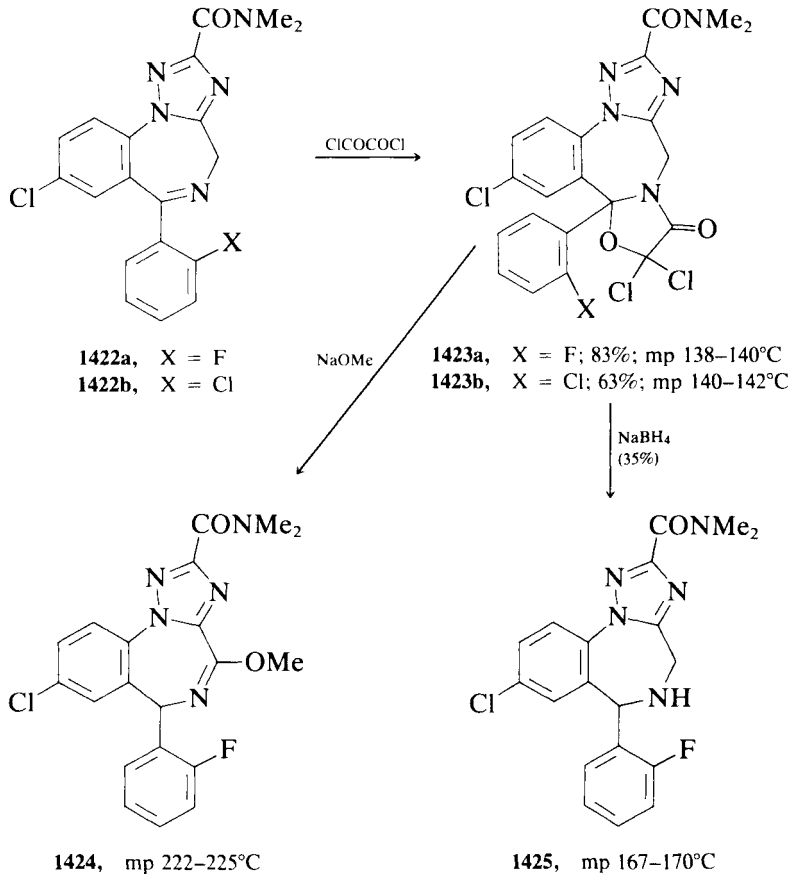


| *n* | $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) |
|---|---|---|---|---|---|
| 1 | H | H | Cl | Cl | 200–202 |
| 1 | H | H | H | Cl | 268–270 |
| 1 | Me | H | Cl | Cl | 248–250 |
| 0 | $CH_2CN$ | H | Cl | Cl | 198–200 |
| 0 | $CH_2CH{=}CH_2$ | H | Cl | Cl | 142–144 |
| 0 | $CH_2C{\equiv}CH$ | H | Cl | Cl | 160–162 |
| 0 | $CH_2OMe$ | H | Cl | Cl | 180–182 |
| 0 | $CH_2COCH_3$ | H | Cl | Cl | 178–180 |
| 0 | $CH_2CH_2NMe_2$ | H | Cl | Cl | 216–218 (HCl) |
| 0 | H | OH | Cl | Cl | 260–262 |
| 1 | H | H | Cl |  | 20 (HCl) |
| 0 | H | H | Cl |  | 228–230 |
| 0 | H | H | Cl | $NMe_2$ | 244–246 |
| 0 | H | H | Cl | Cl | 222–224 |
| 0 | Me | H | Cl | Cl | 200–202 |
| 0 | H | H | H | Cl | 222–224 |
| 0 | H | OAc | Cl | Cl | 232–236 |

## 6. [1,2,4]Triazolo[1,5-*a*][1,4]benzodiazepines (see Section VI.10)

Several additional publications detailing the synthesis of [1,2,4]triazolo[1,5-*a*][1,4]benzodiazepines have appeared, including 4-substituted analogs of **185** (Eq. 42) (819), 6-pyridyl analogs of **192** (Fig. 12) (820), 6-pyridyl analogs of **185** (Eq. 42) (821), and 2-carboxy analogs of **202** (Eq. 43) (822). Several ring-opened compounds (**201**) derived from tricyclic members of this ring system were also reported (823–827).

It was reported that triazole **1422** was converted to the tetracyclic structure **1423** (Fig. 131) with oxalyl chloride. Reaction of **1423** (X = F) with sodium methoxide led to the 4-methoxy analog **1424**. Reduction of **1423** with sodium borohydride produced the dihydro derivative **1425** in 35% yield (828).




**1422a**, X = F
**1422b**, X = Cl

**1423a**, X = F; 83%; mp 138–140°C
**1423b**, X = Cl; 63%; mp 140–142°C

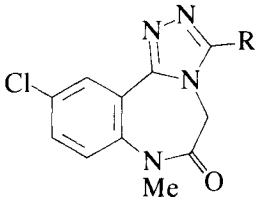
**1424**, mp 222–225°C

**1425**, mp 167–170°C

**Figure 131**

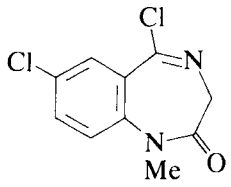
## 7. [1,2,4]Triazolo[1,5-*d*][1,4]benzodiazepines (see Section VI.11)

Additional derivatives of the [1,2,4]triazolo[1,5-*d*][1,4]benzodiazepine ring system were prepared from the intermediate **1426**, which was prepared by



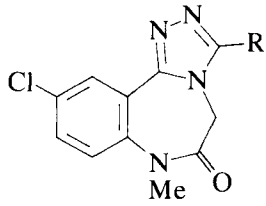
| | R | mp (°C) |
|---|---|---|
| **1428a** | $CF_3$ | 186–187 |
| **1428b** | $CH_2Cl$ | 193–194.5 |

(1) $H_2NNHCO_2Bu$-*t*
(2) $RCO_2H$



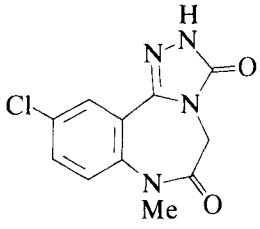
**1426**

$RCONHNH_2$



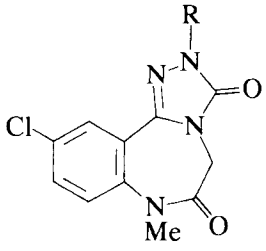
| | R | mp (°C) |
|---|---|---|
| **1427a** | H | 272–274 |
| **1427b** | Me | 228.5–229.5 |
| **1427c** | Ph | 204.5–205.5 |
| **1427d** | $CH_2CN$ | 252–253.5 |
| **1427e** | $CONH_2$ | 303–304 |

$H_2NNHCO_2Et$



**1429**, mp 268–269°C

RX



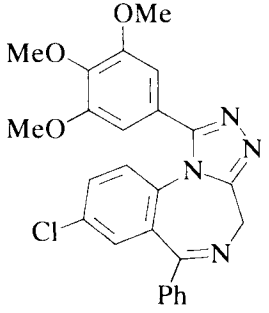
| | R | mp (°C) |
|---|---|---|
| **1430a** | Me | 292–294 |
| **1430b** | $CH_2CH_2OH$ | 171–172 |
| **1430c** | $CH_2CH_2NMe_2$ | 160.5–162 |
| **1430d** | $CH_2CH_2CH_2NMe_2$ | 178–179 |
| **1430e** | Ph | 174–175 |

**Figure 132**

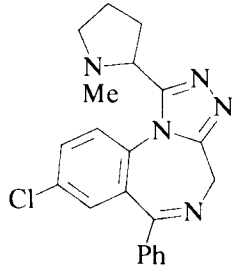
treatment of the corresponding lactam with phosphorous oxychloride. As shown in Fig. 132, addition of acyl hydrazides generated the triazoles **1427a–e**. Alternatively, addition of *tert*-butyl carbazate to **1426** followed by acid-catalyzed removal of the *tert*-butyl group gave **1428a** and **1428b**. Similarly, the use of ethyl carbazate produced triazolone **1429**, which could be alkylated to derivatives **1430a–e**. Temperature-dependent nmr studies of these and related derivatives were used to determine the barriers to diazepine ring inversion (829).

### 8. [1,2,4]Triazolo[4,3-*a*][1,4]benzodiazepines (see Section VI.12)

Details of the synthesis of 1-substituted [1,2,4]triazolo[4,3-*a*][1,4] benzodiazepine derivatives, which have appeared in patents and are listed in Tables 28 and 30, have been published (830). A variety of 1-substituted analogs have been reported, including 1-halomethyl (831), 1-thiomethyl (832), 1-aminoalkyl (833), 1-hydroxyaminomethyl (834), 1-(2,3-dihydroxypropoxymethyl) (835), and 1-(2-aminoethyl) (836,837) derivatives. In addition, a paper has appeared that describes the synthesis of a number of miscellaneous 1-substituted derivatives related to **219**, such as **1431** and **1432**




**1431**

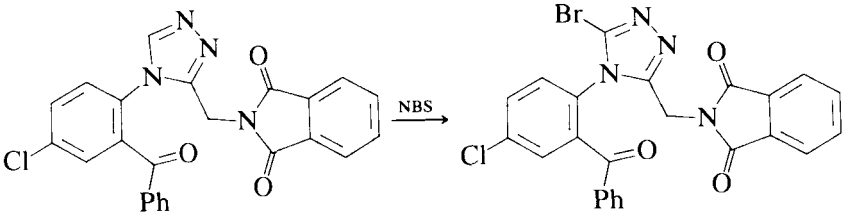



**1432**

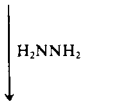
(which are undergoing clinical studies), as well as several triazolones related to **260** (838). Also, a paper has appeared describing earlier patented analogs that were prepared by alkylation of 260 and related triazolones, which are listed in Table 33 (839).

An alternate preparation of 1-halo analogs is outlined in Eq. 342. For example, reaction of **1433** with *N*-bromosuccinimide gave **1434**, which was deprotected with hydrazine and cyclized to **1435** (840).

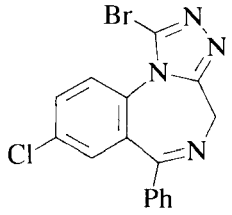
An improved method for the synthesis of 1-(2-dimethylaminoethyl) derivatives was found, starting with **1436** (Eq. 343) and dimethyl (methylene) ammonium chloride to give **1437** (841,842). A paper has appeared that pro-



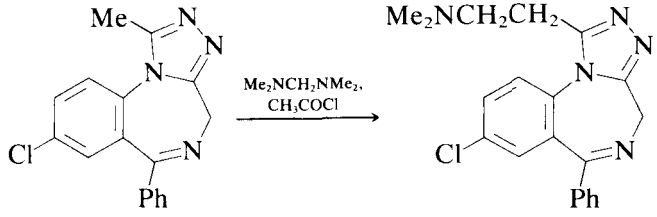

**1433** **1434**




(342)




**1435**, mp 205–206°C

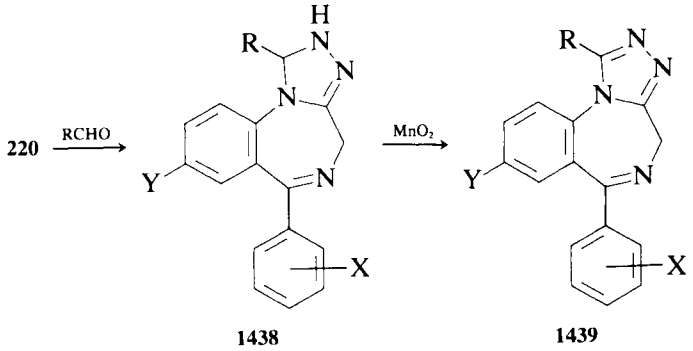



**1436** **1437**

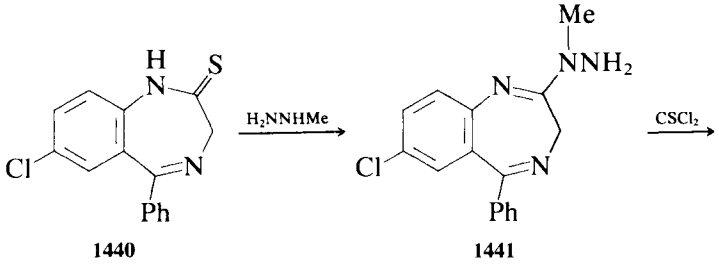
(343)

vides additional details of the work illustrated in Eq. 48 (843). In a related paper an alternate preparation of 1-substituted analogs was described in which the hydrazines **220** were treated with aldehydes to give triazolines **1438** (Eq. 344). These were oxidized with manganese dioxide to triazoles **1439** (844).

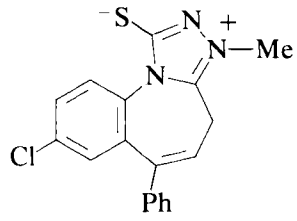
The synthesis of 3-methyltriazolobenzodiazepinium derivatives was achieved as shown in Eq. 345. Condensation of the thioamide **1440** with




1438 1439 (344)



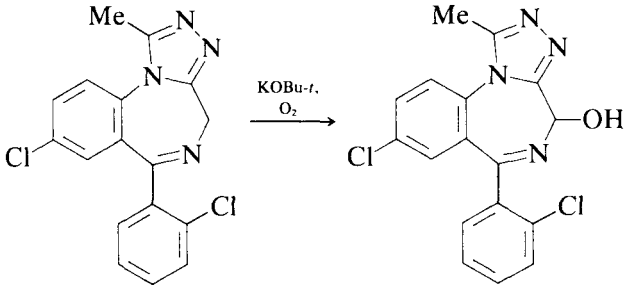

1440 1441




1442 (345)

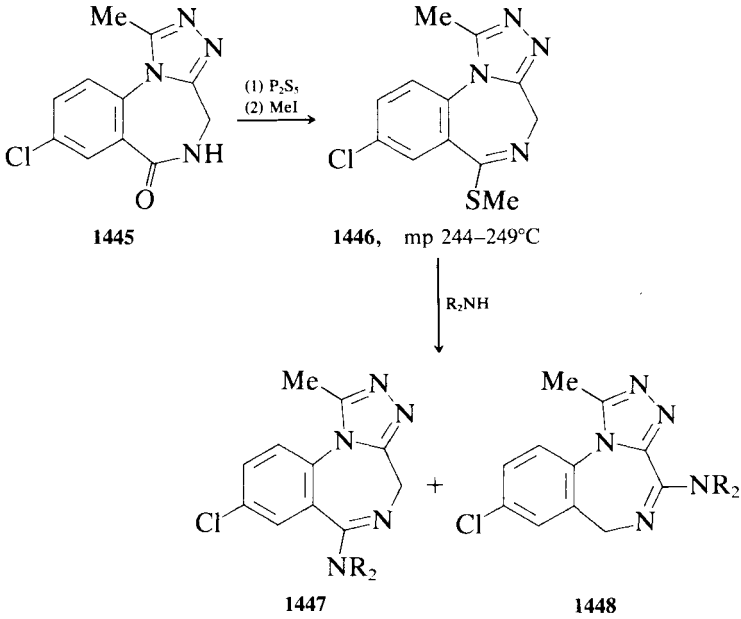
methylhydrazine produced **1441**. Reaction of **1441** with thiophosgene generated the inner salt **1442**. Also prepared were the analogous 1-oxy and 1-amino compounds (845,846).

Details of the preparation of 4-substituted analogs such as **264, 265, 268, 270,** and **273** (listed in Tables 37 and 38) have been published (847). In addition, a one-step $C_4$ oxidation was achieved by treatment of triazoles such as **1443** (Eq. 346) with potassium *t*-butoxide and oxygen to give **1444** (848).




1443 1444 (346)

At the 6-position, 6-(*o*-halophenyl) (849), 6-pyridyl (850,851), and 6-amino (852,853) derivatives were reported. The latter compounds (**1447**) were prepared from **1445** as shown in Eq. 347. During the reaction, the isomeric 4-amino derivatives **1448** were also formed.




1445 1446, mp 244–249°C (347)

1447 1448

A series of 8-hydroxyamino derivatives of structure **219** were patented (854).

A modified synthetic approach to this ring system, partly described earlier in Fig. 18, was achieved starting with the 2-hydroazinoquinoline **1449** (Fig. 133). Triazole formation led to **1450**, which was oxidatively cleaved to yield **1451**. Hydroxymethylation of **1451** produced **1452**, which was converted to

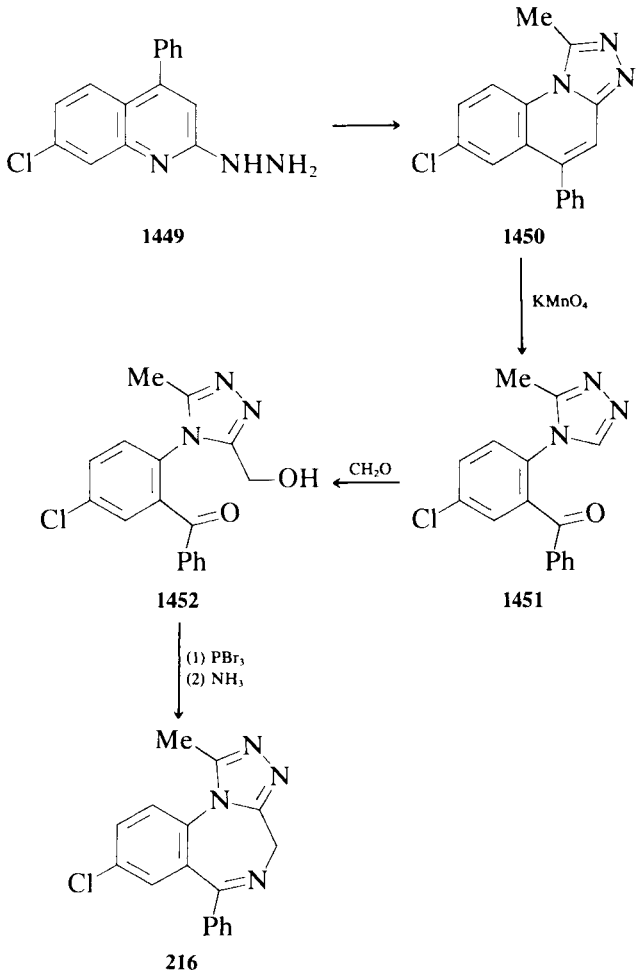



Figure 133

**216** by treatment with phosphorus tribromide followed by ammonia. Several related analogs were prepared similarly (855).

A number of ring-opened analogs have appeared (856)—including compounds such as **284** and **285**, resulting from hydrazine-induced reductive rearrangement (857,858), and compounds described in Eq. 61, involving formaldehyde/formic acid–mediated ring opening (859).

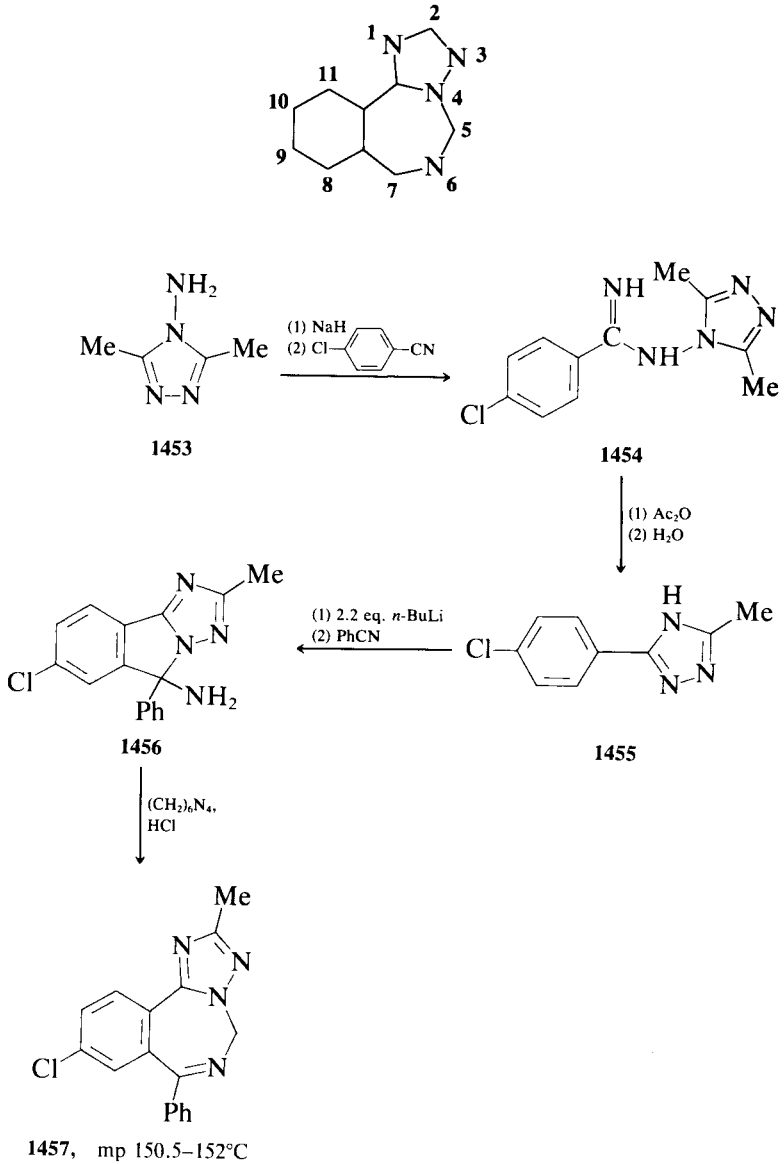
### 9. [1,2,4]Triazolo[4,3-*a*][1,5]benzodiazepines (see Section VI.13)

Several additional examples of the transformation described in Eq. 64 have been patented (860). In addition, a paper providing further details of the synthesis (Fig. 21) of compounds related to **294** has appeared (861).

## 10. [1,2,4]Triazolo[4,3-*d*][1,4]benzodiazepines (see Section VI.14)

A number of papers have appeared providing additional details of the work described in Eqs. 66 and 67 (817,829,862).

## 11. [1,2,4]Triazolo[5,1-*a*][2,4]benzodiazepines




1453 1454 1455 1456

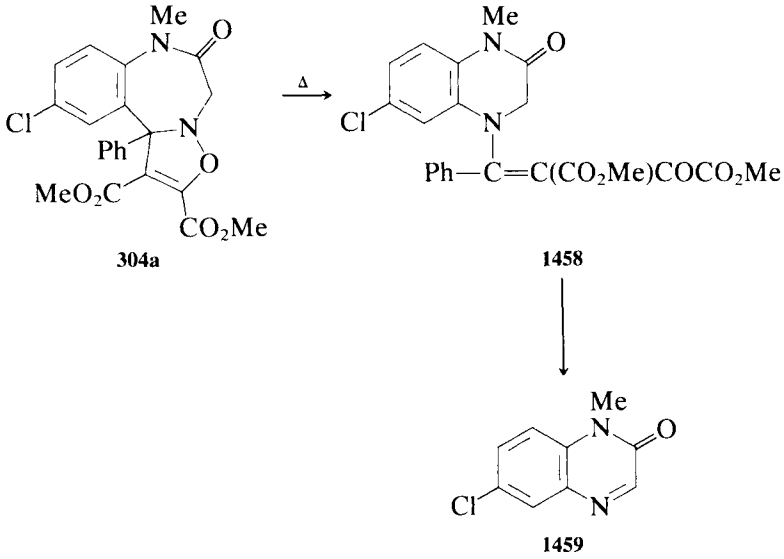
**1457**, mp 150.5–152°C

**Figure 134**

[1,2,4]triazolo[5,1-*a*][2,4]benzodiazepines are claimed to have anti-inflammatory and anxiolytic properties. Only one example is specified. Reaction of hydrazine and acetonitrile under pressure gave the triazole **1453**. Metallation of **1453** followed by addition of 4-chlorobenzonitrile produced **1454** (Fig. 134), which was rearranged to triazole **1455** using acetic anhydride. Generation of the *N*,α-dianion of **1455** with *n*-butyllithium, followed by addition of benzonitrile, led to the isoindole **1456**. Conversion of **1456** to **1457** was accomplished with hexamethylenetetramine (863,864).

## 12. Isoxazolo[2,3-*d*][1,4]benzodiazepines (see Section VI.15)

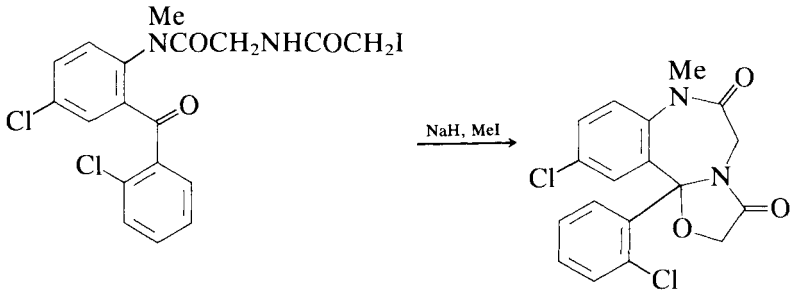
Further details concerning the preparation of compounds **304** are described. In addition, the mild thermal rearrangement of **304a** to **1458** (Eq. 348) and then to **1459** is discussed (765).




**304a** **1458** **1459** (348)

## 13. Oxazolo[3,2-*d*][1,4]benzodiazepines (see Section VI.18)

Additional patents (866–868) as well as a paper (869) describing the transformations outlined in Fig. 23 have appeared. During attempted methylation of **1460**, the ring system **1461** (Eq. 349) was obtained instead (870). Quantitative structure–activity relationships for compounds of the type described in Table 50 have been determined (871).

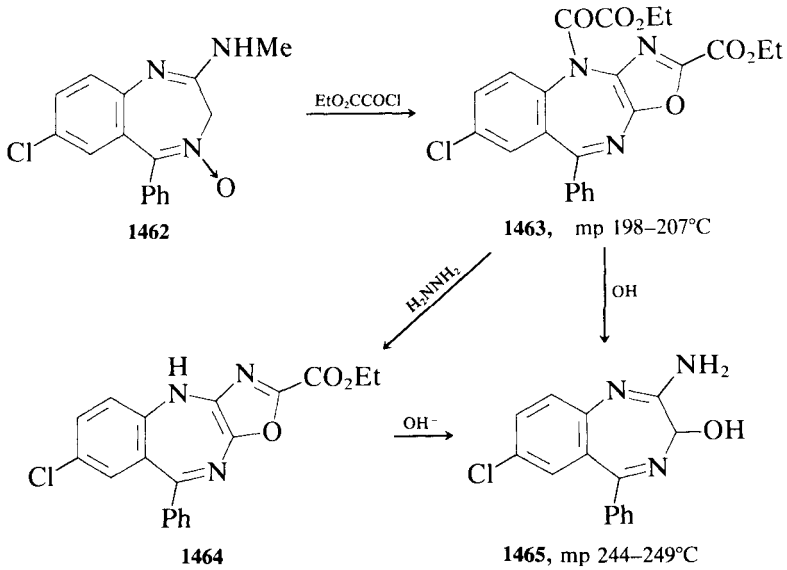



(349)

**1460** **1461**, 66%; mp 198–199°C

### 14. Oxazolo[4,5-*b*][1,4]benzodiazepines (see Section VI.19)

A process related to Eq. 74 was described. Thus, benzodiazepine **1462** (Eq. 350) was treated with ethyloxalyl chloride in refluxing benzene to give




(350)

**1462** **1463**, mp 198–207°C

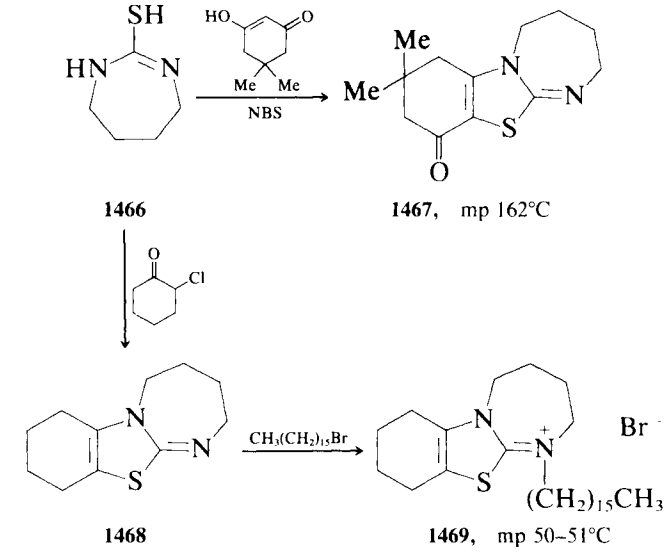
**1464** **1465**, mp 244–249°C

**1463** (54% yield), which could be hydrolyzed to **1464** with hydrazine. Cleavage of **1463** or **1464** with sodium hydroxide gave **1465** (872).

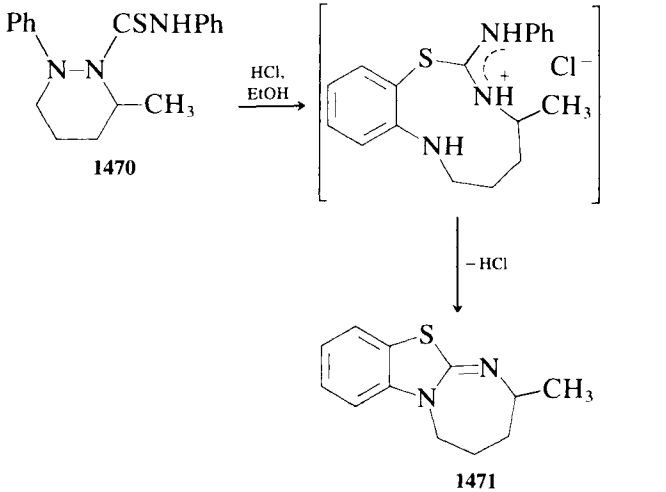
### 15. [1,3]Diazepino[2,1-*b*]benzothiazoles (see Section VI.21)

A number of new examples of the [1,3]diazepino[2,1-*b*]benzothiazole ring system have appeared. Condensation of 2-mercapto-4,5,6,7-tetrahydro-1,3-

diazepine (**1466**) with 2-bromodimedone or with dimedone and *N*-bromosuccinimide gave the tricyclic product **1467** in 70 and 68% yields, respectively (873,874). Reaction of **1466** (Eq. 351) with 2-chlorocyclohexanone produced **1468**, which was quaternized with cetyl bromide to yield **1469**. The latter product is claimed to possess acaricidal activity (875,876). Finally, pyridazine **1470** (Eq. 352) was converted to **1471** in ethanolic hydrochloric acid. Numerous other products were also formed, and the method does not appear to be synthetically useful (877).




(351)




(352)

### 16. [1,3]Diazepino[2,1-*f*]purines (see Section VI.30)

Several additional compounds were prepared by the route described in Eq. 85. Thus 8-chlorotheophylline (**1472**) was alkylated with *N*-(4-bromobutyl)phthalimide to give **1473** (Fig. 135), which was deprotected and cyclized to **1474** in 80% yield. Diazepine **1474** was in part characterized by conversion to the acetyl analog **1475** and the *N*-nitroso derivative **1476** (878).

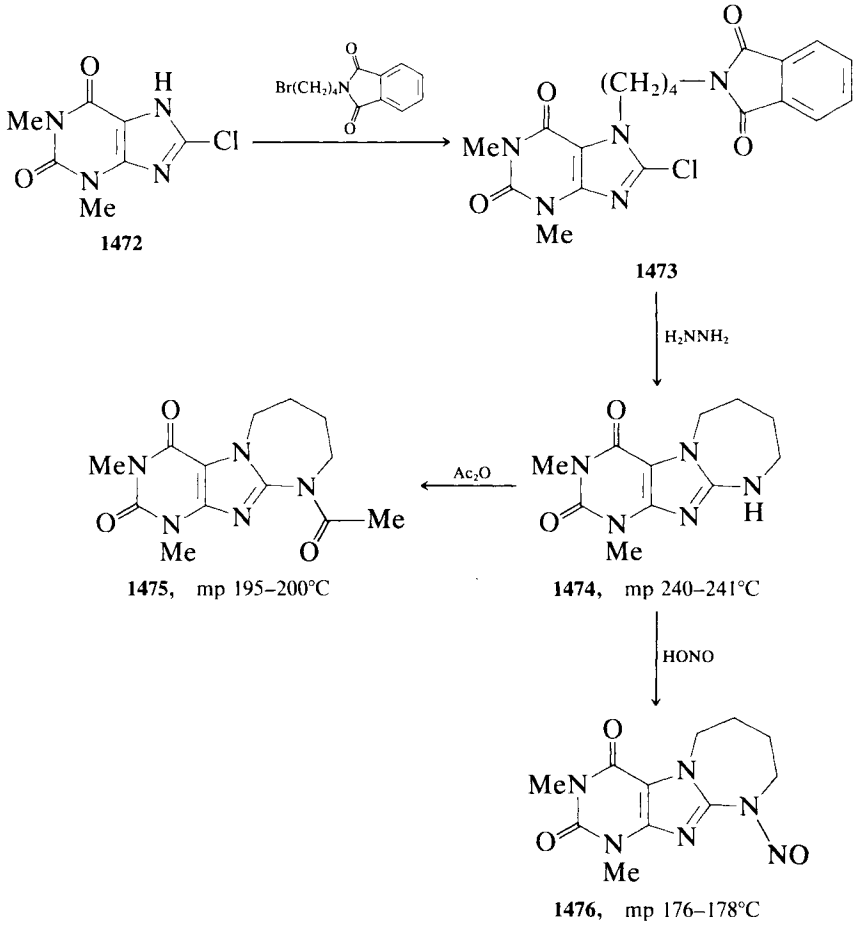


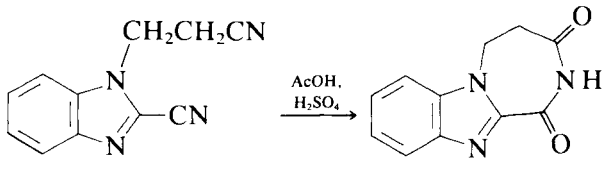

**Figure 135**

### 17. [1,2]Diazepino[1,7-*a*]benzimidazoles (see Section VI.33)

The full paper discussing the work outlined in Fig. 32 has appeared (879).

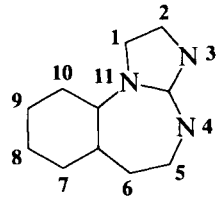
## 18. [1,4]Diazepino[1,2-*a*]benzimidazoles (see Section VI.35)

Another approach to the [1,4]diazepino[1,2-*a*]benzimidazole ring system has appeared. Reaction of dinitrile **1477** (Eq. 353) in acetic acid–sulfuric acid at 120°C for 45 min produced the tricyclic imide **1478** in 28% yield (880).

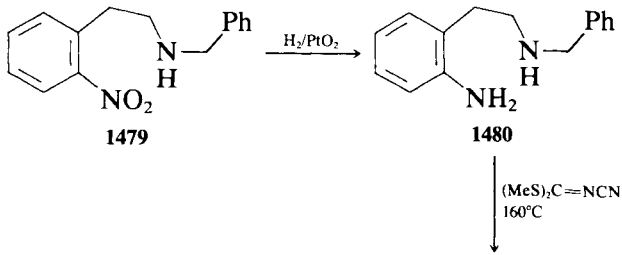



**1477** **1478**, mp 275–276°C (353)

## 19. Imidazo[1,2-*a*][1,3]benzodiazepines




Imidazo[1,2-*a*][1,3]benzodiazepines were prepared as shown in Fig. 136. Reduction of **1479** gave **1480,** which was cyclized to benzodiazepine **1481** with dimethyl cyanoimidodithiocarbonate at 160°C. Alkylation of **1481** with ethyl bromoacetate to give **1482**, followed by ring formation with hydrochloric acid in *t*-butanol, yielded **1483**. In the latter reaction the cyano group was removed in the presence of the ethyl ester, thus permitting the desired cyclization. Finally, debenzylation of **1483** produced the target compound **1484**, which showed some platelet aggregation inhibitory activity (881).




**1479** **1480**

Figure 136 *(cont'd on next page)*

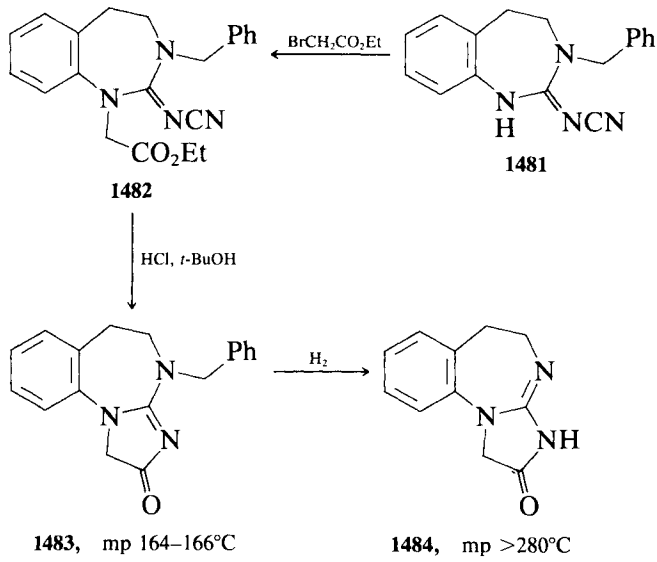



**Figure 136** *(continued)*

## 20. Imidazo[1,2-*a*][1,4]benzodiazepines (see Section VI.36)

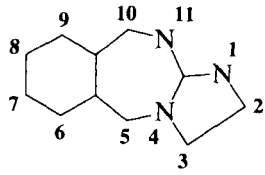
2-Amino analogs of **431** were prepared from **429** and 4-amino-2-butyn-1-ol (882). 6-Oxo derivatives of **429** were converted to 6-oxo derivatives of **431** (883). In addition to the synthesis of **433** (884), the preparation of 6-oxo-derivatives of **433** from 6-oxo derivatives of **429** was described (885,886). Several publications describing the preparation of **441** and related compounds listed in Table 62 have appeared (887,888).

1-Dimethylamino analogs were prepared by reaction of **433** with bis(dimethylamino)methane and acetyl chloride to yield **438** (889). Oxidation of **433** to the 4-hydroxy analog **461** (R = H), a likely metabolite, was carried out in 50% yield by treatment with lithium diisopropylamide followed by oxygen (848).

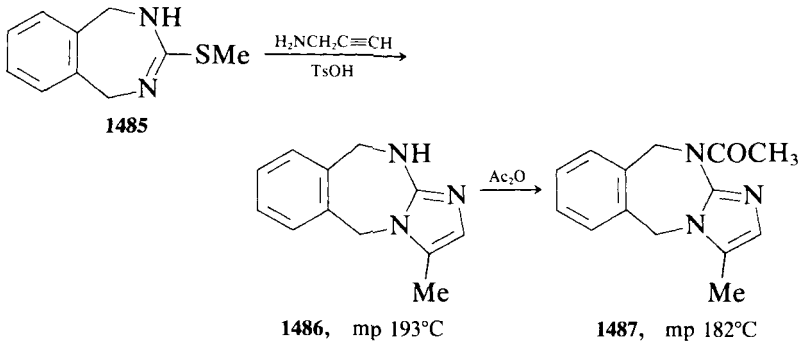
## 21. Imidazo[1,2-*a*][1,5]benzodiazepines (see Section VI.37)

Several publications describing the work outlined in Fig. 35 for compounds listed in Table 64 have appeared (890–892).

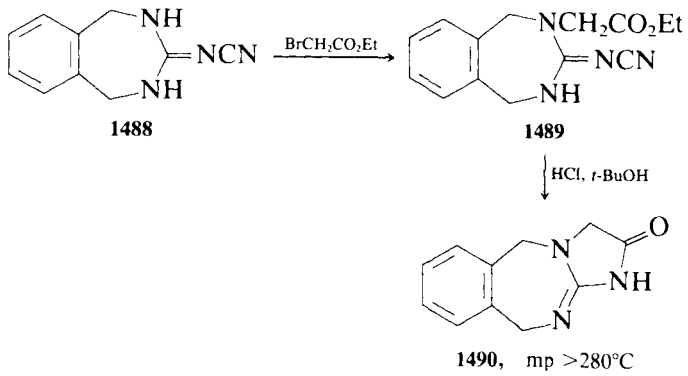
## 22. Imidazo[1,2-*b*][2,4]benzodiazepines




Several methods were used to prepare the imidazo[1,2-*b*][2,4]benzodiazepine ring system. In one of these, condensation of the isothiourea **1485** (Eq. 354) with propargylamine in the presence of *p*-toluenesulfonic acid gave **1486** in 43% yield. Compound **1486** was acetylated to produce **1487** (893). In another method, treatment of **1488** (Eq. 355) with ethyl bromoacetate led to **1489**, which was converted to **1490** in 59% yield with hydrochloric acid in *t*-butanol (881).




(354)




(355)

### 23. Imidazo[1,2-*d*][1,4]benzodiazepines (see Section VI.38)

Several additional patents describing Eq. 107 have appeared (866,867).

### 24. Imidazo[1,5-*a*][1,4]benzodiazepines (see Section VI.39)

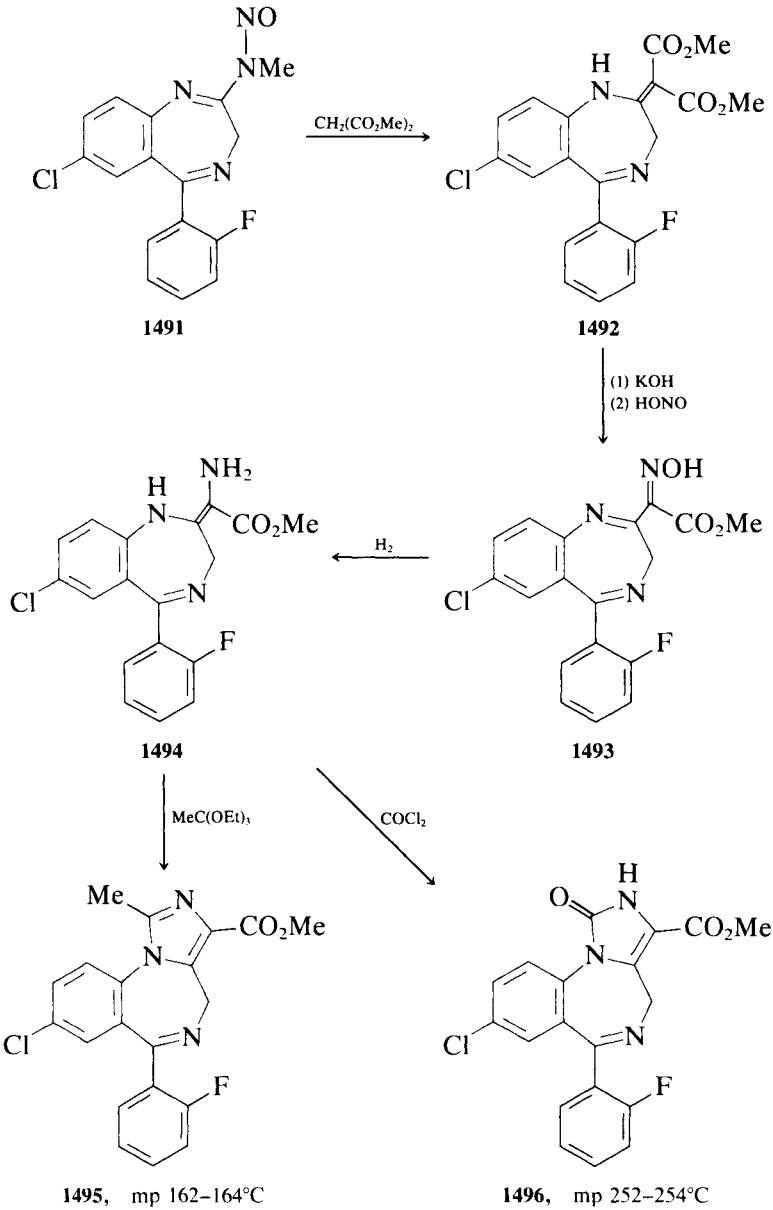
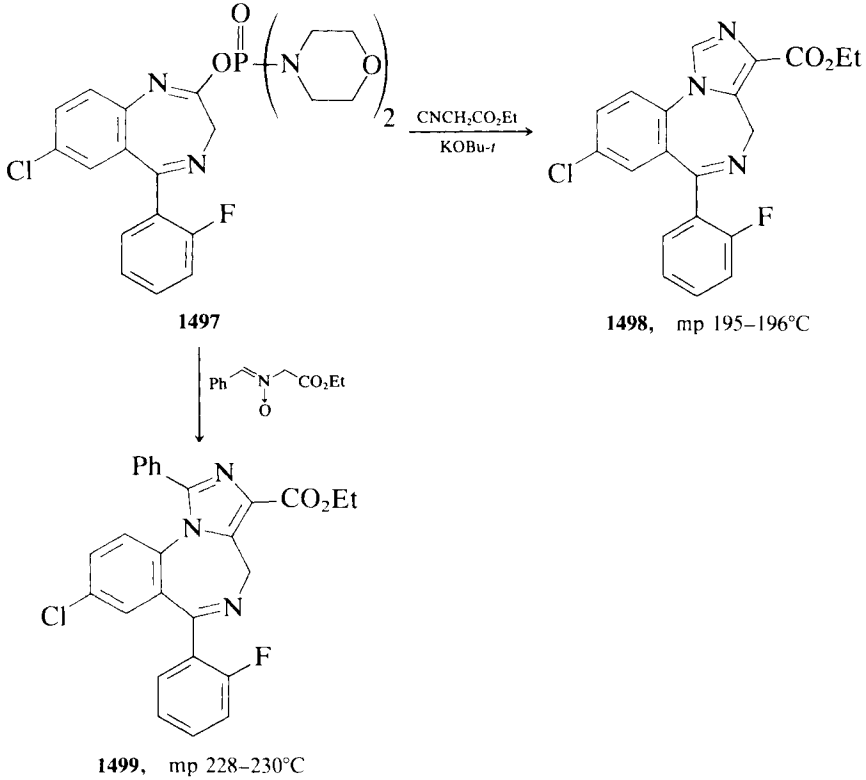



**Figure 137**

A patent and several papers describing and expanding the work set forth in Fig. 36 have been published (809,894,895). A number of new syntheses of 3-carboxy analogs of the kind prepared in Eq. 34 have appeared. One sequence is illustrated in Fig. 137. Dimethyl malonate was condensed with benzodiazepine **1491** to give **1492.** Selective hydrolysis, decarboxylation, and nitrosation of **1492** generated oxime **1493,** which was reduced to enamine **1494.** Reaction of **1494** with triethyl orthoacetate produced the target compound **1495** (806,896). Intermediate **1494** could also be converted to the 1-oxo derivative **1496** by treatment with phosgene (897). Numerous compounds analogous to **1495** and **1496** were prepared.

A one-step synthesis of the ring system has also been reported. Condensation of benzodiazepine **1497** (Eq. 356) with ethyl isocyanatoacetate in the presence of potassium *t*-butoxide yielded the tricyclic diazepine **1498** (898). Another direct approach was achieved by treatment of **1497** with the *N*-oxide of ethyl *N*-benzylideneglycinate to yield **1499** (806,899).

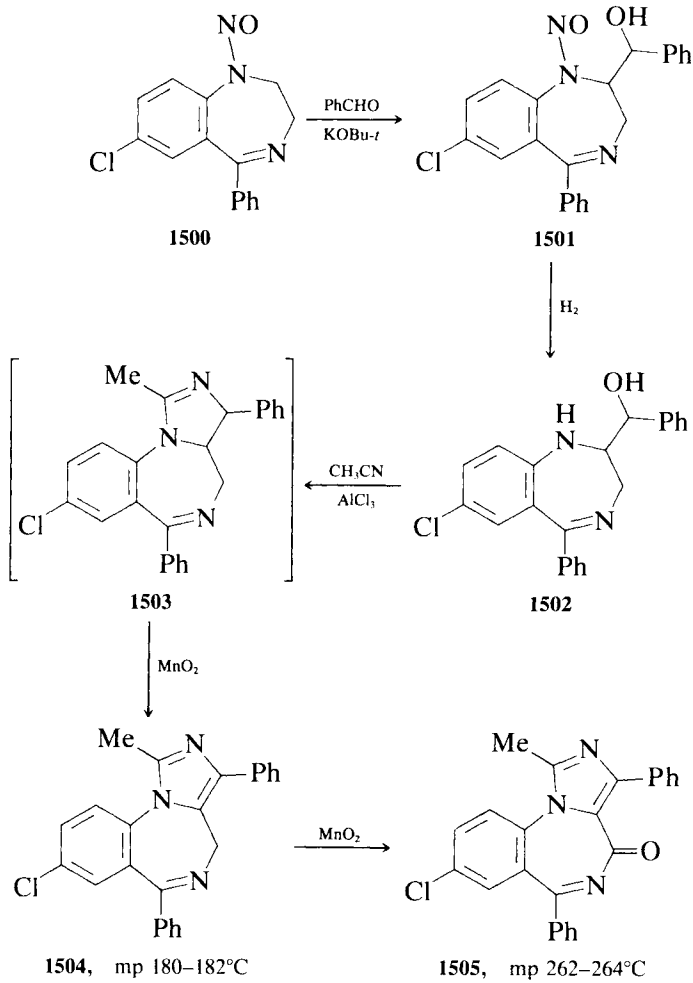
The ring system was also prepared by condensation of *N*-nitrosobenzodiazepine **1500** with benzaldehyde to yield **1501** (Fig. 138). Reductive removal of the nitroso group produced **1502,** which was converted to dihydroimi-




**1497** **1498,** mp 195–196°C

(356)

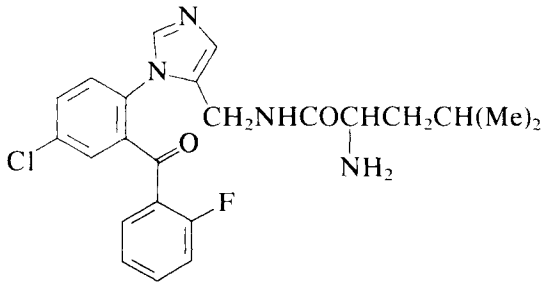
**1499,** mp 228–230°C




**1500** **1501** **1503** **1502**

**1504**, mp 180–182°C **1505**, mp 262–264°C

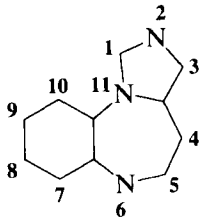
**Figure 138**




**1506**

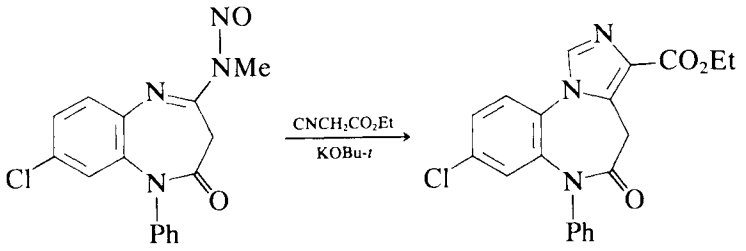
dazole **1503** with acetonitrile and aluminum chloride. Oxidation of **1503** with manganese dioxide generated the desired product **1504** as well as varying amounts of the overoxidized compound **1505** (899). Acid-catalyzed ring opening of compounds such as **488** followed by amidation gave amino acid derivatives illustrated by compound **1506** (900).

## 25. Imidazo[1,5-*a*][1,5]benzodiazepines

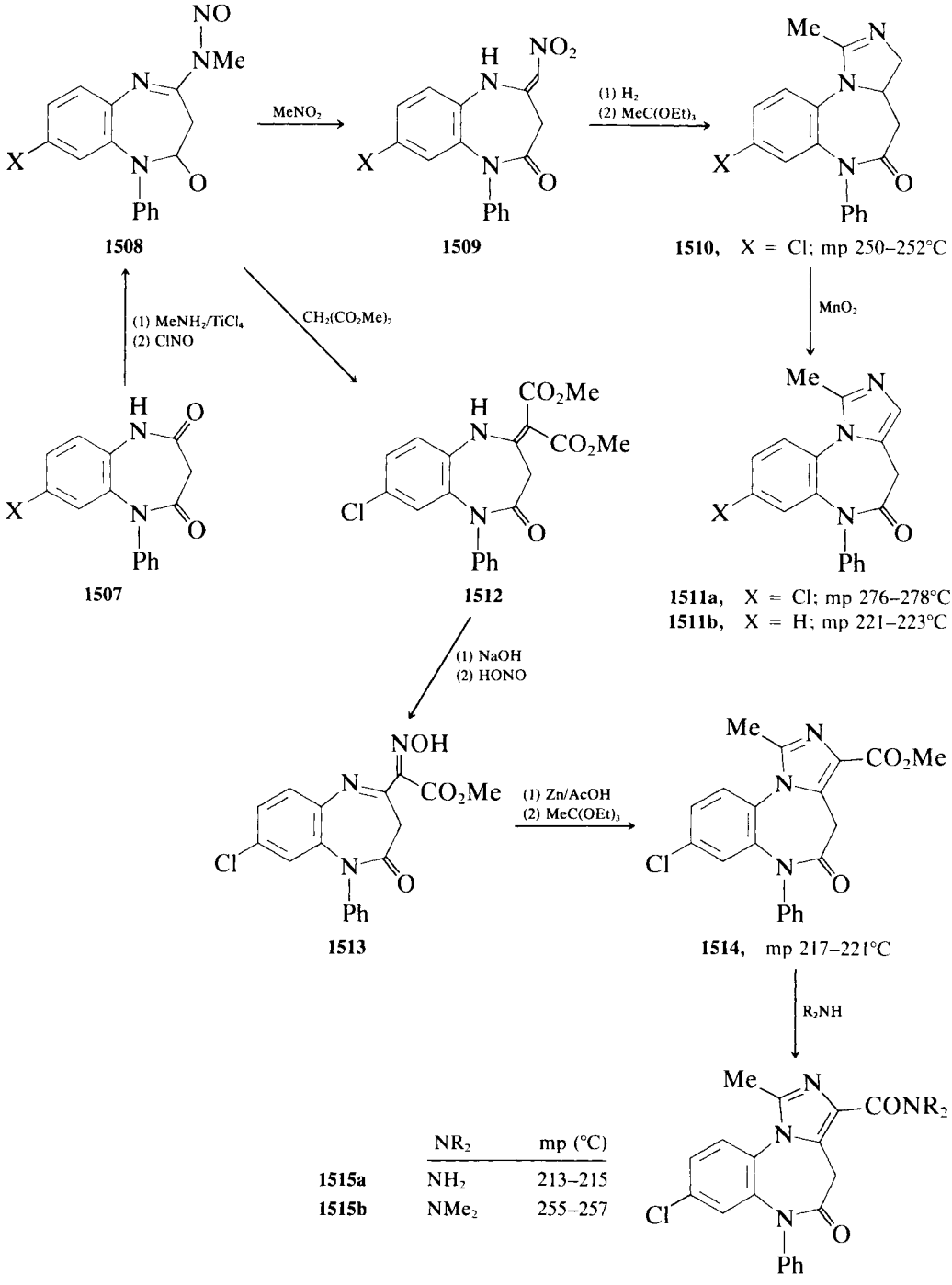



Imidazo[1,5-*a*][1,5]benzodiazepines were patented for their anxiolytic properties. Their preparation (Fig. 139) is analogous to that of the corresponding imidazo[1,5-*a*][1,4]benzodiazepines. Thus benzodiazepinedione **1507** was activated to **1508** and condensed with nitromethane to give **1509.** Reduction of **1509** followed by cyclization with triethyl orthoacetate led to **1510,** which on oxidation yielded the imidazole derivatives **1511.** In addition, treatment of **1508** with dimethyl malonate generated **1512.** Hydrolysis and decarboxylation of **1512** followed by oxiamation gave **1513.** Zinc reduction of **1513** followed by imidazole formation with triethyl orthoacetate produced the ester **1514,** which could be converted with ammonia and dimethylamine to the corresponding amides **1515a** and **1515b,** respectively (901).

An alternate synthesis, which fuses the imidazole onto the benzodiazepine substrate in one step, is outlined in Eq. 357. Treatment of **1516** with ethyl isocyanatoacetate in the presence of potassium *t*-butoxide led directly to the product **1517** (898).




**1516** **1517,** mp 256–258°C (357)




**1508** **1509** **1510**, X = Cl; mp 250–252°C

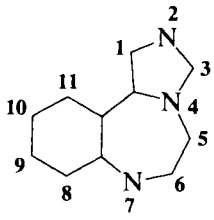
**1507** **1512** **1511a**, X = Cl; mp 276–278°C
**1511b**, X = H; mp 221–223°C

**1513** **1514**, mp 217–221°C

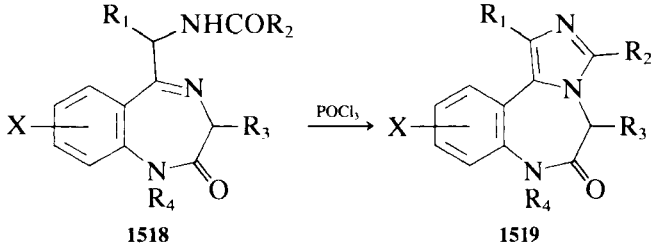
| | $NR_2$ | mp (°C) |
|---|---|---|
| **1515a** | $NH_2$ | 213–215 |
| **1515b** | $NMe_2$ | 255–257 |

**Figure 139**

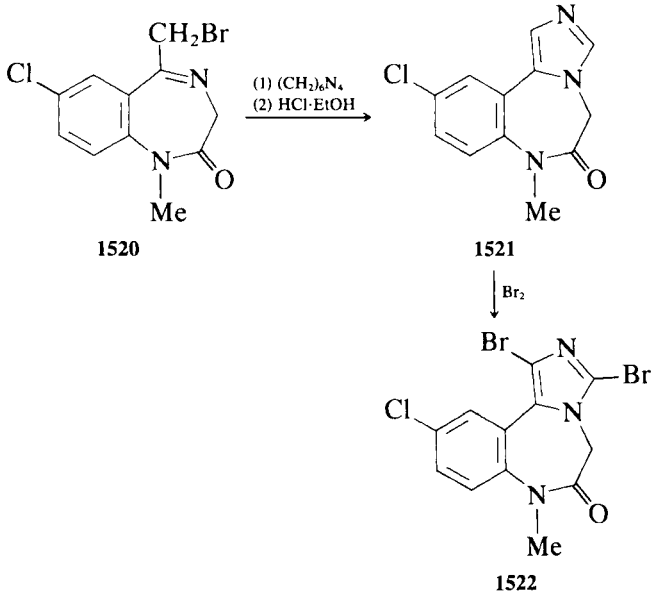
## 26. Imidazo[1,5-*d*][1,4]benzodiazepines



Several syntheses of the new imidazo[1,5-*d*][1,4]benzodiazepine ring system were described (902). In one route imine **1518** was converted to the tricyclic imidazole **1519** (Eq. 358) on treatment with hot phosphorous oxychloride. In another route, described as a new imidazole synthesis, imine **1520** was treated with hexamethylenetetramine followed by ethanolic hy-



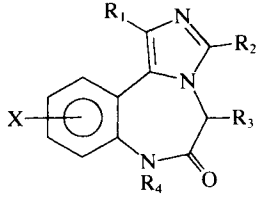
**1518** **1519** (358)



**1520** **1521** **1522** (359)

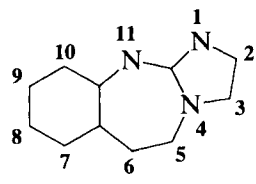
drochloric acid to yield **1521** (Eq. 359). Several transformations of the tricyclic system were also reported. Alkylation of **1519** ($R_4$ = H) led to several 7-alkyl or 7-aminoalkyl derivatives. In addition, bromination of **1521** was found to produce the dibromo analog **1522.** All of the tricyclic products prepared as described above are listed in Table 187.

TABLE 187. IMIDAZO[1,5-*d*][1,4]BENZODIAZEPINES

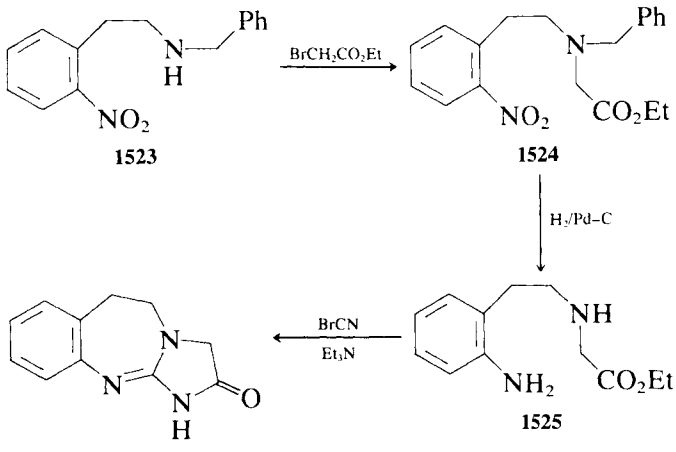


| X | $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) |
|---|---|---|---|---|---|
| 10-Cl | H | H | H | H | <310 |
| 10-Cl | H | Me | H | H | 100 |
| 10-Cl | H | Ph | H | H | 308–311 |
| 10-Cl | H | $CH_2Ph$ | H | H | 211–212 |
| 10-Cl | H | $CO_2Me$ | H | H | 120 |
| 10-Cl | H | $CO_2Et$ | H | H | 130 |
| 10-Cl | H | H | H | Me | 247–248 |
| H | H | H | H | Me | 185–187 |
| 9,10-$(OMe)_2$ | H | H | H | Me | 282–284 |
| 10-Cl | H | H | Me | Me | 226–227 |
| 10-OMe | H | H | H | Me | 159–160 |
| 10-Cl | H | Me | H | Me | 255–256 |
| 10-Cl | H | Ph | H | Me | 176–177 |
| 10-Cl | H | OEt | H | Me | 181–182 |
| 10-Cl | H | H | H | $CH_2CH_2NMe_2$ | 280–283 |
| 9,10-$(OMe)_2$ | H | H | H | $CH_2CH_2NMe_2$ | 143–145 |
| 10-Cl | Br | Br | H | Me | <310 |

## 27. Imidazo[2,1-*b*][1,3]benzodiazepines (see Section VI.41)



The imidazo[2,1-*b*][1,3]benzodiazepine ring system was prepared by starting with **1523.** Alkylation of **1523** with ethyl bromoacetate afforded **1524** (Eq. 360), which was hydrogenated in the presence of palladium to give **1525.**

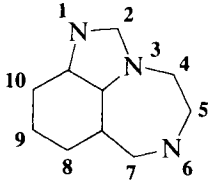



(360)

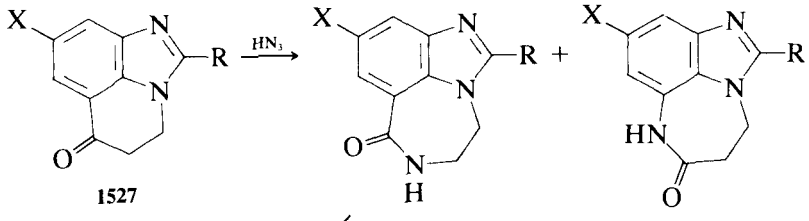
The conversion of **1525** to the product **1526** was carried out in 17% yield using cyanogen bromide (881).

### 28. Imidazo[1,5,4-*ef*][1,5]benzodiazepines (see Section VI.45)

### 29. Imidazo[4,5,1-*jk*][1,4]benzodiazepines



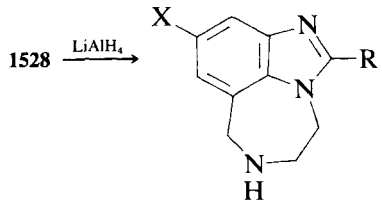

Imidazo[1,5,4-*ef*][1,5]benzodiazepines and imidazo[4,5,1-*jk*]benzodiazepines were prepared as possible anxiolytics. Schmidt reaction on **1527** gave the isomeric diazepines **1528** and **1529** (Fig. 140). The ratio of products was dependent on the aromatic substituent. Compounds **1528** were converted to the imines **1530** by treatment with triethyloxonium fluoroborate followed by phenylmagnesium bromide. In addition, compounds **1528** and **1529** were reduced to give amines **1531** and **1532**, respectively, (Eqs. 361 and 362) (903). Mass spectra of several members of each ring system were determined. Differences in the fragmentation pattern provide a means of identifying the isomeric structures (903).




| R | X | Yield (%) 1528 | 1529 |
|---|---|---|---|
| Me | X | 50 | 46 |
| Me | Cl | 78 | 14 |
| Me | $NO_2$ | 70 | — |
| $PhCH_2$ | Cl | 76 | 10 |
| $PhCH_2$ | $NO_2$ | 74 | 1 |

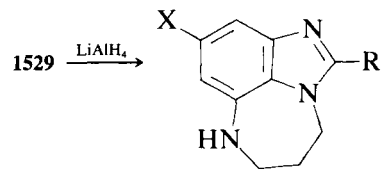
| | R | X | mp (°C) |
|---|---|---|---|
| **1530a** | Me | H | 219–221 |
| **1530b** | Me | Cl | 267–268 |

**Figure 140**




(361)

| | R | X | mp (°C) |
|---|---|---|---|
| **1531a** | Me | H | 184–185 |
| **1531b** | Me | Cl | 153–155 |
| **1531c** | $PhCH_2$ | Cl | 159 |



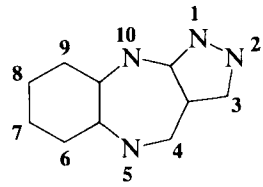

(362)

| | R | X | mp (°C) |
|---|---|---|---|
| **1532a** | Me | H | 229–231 |
| **1532b** | $PhCH_2$ | Cl | 164–166 |

## 30. Pyrazolo[1,5-*a*][1,4]benzodiazepines (see Section VI.46)

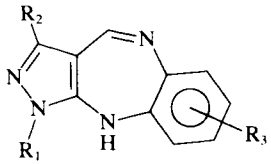
A patent has appeared covering the reactions described in Figs. 38 and 39 (905).

## 31. Pyrazolo[3,4-*b*][1,5]benzodiazepines

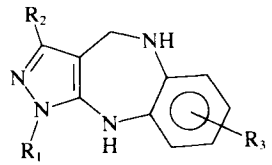



Pyrazolo[3,4-*b*][1,5]benzodiazepines are claimed to lower uric acid levels. Their preparation is illustrated in Fig. 141. Condensation of pyrazole **1533** with *o*-phenylenediamine produced **1534.** Sodium borohydride reduction of **1534** generated the key intermediate **1535.** Compounds prepared by this method are listed in Table 188. Bisalkylation of **1535** could be carried out

TABLE 188. TETRAHYDRO- AND DIHYDROPYRAZOLO[3,4-*b*][1,5]-BENZODIAZEPINES

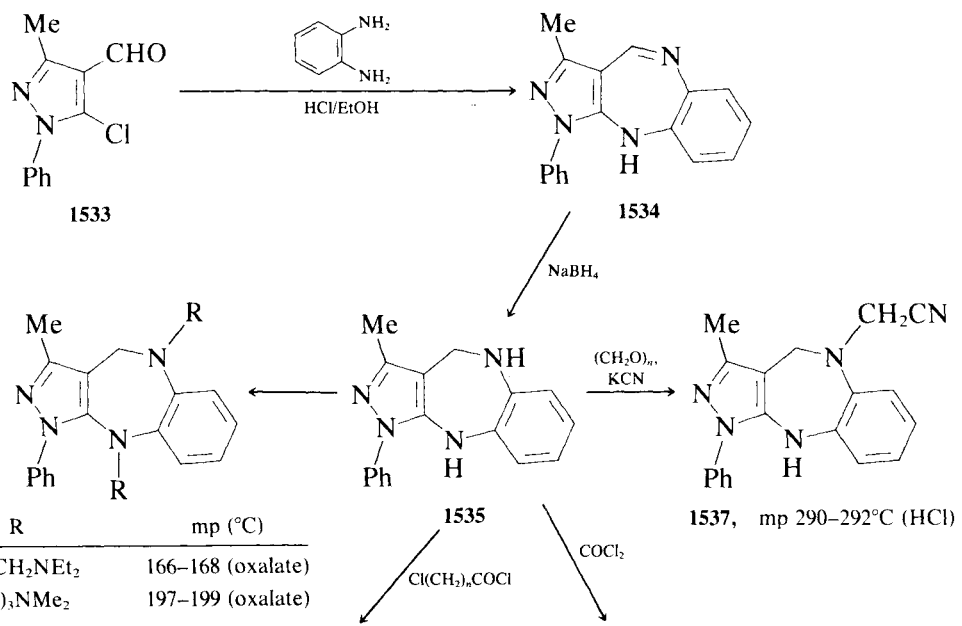



A




B

| | | | mp (°C) | |
|---|---|---|---|---|
| $R_1$ | $R_2$ | 7,8-$R_3$ | A | B |
| Ph | Me | H | 290–292 (HCl) | 165 |
| Ph | Me | Cl | 282–284 | 141–142 |
| Ph | Me | Me | 270–271 | 160 |
| Ph | Me | OMe | 274–276 | 230–231 |
| Ph | Me | $CO_2Me$ | 268–270 | |
| Ph | Me | $H_2NC(=NH)$— | >280 (2HCl) | |
| Me | Ph | H | 220–222 | >230 |
| Ph | H | H | 206–211 | >200 |
| $PhCH_2$ | Me | H | 198–203 | 211–214 |
| Et | Et | H | >190 | 195–196 |
| $C_6H_{11}$ | $Me_2CH$ | H | >170 | >190 |




| | R | mp (°C) |
|---|---|---|
| **1536a** | $CH_2CH_2NEt_2$ | 166–168 (oxalate) |
| **1536b** | $(CH_2)_3NMe_2$ | 197–199 (oxalate) |

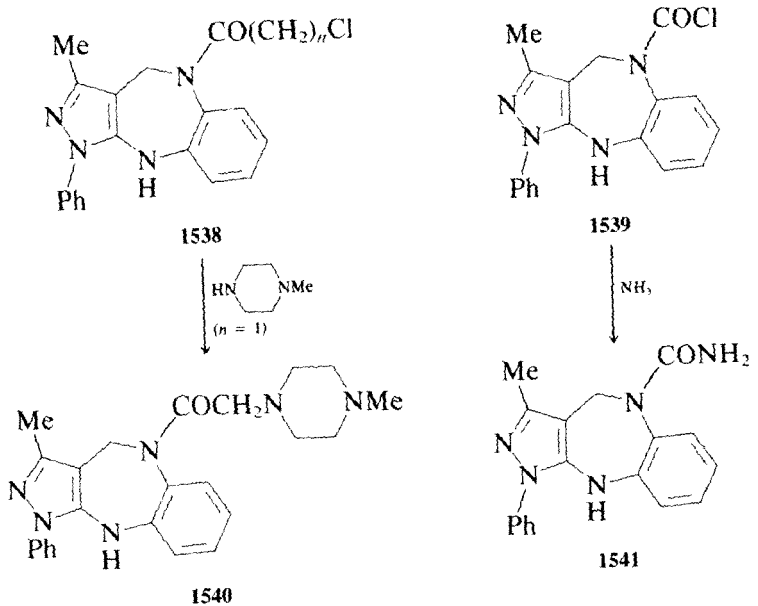
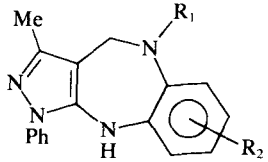
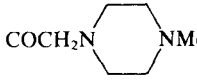
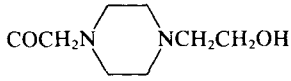
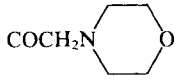
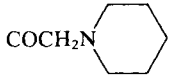
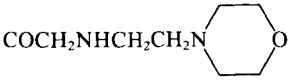
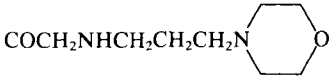
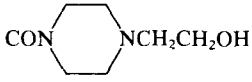

Me
CO(CH2)nCl
N
N
N
Ph
H
1538
HN
NMe
(n = 1)
COCH2N
NMe
1540
COCl
1539
NH3
CONH2
1541

Figure 141

by treatment with sodium hydride and an alkyl halide to give compounds **1536.** Cyanomethylation of **1535** was achieved with paraformaldehyde and potassium cyanide to yield **1537.** Acylation of **1535** with chloroacetyl chloride or 3-chloropropionyl chloride gave amides **1538,** and acylation of **1535** with phosgene generated **1539.** Treatment **1538** or **1539** with amines produced the aminoamide **1540** and the urea **1541,** respectively. 5-Substituted derivatives prepared by these methods are listed in Table 189 (906).

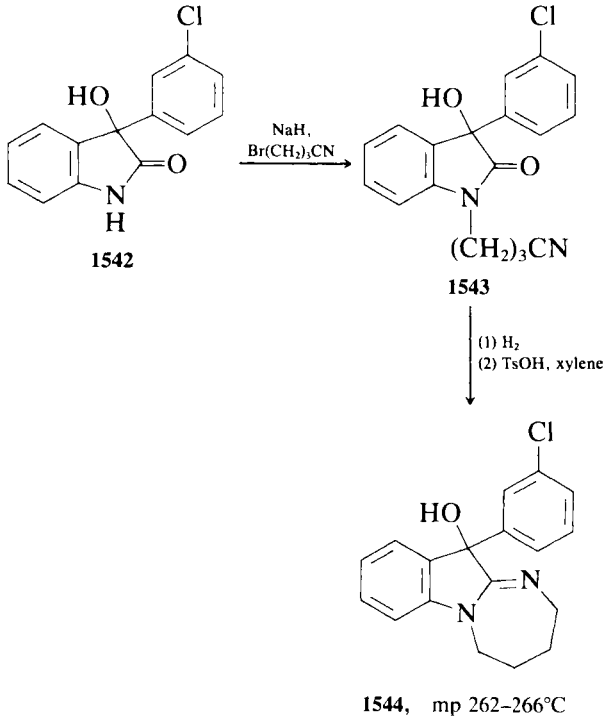
TABLE 189. 5-SUBSTITUTED PYRAZOLO[3,4-*b*][1,5]BENZODIAZEPINES




| $R_1$ | 7,8-$R_2$ | mp (°C) |
|---|---|---|
| COCl | H | 224–225 |
| COCl | Cl | 120 |
| $COCH_2Cl$ | H | 214 |
| $COCH_2CH_2Cl$ | H | 202–203 |
|  | H | 217 |
|  | H | 152–154 |
|  | H | 282–283 |
|  | H | 215–216 |
| $COCH_2NHCH_2CH_2NEt_2$ | H | |
|  | H | |
|  | H | |
| $COCH_2NMe_2$ | H | 226–228 |
|  | H | 152 |
| $CONHCH_2CH_2NEt_2H$ | H | 148 |
| $CONHNH_2$ | H | 140–142 |
| $CONH_2$ | H | 170–173 |
| $CONH_2$ | Cl | 190–194 |
| $CONHNHCOCH_3$ | H | 233 |

### 32. [1,3]Diazepino[1,2-*a*]indoles (see Section VI.50)

In addition to the route described in Eq. 121, diazepinoindole **1544** was prepared by alkylation of oxindole **1542** (Eq. 363) with 4-bromobutyronitrile followed by hydrogenation and cyclization of **1543** (907).




**1542** **1543** **1544**, mp 262–266°C (363)

### 33. [1,4]Diazepino[1,2-*a*]indoles (see Section VI.52)

It was found that bis(trifluoroacetoxy)borane reduced indoles **605** to indoline **631.** A number of other reducing agents were less satisfactory (908,909).

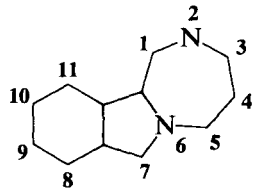
### 34. [1,4]Diazepino[1,7-*a*]indoles (see Section VI.53)

A full paper describing earlier reported results (Eq. 129) has appeared (910).

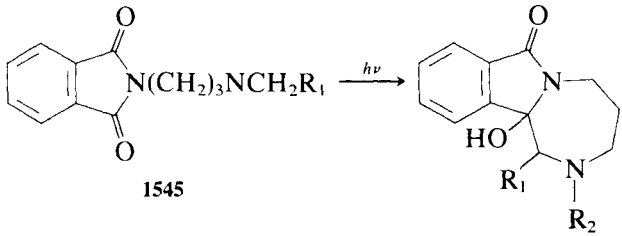
### 35. [1,3]Diazepino[2,1-*a*]isoindoles (see Section VI.56)

The transformation **661** → **660** (R = Ph) has appeared in another patent (911).

## 36. [1,4]Diazepino[2,1-*a*]isoindoles

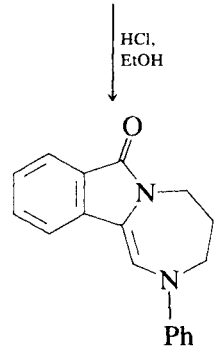



Several examples of the [1,4]diazepino[2,1-*a*]isoindole ring system were obtained in low yield by photocyclization of **1545** (Eq. 364). In addition, the product **1546a** was dehydrated in ethanolic hydrochloric acid to give **1547**, further supporting the identity of the structure (912,913).




**1545**

| | $R_1$ | $R_2$ | Yield (%) | Refs. |
|---|---|---|---|---|
| **1546a** | H | Ph | 20 | 912 |
| **1546b** | Ph | $CH_2Ph$ | 11 | 913 |



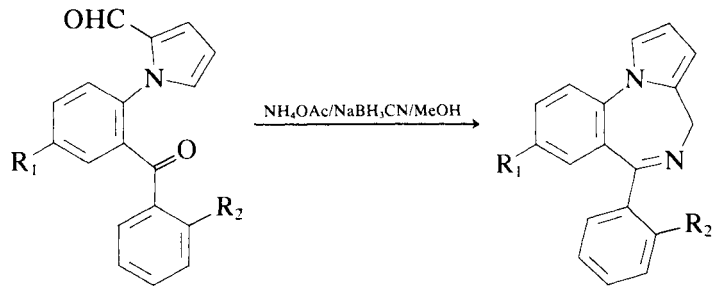

**1547**

(364)

## 37. Pyrrolo[1,2-*a*][1,4]benzodiazepines (see Section VI.57)

A patent (914) describes the preparation of analogs of **683** using the methodology previously reported (340). The same group of compounds (**1548**) has

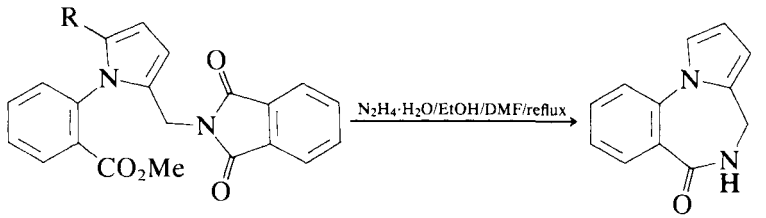
also been prepared (915) by treatment of ketoaldehyde **1549** with ammonium acetate in the presence of cyanoborohydride (Eq. 365). Other publications (916) describe the preparation of a larger group of analogs. Intermediates analogous to **682** were prepared from α-diketones, in addition to the 2,5-dialkoxytetrahydrofurans previously described. This route was also investigated by a German group (917), who prepared a series of ester intermediates (**1550**) and converted these to tricyclic lactams (**1551**) by treatment with hydrazine hydrate (Eq. 366). A variation of the synthetic methods previously described involves Vilsmeier formylation of the cyano compound **1552** (813). Hydrogenation of the formyl compound gave the target tricyclic product **1553** (Eq. 367). Condensation of the aminomethyl compound **670** with ketones gave a series of tricyclic derivatives (**1554**) (918). Dehydrogenation with manganese dioxide gave imine **1555** (Eq. 368).




(365)

**1549**

**1548a**, $R_1$ = Cl, $R_2$ = H
**1548b**, $R_1$ = $R_2$ = H
**1548c**, $R_1$ = $R_2$ = Cl

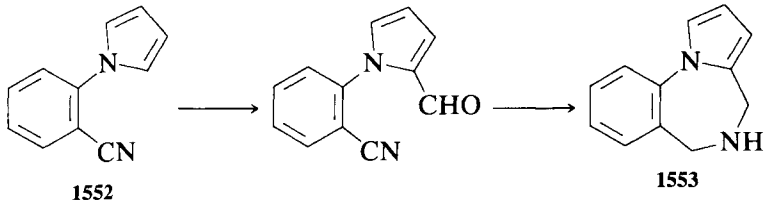



(366)

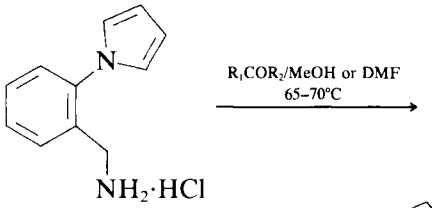
**1550**, R = Me, Et, Ph

**1551**

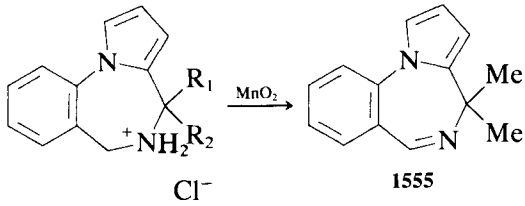
A related synthesis (919) involved acylation of benzhydroxylamine **1556**, followed by a Bischler–Napieralski reaction, to give the tricyclic imines **1557**, which were reduced with lithium aluminum hydride to the saturated amines **1558** (Eq. 369). The phenyl analog **1558** (R = Ph) was also prepared by condensation of the hydrochloride of **1556** with benzaldehyde in methanol at room temperature, or from the corresponding Schiff base by reaction with hydrogen chloride in ether (919).



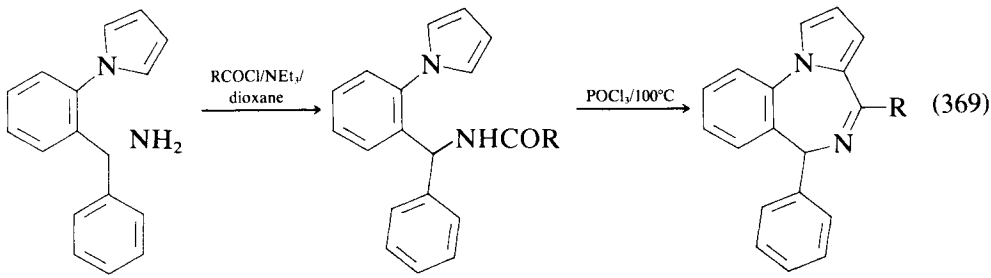

1552 1553 (367)



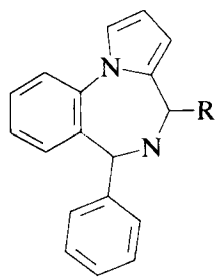

670·HCl




1554 1555 (368)




1556 R = Me, Et, Ph 1557 (369)




1558

## 38. Pyrrolo[1,2-*a*][1,5]benzodiazepines (see Section VI.58)

A new synthesis of pyrrolo[1,2-*a*][1,5]benzodiazepine derivatives involves a Mannich condensation on 1-(2-acetaminophenyl)pyrrole (920). The corresponding quaternary salt was converted to the cyano compound **1559**, which was not obtained pure but gave the tricyclic lactam **1560** on hydrolysis. Reduction with lithium aluminum hydride gave the secondary amine, which was acylated with acetic anhydride or acid chlorides. Vilsmeier reaction of the acetyl compound gave the 1-formyl derivative, which gave a condensation product with ethyl cyanoacetate (Fig. 142).

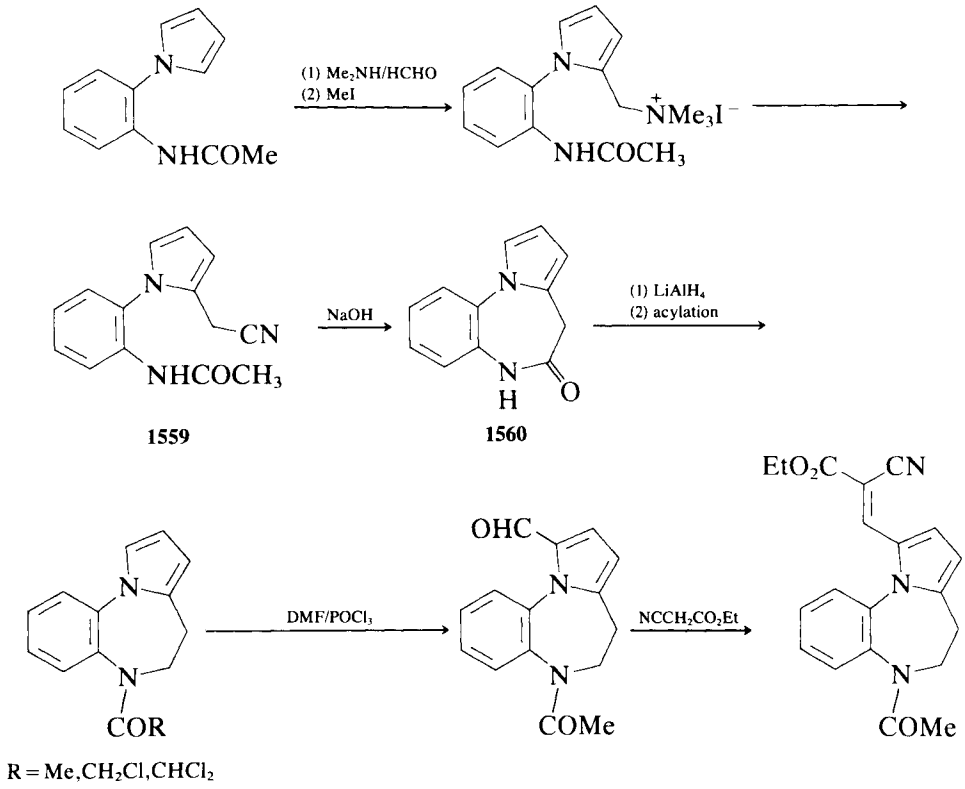
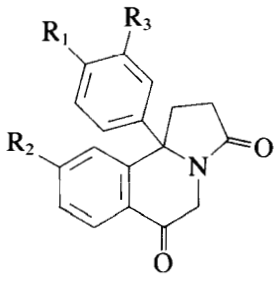


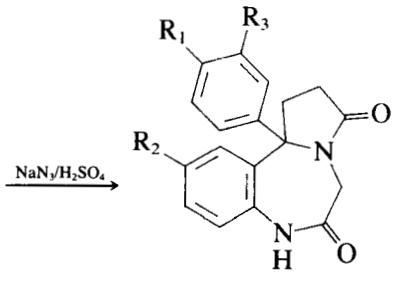

Figure 142

## 39. Pyrrolo[1,2-*d*][1,4]benzodiazepines (see Section VI.60)

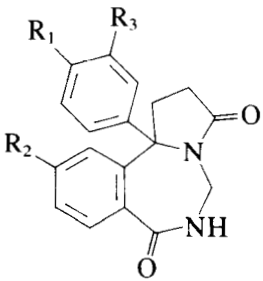
Further details of the chemistry described earlier (344) and leading to the preparation of **699** and **700** have now been provided (921). Schmidt reaction of **698a** gave 41% of **699a**, 4% of **1561a**, and 16% of **1563**; **698b** gave 55% of



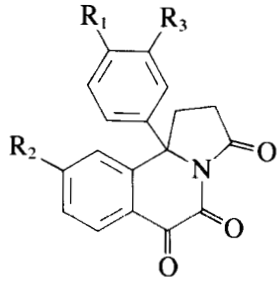
**698a**, $R_1 = R_2 = R_3 = H$
**698b**, $R_1 = R_3 = H$, $R_2 = Cl$
**698c**, $R_1 = R_3 = Cl$, $R_2 = H$



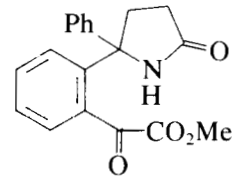
**699a,b**



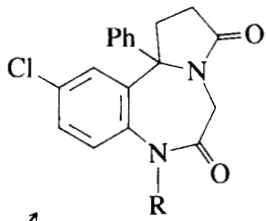
**1561a,b**



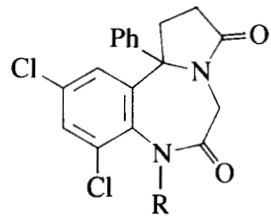
**1562**



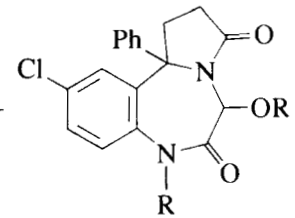
**1563**



**1564a**, R = H (89%)
**1564b**, R = COMe



**1565**, 1%

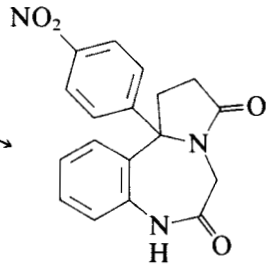


**1566a**, R = H (4%)
**1566b**, R = COMe

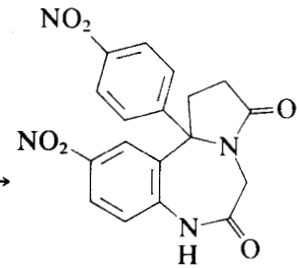
NCS/DMF
95°C

**698a**

$KNO_3/H_2SO_4$,
−15°C



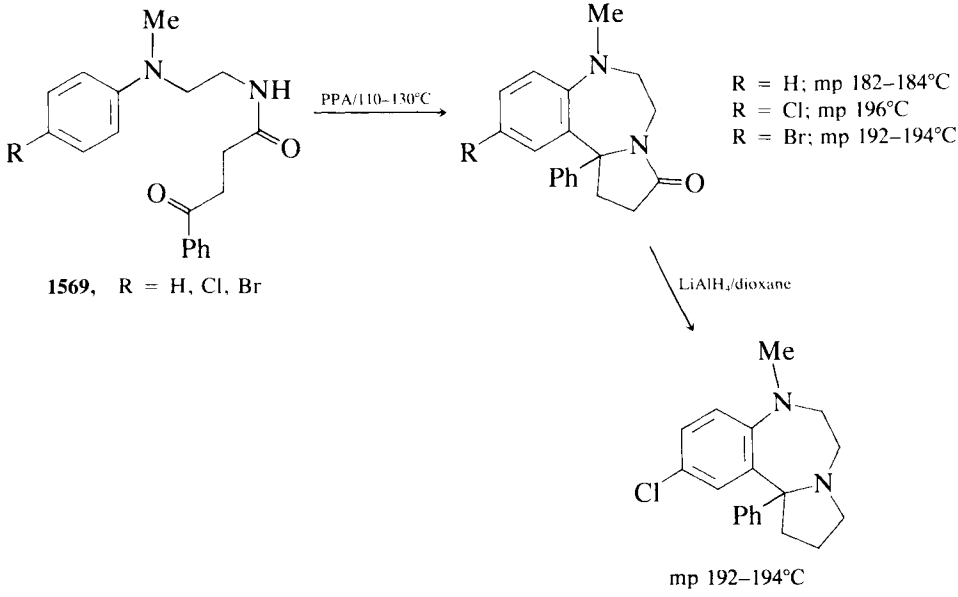
**1567**, 83%



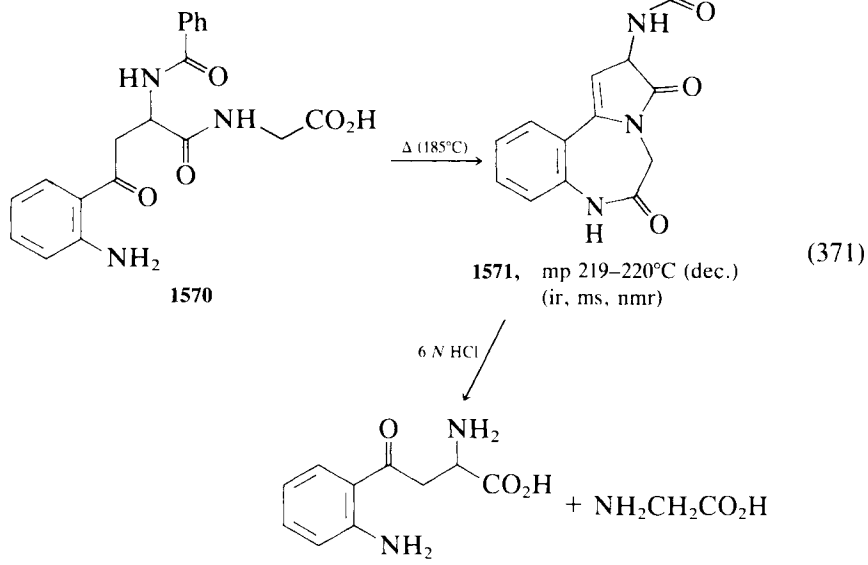
**1568**

**Figure 143**

**699b,** 4% of **1561b,** and 2% of **1562b; 698c** gave only **1562** in 37% yield (Fig. 143). Chlorination of **698a** with *N*-chlorosuccinimide gave **1564a** as the main product. Acetylation of **1564a** and **1566a** gave **1564b** and **1566b,** respectively. Nitration of **698a** gave **1567,** which was converted to the dinitro compound **1568.**




**1569,** R = H, Cl, Br (370)




**1570** **1571,** mp 219–220°C (dec.) (ir, ms, nmr) (371)

An additional group of compounds was prepared (922) by cyclization of **1569** (Eq. 370). Pyrolysis of the DL-kynurenine derivative **1570** gave the tricyclic pyrrolone **1571** (923). Hydrolysis of **1571** gave DL-kynurenine and glycine (Eq. 371).

Reaction of the diketones **1572** with ammonium acetate gave the 2-(2-nitrophenyl)pyrroles **1573,** which on catalytic hydrogenation gave the anilines **1574** (924). Treatment with bromoacetyl bromide gave the desired tricyclic derivatives **1575** ($R_2$ = H) in low yield. Condensation of the original diketones **1572** with either glycine or alanine gave pyrroles **1576,** from which the tricyclic lactams **1575** ($R_2$ = H, Me) were obtained in good yield on catalytic hydrogenation (Fig. 144).

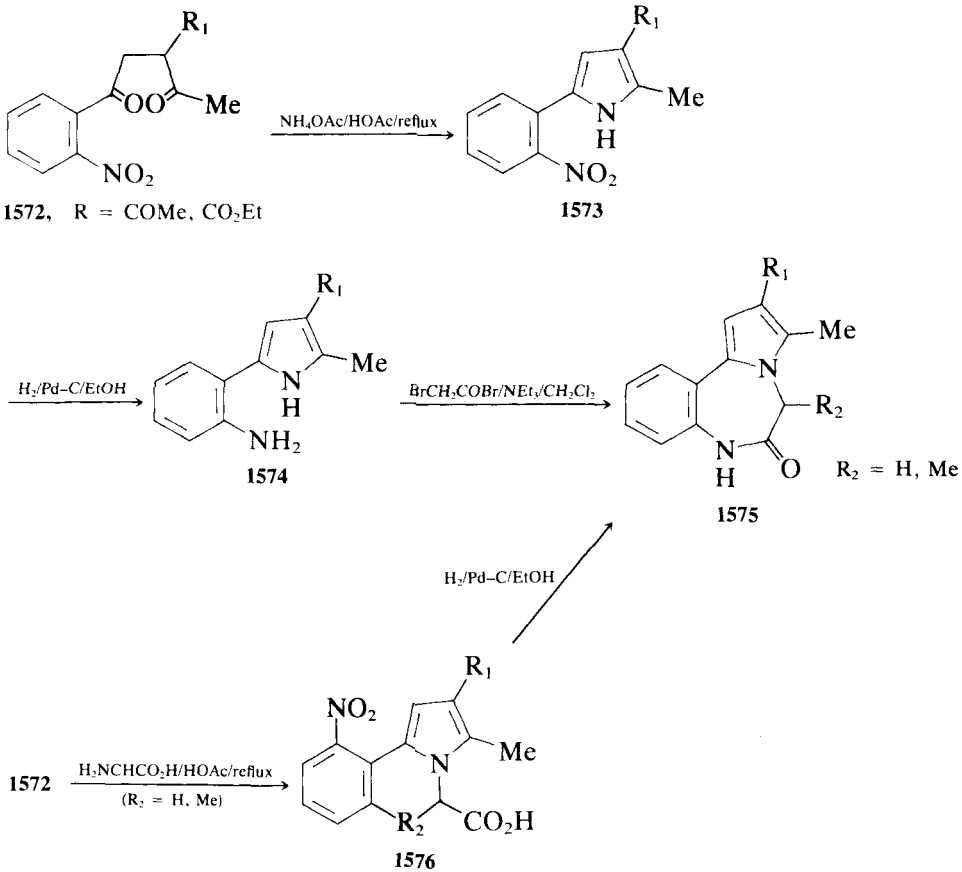
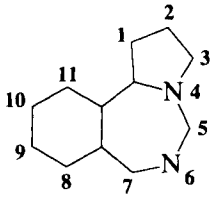



**Figure 144**

## 40. Pyrrolo[2,1-*a*][2,4]benzodiazepines




As described in the previous section and indicated in Fig. 143, derivatives of the pyrrolo[2,1-*a*][2,4]benzodiazepine ring system were obtained as low-yield by-products of the Schmidt reaction of keto lactams **698a** and **698b** (921).

## 41. Pyrrolo[2,1-*b*][1,3]benzodiazepines (see Section VI.61)

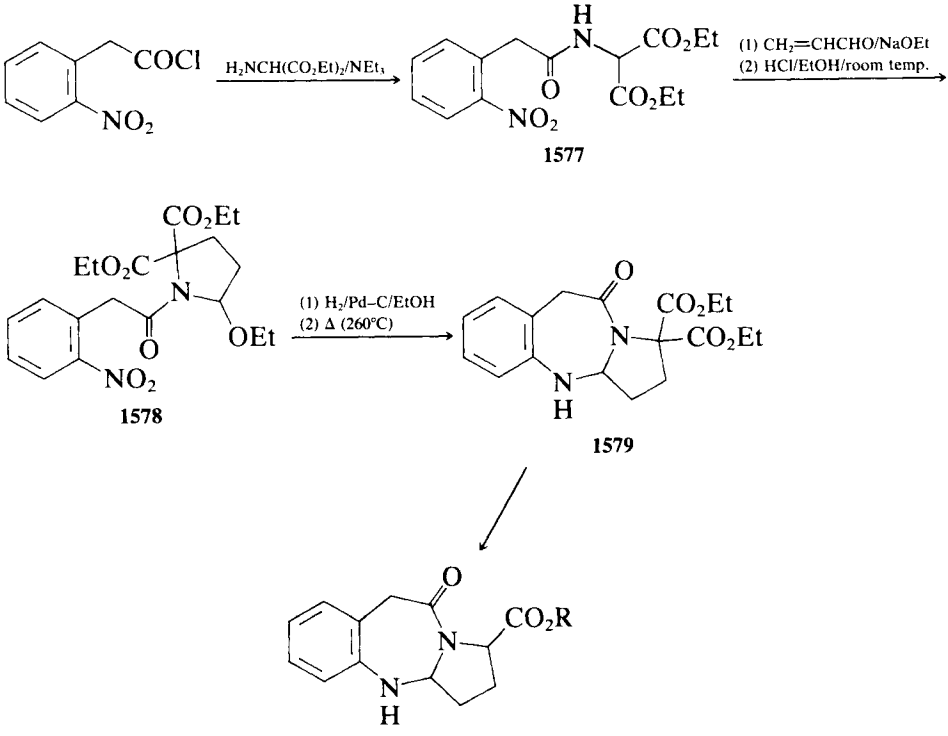
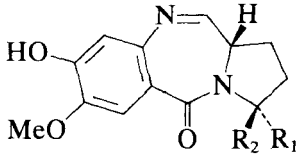



**Figure 145**

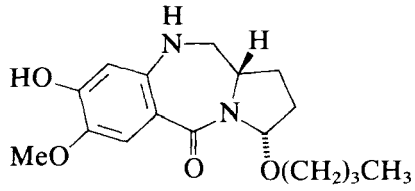
A new synthesis of pyrrolo[2,1-*b*][1,3]benzodiazepines is indicated in Fig. 145. Acylation of diethyl aminomalonate with 2-nitrophenylacetyl chloride gave **1577.** Michael reaction with acrolein gave an adduct that was cyclized under acidic conditions to the acylated aminal **1578.** The nitro group was reduced by catalytic hydrogenation, and the aniline was cyclized by pyrolysis to **1579.** This substance could be hydrolyzed either to the monoester or the monocarboxylic acid (925).

## 42. Pyrrolo[2,1-*c*][1,4]benzodiazepines (see Section VI.62)

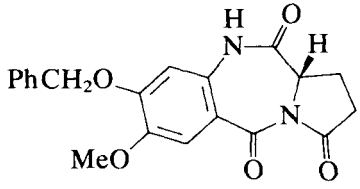
Structure elucidation and total synthesis of two new antibiotics, neothramycins A and B (**1580a,b**), have been described (926). Either substance gave



**1580a,** $R_1$ = OH, $R_2$ = H
**1580b,** $R_1$ = H, $R_2$ = OH
**1581a,** $R_1$ = OMe, $R_2$ = H
**1581b,** $R_1$ = H, $R_2$ = OMe
**1582a,** $R_1$ = $O(CH_2)_3CH_3$, $R_2$ = H
**1582b,** $R_1$ = H, $R_2$ = $O(CH_2)_3CH_3$



**1583**



**1584**

a mixture of neothramycins A and B methyl ethers (**1581a,b**) on treatment with methanol; the *n*-butyl ether derivatives **1582a,b** were obtained analogously. Catalytic hydrogenation of **1582a** gave dihydro compound **1583.** Alkaline hydrolysis of **1582a** gave 4-hydroxy-5-methoxyanthranilic acid. Treatment of **1582a** with phenyldiazomethane followed by mild hydrolysis gave a mixture of *O*-benzyl derivatives, which were oxidized with potassium permanganate to a single tricarbonyl compound (**1584**). Acid hydrolysis of **1584** gave L-glutamic acid, thus defining the stereochemistry at $C_{11a}$. Configurations at $C_3$ were determined from nmr studies. The imine function in **1580a,b** was readily hydrated in aqueous solution.

The synthetic work is outlined in Fig. 146. Nitro acid **1585** was obtained by nitration of *O*-benzylvanillic acid. This substance was converted to the acid chloride, which was condensed with γ-methyl L-glutamate to give the amide acid **1586.** Reduction of the carboxylic acid function to the aldehyde,

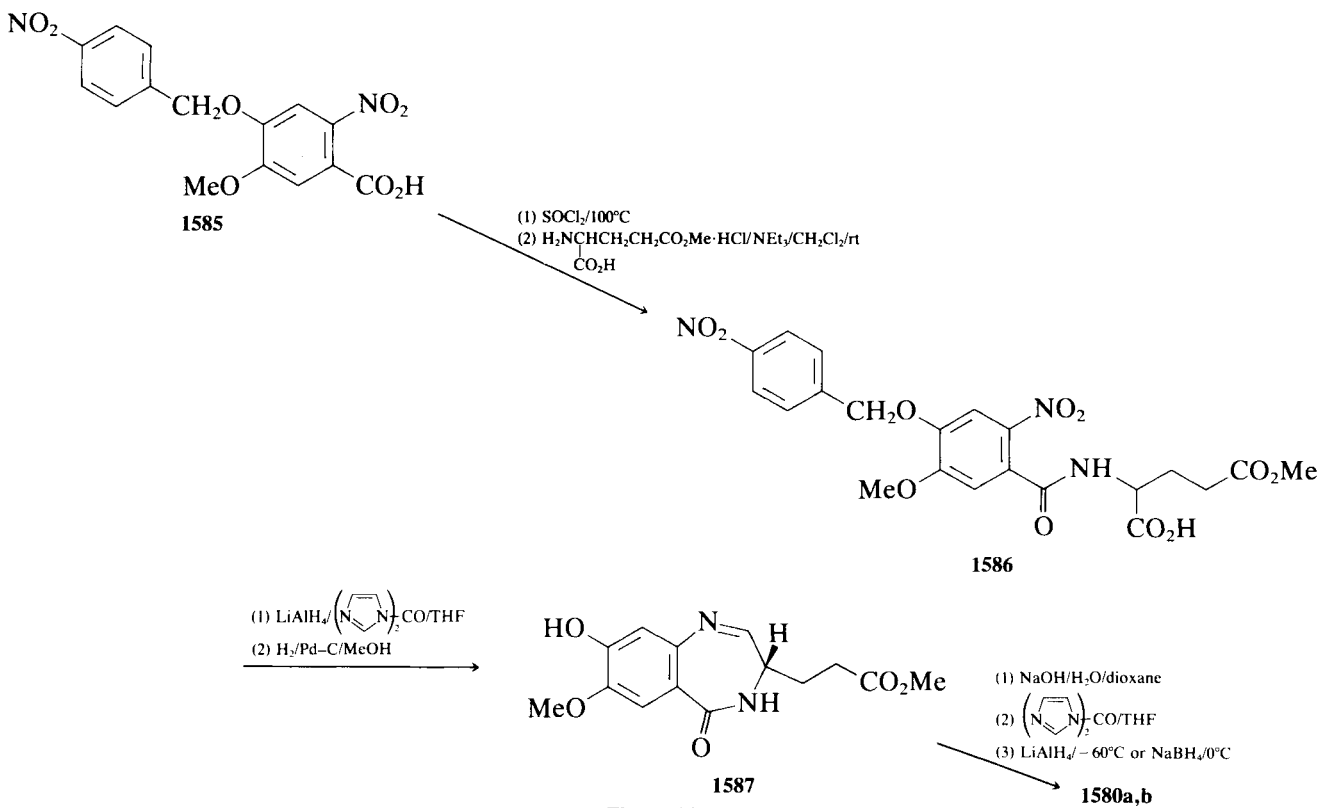
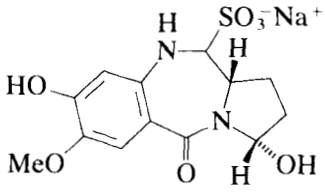

NO2
CH2O
NO2
MeO
CO2H
1585
(1) SOCl2/100°C
(2) H2NCHCH2CH2CO2Me·HCl/NEt3/CH2Cl2/rt
CO2H
NO2
CH2O
NO2
MeO
NH
CO2Me
O
CO2H
1586
(1) LiAlH4/(N N)2CO/THF
(2) H2/Pd–C/MeOH
HO
N
H
CO2Me
MeO
NH
O
1587
(1) NaOH/H2O/dioxane
(2) (N N)2CO/THF
(3) LiAlH4/ – 60°C or NaBH4/0°C
1580a,b

**Figure 146**

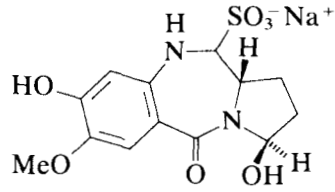
followed by catalytic hydrogenation, gave imine **1587.** The ester function in **1587** was hydrolyzed to the carboxylic acid. Reduction to the aldehyde stage gave a mixture of **1580a** and **1580b.**

A patent (927) describes the preparation and biological properties of the neothramycin sodium sulfite adducts **1588a** and **1588b.**The structure of mazethramycin (**1589**) was determined from spectroscopic data (928). A patent describes the methodology for isolating the antibiotic (929).

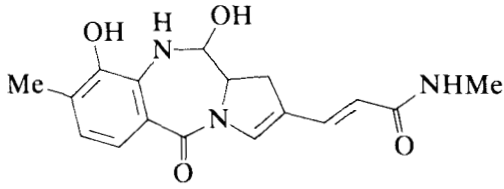
The key step in the synthesis of anhydrosibiromycinone (**1590**) was first investigated on a model system (930). The sodium salt of pyrrole-2-aldehyde was condensed with the sulfinamide anhydride **1591** (Eq. 372a). This pro-



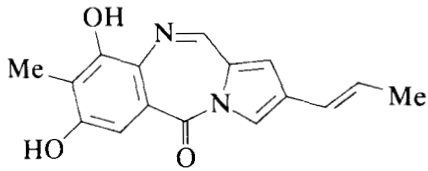
**1588a**



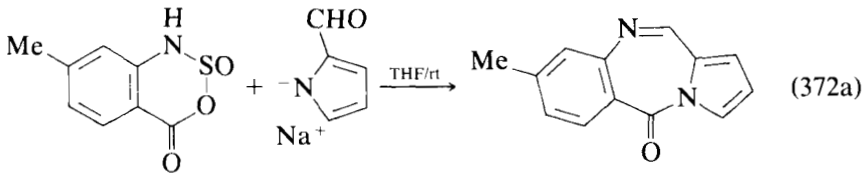
**1588b**



**1589**



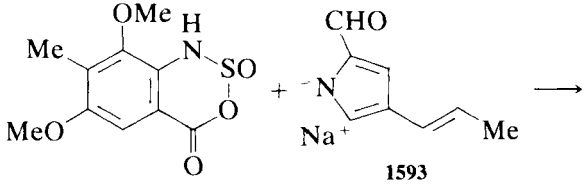
**1590**



**1591**

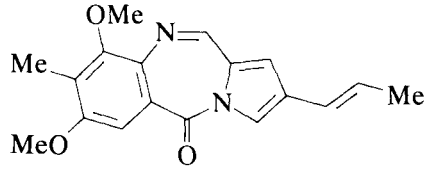
(372a)

cedure was then applied to the anthranilic acid derivative **1592** and the aldehyde **1593** (Eq. 372b). The condensation product **1594** was demethylated with boron tribromide to give **1590.**



**1592** **1593**

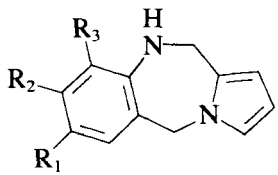
(372b)



**1594**

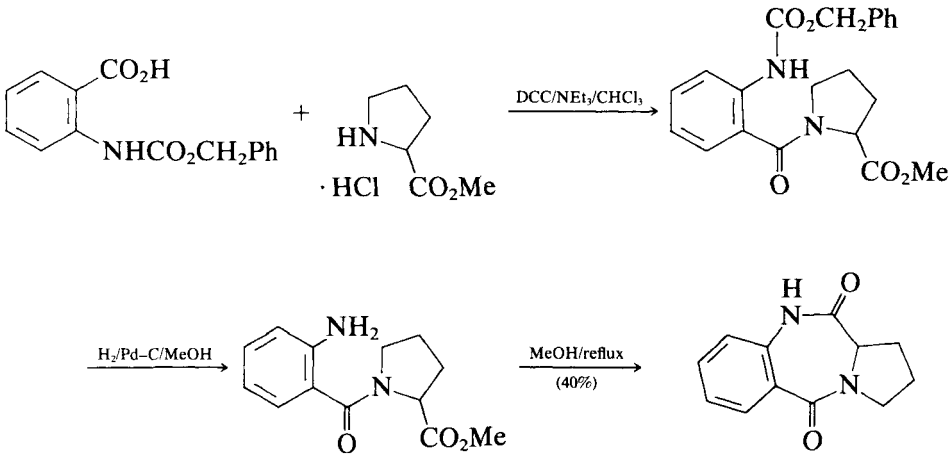
Reviews on pyrrolo[2,1-*c*][1,4]benzodiazepine antibiotics covering chemistry, biosynthesis, and biological effects have been published (931). Further biosynthetic studies have been described (932). X-ray crystallographic studies of anthramycin (933) and anthramycin methyl ether (934) have been reported, and a detailed proposal for the structure of the anthramycin–DNA adduct has been made (935).

Using methodology previously described, a series of simplified analogs of tomaymycin (**708**) has been prepared (936). These include **753** (X = 7-MeO, 8-OH; R = H, OH), **757** [X = 7-MeO, 8-$PhCH_2O$; 8-$PhCH_2O$, 9-MeO; 7,8-$(PhCH_2O)_2$], as well as the reduced compounds **1595a–e.** Debenzylation of **1595e** could not be effected.



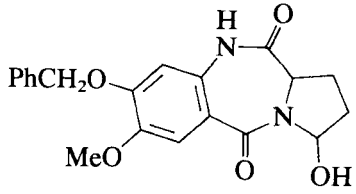
**1595a,** $R_1$ = MeO, $R_2$ = OH, $R_3$ = H
**1595b,** $R_1$ = MeO, $R_2$ = $PhCH_2O$, $R_3$ = H
**1595c,** $R_1$ = H, $R_2$ = $PhCH_2O$, $R_3$ = MeO
**1595d,** $R_1$ = H, $R_2$ = OH, $R_3$ = MeO
**1595e,** $R_1$ = $R_2$ = $PhCH_2O$, $R_3$ = H

The simple dilactam **1596** was prepared by condensation of *N*-benzyloxycarbonylanthranilic acid with proline methyl ester hydrochloride followed by hydrogenolysis and thermal cyclization (Eq. 373). A detailed analysis of the circular dichroism spectrum was provided (937). The hydroxy dilactam **1597** was prepared using methodology described earlier (938).




(373)

**1596,** mp 209–211°C (uv, ms)




**1597**

Hydroboration of the unsaturated diester **754a** gave a mixture of the anticipated alcohol **1598** and the diol **1599** (939). Both substances were converted to the tricyclic trione **1600** (Fig. 147), analogous to **747,** which was used in the synthesis of anthramycin.

Reduction of diester **754a** with ferrous sulfate gave the tricyclic olefin **1601.** This substance was brominated, and the dibromo compound was converted to the bromohydrin (940). Dehydration gave vinyl bromide **754b.** Hydrolysis of **1601** gave the decarbethoxylated product **1602** (Fig. 148).

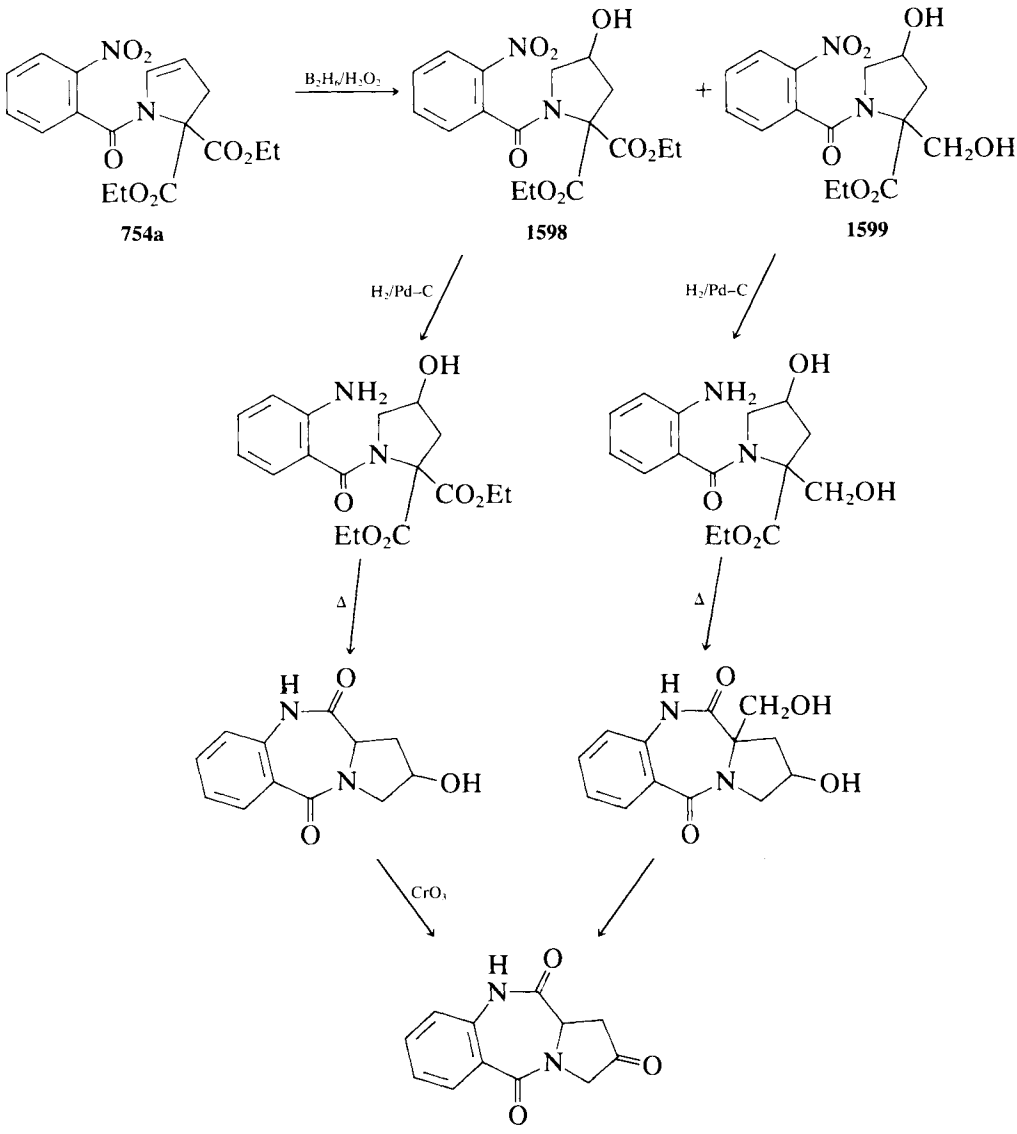



**Figure 147**

Condensation of isatoic anhydrides with proline derivatives (Eq. 374) led to the formation of the tricyclic dilactams **1603,** which were found to exhibit anxiolytic properties in animals (941). Simplified antibiotic analogs (**1604** and **1604a**) lacking substituents on the five-membered ring were prepared by standard methods. Antileukemic activity was claimed for these compounds (942).

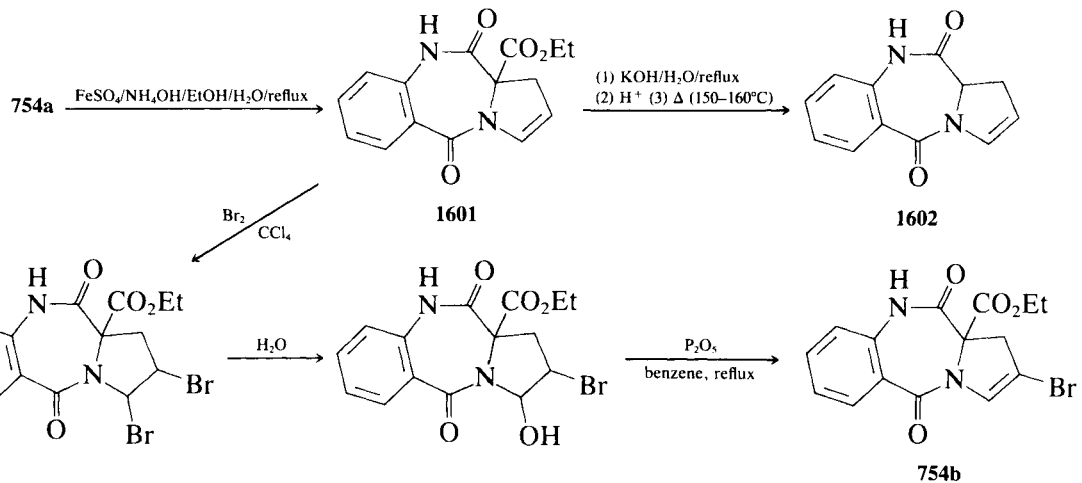
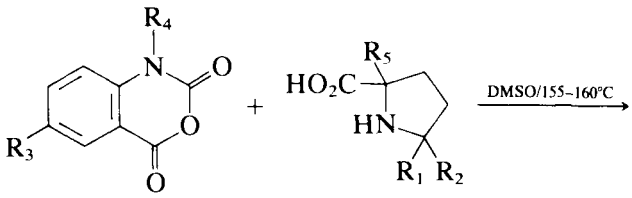
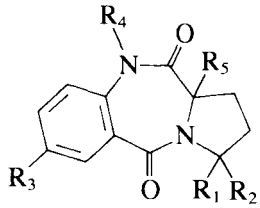

754a
FeSO4/NH4OH/EtOH/H2O/reflux
1601
(1) KOH/H2O/reflux
(2) H+ (3) Δ (150–160°C)
1602
Br2
CCl4
H2O
P2O5
benzene, reflux
754b

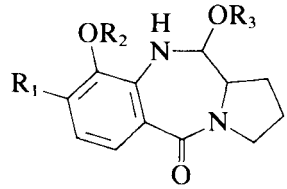
**Figure 148**



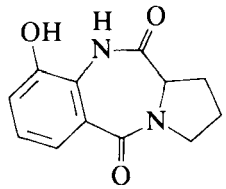

(374)



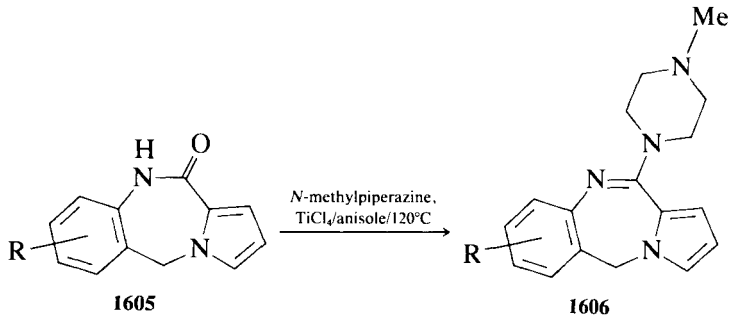

**1603,** $R_1 = R_2 = H$, Me; $R_3 = H$, F; $R_4 = H$, Me; $R_5 = H$, Me




**1604,** $R_1 = H$, OH, alkyl, alkoxy; $R_2 = H$, acyl; $R_3 = H$, alkyl, phenyl




**1604a**




(375)

Analogs of the neuroleptic agent clozapine were prepared (943) from the tricyclic lactams **1605,** obtained by methods essentially those of Artico and coworkers. (373,375) The target amidines **1606** were prepared from **1605** with titanium tetrachloride (Eq. 375).

The Italian group (944) has prepared a series of tricyclic cyanoimines (**1607**) by cyclization of cyanoamides **1608** (Fig. 149). Hydrolysis of **1607** gave amides **1609** and carboxylic acids **1610.** The acids could be thermally decarboxylated. The imine function of **1607** could be reduced by catalytic hydrogenation.

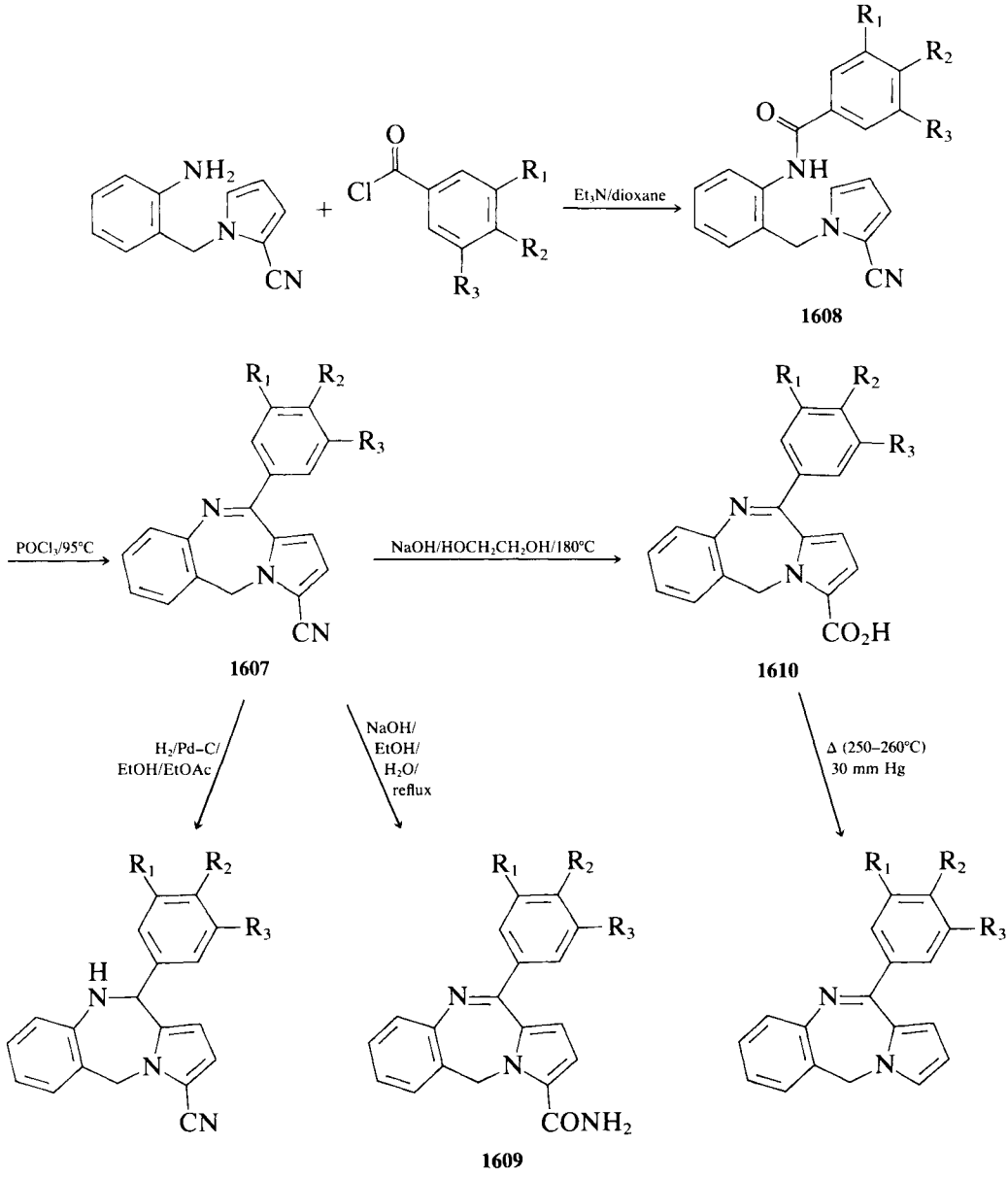
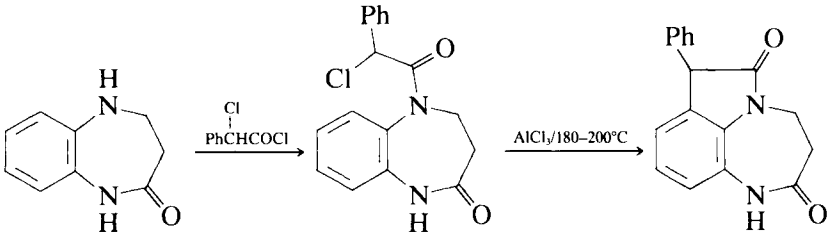

NH2
N
CN
O
Cl
R1
R2
R3
Et3N/dioxane
O
NH
1608
POCl3/95°C
NaOH/HOCH2CH2OH/180°C
1607
1610
H2/Pd-C/
EtOH/EtOAc
NaOH/
EtOH/
H2O/
reflux
Δ (250–260°C)
30 mm Hg
CONH2
CO2H
1609

**Figure 149**

## 43. Pyrrolo[1,2,3-*ef*][1,5]benzodiazepines (see Section VI.66)

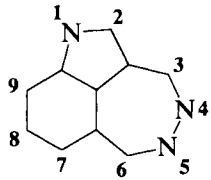
An additional derivative has been synthesized from the benzodiazepinone **1611** by acylation with α-chloro-α-phenylacetyl chloride followed by cyclization with aluminum chloride at 180–200°C (945). The substance exhibited anti-inflammatory activity and inhibited platelet aggregation *in vivo* (Eq. 376).



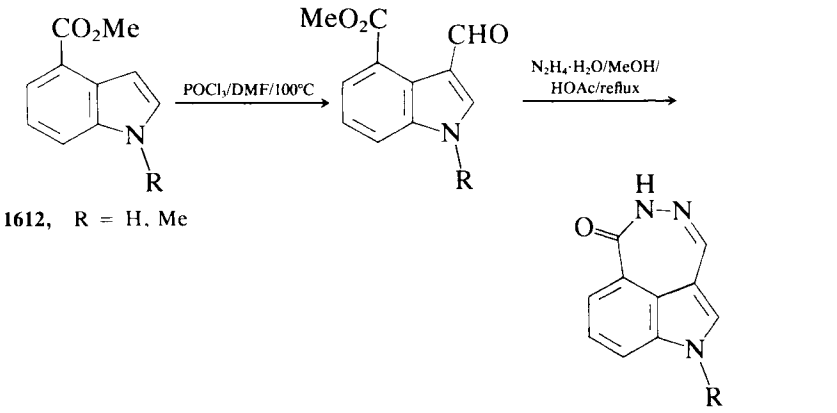

(376)

**1611**

## 44. Pyrrolo[4,3,2-*ef*][2,3]benzodiazepines




Vilsmeier formylation of the indole derivatives **1612** gave the 3-formyl compounds (946). Treatment with hydrazine gave the tricyclic diazepinones **1613** (Eq. 377).



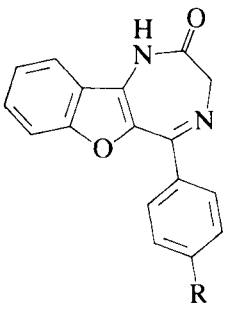

(377)

**1612**, R = H, Me

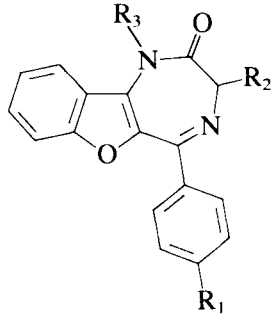
**1613**, R = H (94%); mp 327°C
(ir, ms)
R = Me (80%); mp 253–255°C

## 45. Benzofuro[3,2-*e*][1,4]diazepines (see Section VI.68)

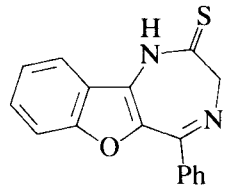
In a recent study of the synthesis of derivatives of the benzofuro[3,2-*e*][1,4]diazepine ring system (947), the diazepinone **830** and a chloro analog (**830a**) were prepared by a method similar to that previously described (405). The alkylated derivatives **1614** and the thiolactam **1615** were also prepared.



**830**, R = H
**830a**, R = Cl



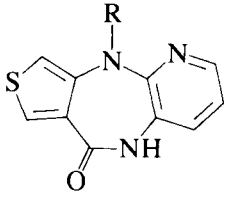
**1614a**, R = $R_1$ = H; $R_2$ = Me
**1614b**, R = H; $R_1$ = $R_2$ = Me
**1614c**, R = Cl; $R_1$ = H; $R_2$ = Me



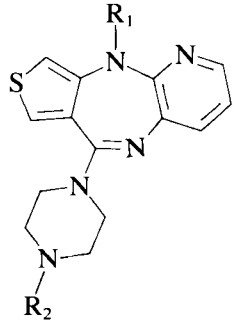
**1615**

## 46. Pyrido[3,2-*b*]thieno[3,4-*e*][1,4]diazepines (see Section VI.73)

Lactams **852** and **1616**, prepared as described previously (414), were converted to the clozapine analogs **1617** via the thiolactams and the thioimino ethers (948).

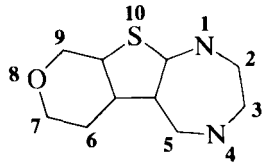


**852**, R = H
**1616**, R = Me

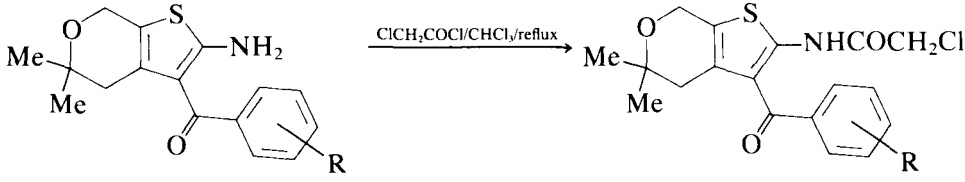


**1617a**, $R_1$ = $R_2$ = H
**1617b**, $R_1$ = H, $R_2$ = Me
**1617c**, $R_1$ = H, $R_2$ = $CH_2CH_2OH$
**1617d**, $R_1$ = $R_2$ = Me

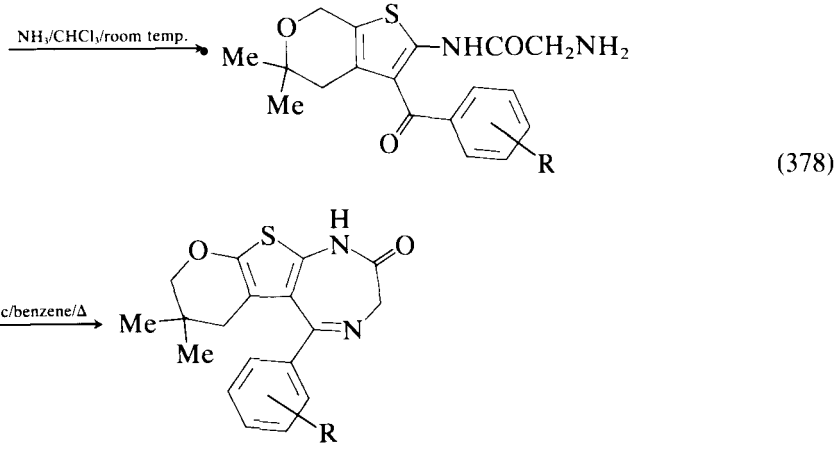
## 47. Pyrano[4′,3′:4,5]thieno[2,3-*e*][1,4]diazepines



Derivatives of the pyrano[4′,3′:4,5]thieno[2,3-*e*][1,4]diazepine ring system have been prepared using standard methodology. Ketones **1618** were prepared by the Gewald procedure (59). Reaction with chloracetyl chloride and then ammonia, followed by cyclization, gave the tricyclic targets (949). No comment was made about the regiochemistry of the thiophene ring-formation reaction (Eq. 378).



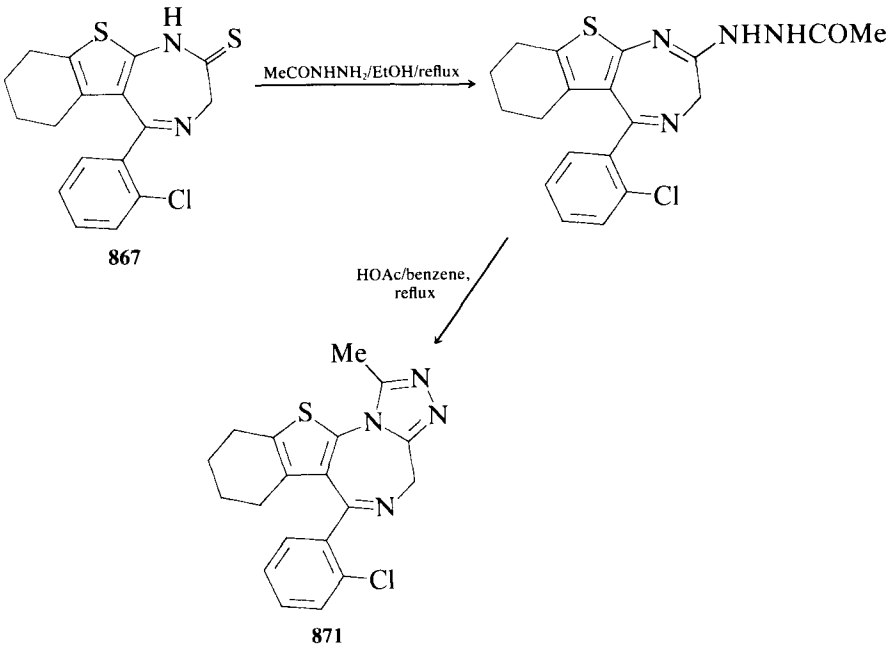
**1618**, R = H, 2-Cl, 4-Br, 2-Br, 3-$NO_2$



(378)

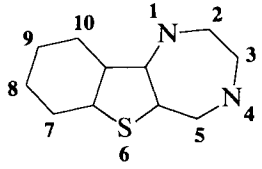
## 48. [1]Benzothieno[2,3-*e*][1,4]diazepines (see Section VI.76)

An additional procedure for the conversion of thiolactam **867** to the tetracyclic tetrazole **871** is shown in Eq. 379 (801).

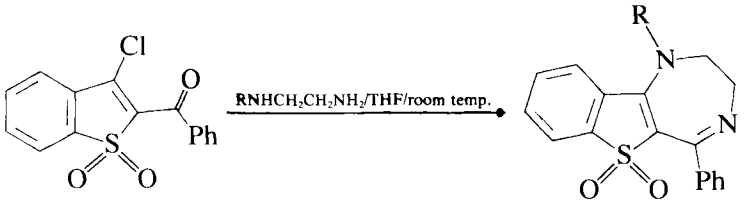



867 871 (379)

## 49. [1]Benzothieno[3,2-*e*][1,4]diazepines



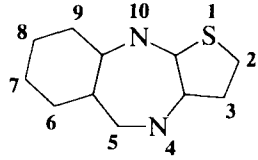
Condensation of benzothiophene dioxide **1619** with ethylenediamine and *N*-methylethylenediamine gave the tricyclic targets **1620a** and **1620b** (950). Treatment of **1620a** with methyl iodide gave **1620b** (Eq. 380).



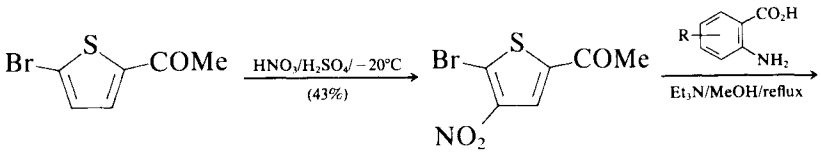

**1619** (380)

**1620a**, R = H (60% from **1619**); mp 235°C
**1620b**, R = Me; (66% from **1619**); mp 231°C

## 50. Thieno[2,3-*b*][1,4]benzodiazepines




For the synthesis of derivatives of the thieno[2,3-*b*][1,4]benzodiazepine ring system, an acetyl function on the thiophene ring was introduced in order to provide an appropriately substituted starting material (951). Thus nitration of 5-acetyl-2-bromothiophene gave the desired 3-nitro compound (**1621**) together with a small amount of 2-bromo-3,5-dinitrothiophene. Condensation of **1621** with anthranilic acid derivatives proceeded in high yield. The adducts were esterified, and the nitro groups were reduced to amines by catalytic hydrogenation. Cyclization was effected with sodium hydride in dimethyl sulfoxide (Fig. 150a). Substances with the acetyl function reduced to ethyl were prepared by first reducing the keto function of the nitro esters **1623a,c** with aluminum isopropoxide (Fig. 150b). Chlorination of **1625c** with thionyl chloride gave the elimination product **1626c.** Treatment of **1625a** with *p*-

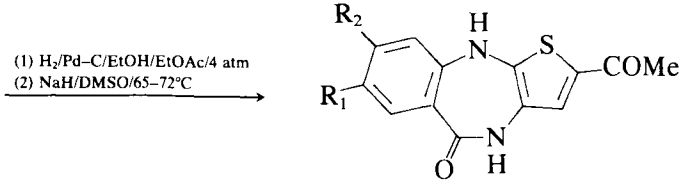



**1621**




**1622a,** $R_1 = R_2 = H$ (98%)
**1622b,** $R_1$ = Me, $R_2$ = H (95%)
**1622c,** $R_1$ = Cl, $R_2$ = H (96%)
**1622d,** $R_1$ = H, $R_2$ = Cl (82%)

**1623a,** $R_1 = R_2 = H$, 73%
**1623b,** $R_1$ = Me, $R_2$ = H, 71%
**1623c,** $R_1$ = Cl, $R_2$ = H, 57%
**1623d,** $R_1$ = H, $R_2$ = Cl, 18%




**1624a,** $R_1 = R_2 = H$, 74%; mp >260°C (nmr)
**1624b,** $R_1$ = Me, $R_2$ = H, 72%; mp >260°C (nmr)

**Figure 150a**

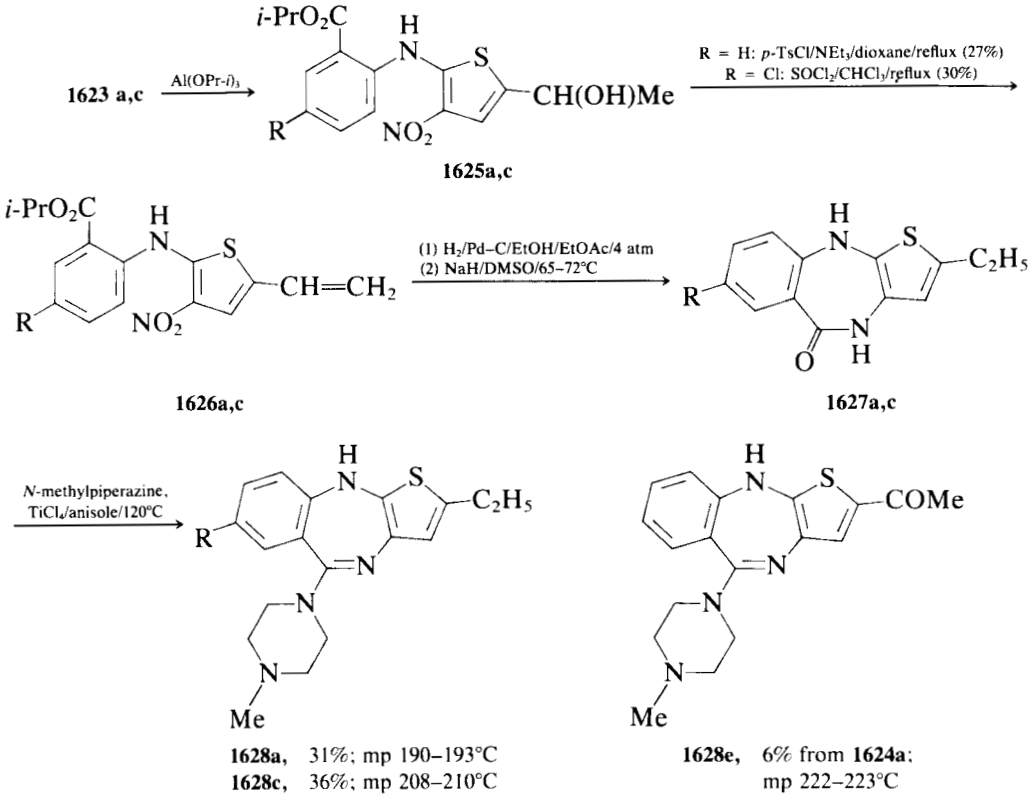


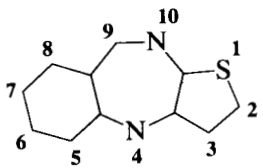

**Figure 150b**

toluenesulfonyl chloride and triethylamine in dioxane gave the vinyl compound **1626a.** Hydrogenation and cyclization gave the ethyl-substituted tricyclic lactams **1627a,c.** A later publication (952) describes the conversion of **1627a,c** and **1624a** to the amidines **1628a,c** and **1628e,** respectively.

## 51. Thieno[2,3-*b*][1,5]benzodiazepines (see Section VI.77)

Two papers have appeared (952,953) giving further details of the chemistry previously described in a patent (422). Additional patents (954) describe the preparation of further substances of the types indicated in Eq. 157.

## 52. Thieno[3,2-*b*][1,4]benzodiazepines



Derivatives of the thieno[3,2-*b*][1,4]benzodiazepine ring system were prepared by first condensing anthranilic acid and the methyl-substituted compound shown in Fig. 151 with 3-bromo-2-nitrothiophene (951). The products (**1630a,b**) were esterified, and the nitro groups were reduced by catalytic hydrogenation. Cyclization under basic conditions gave the tricyclic lactams **1629a,b.** Alternatively, nitro acid **1630a** was converted to the mixed anhydride, which on hydrogenation gave lactam **1629a** directly. This substance was converted to amidine **1629c** (955).

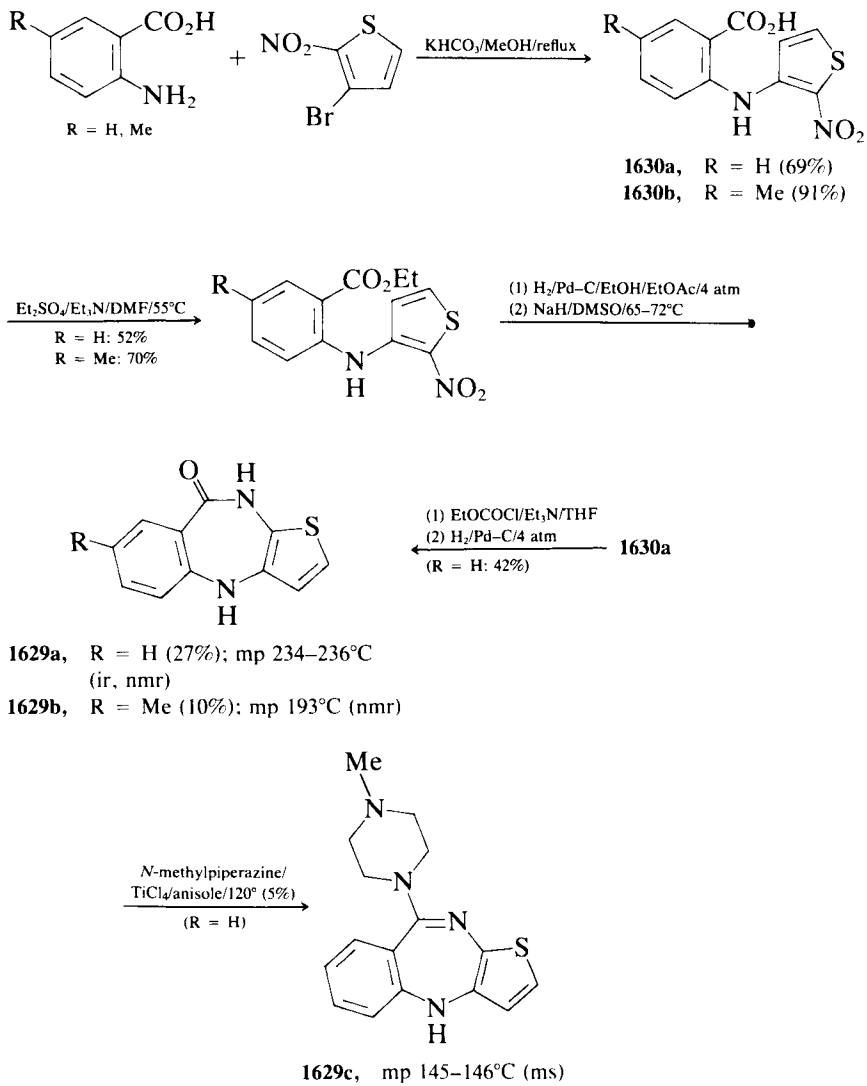



**Figure 151**

## 53. Thieno[3,2-*b*][1,5]benzodizepines (see Section VI.78)

Two papers have appeared (952,953) giving further details of the chemistry previously disclosed in a patent (422). Additional patents (954) describe the preparation of other substances of the types indicated in Eq. 158.

## 54. Thieno[3,4-*b*][1,4]benzodiazepines

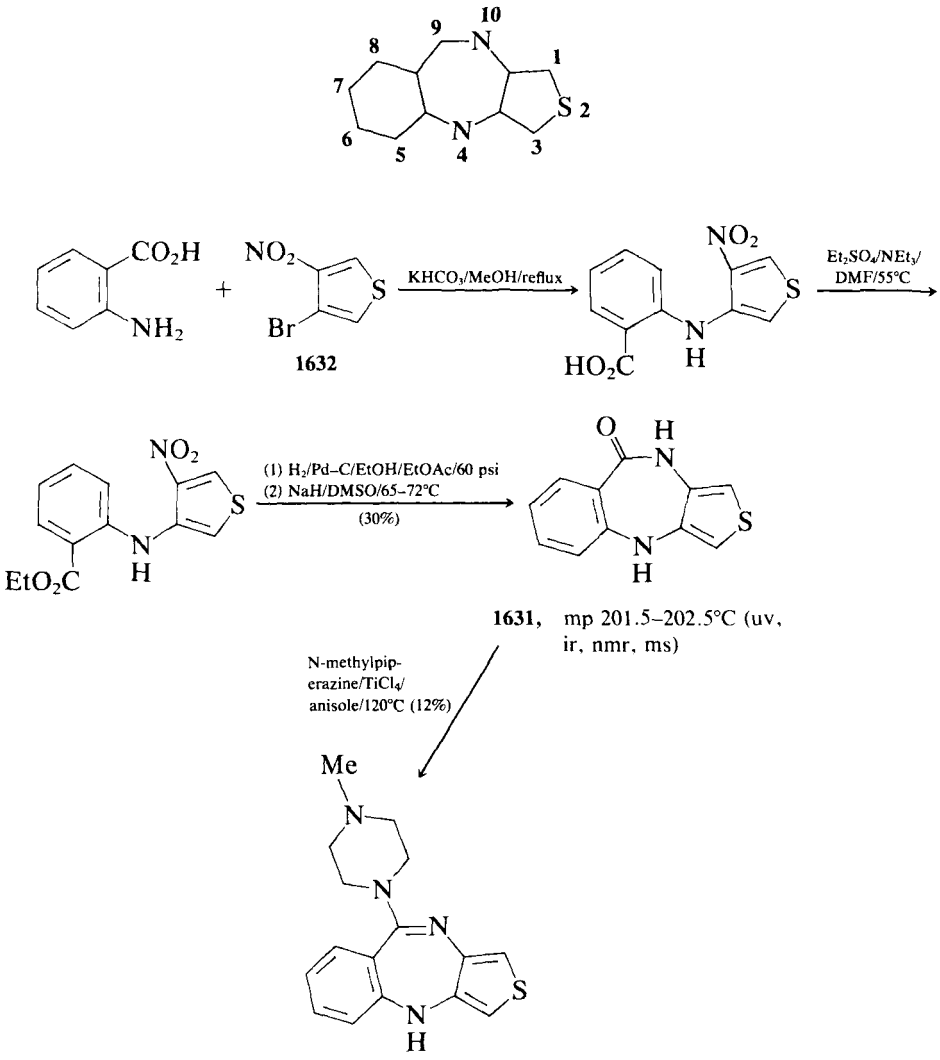
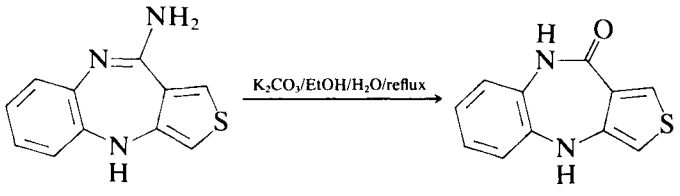



**Figure 152**

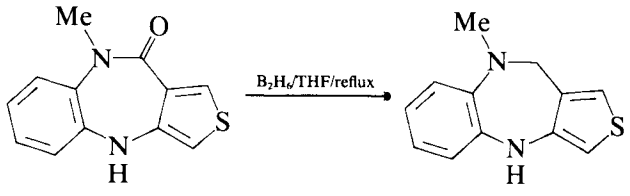
A derivative of the thieno[3,4-*b*][1,4]benzodiazepine ring system (**1631**) was prepared by condensation of bromonitrothiophene (**1632**) with anthranilic acid followed by esterification, reduction of the nitro group, and cyclization (951). Reaction of **1631** with *N*-methylpiperazine gave the clozapine analog **1633** (955), which was found to lack biological activity (Fig. 152).

### 55. Thieno[3,4-*b*][1,5]benzodiazepines (see Section VI.79)

Further details of chemistry previously described have now been presented (953-956). As indicated in Eq. 381, tricyclic amidines such as **891** have been converted to the corresponding lactams (**1633a**) by hydrolysis under basic conditions (954,955). The preparation of 1,3-dihydro compounds, using routes similar to those given in Fig. 63 but starting with 3-cyanotetrahydrothiophen-4-one, have been described (954,955). Dehydrogenation of the tricyclic lactam **887** may be accomplished with sulfuryl chloride (957), in addition to the reagents described earlier. Tricyclic amidines such as **894** were prepared directly from lactams using titanium tetrachloride, and descriptions of the neuroleptic properties of these substances (clozapine analogs) have been provided (955,956). As shown in Eq. 382, the tricyclic lactam **889** has been reduced to the corresponding amine (958).




**891** **1633a** (381)

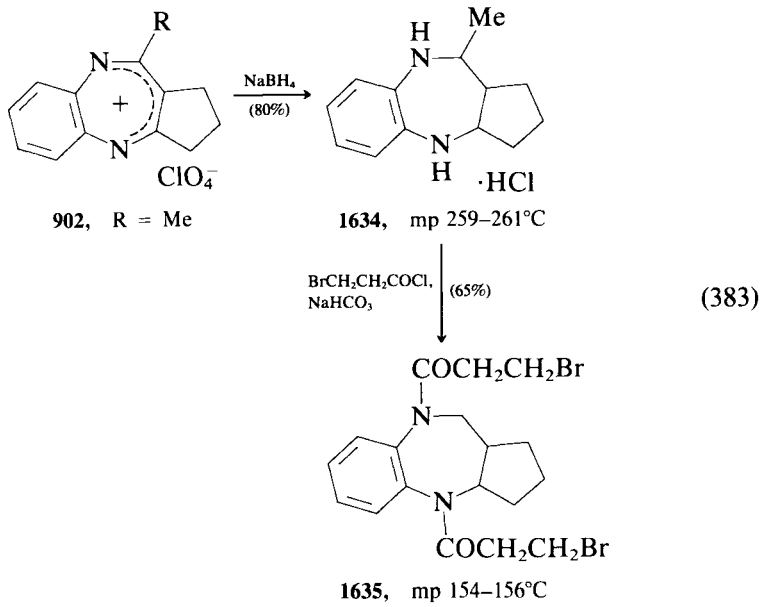



**889** mp 110–112°C (382)

### 56. Benzo[*b*]cyclopenta[*e*][1,4]diazepines (see Section VI.81)

Reduction of **902** (R = Me) with sodium borohydride (959) gave the tetrahydro derivative **1634** (Eq. 383). No comment was made concerning the stereochemistry of the product. An acylated derivative (**1635**) was prepared.

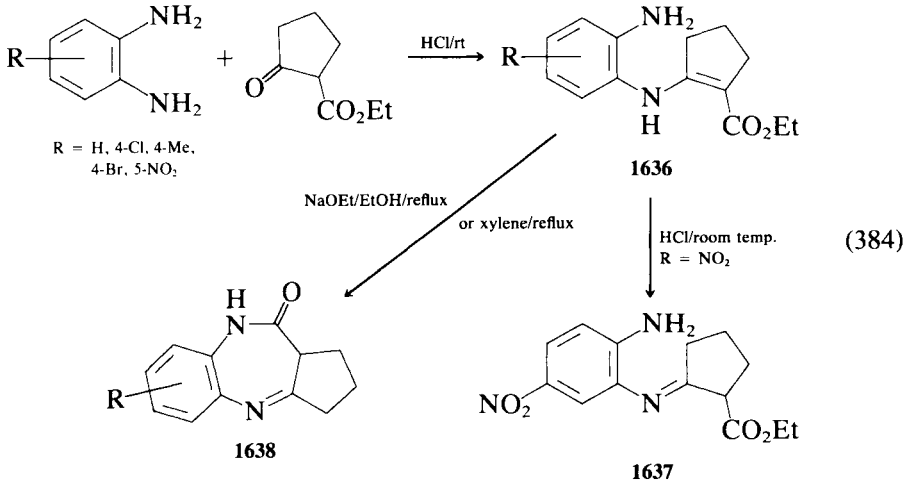
Condensation of *o*-phenylenediamines with ethyl cyclopentanone-2-car-




(383)

boxylate at room temperature under acidic conditions gave the enamino esters **1636** (960). In the case of 4-nitro-1,2-phenylenediamine, longer reaction times produced the isomeric substance **1637** (Eq. 384). Cyclization of the adducts **1636** with sodium ethoxide in refluxing ethanol or by refluxing in xylene gave products formulated as **1638,** in contrast to the $\alpha,\beta$-unsaturated structure (**903**) reported earlier (429,430).

In a patent (961) the chemistry described above was further developed. Treatment of ethyl cyclopentanone-2-carboxylate with *N*-methyl-*o*-phenylenediamine gave the two products shown in Fig. 153. Ethylation of **1638** (R = H) gave the immonium salt **1641,** which on treatment with base gave the




(384)

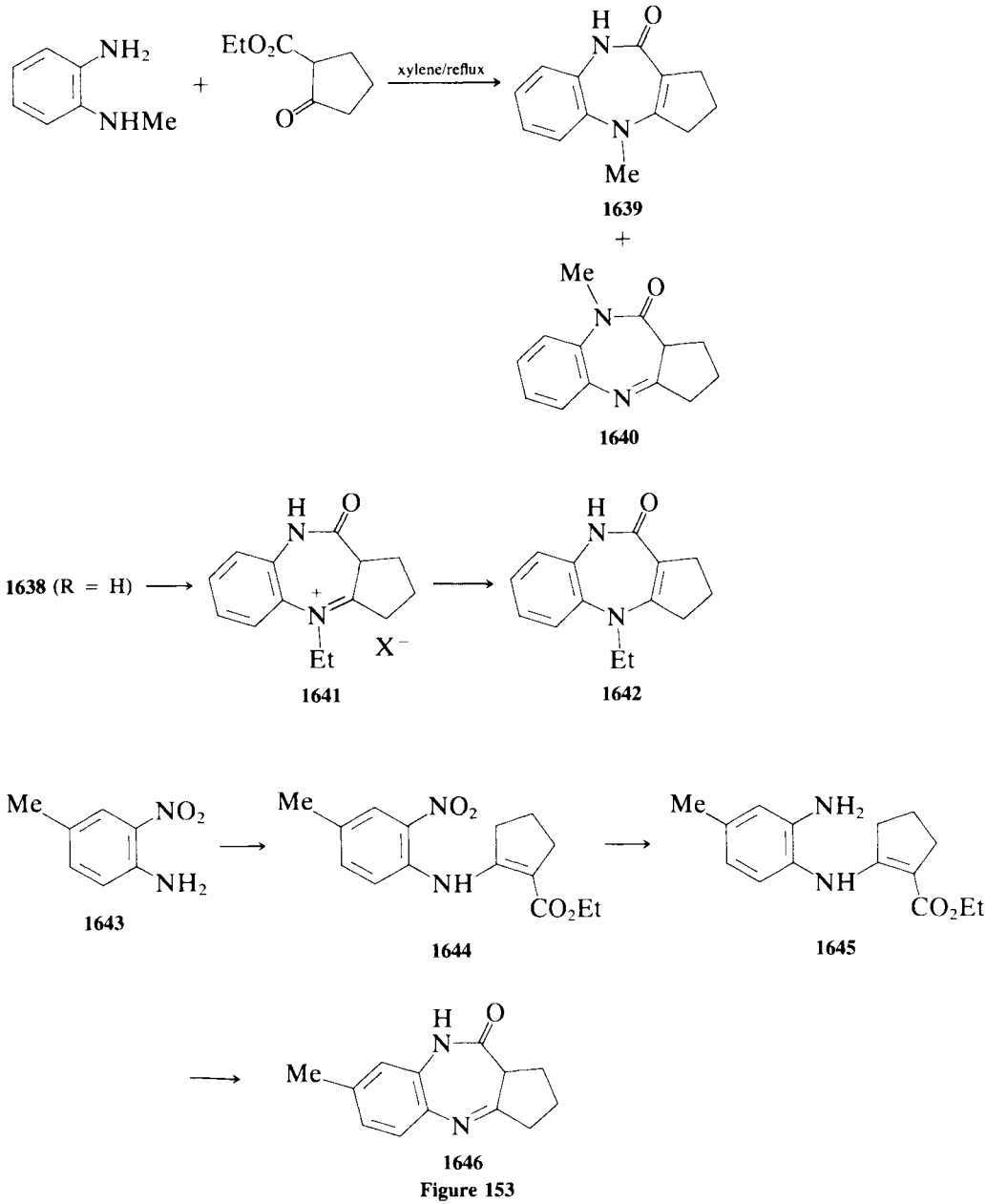
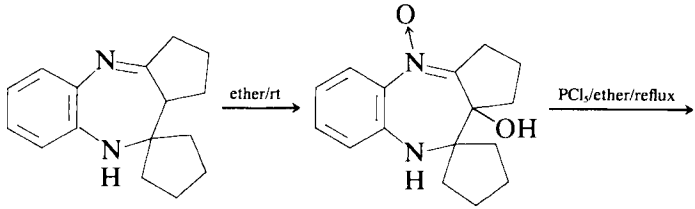



Figure 153

$\alpha,\beta$-unsaturated lactam **1642.** Use of nitroaniline **1643** gave initially the enamino ester **1644** (analogous to **1636**). The nitro group was reduced to give **1645,** which on cyclization gave the $\beta,\gamma$-unsaturated lactam **1646.** Numerous analogs were prepared.

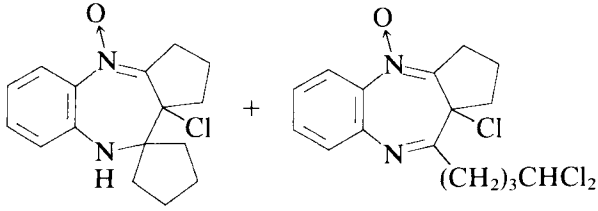
Oxidation of **1647** (formed by reaction of *o*-phenylenediamine with cy-

clopentanone), by leaving a solution in ether at room temperature, gave the hydroxy *N*-oxide **1648** (961). This substance, on treatment with phosphorus pentachloride (Eq. 385), gave a mixture of two compounds that were assigned structures **1649** and **1650.** It is difficult to envision a mechanism for the formation of the *gem*-dichloro function of **1650.**




**1647** **1648**

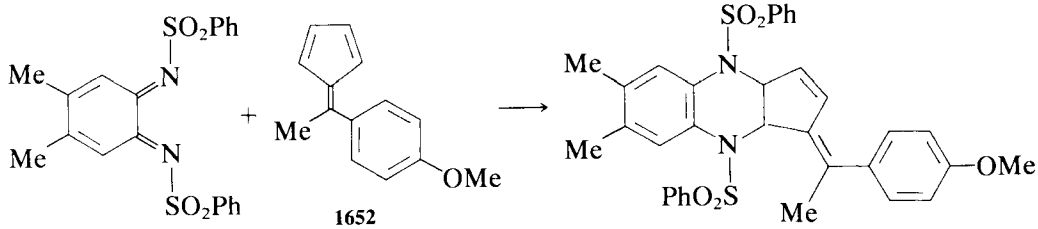
(385)



**1649** **1650,** 11%; mp 210°C (nmr)

Further details of the *N,N'*-dibenzenesulfonyl-*o*-benzoquinonediimine/fulvene cycloaddition have now been described (963). Reaction of **1651** with **1652** gave two products (**1653, 1654**), of which only the indicated isomers were obtained (Fig. 154). In refluxing chloroform, **1654** produced a dimer (spiroimidazoline **1655**) and the epimer of the starting material (**1656**). Structural assignment was based on detailed nmr analysis. Further heating of **1656** in refluxing chloroform gave fulvene **1657.** The adduct **1658** reacted at the less hindered double bond with an additional mole of diimine **1651** to give **1659.**

The studies were then extended to adducts derived from monosubstituted fulvenes (Eq. 386). The adducts **1660** were unstable and rearranged at room temperature, via a 1,5-sigmatropic rearrangement, to **1661.** At higher temperatures, an equilibrium between **1661** and **1662** was attained.



**1651** **1652** **1653**

**Figure 154** (*continued on next page*)

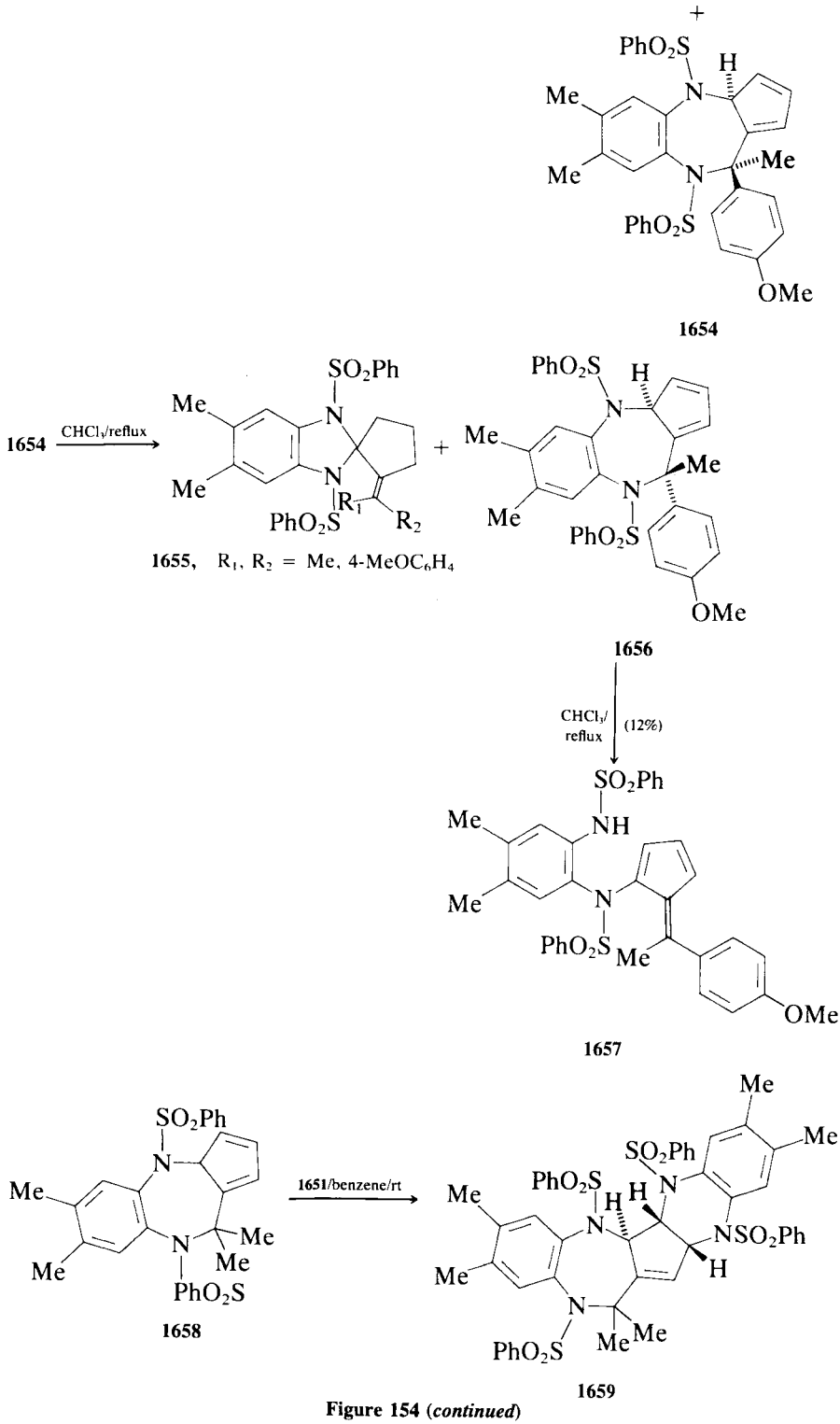
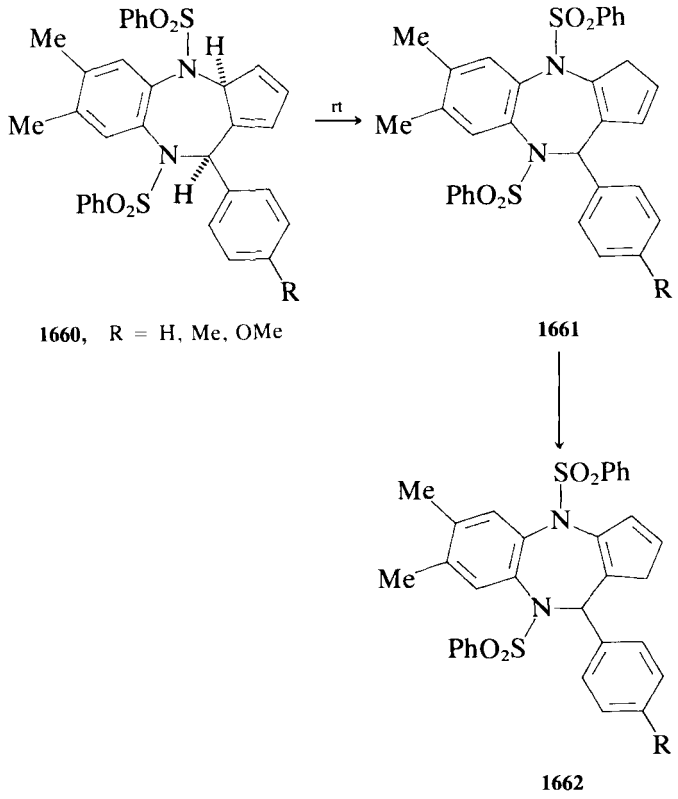



**Figure 154** (*continued*)




**1660**, R = H, Me, OMe

**1661**

**1662**

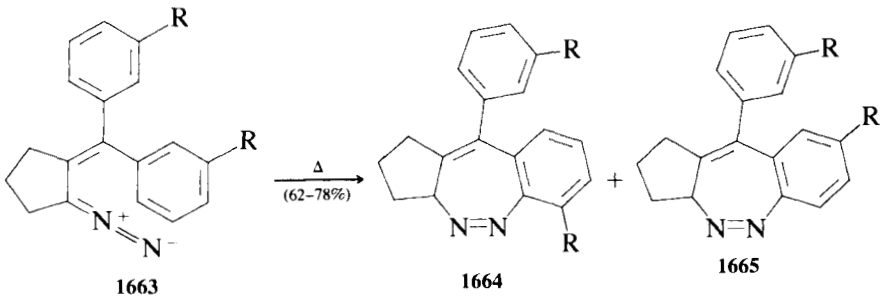
(386)

### 57. Benzo[*c*]cyclopenta[*e*][1,2]diazepines (see Section VI.82)

A more detailed discussion of the results obtained earlier (437) is now available (964).

### 58. Benzo[*c*]cyclopenta[*f*][1,2]diazepines (see Section VI.83)

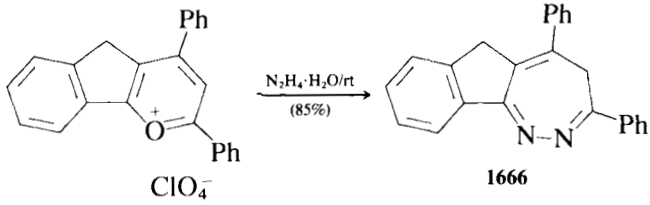
In an extension of the study reported earlier (438), it has now been disclosed (965) that the *m*-substituted diazo compounds **1663** on thermolysis in refluxing cyclohexane rearrange to give the isomers of the tricyclic diazepines **1664** and **1665** (Eq. 387). The isomer ratio (**1664** : **1665**) ranged from 4.3 for R = Me to 0.5 for R = $CF_3$. For R = *t*-Bu, only compound **1665** was formed. Furthermore, certain of the *o*-substituted products (**1664**; R = MeO, EtO, Cl) slowly rearranged to the corresponding *para*-isomers at 80–110°C.




1663 1664 1665 (387)

### 59. Indeno[1,2-*c*][1,2]diazepines (see Section VI.85)

As shown in Eq. 388, an additional derivative of the indeno[1,2-*c*]-[1,2]diazepine ring system (**1666**) was obtained by treatment of the fused pyrylium salt **1667** with hydrazine hydrate (966).




1667 1666 (388)

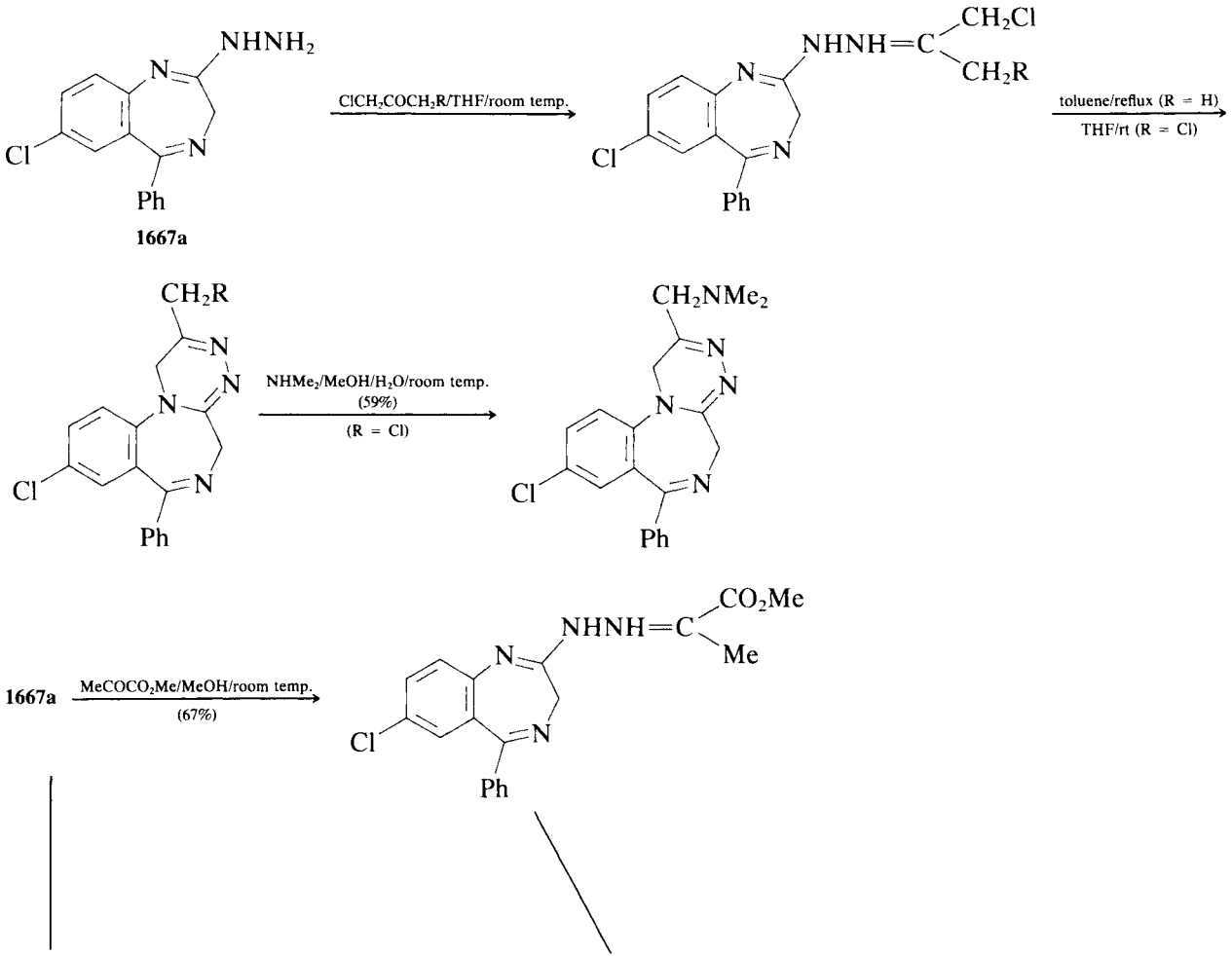
## XVI. 6,6,7-SYSTEMS

### 1. [1,2,4]Triazino[4,3-*a*][1,4]benzodiazepines (see Section IX.3)

A variety of derivatives of the [1,2,4]triazino[4,3-*a*][1,4]benzodiazepine ring system have now been synthesized from 2-hydrazinobenzodiazepines (967). Representative examples are shown in Fig. 155.

### 2. [1,2,4]Triazino[4,3-*d*][1,4]benzodiazepines (see Section IX.4)

Two papers have appeared (829) providing further details of the chemistry described earlier (454). The preparation of additional derivatives was also described.


NHNH2
N
N
Cl
Ph
1667a
ClCH2COCH2R/THF/room temp.
NHNH=C
CH2Cl
CH2R
toluene/reflux (R = H)
THF/rt (R = Cl)
CH2R
NHMe2/MeOH/H2O/room temp.
(59%)
(R = Cl)
CH2NMe2
1667a
MeCOCO2Me/MeOH/room temp.
(67%)
CO2Me
Me

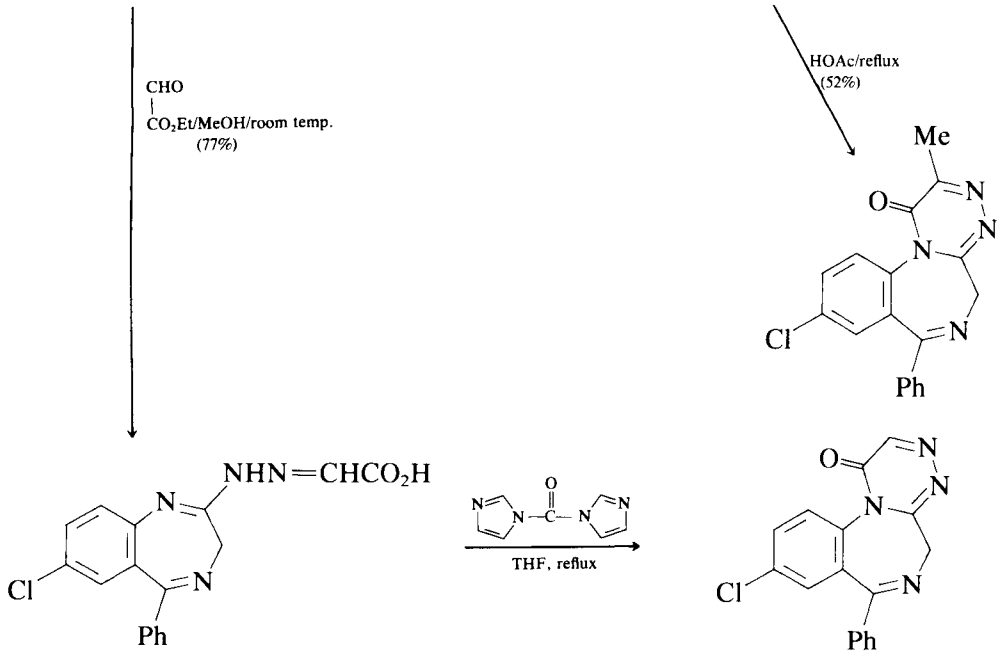



**Figure 155 (*cont'd*)**

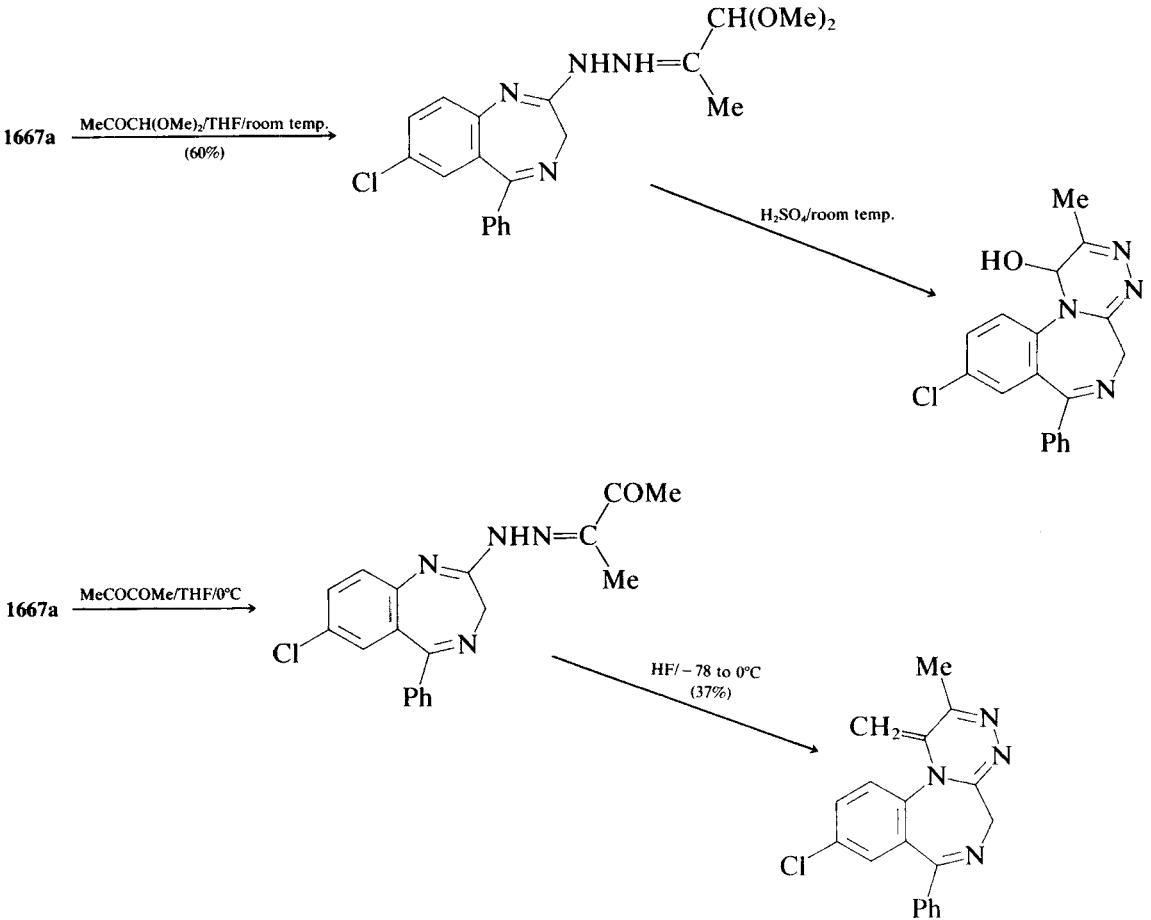



**Figure 155** (*cont'd*)

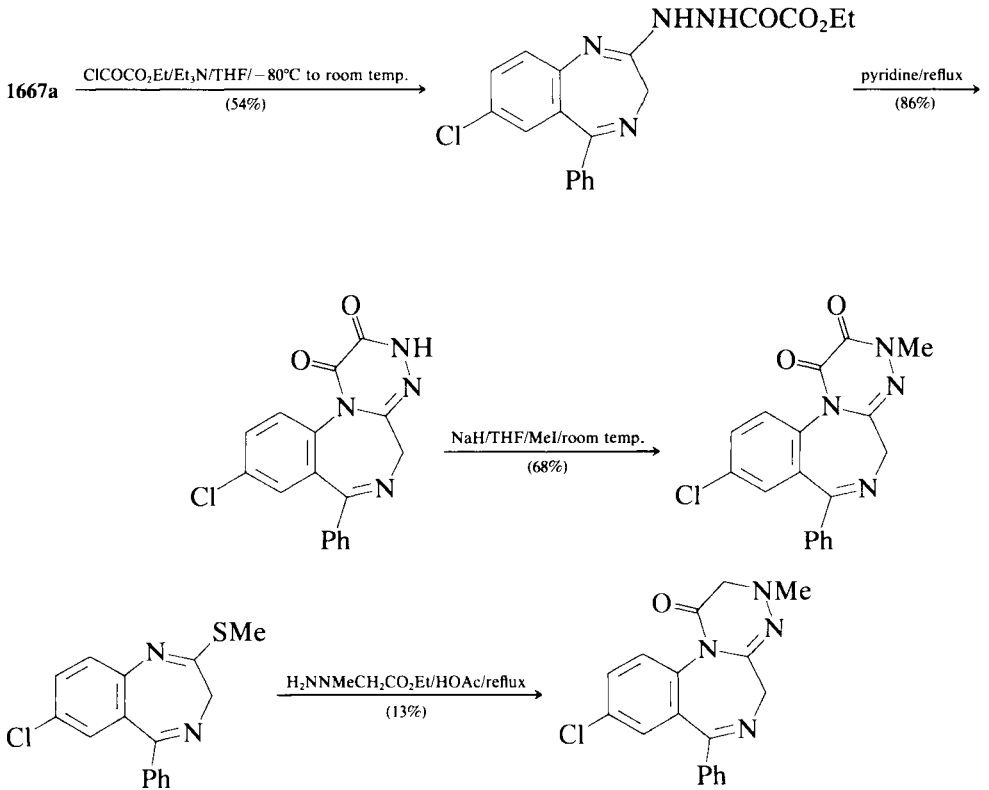
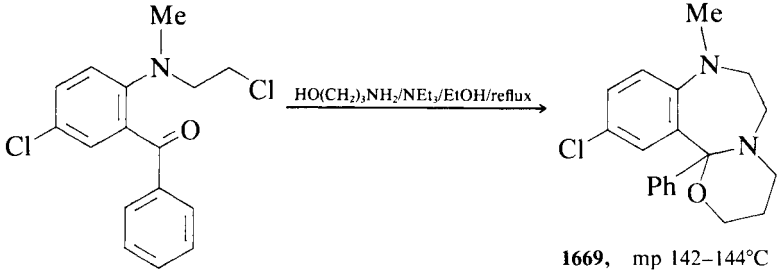



**Figure 155 (*cont'd*)**

### 3. [1,3]Oxazino[3,2-*d*][1,4]benzodiazepines (see Section IX.6)

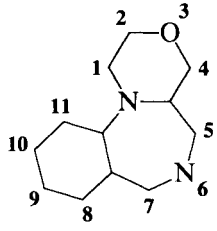
As shown in Eq. 389, reaction of benzophenone **1668** with 3-aminopropanol in refluxing ethanol in the presence of triethylamine gave the tricyclic oxazine **1669** (867,868).

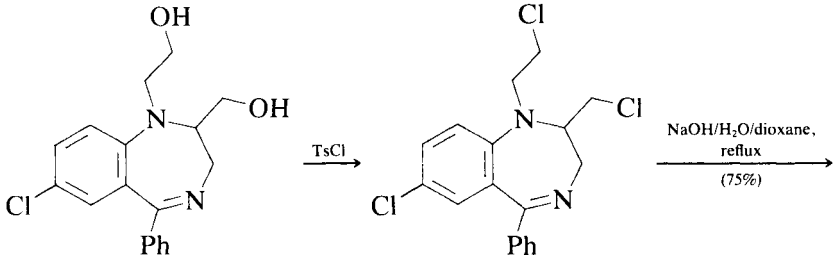



**1668**

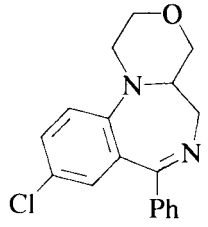
**1669**, mp 142–144°C (389)

### 4. [1,4]Oxazino[4,3-*a*][1,4]benzodiazepines



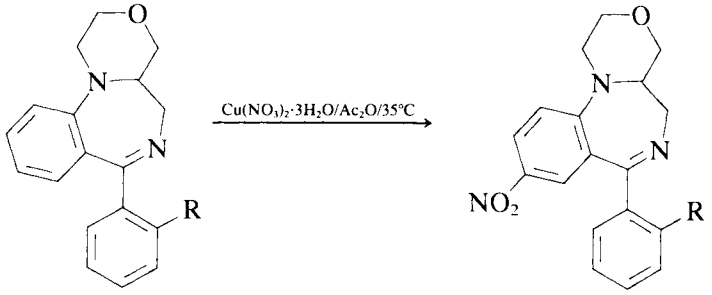




**1671** **1670** (390)



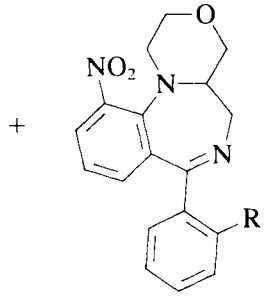

**1672**, mp 156–158°C;
maleate, mp 143–145°C

As shown in Eq. 390, cyclization of **1670** (obtained from diol **1671**) with sodium hydroxide in aqueous dioxane gave the tricyclic morpholine **1672** (968). Other substances were prepared by treating diols with *p*-toluenesulfonyl chloride and sodium hydroxide in aqueous dioxane at reflux. Substances prepared by these procedures are listed in Table 190. Additional compounds were prepared by nitration of tricyclic derivatives (Eq. 391).



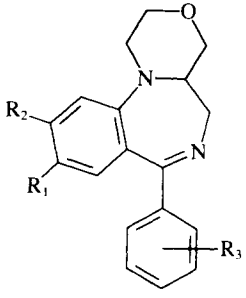

R = H: mp 142–145°C
R = Cl: mp 164–166°C (32%)

(391)




R = H: mp 184–186°C
R = Cl: oil, 19% yield (ir)

TABLE 190. 7-ARYL-1,2,4,4a-TETRAHYDRO-5*H*-[1,4]OXAZINO[4,3-*a*][1,4]-BENZODIAZEPINES

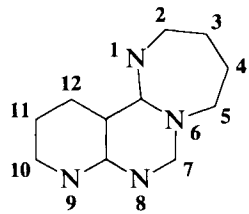



*(continued)*

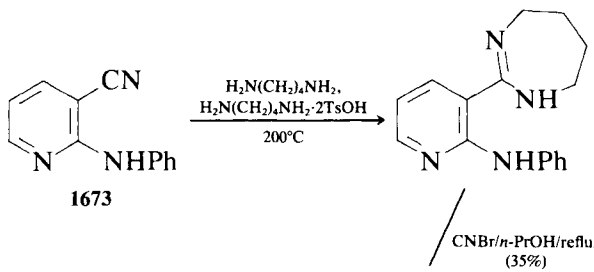
TABLE 190. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | mp (°C) |
|---|---|---|---|
| H | H | H | 102–105 |
| F | H | H | 154–156 |
| Br | H | H | 176–179 |
| $NO_2$ | H | H | 142–145 |
| Me | H | H | 174–176 |
| H | Me | H | 123–124 |
| Me | Me | H | 132–134 |
| H | OMe | H | 107–110 |
| Cl | Cl | H | 163–165 |
| Me | Cl | H | 115–118 |
| Br | Me | H | 117–119 |
| —$OCH_2O$— | | H | 156–158 |
| Cl | H | 3-$CF_3$ | 104–107 |
| Cl | H | 3,4-$Cl_2$ | 145–148 |
| F | H | 3,4,5-$(OMe)_3$ | 165–166 |
| Cl | H | 2-Cl | 140–141 |

## 5. Pyrido[2′,3′:4,5]pyrimido[1,6-*a*][1,3]diazepines

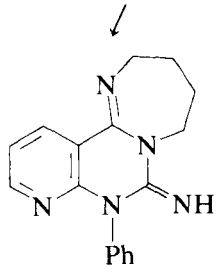



The single known derivative of the pyrido[2′,3′:4,5]pyrimido[1,6-*a*][1,3]-diazepine ring system was obtained as shown in Eq. 392. 2-Anilinonicotinonitrile (**1673**) was treated with 1,4-diaminobutane, and the resulting amidine was treated with cyanogen bromide to give the tricyclic guanidine **1674** (969).




(392)

*(see next page)*

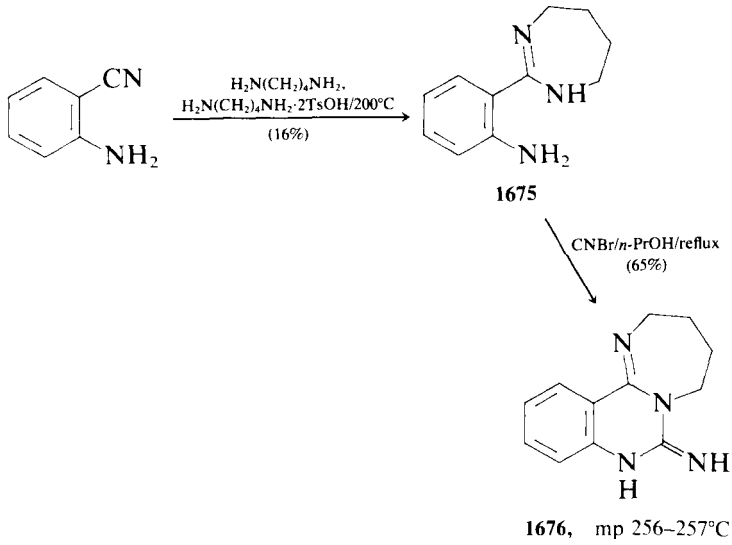


(392 *cont'd*)

**1674**, mp 161–163°C

## 6. [1,3]Diazepino[1,2-*c*]quinazolines (see Section IX.11)

A new synthesis has been used for the preparation of a derivative of the [1,3]diazepino[1,2-*c*]quinazoline ring system (969). Anthranilonitrile was converted to the cyclic amidine **1675**, and this substance was treated with cyanogen bromide to give the cyclic guanidine **1676** (Eq. 393).

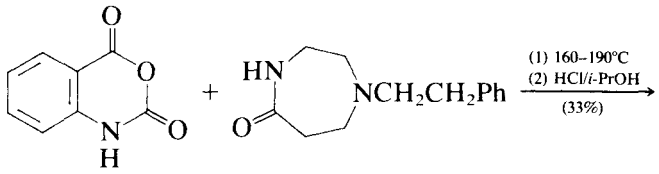


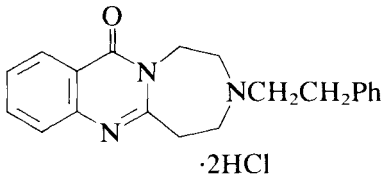
(393)

**1676**, mp 256–257°C

## 7. [1,4]Diazepino[5,4-*b*]quinazolines (see Section IX.13)

As shown in Eq. 394, an additional derivative of the [1,4]diazepino[5,4-*b*]-quinazoline ring system (**1677**) was prepared by a variant of the procedure used previously (970).

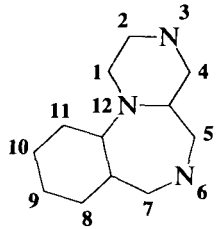


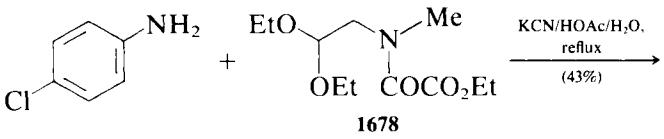

(394)

**1677,** mp 260°C (uv, ir)

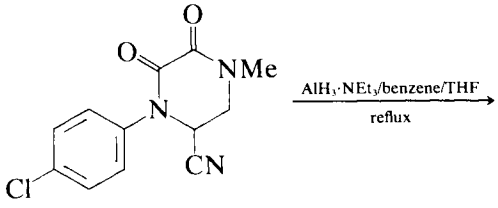
## 8. Pyrazino[1,2-*a*][1,4]benzodiazepines



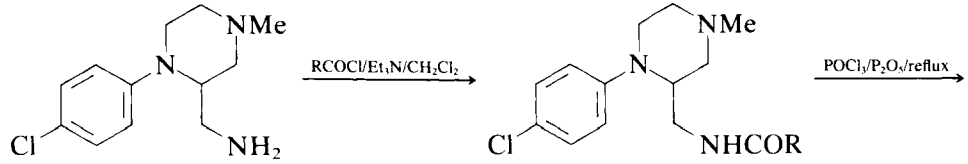

Derivatives of the pyrazino[1,2-*a*][1,4]benzodiazepine ring system were prepared as shown in Fig. 156. Condensation of *p*-chloroaniline with oxamide **1678** and potassium cyanide gave the piperazinedione **1679,** which was reduced to the aminomethyl compound **1680** with alane-triethylamine (971). Compound **1680** was acylated with a variety of acid chlorides, and the amides were cyclized to the desired tricyclic compounds **1681** (Table 191). One substance (**1681,** R = Ph) was reduced with sodium cyanoborohydride, and the reduced amine was acetylated to **1682.** Treatment of the dichloro compound **1683** with ammonia gave the tricyclic pyrazine **1684** (968). Additional compounds prepared by this procedure are listed in Table 192.



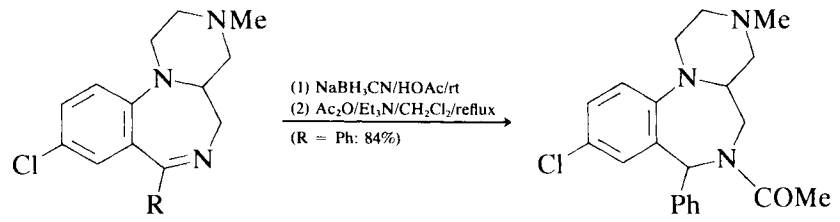

**1678**




**1679**

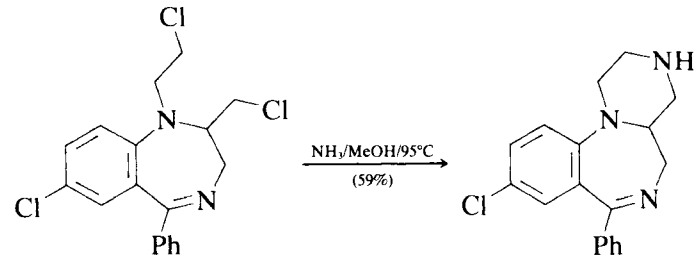



**1680**




**1681** (nmr, ms)

**1682,** mp 210–211°C (fumarate) (nmr)

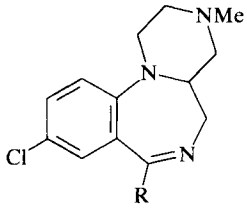



**1683**

**1684,** mp 132–135°C

**Figure 156**

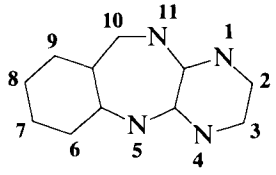
TABLE 191. 7-SUBSTITUTED 9-CHLORO-1,2,3,4,4a,5-HEXAHYDROPYRAZINO-[1,2-*a*][1,4]BENZODIAZEPINES




| R | mp (°C)[a] | Yield (%) |
|---|---|---|
| Ph | 221–222 | 89 |
| 2-ClPh | 201–202 | 97 |
| 4-ClPh | 225–226 | 97 |
| $PhCH_2$ | 113–115 | 38 |
| Me | 167–168 | 75 |

[a]Fumarate salts.

## 9. Pyrazino[2,3-*b*][1,4]benzodiazepines

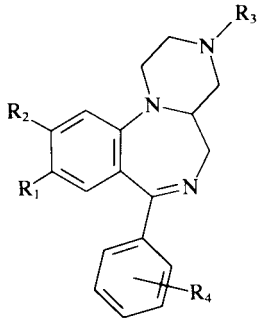



A single derivative of the pyrazino[2,3-*b*][1,4]benzodiazepine ring system has been reported (872). Treatment of the imidazodiazepinone **1685** with ethylenediamine gave a mixture of the tetracyclic compound **1686** and the pyrazino[2,3-*b*][1,4]benzodiazepine **1687,** presumably via the mechanism shown in Fig. 157. In a separate experiment **1686** was converted to **1687** with diethylamine in refluxing methanol.

## 10. Pyrimido[1,2-*a*][1,4]benzodiazepines (see Section IX.16)

Details of the reaction of benzodiazepine **1688** with diketene in chloroform at room temperature have now been published (972). The main product (92% yield) of this reaction was the 2-acetoacetamido derivative **1689.** Pyrimidodiazepine **985a** was isolated in 1% yield, but its precursor, the 1-acetoacetylated compound, was not obtained. Treatment of **1689** with methanolic

TABLE 192. 1,2,3,4,4a,5-HEXAHYDROPYRAZINO[1,2-*a*][1,4]BENZODIAZEPINES



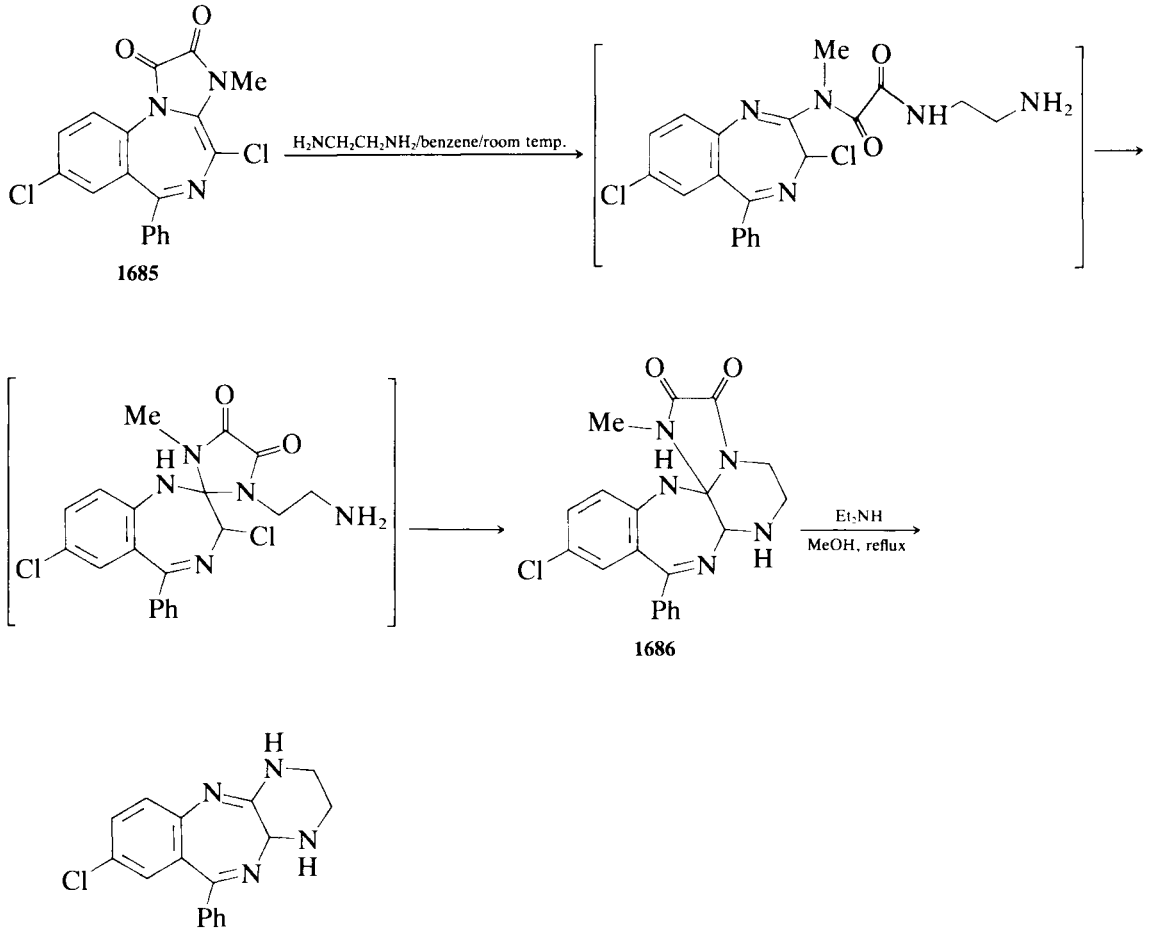

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) | Salt | Yield (%) |
|---|---|---|---|---|---|---|
| Br | H | H | H | 133–138 | | |
| Me | H | H | H | 192–198 | Ditosylate | |
| H | H | H | H | 232–234 | Ditosylate | |
| Br | Me | H | H | 260–263 | Ditosylate | |
| Cl | H | H | 2-Cl | 131–137 | | |
| Br | H | H | 3,4-$Cl_2$ | 210–212 | 2HCl | |
| Cl | H | Me | H | 262 (dec.) | 2HCl | 58 |
| Cl | H | *i*-Pr | H | 236–245 (dec.) | 2HCl | |
| Cl | H | *n*-Bu | H | 104–106 | | |
| Cl | H | *t*-Bu | H | 143–146 | | |
| Cl | H | $CH_2CH{=}CH_2$ | H | 230–233 (dec.) | 2HCl | |
| Cl | H | $CH_2CH_2OH$ | H | 129–131<br>216 (dec.) | 2HCl | |
| Cl | H | 3,4-$(MeO)_2C_6H_3CH_2CH_2$ | H | 180 (dec.) | 2HCl | |
| Cl | H | Me | 2-Cl | 137–138 | | |
| Me | H | Me | H | 230–233 | 2HCl | |
| H | Me | Me | H | 164–165 | | |
| H | Me | Me | 2-Cl | 145–147 | | |

*(continued)*

TABLE 192. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) | Salt | Yield (%) |
|---|---|---|---|---|---|---|
| Br | Me | Me | 2-Cl | 106–108 | | |
| Me | Me | Me | H | 139–140 | | |
| H | H | Me | H | 111–114 | | |
| F | H | Me | H | 200 (dec.) | 2HCl | |
| $NO_2$ | H | Me | H | 191–194 | | |
| Cl | Cl | Me | H | 158–160 | | |
| H | OMe | Me | H | 121–123 | | |
| H | H | Me | 2-Cl | 136–138 | | |
| Cl | H | $PhCH_2$ | H | 236–239 (dec.) | 2HCl | 55 |
| Cl | H | $MeOCH_2CH_2$ | H | 237–240 | 2HCl | |
| Cl | H | $HOCH_2CH_2CH_2$ | H | 205 (dec.) | 2HCl | |
| Cl | H | $PhCH_2CH_2$ | H | 119–121 | | |
| Cl | H | $CH_2CH_2CHMe_2$ | H | 240–245 | 2HCl | |
| Cl | H | $CH_2CMe_3$ | H | 215 (dec.) | 2HCl | |
| Cl | H | $ClCH_2CH_2$ | H | 220 (dec.) | 2HCl | 64[a] |
| Cl | H | $MeOCH_2CH_2$ | H | 237–240 | 2HCl | 68[b], 50[c] |

[a]Prepared from the hydroxy compound with $SOCl_2$ under reflux.
[b]Prepared from the chloro compound with NaOMe/MeOH under reflux.
[c]Prepared from the hydroxy compound with NaH/DMF followed by addition of MeI.



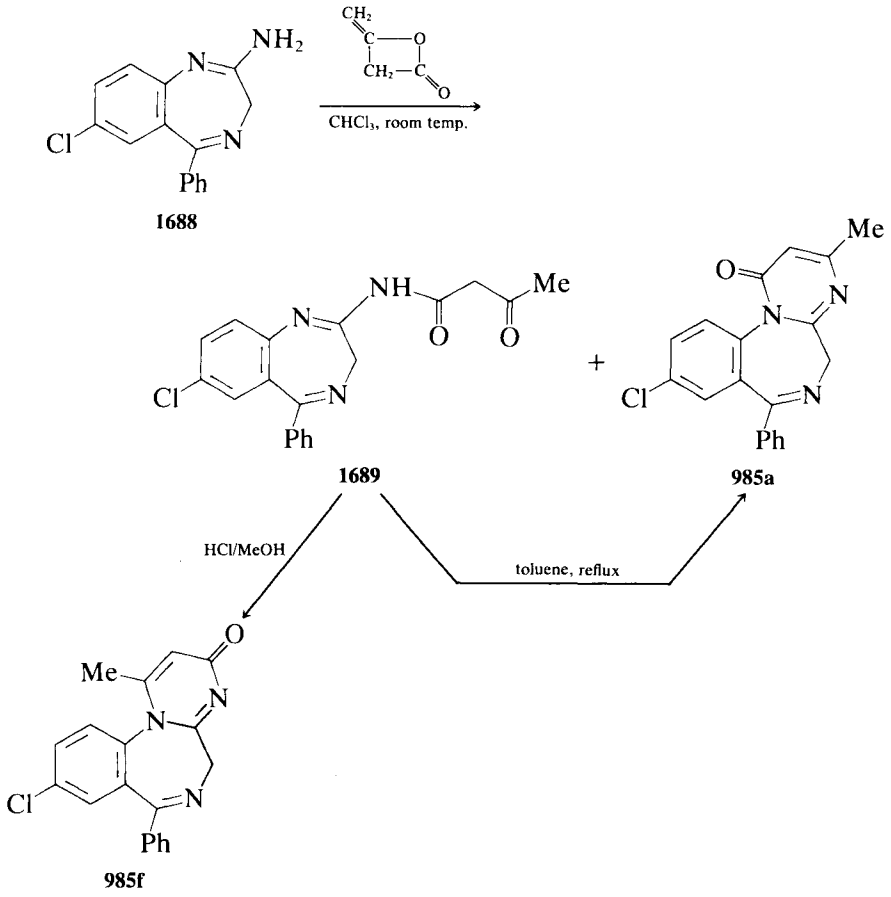

**1685**

**1686**

**1687** 4% from 1685, 60% from **1686**; mp 194–198°C (ir, nmr, uv, ms)

**Figure 157**

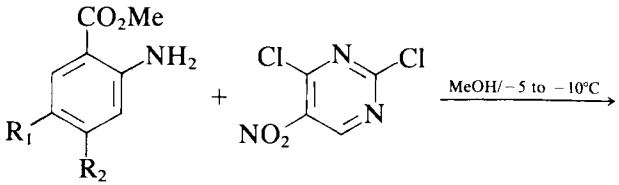
hydrogen chloride gave **985f.** Thermolysis of **1689** in refluxing toluene gave the rearrangement product **985a** and **1688** (Eq. 395).




(395)

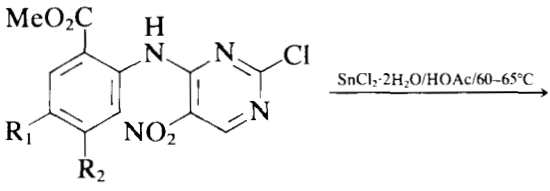
### 11. Pyrimido[4,5-*b*][1,4]benzodiazepines (see Section IX.18)

A series of compounds has been prepared (973) using procedures similar to those described earlier (Fig. 71). Stannous chloride reduction of the nitro esters **1690** to **1691** allowed retention of the chloro function. Cyclization of **1691** to **1692** was effected in sulfuric acid at 100–105°C (Eq. 396).



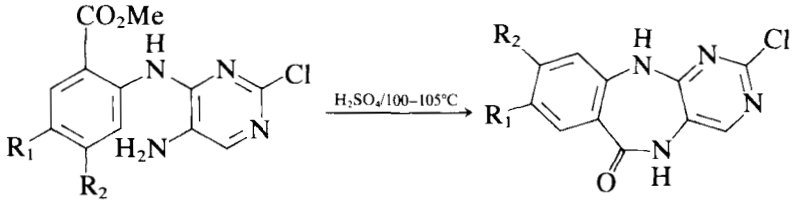

(396)

*(see next page)*




**1690**

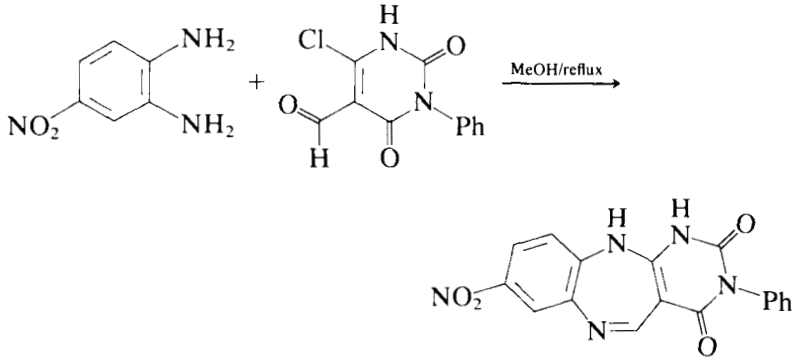
(396 *cont'd*)




**1691** **1692**, $R_1$ = H, Cl; $R_2$ = H, Cl, Me

## 12. Pyrimido[4,5-*b*][1,5]benzodiazepines (see Section IX.19)

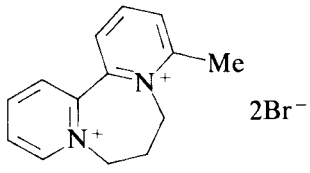
A Russian patent (974) describes the synthesis of further examples of the pyrimido[4,5-*b*][1,5]benzodiazepine ring system. The procedure shown in Eq. 397 is illustrative.



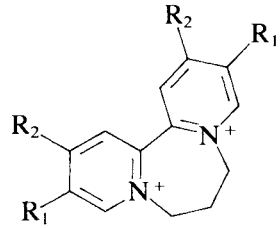

(397)

## 13. Dipyrido[1,2-*a*:2′,1′-*c*][1,4]diazepines (see Section IX.23)

A monosubstituted diquaternary salt (**1693**) was prepared by the procedure used earlier, and the redox and herbicidal properties of the substance were described (975). The electrochemical properties of **1694a** and **1694b** were compared with those of the parent compound **1694c** (976).

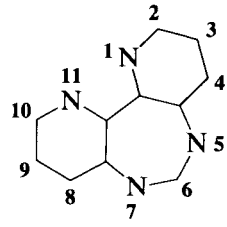


1693

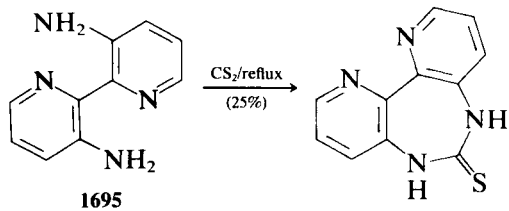


**1694a,** $R_1$ = Me, $R_2$ = H
**1694b,** $R_1$ = H, $R_2$ = Me
**1694c,** $R_1$ = $R_2$ = H

## 14. Dipyrido[3,2-*d*:2′,3′-*f*][1,3]diazepines



As shown in Eq. 398, treatment of the diamine **1695** with carbon disulfide gave the tricyclic thiourea **1696** (977).

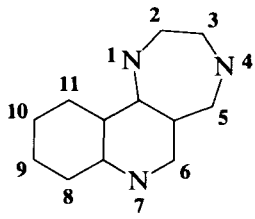


**1695**

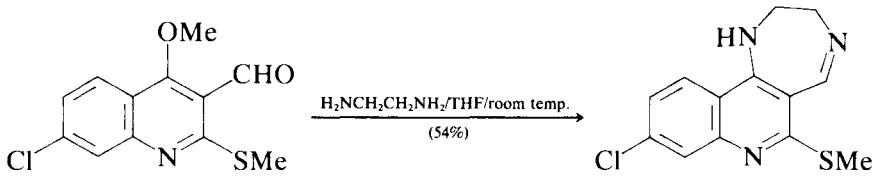
**1696,** mp 263–264°C (ir, ms)

(398)

## 15. [1,4]Diazepino[6,5-*c*]quinolines



As shown in Eq. 399, reaction of ethylenediamine with the quinoline derivative **1697** gave the tricyclic imine **1698** (978).




(399)

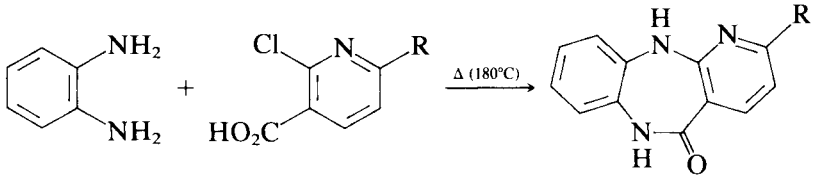
**1697** **1698**, mp 245–246°C (nmr, ms)

## 16. Pyrido[2,3-*b*][1,4]benzodiazepines (see Section IX.40)

Three patents (979) give details of additional pirenzepin analogs similar to those described in Table 133. The metabolism of pirenzepin in various species, including man, has been studied (980).

## 17. Pyrido[2,3-*b*][1,5]benzodiazepines (see Section IX.41)

A patent (981) describes the preparation of an additional group of compounds similar to those listed in Table 140. Tricyclic lactams with an aryl substituent in the 2-position (**1699**) have been prepared by the standard procedure, as shown in Fig. 158. Additional analogs (**1700**) were prepared by nitration of 2-anilinonicotinic acids, reduction of the nitro group, and cyclization (982).




**1699**, R = Ph, 3-$NO_2$Ph, 3-Py

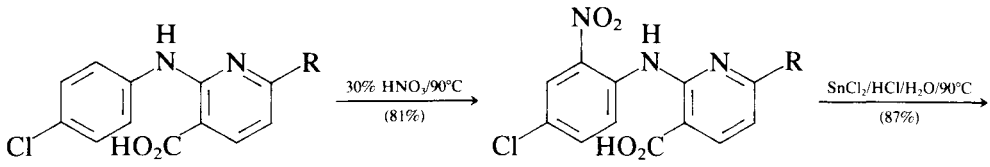
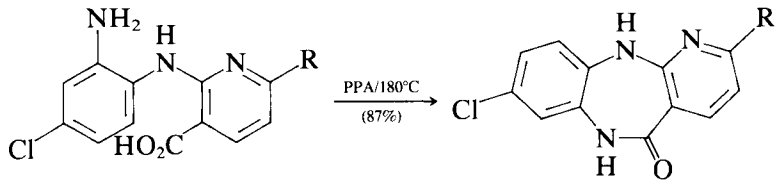



**Figure 158** (*continued on next page*)

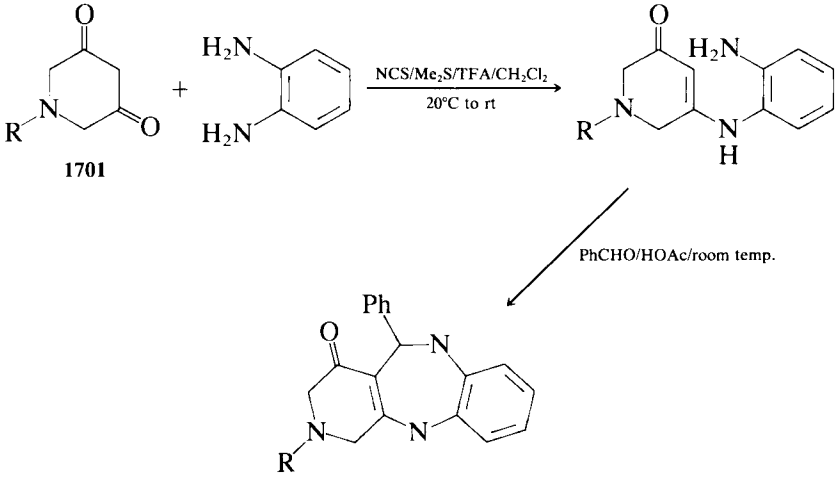



**1700,** R = Ph, 3-Py

**Figure 158 (*continued*)**

## 18. Pyrido[3,4-*b*][1,5]benzodiazepines (see Section IX.43)

A new synthesis of pyrido[3,4-*b*][1,5]benzodiazepine derivatives involves condensation of the 3,5-piperidinediones **1701** with *o*-phenylenediamine (983). Reaction of the products with benzaldehyde gave the tricyclic compounds **1702** (Eq. 400).




(400)

**1702,** R = $PhCH_2$, MeCO, $EtO_2C$, 4-$MeC_6H_4O_2S$

## 19. Pyrido[4,3-*b*][1,5]benzodiazepines (see Section IX.44)

A Japanese patent (984) describes the preparation of the *N*-benzyl analog of **1116** (Fig. 159). This substance (**1703**) could be hydrogenated either to the saturated derivative **1704** or to the saturated debenzylated compounds **1705**. The latter was converted to various *N*-alkylated derivatives, such as **1706.** Additional substances shown in Fig. 159 were prepared by standard

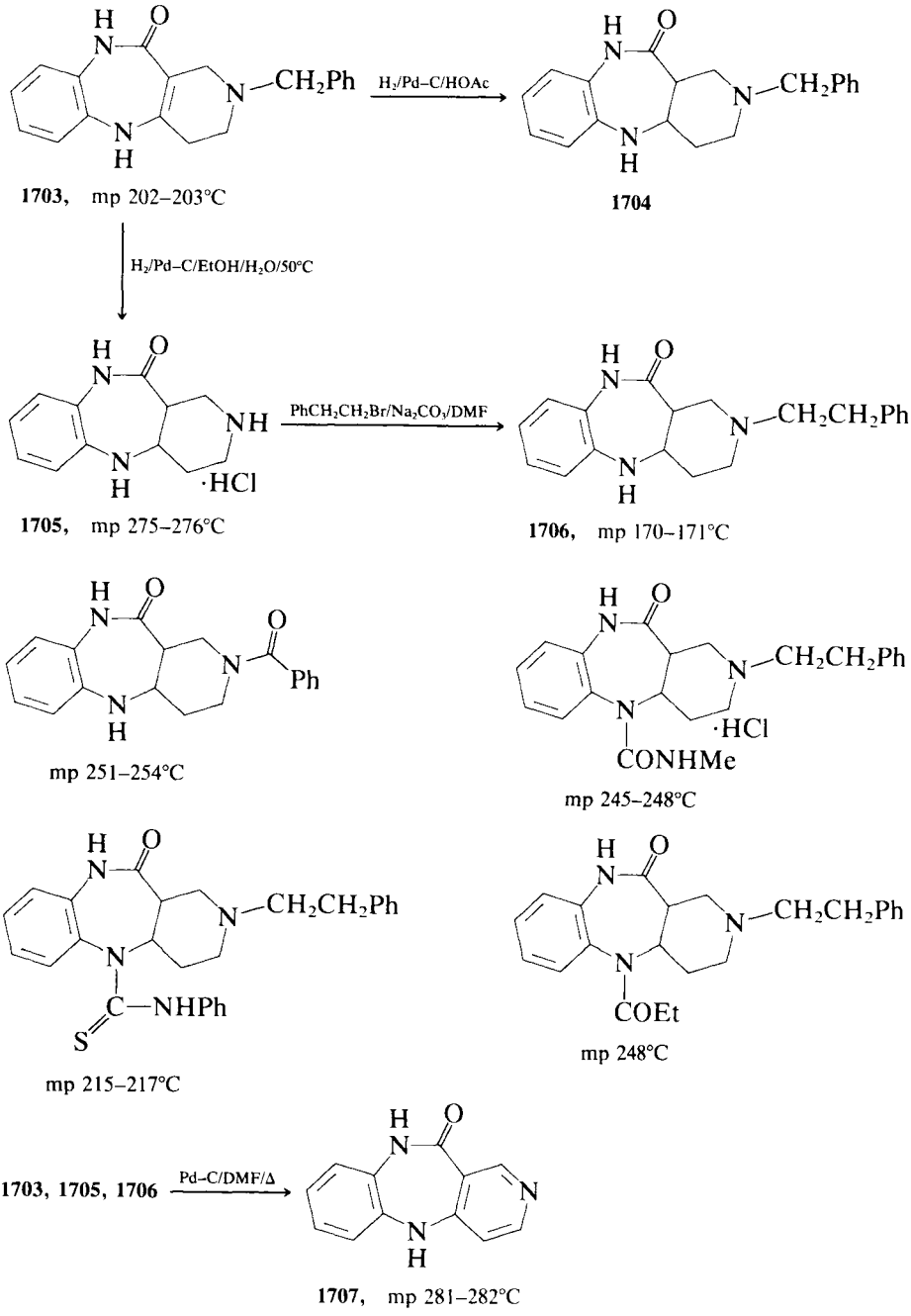
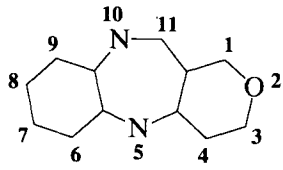

H
O
N
N
N
CH2Ph
H
H2/Pd–C/HOAc
1703, mp 202–203°C
1704
H2/Pd–C/EtOH/H2O/50°C
NH
·HCl
PhCH2CH2Br/Na2CO3/DMF
1705, mp 275–276°C
CH2CH2Ph
1706, mp 170–171°C
Ph
mp 251–254°C
CONHMe
mp 245–248°C
C
S
NHPh
mp 215–217°C
COEt
mp 248°C
1703, 1705, 1706
Pd–C/DMF/Δ
1707, mp 281–282°C

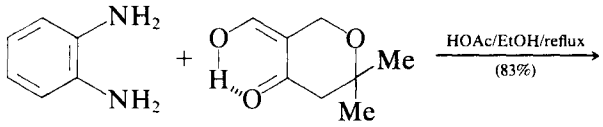
**Figure 159**

methods. A second patent (985) describes dehydrogenation of **1703, 1705,** and **1706** with 10% Pd–C in dimethylformamide to give the fused pyridine derivative **1707.**

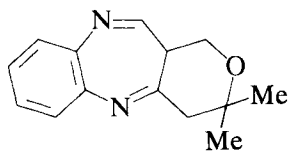
## 20. Pyrano[4,3-*b*][1,5]benzodiazepines




As shown in Eq. 401, reaction of the tetrahydropyranone **1708** with *o*-phenylenediamine gave the tricyclic diamine **1709** (986).




**1708**




**1709,** mp 155°C (ir)

(401)

## 21. Thiopyrano[4,3-*b*][1,5]benzodiazepines (see Section IX.47)

Reduction of the enaminolactam **1149** (Fig. 160) with sodium borohydride gave the saturated lactam **1710** (987). Acetylation of **1710** gave **1711** or **1712,** depending on the conditions employed. Reduction of **1149** with lithium aluminum hydride gave two isomeric diamines **1713a,** and **1713b.** Reduction of **1710** with lithium aluminum hydride gave only **1713b** (the higher-melting isomer). Both **1713a** and **1713b** were acetylated to give the diacetyl compounds **1714a** and **1714b.** These transformations excluded the formation of a tetrahydrothiopyranobenzimidazoline derivative analogous to **1153** and **1154.** Attempts to prepare the sulfone derivative of **1149** were not successful.

As shown in Eq. 402, the reaction of tetrahydrothiopyranone **1715** with *o*-phenylenediamine gave the tricyclic diazepine **1716** (986).

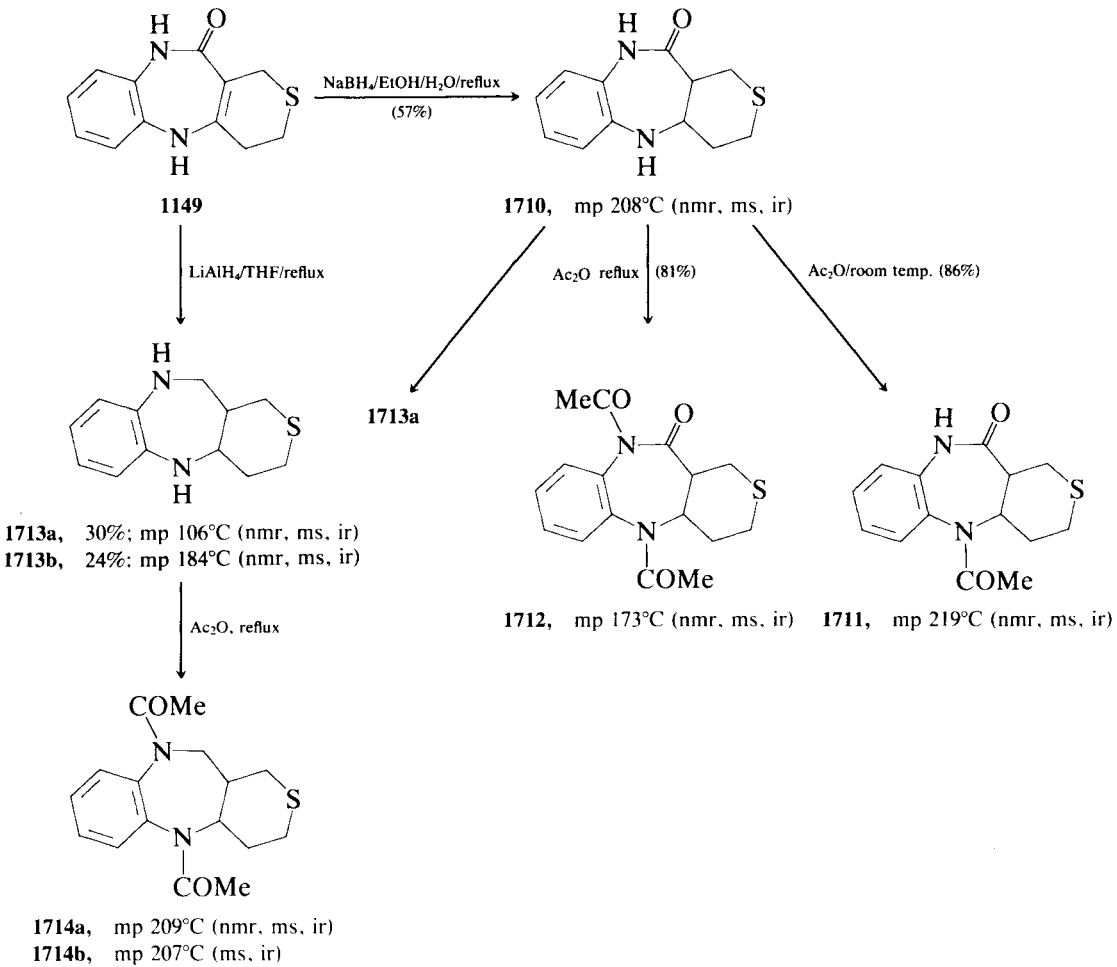
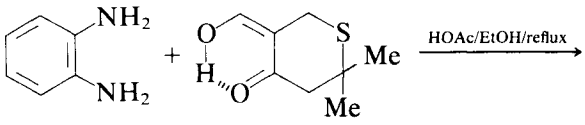
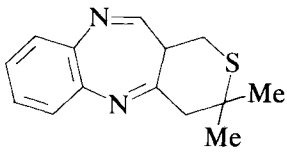

NaBH4/EtOH/H2O/reflux
(57%)
1149
1710, mp 208°C (nmr, ms, ir)
LiAlH4/THF/reflux
Ac2O reflux (81%)
Ac2O/room temp. (86%)
1713a
1713a, 30%; mp 106°C (nmr, ms, ir)
1713b, 24%: mp 184°C (nmr, ms, ir)
Ac2O, reflux
1712, mp 173°C (nmr, ms, ir)
1711, mp 219°C (nmr, ms, ir)
1714a, mp 209°C (nmr, ms, ir)
1714b, mp 207°C (ms, ir)

**Figure 160**



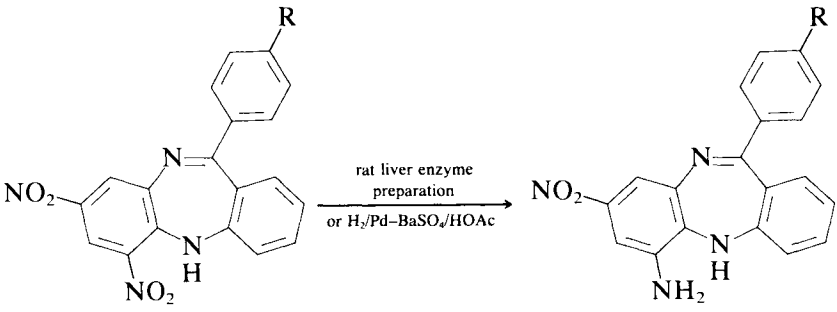

1715




1716 (402)

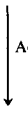
## 22. Dibenzo[b,e][1,4]diazepines (see Section IX.48)

Additional derivatives of the tricyclic lactam **1155a** have been prepared (988).

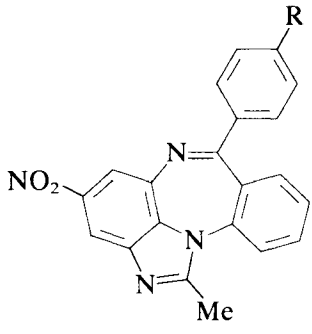



1717, R = Cl, Br, H, Me

1718



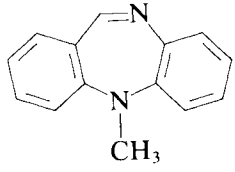

(403)




1719

Dinitro compounds **1717** were prepared by standard methods (989). Reduction of these substances either with a rat liver enzyme preparation or by catalytic hydrogenation over palladium on barium sulfate gave the nitroanilines **1718,** which gave the tetracyclic imidazoles **1719** on treatment with acetic anhydride (Eq. 403).

A photoelectron spectroscopic study of imine **1180g** has been described (990).



**1180g**

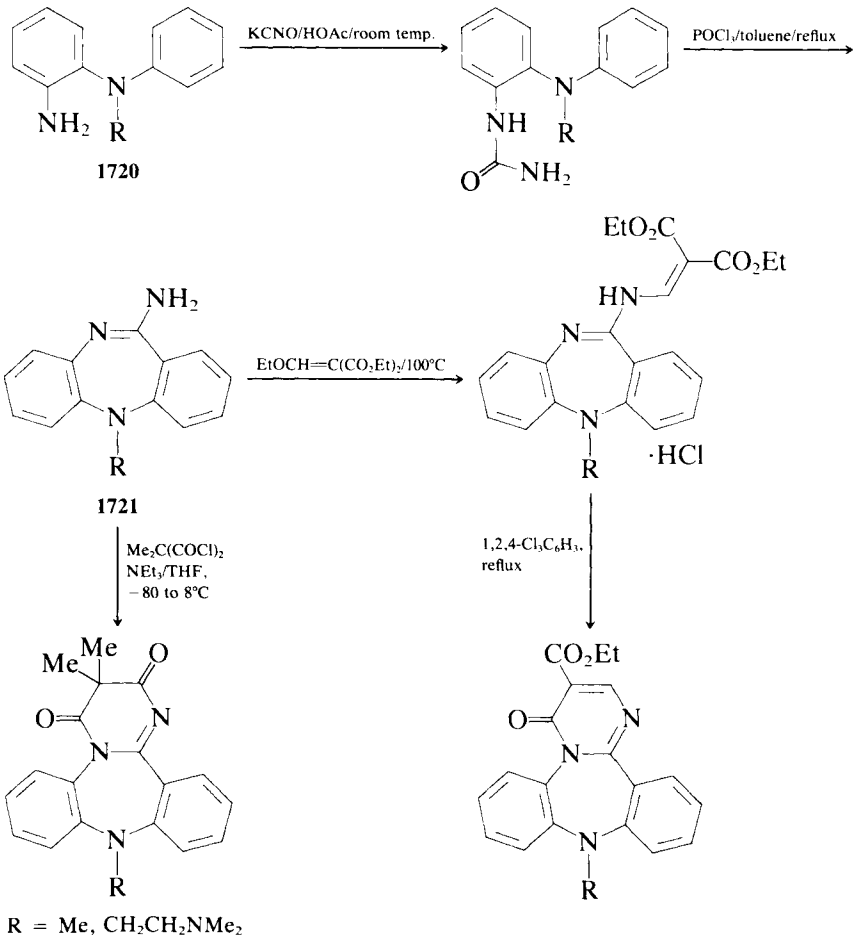
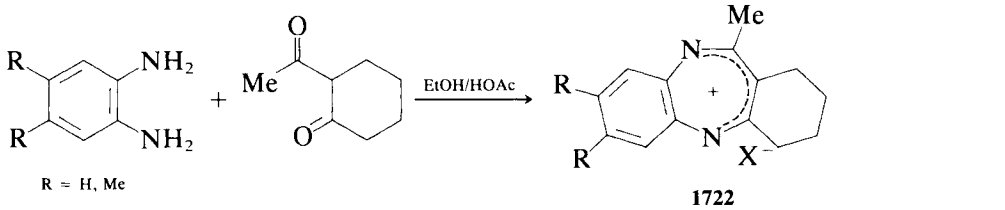
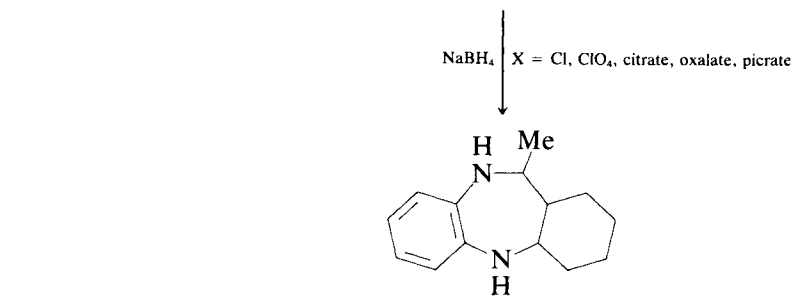


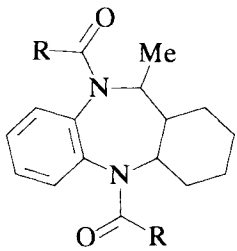

**Figure 161**



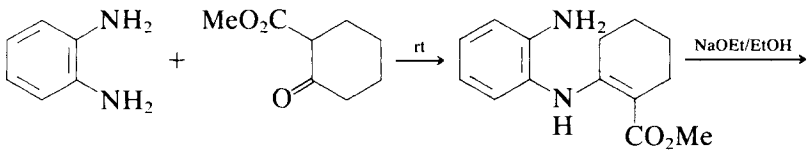

**1722**



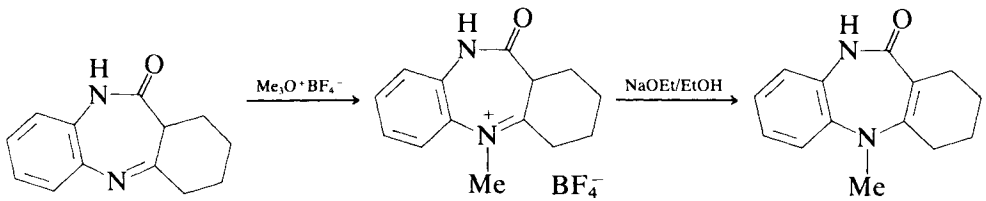

**1723**




**1724,** R = $CH_2CH_2Br$
**1725,** R = Ph




**1726**




**1727,** mp 178–184°C
**1728,** mp 265–268°C
**1729,** mp 150–169°C (dec.)

**Figure 162**

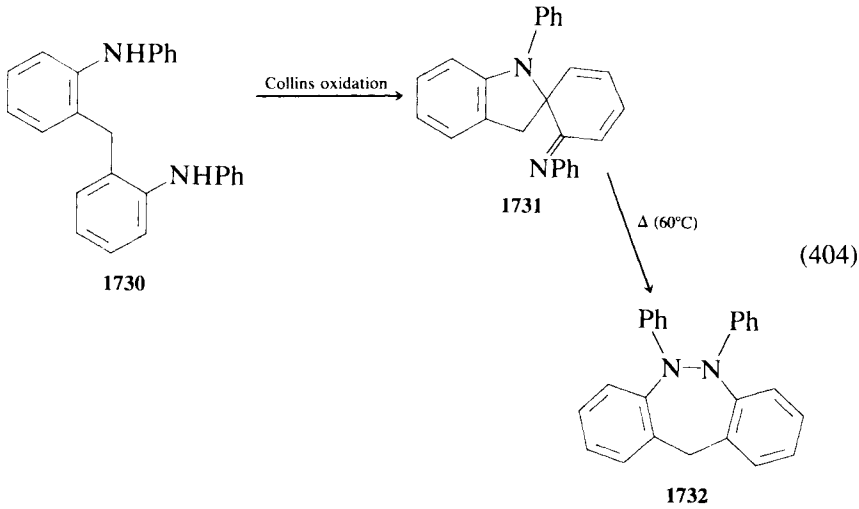
Further studies on the metabolism of clozapine (**1183b**) in man have been described (991). Metabolites in which the chloro substituent was converted to hydroxy or methylthio groups were detected. Two papers presenting detailed analyses of structure–activity relationships in the clozapine area have appeared (992). Additional analogs of clozapine were prepared using procedures previously described (993).

Further examples of the conversion of dibenzo[*b,e*][1,4]diazepines to imidazo[1,2-*d*]dibenzo[*b,f*][1,4]diazepines have been described (994). 11-Aminodibenzo[*b,e*][1,4]diazepine derivatives were prepared by treatment of 2-aminodiphenylamines (**1720**) with potassium cyanate followed by cyclization of the urea with phosphorous oxychloride (Fig. 161). These substances (**1721**) were converted to tetracyclic pyrimidine and triazine derivatives using standard benzodiazepine annelation methodology (995).

Condensation of *o*-phenylenediamine with 2-acetylcyclohexanone gave the tricyclic salts **1722** (949). Reduction of **1722** (Fig. 162) with sodium borohydride gave the tetrahydro derivative **1723,** which was acylated to give **1724** and **1725.** In a Japanese patent (961) the product obtained by reaction of 2-carbomethoxycyclohexanone with *o*-phenylenediamine was formulated as **1726.** Cyclization of **1727** was effected under basic conditions. This imine was converted to the quaternary salt **1728,** which gave the enaminolactam **1729** on treatment with base.

## 23. Dibenzo[*c,f*][1,2]diazepines (see Section IX.49)

A new synthetic method for dibenzo[*c,f*][1,2]diazepine derivatives is shown in Eq. 404. Oxidation of **1730** with Collins reagent gave the cyclohexadienone



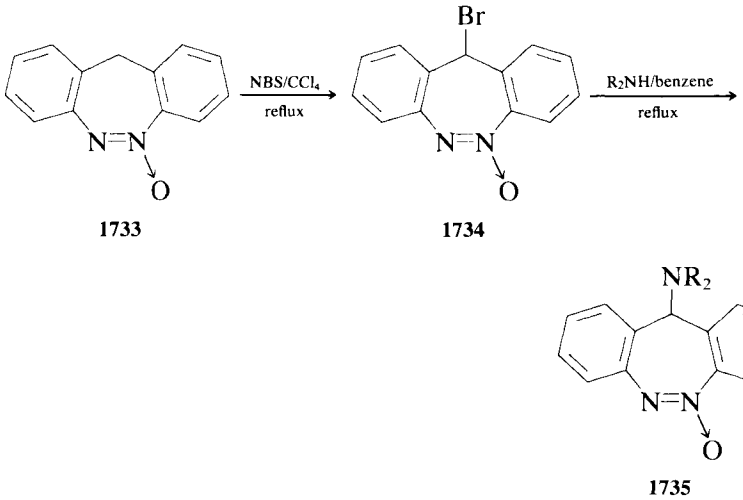

**1730** **1731** **1732** (404)

imine **1731**, which rearranged thermally to the dibenzodiazepine derivative **1732** (996). The equilibrium between **1731** and **1732** was studied by nmr, and a detailed analysis of the thermodynamic parameters for the interconversion was provided.

Further details of the photochemical conversion of **1219** to dibenzodiazepine derivatives have been provided (997).

Treatment of the *N*-oxide **1733** with *N*-bromosuccinimide gave the bromo derivative **1734** (998). This substance gave the amino derivatives **1735** on reaction with secondary amines in refluxing benzene (Eq. 405).

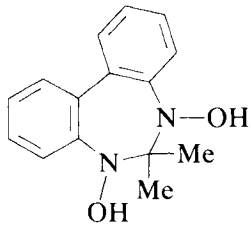
Studies describing the metabolic fate of certain dibenzo[*c*,*f*][1,2]diazepine derivatives have been published (999).




**1733** **1734** **1735** (405)

## 24. Dibenzo[*d*,*f*][1,3]diazepines (see Section IX.50)

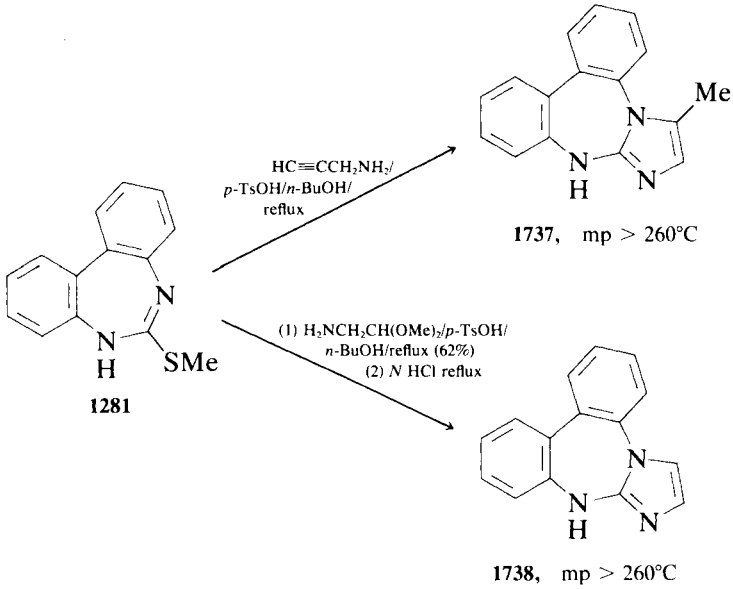
An X-ray crystallography study of **1736** has been published (1000).




**1736**

As shown in Fig. 163, *S*-methylisothiourea **1281** was converted to the tetracyclic imidazoles **1737** and **1738** by standard methodology (893), while the pentacyclic thiazole **1739** was obtained by treatment of thiourea **1260** with 2,3-dichloroquinoxaline (1001).

Pyrolysis of the tricyclic azide **1740** (Eq. 406) gave the remarkable cyclic carbodiimide **1741,** characterized by a strong absorption at 2010 $cm^{-1}$ and stable in the solid state at $-40°C$. Above $-40°C$, rapid dimerization occurred (1002).



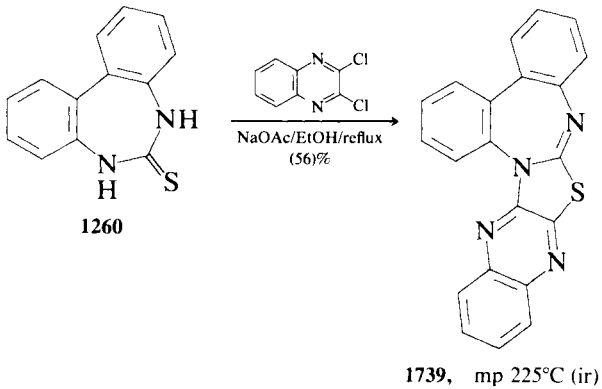
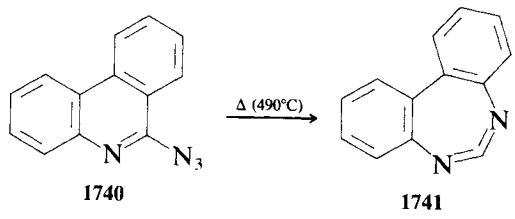



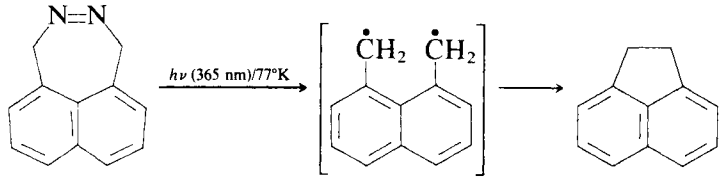

**Figure 163**




1740 1741 (406)

## 25. Naphtho[1,8-*de*][1,2]diazepines (see Section IX.53)

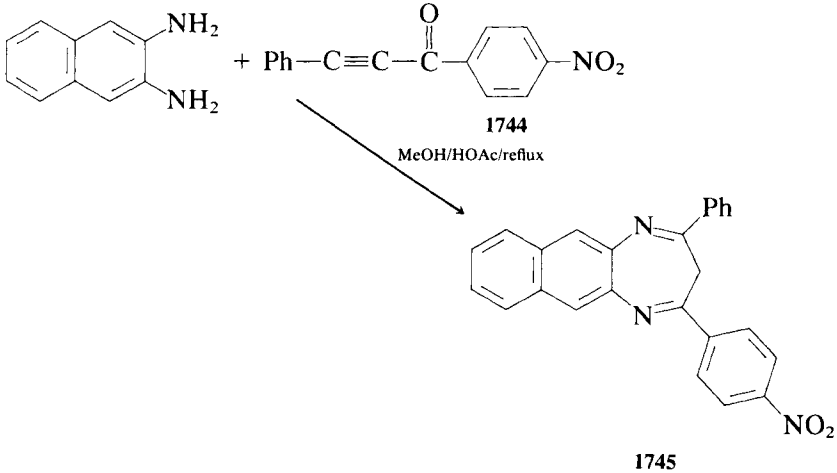
Irradiation of **1310** at 77°K resulted in the formation of the diradical **1742,** which then collapsed to acenaphthene **1743** (Eq. 407). Apparently, only a small fraction of the photochemical conversion proceeds via **1742,** so that sufficient quantities for a proper determination of its ultraviolet and visible spectrum could not be accumulated (1003).




1310 1742 1743 (407)

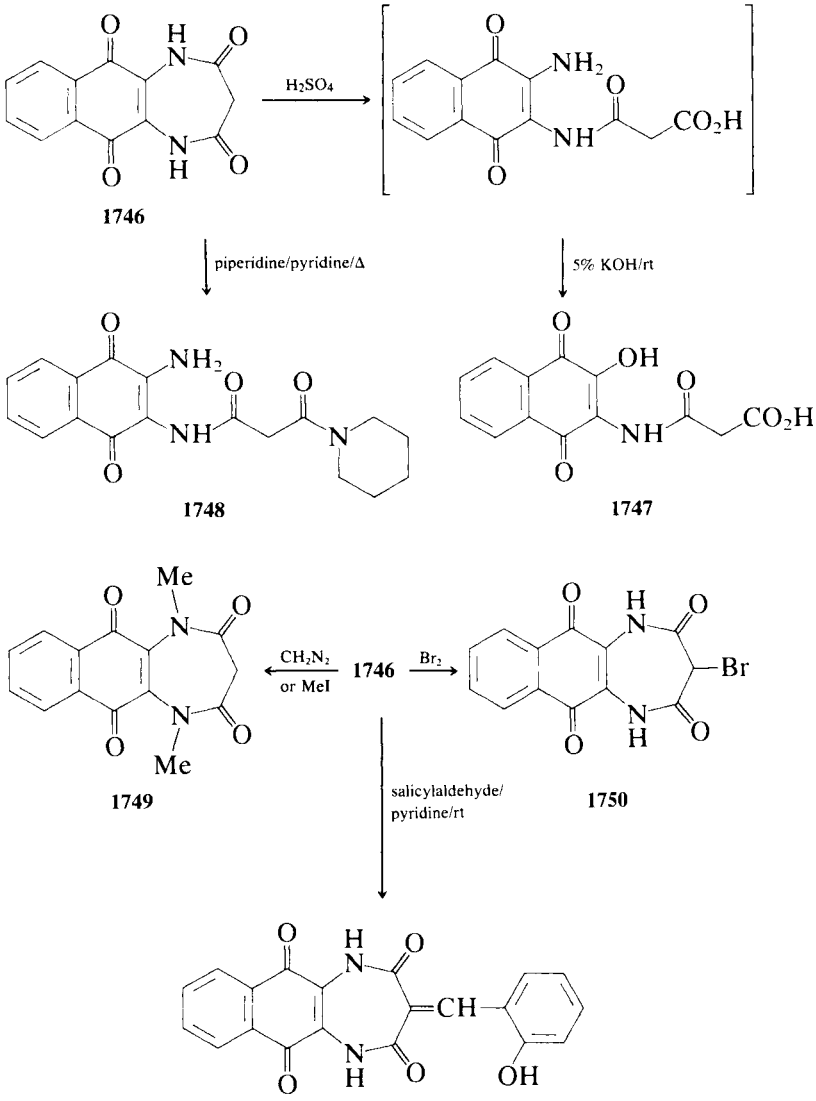
## 26. Naphtho[2,3-*b*][1,4]diazepines (see Section IX.54)

As shown in Eq. 408, reaction of 2,3-diaminonaphthalene with acetylenic ketone **1744** gave the tricyclic diazepine **1745** (1004).




1745 (408)

Diazepinetetraone **1746** was hydrolyzed to 2,3-diaminonaphthoquinone with concentrated sulfuric acid (Fig. 164). Treatment with aqueous potassium hydroxide gave the ring-opened acid **1747,** while heating with secondary amines in pyridine solution gave ring-opened amides such as **1748** (1005). Alkylation with diazomethane or methyl iodide gave the *N,N*-dimethyl derivative **1749.** Treatment of **1746** with bromine gave the 3-bromo derivative **1750** (which was not obtained in a pure state), while reaction with salicaldehyde gave the benzylidene derivative **1751.**




**1746** **1748** **1747** **1749** **1750** **1751**

**Figure 164**

Reaction of 2,3-diaminonaphthoquinone with acetoacetic ester was shown to give trione **1752,** in which the double bond is conjugated with the carbonyl group (1006). The product had a melting point similar to that of the diketene addition product **1318,** formulated as the imine isomer, but no direct comparison was made. Hydrogenation of **1752** gave **1319,** while treatment with methanol gave the addition product **1753** (Fig. 165).

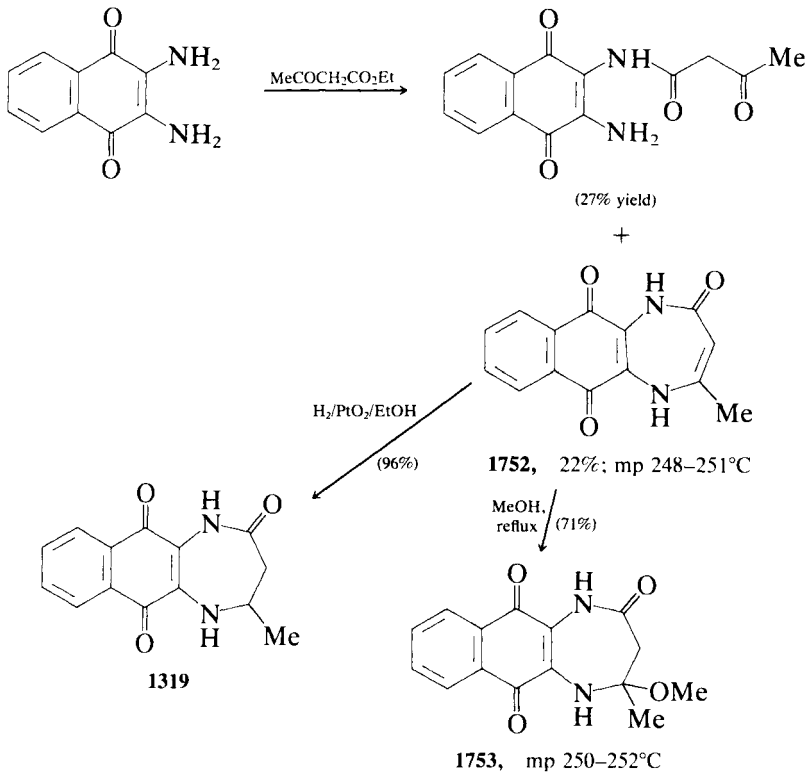
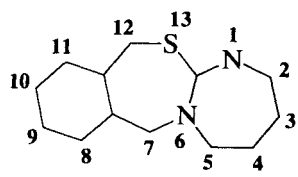


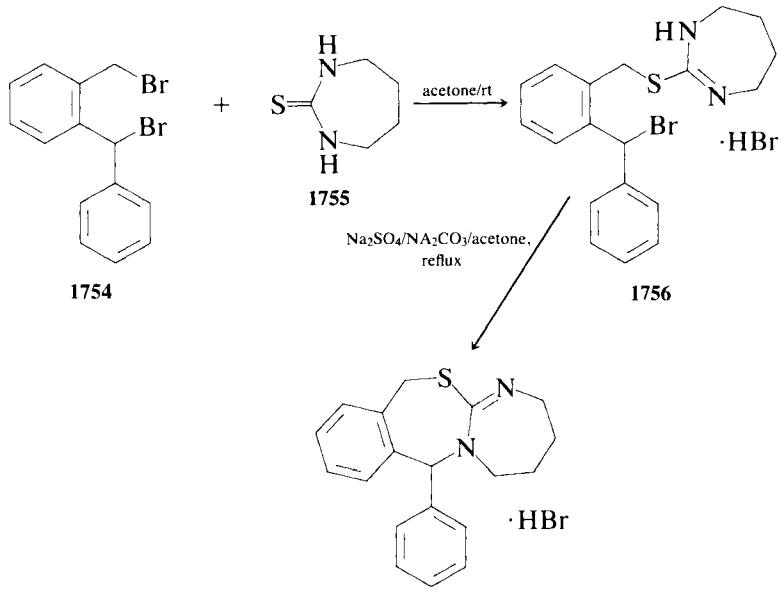

**Figure 165**

## XVII. 6,7,7-SYSTEMS

### 1. [1,3]Diazepino[2,1-*c*][2,4]benzothiazepines

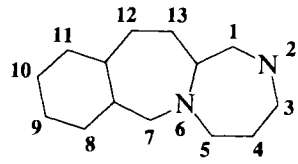


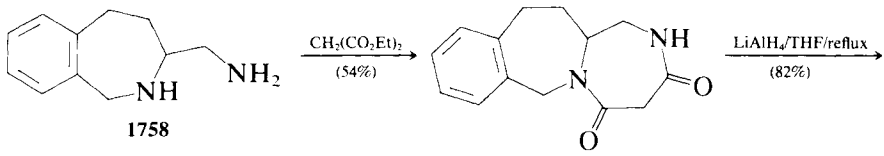
As shown in Eq. 409, condensation of dibromide **1754** with the cyclic urea **1755** gave the adduct **1756,** which was cyclized under basic conditions to the tricyclic diazepine **1757** (1007).



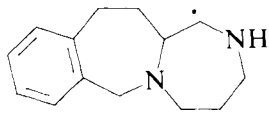

1757, mp 254–256°C (409)

## 2. [1,4]Diazepino[1,2-*b*][2]benzazepines



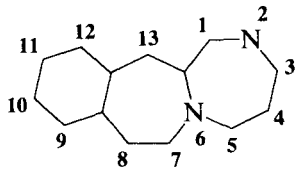

1759, mp 91–93°C (410)



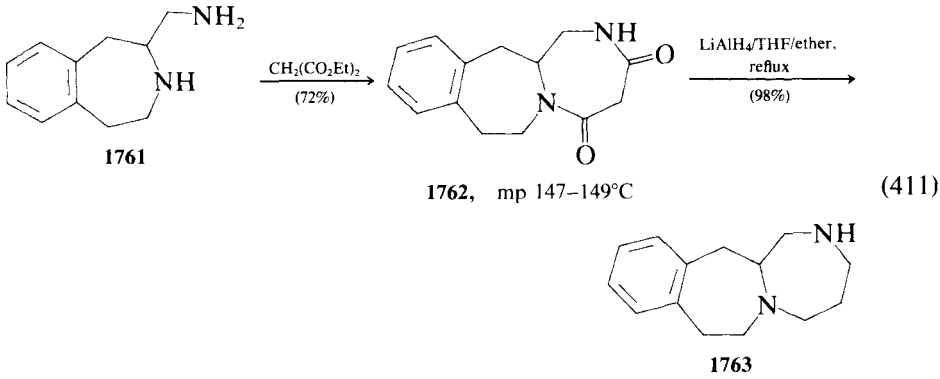

1760

As shown in Eq. 410, condensation of the diamine **1758** (1008) with diethyl malonate gave the dilactam **1759,** which was reduced with lithium aluminum hydride to the diamine **1760** (1009).

### 3. [1,4]Diazepino[2,1-*b*][3]benzazepines



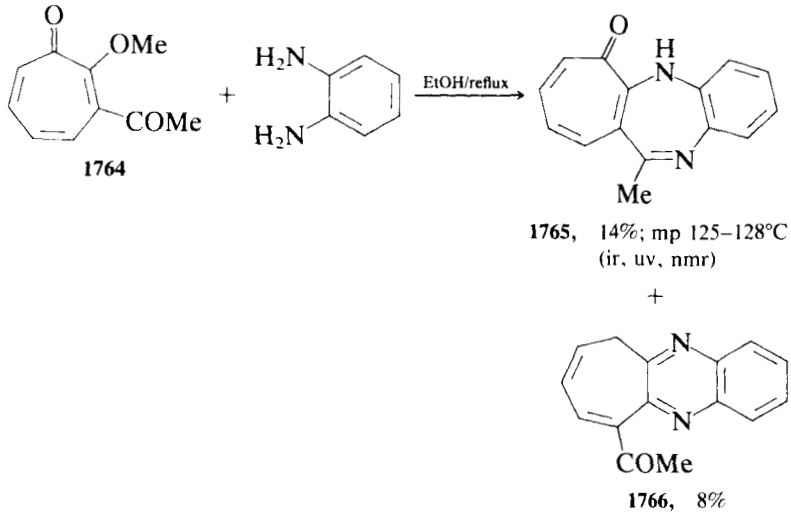

As shown in Eq. 411, condensation of the diamine **1761** (1008) with diethyl malonate gave the dilactam **1762,** which was reduced with lithium aluminum hydride to the diamine **1763** (1009).




(411)

### 4. Benzo[*b*]cyclohepta[*e*][1,4]diazepines (see Section X.8)

Condensation of tropone **1764** with *o*-phenylenediamine gave the adducts **1765** and **1766** (Eq. 412). Prolonged reaction gave **1767** as the major product (33% yield), with only trace amounts of **1765** and **1766** remaining (1010). Use

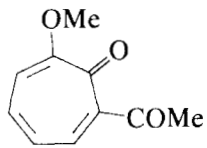



(412)

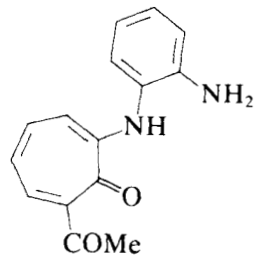
of the isomeric tropone **1768** resulted in the formation of **1769** in 58% yield, with trace amounts of **1766** and **1767.** Prolonged reaction (24 h) gave **1765** (37%), **1766** (11%), **1767** (24%), and **1769** (7%). Adduct **1766** was converted to **1765** under acidic conditions.




**1767**




**1768**




**1769**

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CHAPTER II

# Monocyclic and Condensed Triazepines and Tetrazepines

NORTON P. PEET

*Pharmaceutical Research and Development—Medicinal Chemistry*
*Merrell Dow Pharmaceuticals*
*Indianapolis, Indiana*

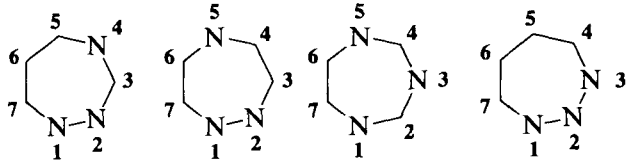
## I. TRIAZEPINES

### 1. Introduction

The history of the construction of seven-membered rings containing three nitrogen atoms, or triazepines, is a fascinating area for review. Triazepine ring systems, in general, are difficult to synthesize. It appears that when the potential for smaller-sized ring formation exists, in experiments designed to produce triazepines, the smaller-sized rings will often result. Thus structural misassignments are prevalent in reports dealing with triazepine synthesis. As a result, many literature reports dealing with triazepine synthesis have been subsequently reinvestigated.

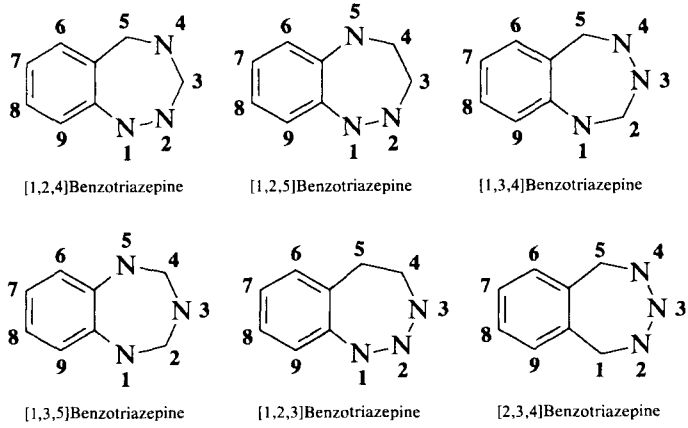
As with many areas of synthesis, several of the synthetic studies in the triazepine area were designed to produce compounds for biological evaluation. Many of the monocyclic triazepines have been evaluated as agricultural products. The synthesis of benzotriazepines blossomed after the discovery that certain benzodiazepines were active as central nervous system agents. And, certainly, some of the interest in the dibenzotriazepines and other fused-ring triazepine systems was engendered by the tricyclic antidepressants. Information regarding the proposed or realized biological activities of the triazepines will be cited in this review.

The four possible classes of monocyclic triazepine ring systems are [1,2,4]-, [1,2,5]-,[1,3,5]-, and [1,2,3]triazepines. Representatives of all of these classes have been reported in the literature. In the older literature [1,2,4]triazepines were termed "heptatriazines", and [1,3,5]triazepines have even recently been labeled "triazacycloheptanes."



[1,2,4]Triazepine [1,2,5]Triazepine [1,3,5]Triazepine [1,2,3]Triazepine

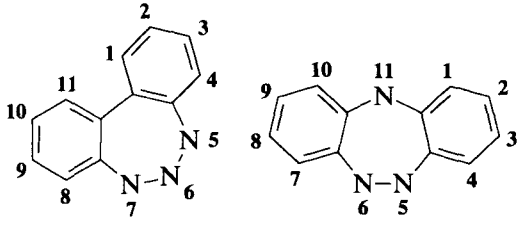
There are, theoretically, six possible classes of benzotriazepines. These are [1,2,4]-, [1,2,5]-,[1,3,4]-,[1,3,5]-,[1,2,3]- and [2,3,4]benzotriazepines, as illustrated. The first four classes are well known in the literature. One report dealing with the latter class, [2,3,4]benzotriazepines, which will be discussed in this review, is undoubtedly erroneous. The [1,2,3]benzotriazepine system, lacking a fused aromatic ring at the 4- and 5-positions, is unknown.



[1,2,4]Benzotriazepine [1,2,5]Benzotriazepine [1,3,4]Benzotriazepine

[1,3,5]Benzotriazepine [1,2,3]Benzotriazepine [2,3,4]Benzotriazepine

Only two classes of dibenzotriazepines are theoretically possible. These are the [1,2,3]- and [1,2,5]dibenzotriazepines, and both are known in the literature.



[1,2,3]Dibenzotriazepine [1,2,5]Dibenzotriazepine

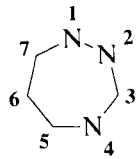
Other fused-ring triazepine and benzotriazepine systems are known in

addition to the benzotriazepines and dibenzotriazepines. A separate section (Section 4) is devoted to these other fused-ring triazepine systems. The fused-ring benzotriazepine systems will be discussed integrally in the section dealing with benzotriazepines (Section 3).

The physical properties of compounds are given in tabular form when several triazepines of a specific class are available. Not included in these tables are compounds that were originally reported as triazepines but were subsequently shown to be misassigned, or compounds of doubtful structure.

## 2. Monocyclic Triazepine Ring Systems

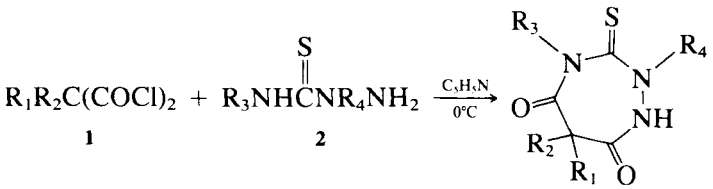
### A. *[1,2,4]Triazepines*



#### a. 3-THIOXO-5H-[1,2,4]TRIAZEPINE-5,7(6H)-DIONES

Losse and Uhlig (1) reported that 2-phenylthiosemicarbazide and 2-methyl-4-phenylthiosemicarbazide, when treated with dialkylmalonyl chlorides (**1**), yielded the 6,6-dialkyl-2-phenyltetrahydro-3-thioxo-5H-[1,2,4]triazepine-5,7(6H)-diones **3–9,** as shown in Eq. 1. These authors stated that polymeric products were obtained when the same malonyl chlorides were allowed to react with 2-methylthiosemicarbazide or 2,4-diphenylthiosemicarbazide.

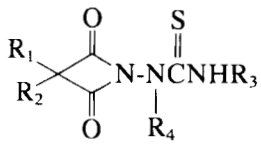
Structural assignments were made on the basis of elemental analyses, molecular weight determinations, and the observation that the cyclization products derived from 2-methyl-4-phenylthiosemicarbazide formed neither



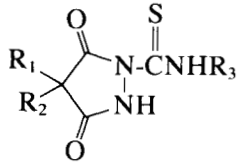
(1)

**3,** $R_1$ = Me, $R_2$ = Et, $R_3$ = H, $R_4$ = Ph
**4,** $R_1$ = $R_2$ = Et, $R_3$ = H, $R_4$ = Ph
**5,** $R_1$ = $R_2$ = *n*-Pr, $R_3$ = H, $R_4$ = Ph
**6,** $R_1$ = $R_2$ = $R_4$ = Me, $R_3$ = Ph
**7,** $R_1$ = $R_4$ = Me, $R_2$ = Et, $R_3$ = Ph
**8,** $R_1$ = $R_2$ = Et, $R_3$ = Ph, $R_4$ = Me
**9,** $R_1$ = $R_2$ = *n*-Pr, $R_3$ = Ph, $R_4$ = Me

hydrochloride nor alkali metal salts. However, this argument does not rigorously exclude general structures **10** or **11** ($R_4$ must be H) from consideration as products of the reaction, especially those derived from semicarbazides other than 2-methyl-4-phenylthiosemicarbazide.

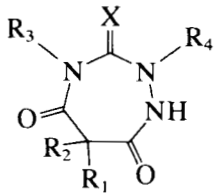


**10**



**11**

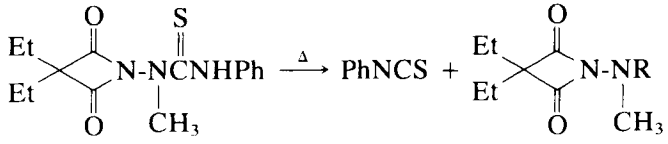
In a subsequent article, Losse, Wottgen, and Just (2) reported the preparation of additional thioxo-[1,2,4]triazepinediones (**12–18**) and [1,2,4]-triazepinetriones (**19–21**) in a similar fashion. However, a later article by



**12**, X = S, $R_1$ = $PhCH_2$, $R_2$ = Et, $R_3$ = H, $R_4$ = Me
**13**, X = S, $R_1$ = $R_2$ = $PhCH_2$, $R_3$ = H, $R_4$ = Me
**14**, X = S, $R_1$ = $R_4$ = Ph, $R_2$ = Et, $R_3$ = H
**15**, X = S, $R_1$ = $PhCH_2$, $R_2$ = Et, $R_3$ = H, $R_4$ = Ph
**16**, X = S, $R_1$ = $R_2$ = $PhCH_2$, $R_3$ = H, $R_4$ = Ph
**17**, X = S, $R_1$ = $R_2$ = $R_4$ = $PhCH_2$, $R_3$ = H
**18**, X = S, $R_1$ = $R_2$ = $PhCH_2$, $R_3$ = Ph, $R_4$ = Me
**19**, X = O, $R_1$ = $R_2$ = $PhCH_2$, $R_3$ = H, $R_4$ = Et
**20**, X = O, $R_1$ = $R_2$ = Et, $R_3$ = H, $R_4$ = Ph
**21**, X = O, $R_1$ = $R_2$ = $PhCH_2$, $R_3$ = H, $R_4$ = Ph

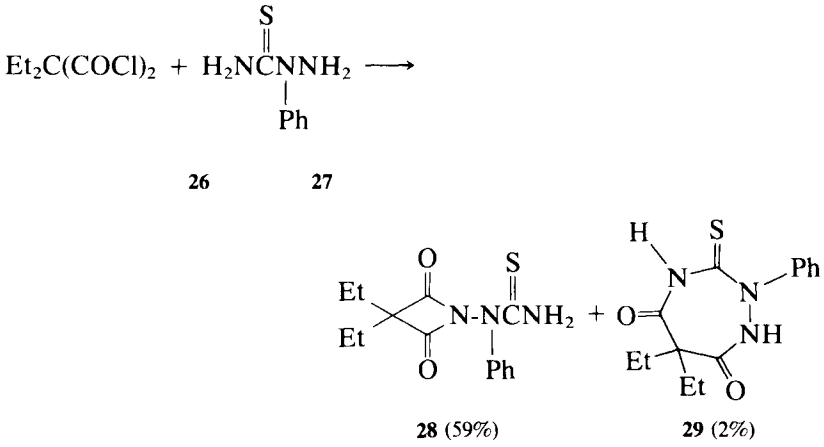
Ebnöther and co-workers (3) took exception to the work of Losse and co-workers (1,2) and indicated that all of the products from the reaction of thiosemicarbazides with disubstituted malonyl chlorides reported by Losse and co-workers are probably azetidinediones of general structure **10.** In repeating some of the preparations of Losse and co-workers, who reported no spectral data for their compounds, Ebnöther and co-workers found that the products displayed infrared carbonyl absorptions at ca. 1755 $cm^{-1}$ (strong) and 1880 $cm^{-1}$ (weak), which are consistent with azetidinedione structures. Moreover, azetidinedione **22,** which was reported to have structure **8** by Losse and Uhlig (1), was shown to thermally decompose to phenyl isothio-

cyanate (**23**) and azetidinedione **24** (Eq. 2). Treatment of **24** with *p*-toluenesulfonyl chloride in pyridine led to the tosyl derivative **25.** Ebnöther and co-workers (3) offered convincing evidence that most or all of the [1,2,4]triazepines reported by Losse and co-workers (1,2) were incorrectly assigned.



**22** **23** **24**, R = H; **25**, R = *p*-$MeC_6H_4SO_2$ (2)

Ebnöther and co-workers (3) isolated a co-product of azetidinedione **28** from the reaction of diethylmalonyl chloride (**26**) with 2-phenylthiosemicarbazide (**27**) which they formulated as 6,6-diethyl-2-phenyltetrahydro-3-thioxo-5H-[1,2,4]triazepine-5,7(6H)-dione (**29**). Thus when the procedure of Losse and Uhlig (1) was followed, **28** was isolated in 59% yield (and had approximately the same melting point as the product assigned structure **4** by Losse and Uhlig (1)) and **29** was isolated in 2% yield (Eq. 3).

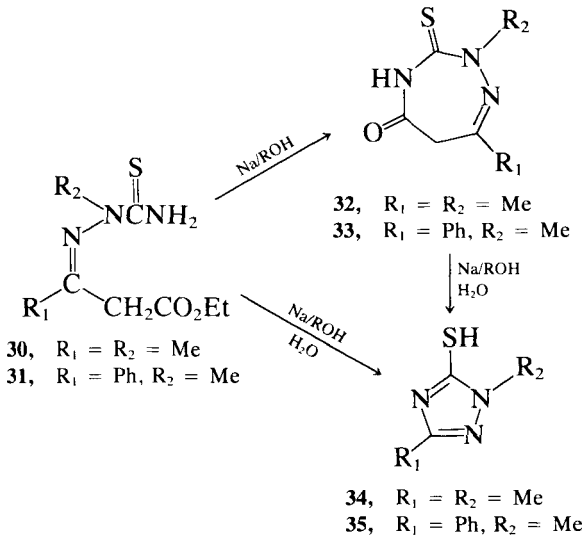


**26** **27** **28** (59%) **29** (2%) (3)

## b. 2,3,4,6-TETRAHYDRO-3-THIOXO-5H-[1,2,4]TRIAZEPIN-5-ONES

Losse and co-workers (4) reported the preparation of 2,7-dimethyl-2,3,4,6-tetrahydro-3-thioxo-5H-[1,2,4]triazepin-5-one (**32**) and the 7-phenyl analog (**33**) from the respective thiosemicarbazones **30** and **31** with sodium in alcohol (Eq. 4). Thus **30** and **31,** which were prepared from 2-methylthiosemicarbazide and the appropriate β-ketoesters, were converted to **32** and **33** in respective yields of 36 and 82%. Structural assignments for **32** and **33** were

made on the basis of elemental analyses, molecular weight determinations, infrared spectra (not reported), base solubility, the propensity of **33** to form an ethyl thioether derivative, and the conversion of **32** and **33** with alcoholic sodium hydroxide to mercaptotriazoles **34** and **35**, respectively. Compounds **34** and **35** could also be prepared from the respective thiosemicarbazones **30** and **31** under the same conditions.



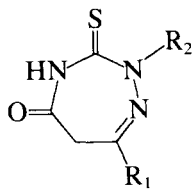

**30**, $R_1 = R_2 = Me$
**31**, $R_1 = Ph$, $R_2 = Me$

**32**, $R_1 = R_2 = Me$
**33**, $R_1 = Ph$, $R_2 = Me$

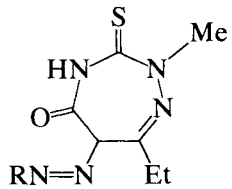
**34**, $R_1 = R_2 = Me$
**35**, $R_1 = Ph$, $R_2 = Me$

(4)

In a subsequent article, Losse and Farr (5) reported additional 2,7-disubstituted 2,3,4,6-tetrahydro-3-thioxo-5H-[1,2,4]triazepin-5-ones (**36–40**) using essentially the same procedure, but sometimes employing a calcium alkoxide as the base. The authors also reported the preparation of azo compounds **41–43** from the reaction of **36** with appropriate diazonium ions. Physical constants for known members of this series are listed in Table 1.

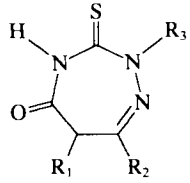


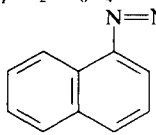
**36**, $R_1 = Et$, $R_2 = Me$
**37**, $R_1 = p\text{-}MeC_6H_4$, $R_2 = Me$
**38**, $R_1 = Me$, $R_2 = PhCH_2$
**39**, $R_1 = Et$, $R_2 = PhCH_2$
**40**, $R_1 = Me$, $R_2 = Ph$



**41**, R = Ph
**42**, R = $p\text{-}NO_2C_6H_4$
**43**, R = α-naphthyl

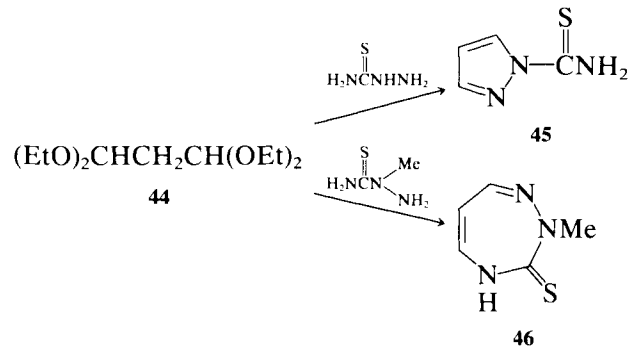
TABLE 1. 2,3,4,6-TETRAHYDRO-3-THIOXO-5H-[1,2,4]TRIAZEPIN-5-ONES



| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|
| H | Me | Me | 147–148 | 8 | 5 |
| H | Me | Me | 137.5–138 | 36 | 4 |
| H | Me | Ph | 198–200 | 10 | 5 |
| H | Me | $PhCH_2$ | 176–177 | 29 | 5 |
| H | Et | Me | 130–131 | 75 | 5 |
| H | Et | $PhCH_2$ | 151–152 | 25 | 5 |
| H | Ph | Me | 180–181 | 63 | 5 |
| H | Ph | Me | 181 | 82 | 4 |
| H | *p*-$MeC_6H_4$ | Me | 198–199 | 30 | 5 |
| PhN=N— | Me | Me | 172–174 | 65 | 5 |
| *p*-$O_2NC_6H_4N$=N— | Me | Me | 216–218 | 30 | 5 |
|  | Me | Me | 181–182 | 35 | 5 |

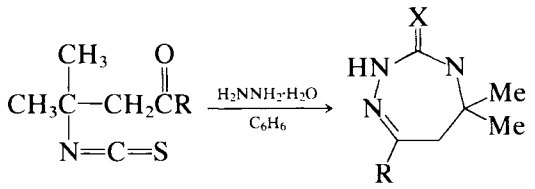
## c. 3H-[1,2,4]TRIAZEPINE-3-THIONES

There has been some recent synthetic interest in 3H-[1,2,4]triazepine-3-thiones (Eq. 5). Stanovnik and Tisler (6) found that 1,1,3,3-tetraethoxypropane (**44**), when treated with thiosemicarbazide (or thiosemicarbazones), yielded pyrazole-1-thiocarboxamide (**45**). However, when **44** was allowed to react with 2-methylthiosemicarbazone the resulting product was reportedly 2-methyl-3H-[1,2,4]triazepine-3-thione (**46**).



(5)

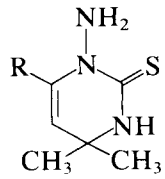
Zigeuner and co-workers (7) also reported the preparation of triazepine-thiones from the reaction of 4-isothiocyanato-4-methyl-2-pentanone (**47**) and its homolog **48** with hydrazine hydrate (Eq. 6). The structures of these products were assigned as 5,5,7-trimethyl-2,4,5,6-tetrahydro-3H-[1,2,4]-triazepine-3-thione (**49**) and the ethyl analog **51,** respectively. Alternate structures **52** and **53** (or their thiol tautomers) were dismissed on the basis of spectra; the products lacked nmr vinyl proton signals which would be expected for structures **52** and **53.** Treatment of **49** with hydrogen peroxide yielded the triazepinone **50.** The authors pointed out that compound **49** was identical to a compound obtained earlier by Mathes and Stewart (8) and Mathes (9), which was prepared from **47** and hydrazine but was formulated as 2-mercapto-3-amino-3,6-dihydropyrimidine (**52**). Physical constants for compound **49** and other 5,5-dimethyl-2,4,5,6-tetrahydro-3H-[1,2,4]triazepine-3-thiones are given in Table 2.




(6)

**47,** R = Me
**48,** R = Et

**49,** R = Me, X = S
**50,** R = Me, X = O
**51,** R = Et, X = S



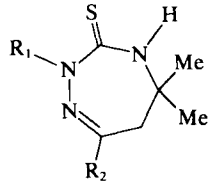

**52,** R = Me
**53,** R = Et

Closely related work is that of Neidlein and Ober (10), who also prepared **49** as well as congeners **54–58** (Eq. 7). In addition, the cyclopentane-fused compound **59** was prepared from the appropriate isothiocyanate. Alkylation of **49** and **54** with methyl iodide gave the methyl thioethers **60** and **61.**

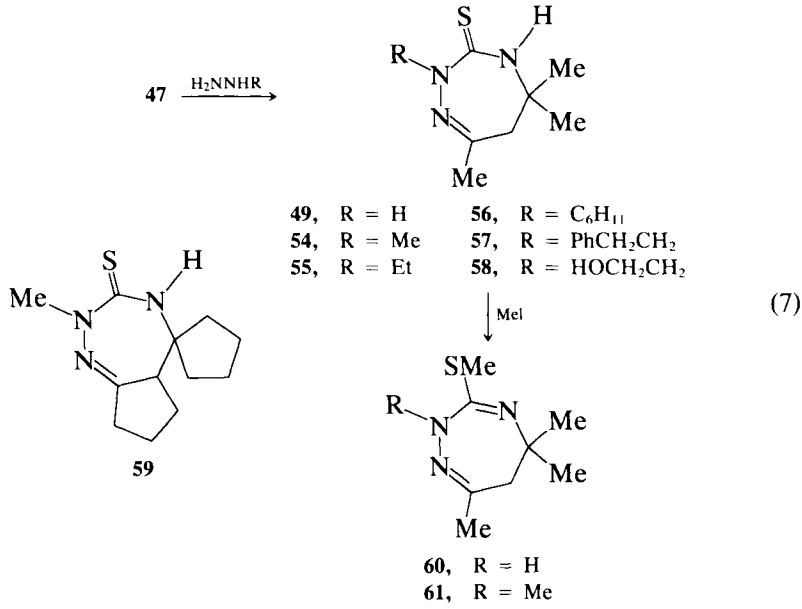
### d. 2H-, 4H- and 6H-[1,2,4]TRIAZEPINES

Fully unsaturated [1,2,4]triazepine systems are compound types that have only recently been synthesized. In 1974 Anderson and Hassner (11) reported that the then unknown [1,2,4]triazepine system was available by the cy-

TABLE 2. 5,5-DIMETHYL-2,4,5,6-TETRAHYDRO-3H-[1,2,4]TRIAZEPINE-3-THIONES

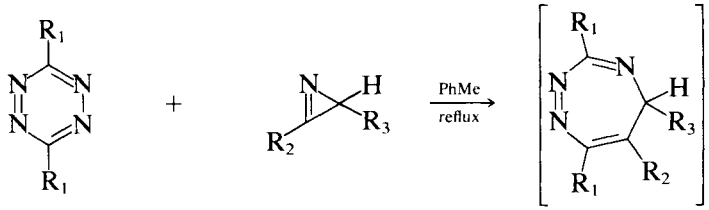


| $R_1$ | $R_2$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|
| H | Me | 209–210 | 75 | 7 |
| H | Me | 213–215 | 47 | 10 |
| H | Me | 209–210 | 80 | 9 |
| H | Et | — | — | 7 |
| Me | Me | 133 | 81 | 10 |
| Et | Me | 105 | 87 | 10 |
| $C_6H_{11}$ | Me | 173 | 88 | 10 |
| $PhCH_2CH_2$ | Me | 100 | 77 | 10 |
| $HOCH_2CH_2$ | Me | 109 | 51 | 10 |



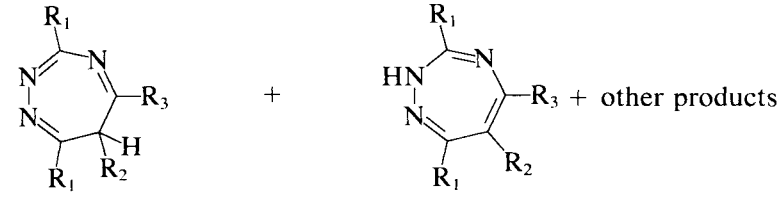

(7)

cloaddition of [1]azirines to [1,2,4,5]tetrazines (Eq. 8). Thus tetrazines **62–64** were allowed to react with azirines **65–67** in toluene at reflux. Reaction products included 6H-[1,2,4]triazepines **69–71** and 2H-[1,2,4]triazepines **72–74.** The intermediacy of the 5H-[1,2,4]triazepines of general structure 68 was envisioned: thermally allowed 1,5-hydrogen shifts could produce the 2H



**62**, $R_1$ = Ph
**63**, $R_1$ = *p*-$MeC_6H_4$
**64**, $R_1$ = 2-$C_5H_4N$
**65**, $R_2$ = Ph, $R_3$ = H
**66**, $R_2$ = Ph, $R_3$ = Me
**67**, $R_2$ = H, $R_3$ = *t*-Bu

**68**

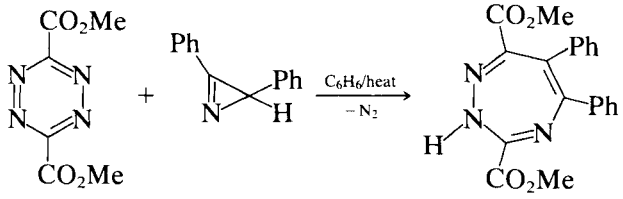


**69**, $R_1$ = $R_2$ = Ph, $R_3$ = Me
**70**, $R_1$ = *p*-$MeC_6H_4$, $R_2$ = Ph, $R_3$ = Me
**71**, $R_1$ = 2-$C_5H_4N$, $R_2$ = H, $R_3$ = *t*-Bu
**72**, $R_1$ = $R_2$ = Ph, $R_3$ = H
**73**, $R_1$ = 2-$C_5H_4N$, $R_2$ = Ph, $R_3$ = Me
**74**, $R_1$ = 2-$C_5H_4N$, $R_2$ = H, $R_3$ = *t*-Bu

(8)

isomers from the postulated 5H isomers, and 6H isomers from the 2H isomers. Other products isolated from these cycloaddition reactions were pyrimidines, pyrazoles, and unidentified adducts. Structural assignments for the isolated triazepines were based on spectral data, elemental analysis, pyrolytic behavior, and literature mechanistic precedent. Other structural possibilities for the NH-containing triazepines (**72–74**), namely isomers in which the nitrogen proton is at positions 1 or 4, were not considered. Physical constants for compounds **72–74** and related [1,2,4]triazepines are presented in Table 3.

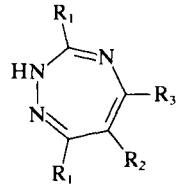
The reaction of dicarbomethoxy-*s*-tetrazine (**75**) with 2,3-diphenylazirine (**76**) was shown by Johnson and Levin (12) to produce a [1,2,4]triazepine (Eq. 9). The authors argued convincingly—on the basis of spectral evidence, precedents from azepine chemistry, and the minimization of 1,5-hydrogen shifts—that the isomer produced (out of four possible isomers) was **77**.



**75** **76** **77**

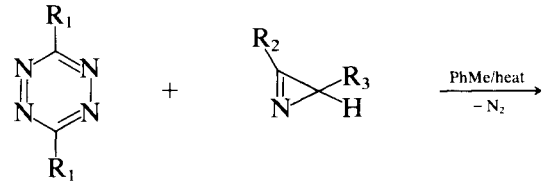
(9)

TABLE 3. SUBSTITUTED 2H-[1,2,4]TRIAZEPINES



| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|
| Ph | Ph | H | — | — | 11 |
| Ph | Ph | H | 208–210 | 58 | 14 |
| Ph | Ph | H | 210 | 68 | 13 |
| Ph | Ph | Me | 198–200 | 55 | 13 |
| Ph | 2-$C_5H_4N$ | H | 190–192 | 63 | 14 |
| Ph | 4-$C_5H_4N$ | H | 218–219 | 83 | 14 |
| 2-$C_5H_5N$ | Ph | Me | — | 95 | 11 |
| 2-$C_5H_5N$ | H | *t*-Bu | — | 82 | 11 |
| $MeO_2C$ | Ph | Ph | 134–136 (dec.) | 67 | 12 |

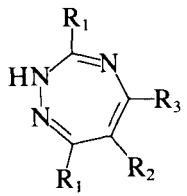
Nair (13) has assigned structures **72** and **79**, respectively, to the [1,2,4]triazepines obtained from the reactions of diphenyl-*s*-tetrazine (**62**) with 2-phenyl[1]azirine (**65**) and 2-phenyl-3-methyl[1]azirine (**66**) in toluene at reflux (Eq. 10). The possibility of the production of double bond isomers




**62**, $R_1$ = Ph
**64**, $R_1$ = 2-$C_5H_4N$
**78**, $R_1$ = 4-$C_5H_4N$

**65**, $R_2$ = Ph, $R_3$ = H
**66**, $R_2$ = Ph, $R_3$ = Me

(10)

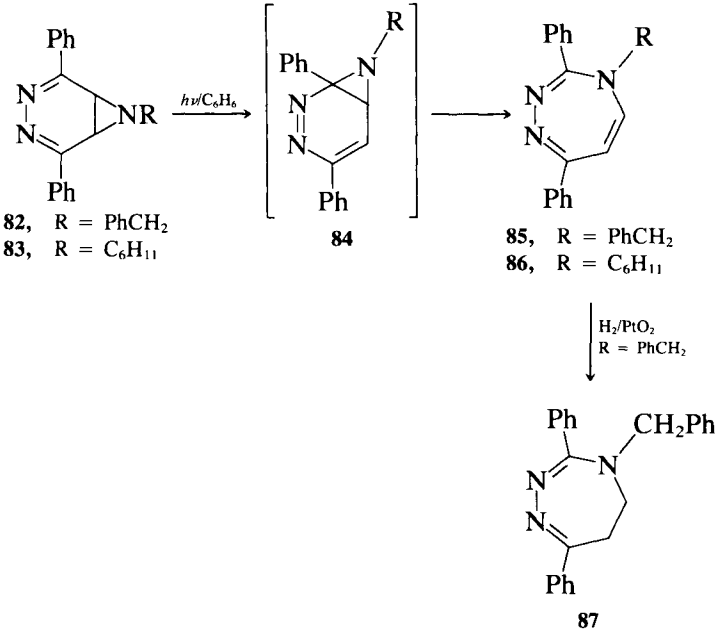


**72**, $R_1 = R_2$ = Ph, $R_3$ = H
**79**, $R_1 = R_2$ = Ph, $R_3$ = Me
**80**, $R_1$ = Ph, $R_2$ = 2-$C_5H_4N$, $R_3$ = H
**81**, $R_1$ = Ph, $R_2$ = 4-$C_5H_4N$, $R_3$ = H

of **72** and **79** was not discussed. The tosylate salt of **72** was also made for thermolysis studies, but these data were not published. It is interesting to note that Anderson and Hassner (11) reported 4-methyl-3,6,7-triphenyl-6H-[1,2,4]triazepine (**69**) as a product from the reaction of diphenyl-*s*-tetrazine (**62**) and 2-phenyl-3-methyl[1]azirine (**66**) without mentioning the 2H isomer **79**, whereas Nair (13) reported only the production of **79** from **62** and **66**.

Takahashi and co-workers (14) independently prepared **72** from **62** and **65** using the same reaction conditions as Nair. These authors also reported the dipyridyl[1,2,4]triazepines **80** and **81**, which were obtained from the reactions of tetrazines **64** and **78**, respectively, with 2-phenyl[1]azirine (**65**). The authors did consider other double bond isomers as structural possibilities for their triazepine products. Invoking arguments similar to those used by Johnson and Levin (12), they concluded that alternate structures were improbable.

Saito and co-workers (15) recently studied the photolysis of norcaradienes **82** (which had earlier been prepared by Heine and co-workers (16)) and **83** in benzene solution (Eq. 11). The authors proposed the intermediacy of **84** in these "photochemical walk" rearrangements which produced as the major products the [1,2,4]triazepines **85** and **86**, respectively. Structural assignments were based on spectral data and the catalytic reduction of **85**, which produced the dihydro derivative **87**. A subsequent report by Saito and co-workers (17) described the thermally induced ring-contraction reactions of **85** and **86**.




**82**, R = $PhCH_2$
**83**, R = $C_6H_{11}$

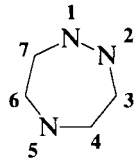
**84**

**85**, R = $PhCH_2$
**86**, R = $C_6H_{11}$

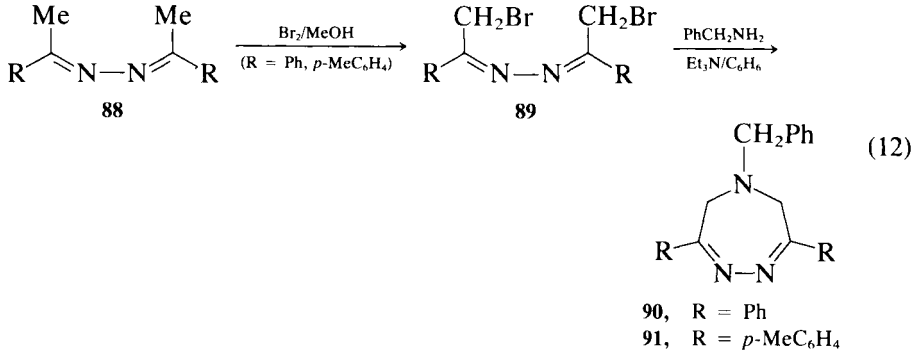
(11)

**87**

## B. [1,2,5]Triazepines



The synthesis of 5-benzyl-4,6-dihydro-3,7-diphenyl-5H-[1,2,5]triazepine (**90**) was reported by Tsuge and co-workers (18). Bromination of acetophenone ketazine (**88**, R = Ph) yielded the dibromo compound **89** (R = Ph), which was treated with benzylamine to produce **90** (Eq. 12). Triazepine **91** was similarly prepared.



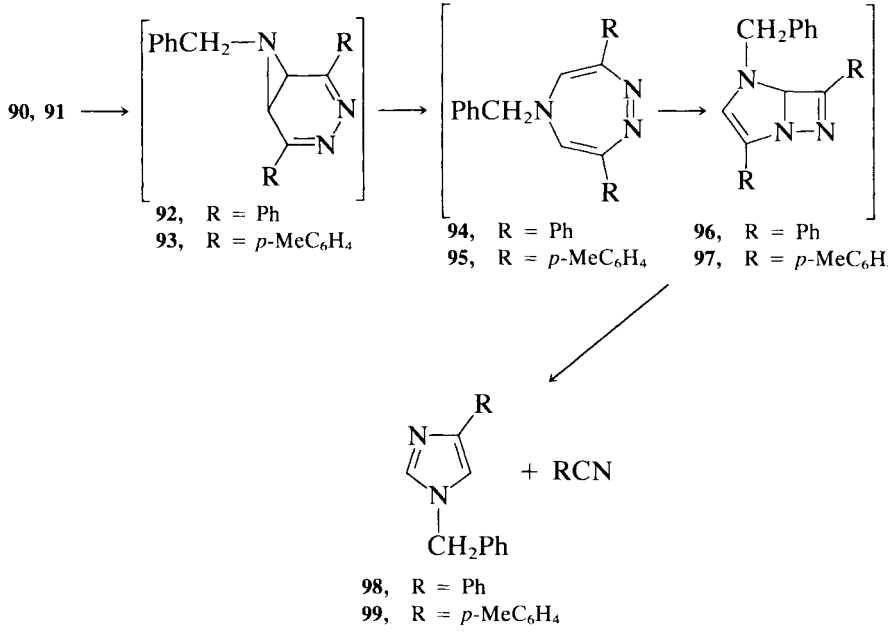
**88** **89**

**90**, R = Ph
**91**, R = *p*-$MeC_6H_4$

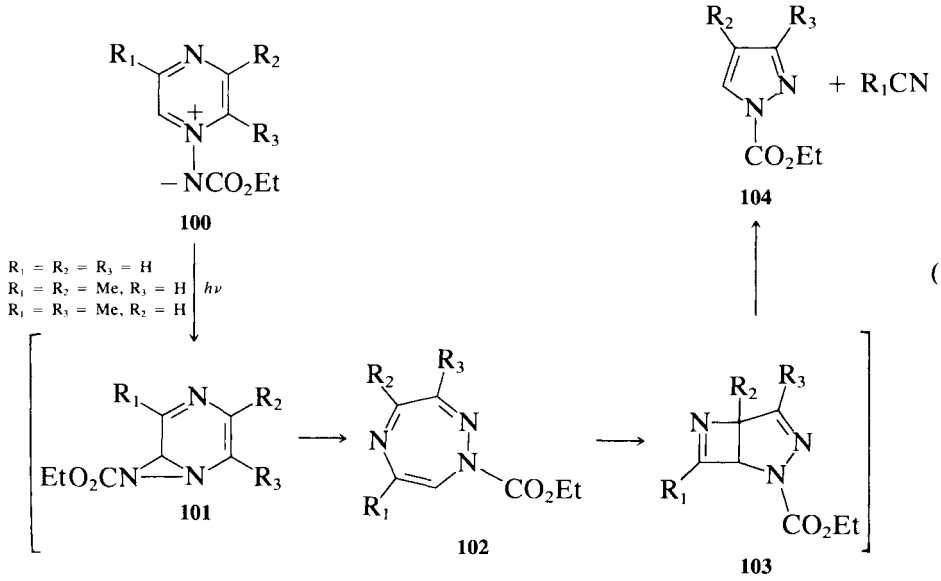
Tsuge and Kamata (19) later used triazepine **90** and its analog **91** in halogenation studies (Eq. 13). Bromination of **90** and **91** led to 1-benzyl-4-arylimidazoles **98** and **99**, respectively. The authors proposed the intermediacy of 7-benzyl-2,5-diaryl[3,4,7]triaza[2,4]norcaradienes **92** and **93** in this transformation. Also proposed as intermediates were [1,2,5]triazepines **94** and **95**, which led to imidazoline intermediates **96** and **97**, the proposed immediate precursors of **98** and **99**, respectively.

Indeed, the proposition of intermediates **92** and **93** seems reasonable in view of earlier work by Heine and Irving (20), who converted triazanorcaradiene **92** to imidazole **98** and benzonitrile in chloroform at 41°C. These authors followed the transformation of **92** to **98** by nmr spectrometry but were unable to detect any signals assignable to intermediates **94** or **96**, which they also proposed. Triazanorcaradiene **92** is a stable, isolable compound which was prepared from 2,3-dibenzoylaziridine and hydrazine in ethanol (16).

It is interesting to note that intermediates similar to those described in the transformation of **90** (or **92**) to **98** were proposed by Tsuchiya and Kurita (21) in the photolytic conversion (Eq. 14) of *N*-ethoxycarbonyliminopyra-




(13)

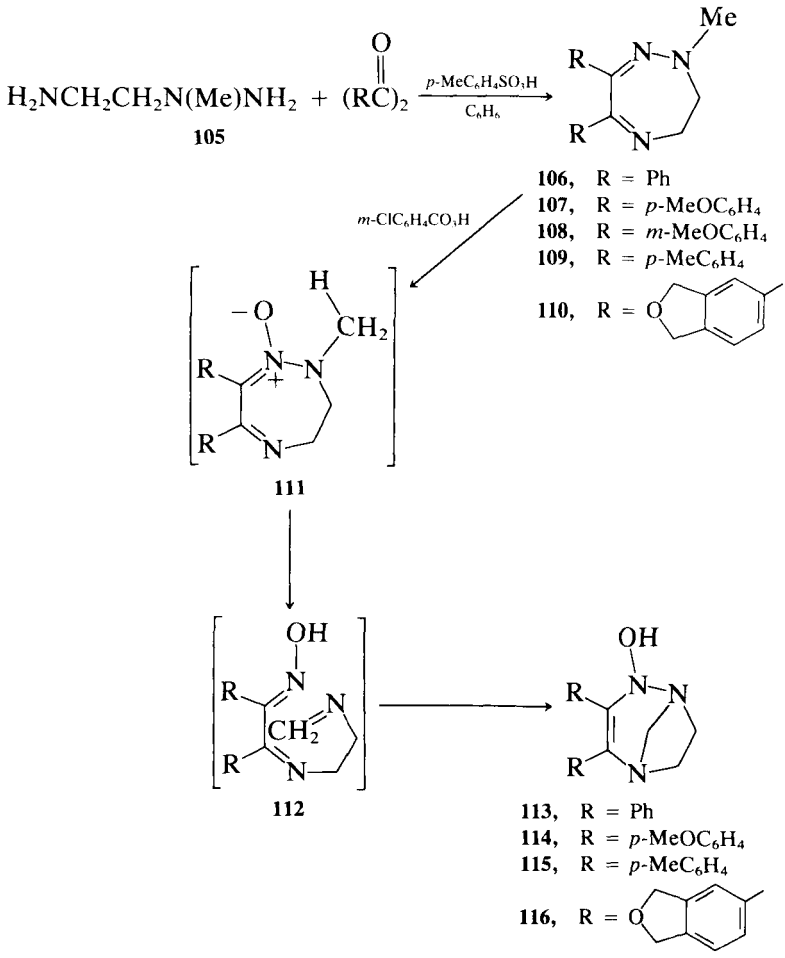



(14)

zinium ylides **100** to pyrazoles **104.** Attempts to isolate the proposed intermediary triazanorcaradienes **101,** [1,2,5]triazepines **102,** or pyrazolines **103** were not successful.

The preparation of 3,4-diaryl-6,7-dihydro-1-methyl-1H-[1,2,5]triazepines from 1-(2-aminoethyl)-1-methylhydrazine (**105**) and benzils has been reported by Trepanier and co-workers (22). A series of methano-bridged triazepines

was generated from compounds **106, 107, 109,** and **110** by treatment with *m*-chloroperbenzoic acid (Eq. 15). In these transformations, the authors envisioned initial *N*-oxide formation at the 2-position (intermediate **111**) followed by proton abstraction by oxygen and rupture of the ring to produce intermediate **112,** which could undergo an internal Diels–Alder addition to produce the bridged products **113–116.** Other transformations of the triazepines included sodium borohydride reduction of **106** to a dihydro derivative, and *O*-acetylation of **113** with acetic anhydride in pyridine at 40°C. Acety-



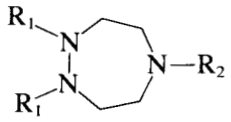

(15)

lation of **113** under more vigorous conditions, using acetic anhydride at 100°C without solvent, led to an interesting triazabicyclo[3.2.0]octadiene.

The synthesis of hexahydro-1H-[1,2,5]triazepine derivatives has been reported by Szotor and Kotelko (23). These authors condensed 1,2-dialkylhydrazines **117** and **118** with di(chloroethyl)amines **119** and **120** to produce the triazepines **121–123** in moderate yield (Eq. 16).

$R_1NHNHR_1 + (ClCH_2CH_2)NR_2$

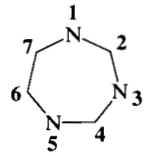
**117**, $R_1$ = Me **119**, $R_2$ = Me
**118**, $R_1$ = $Me_2CH$ **120**, $R_2$ = $PhCH_2$



(16)

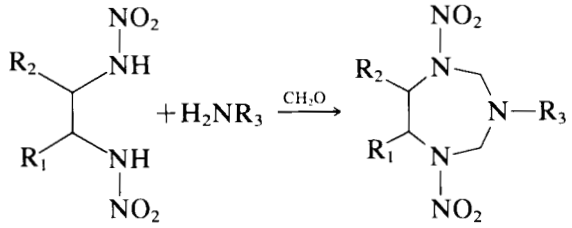
**121**, $R_1$ = $Me_2CH$, $R_2$ = Me
**122**, $R_1$ = $Me_2CH$, $R_2$ = $PhCH_2$
**123**, $R_1$ = Me, $R_2$ = $PhCH_2$

## C. *[1,3,5]Triazepines*



### a. 1,5-DINITRO- AND 1,3,5-TRINITROHEXAHYDRO-1H-[1,3,5]TRIAZEPINES

An important group of [1,3,5]triazepines consists of the biologically active 1,5-dinitrohexahydro derivatives of general structure **126.** A number of these compounds were prepared by Strycker (24–28) as plant growth regulators by condensation of *N,N'*-dinitroethylenediamines (**124**) with primary amines (**125**) and formaldehyde (Eq. 17). Other workers (29–34) have obtained additional derivatives in essentially the same fashion. Physical constants for these compounds are compiled in Table 4.

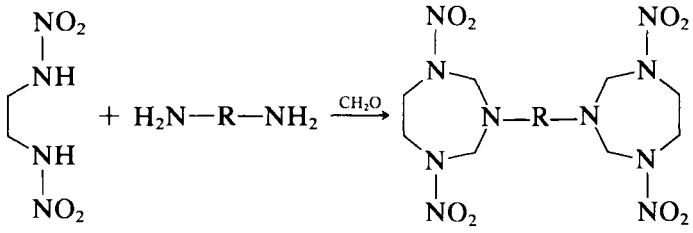


**124** **125** **126**

(17)

When diamines (**128**) were employed in the Mannich condensation with formaldehyde and *N,N'*-dinitroethylenediamine (**127**), the products were 3,3'-alkylenebis(1,5-dinitrohexahydro-1H-[1,3,5]triazepines) of general structure **129** (Eq. 18). Several workers (35–37) have reported derivatives of this type.

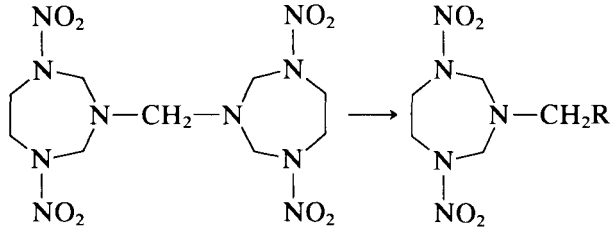
Bell and Dunstan (36,38,39) treated **129** (R = $CH_2$) with acetic anhydride and acetic acid to obtain the acetoxymethyl compound **130,** which on further



(18)

127 128 129

reaction with various nucleophiles (Eq. 19) yielded the products **131–136.** Compounds **137–139** were similarly prepared by Myers and Wright (40). The 3-acetoxymethyl derivative **130** has also been used as an intermediate in an alternative route to compounds of general structure **129.** Thus dinitramines **140–142** reacted with **130** to yield the respective bis compounds **143–145** (36) (Eq. 20).



**129,** R = $CH_2$

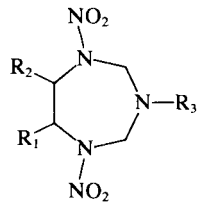
**130,** R = AcO
**131,** R = MeO
**132,** R = CN
**133,** R = $N_3$
**134,** R = Cl
**135,** R = $Me(NO_2)N$
**136,** R = *n*-$Bu(NO_2)N$
**137,** R = EtO
**138,** R = *n*-PrO
**139,** R = *i*-PrO

(19)

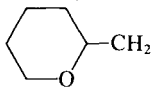
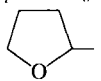
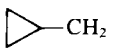
The nitration of **130** was also explored by Bell and Dunstan (38). Evidence for the initially formed, unstable hexahydro-1,5-dinitro-3-nitroxymethyl-1H-[1,3,5]triazepine (**146**) was obtained by performing additional reactions with the cold nitration solution (Eq. 21). Addition of aqueous sodium nitrite gave the nitrosamine **147,** treatment with water at ambient temperature afforded the trinitro derivative **148,** and addition of methanol to the cold solution gave methoxymethyl derivative **131.**

Trinitro derivative **148** has also been prepared by Myers and Wright (40). These authors treated **129** (R = $CH_2$) with nitric acid and obtained a higher

TABLE 4. 1,5-DINITROHEXAHYDRO-1H-[1,3,5]TRIAZEPINES

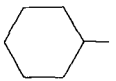
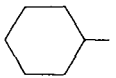


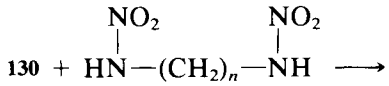
| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Refs. |
|---|---|---|---|---|
| H | H | *p*-$MeC_6H_4$ | 159.5–160.5 | 24 |
| H | H | $HO_2CCH_2CH_2$ | 126.5–127.5 | 24 |
| H | H | 1-Naphthyl | 185–186.5 (dec.) | 24 |
| H | H | 3-Furyl | 127–128 | 24 |
| H | H | *p*-$ClC_6H_4$ | 168–168.5 | 24 |
| H | H | $HOCH_2CH_2$ | 103–104 | 24 |
| H | H | Ph | 159.5–160.5 | 24 |
| H | H | Ph | 200–203 | 32 |
| H | H | $MeCHOHCH_2$ | 127–129 | 24 |
| H | H | $HO_2C(CH_2)_3$ | 146.5–147.5 | 24 |
| H | H | *p*-$MeOC_6H_4$ | 131–132 | 24 |
| H | H | *p*-$BrC_6H_4$ | 163–164.5 | 24 |
| H | H | $HO_2CCH_2$ | 181–182 | 24 |
| H | H | $EtO_2CCH_2$ | 135–136 | 24 |
| H | H | 2-Naphthyl | 177–178.5 | 24 |
| H | H | $HO_2C(CH_2)_{10}$ | 102–105 | 24 |
| H | H | $MeOCH_2CH_2$ | 103.5–105 | 24 |
| H | H | *m*-$ClC_6H_4$ | 148–149 | 24 |
| H | H | $MeOCH_2CHMe$ | 87–87.5 | 24 |
| Me | Me | 2,4,5-$Cl_3C_6H_2$ | — | 24 |
| H | H | *o*-$ClC_6H_4$ | 108.5–109.5 | 24 |
| H | H | 2,4-$Cl_2C_6H_3$ | 111–113.5 | 24 |

| | | | | |
|---|---|---|---|---|
| H | H | $MeO(CH_2)_3$ | 84–85 | 24 |
| H | H | *p*-$EtOC_6H_4$ | 108–109 | 24 |
| H | H | 2-$C_5H_4N$ | 157.5–158 | 24 |
| H | H | *p*-*i*-$PrC_6H_4$ | 125–129 | 24 |
| H | H | *i*-$PrO(CH_2)_3$ | 58–59 | 24 |
| H | H | *p*-$HOC_6H_4$ | 137–139 | 24 |
| H | H | $NaOSO_2(CH_2)_3$ | 92–95 | 24 |
| H | H | 2,4-Xylyl | 155–156.5 | 24 |
| H | H |  | 154–154.5 | 24 |
| H | H | *p*-$NCSC_6H_4$ | 126–127 | 24 |
| H | H |  | 179.5–180 | 24 |
| H | H | *p*-$MeSC_6H_4$ | 120 | 24 |
| H | H |  | 89–90 | 24 |
| H | H |  | 102–103 | 24 |
| H | H | H | — | 26 |
| H | H | Me | — | 26 |
| H | H | Me | 156 | 32 |
| H | H | *n*-Pr | — | 26 |
| H | H | *i*-Pr | — | 26 |
| H | H | *i*-Pr | 107–108 | 29 |
| H | H | *n*-Bu | — | 26 |
| H | H | *n*-Bu | 106–107 | 29 |
| H | H | *n*-Bu | 103–105 | 32 |
| H | H | *t*-Bu | — | 26 |
| H | H | $Me(CH_2)_4$ | — | 26 |
| H | H | $Me(CH_2)_5$ | — | 26 |

(*continued*)

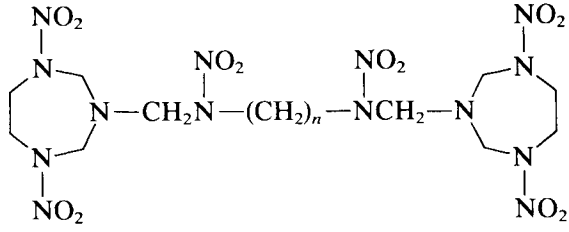
TABLE 4. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Refs. |
|---|---|---|---|---|
| H | H |  | — | 26 |
| H | H |  | 127 | 29 |
| H | H | $Me(CH_2)_{11}$ | — | 26 |
| H | H | $Me(CH_2)_{15}$ | — | 26 |
| H | H | $PhCH_2$ | 170 | 26 |
| H | H | $PhCH_2$ | 175 | 32 |
| H | H | $O_2N$ | — | 26 |
| H | H | $EtOCH_2$ | — | 27 |
| H | H | $EtOCH_2$ | 166.2–166.4 | 40 |
| H | H | $PhCH_2CH(Me)$ | — | 28 |
| H | H | $p$-$ClC_6H_4CHMeCH(Me)$ | — | 28 |
| H | H | Et | 140–142 | 29 |
| H | H | Et | 138–140 | 32 |
| H | H | $MeC(NO_2)_2CH_2CH_2$ | 146–147 | 30 |
| H | H | $(NO_2)_3C(CH_2)_3$ | — | 31 |
| H | H | $HOCH_2CH_2$ | 104–105 | 32 |
| H | H | $HOCH_2CH_2CH_2$ | 84–85 | 32 |
| H | H | $EtO_2CNH$ | 181 | 34 |
| H | H | $AcOCH_2$ | 182.5–184 | 36 |
| H | H | $MeOCH_2$ | 146.5–147 | 36 |
| H | H | $n$-$PrOCH_2$ | 136.8–138.2 | 40 |
| H | H | $i$-$PrOCH_2$ | 182.2–184.6 | 40 |
| H | H | $ClCH_2$ | 134–137 (dec.) | 36 |
| H | H | $NCCH_2$ | 190–193 (dec.) | 36 |
| H | H | $N_3CH_2$ | 119–122 (dec.) | 36 |
| H | H | $MeN(NO_2)CH_2$ | 163–164 | 36 |
| H | H | $n$-$BuN(NO_2)CH_2$ | 147–148.5 | 36 |

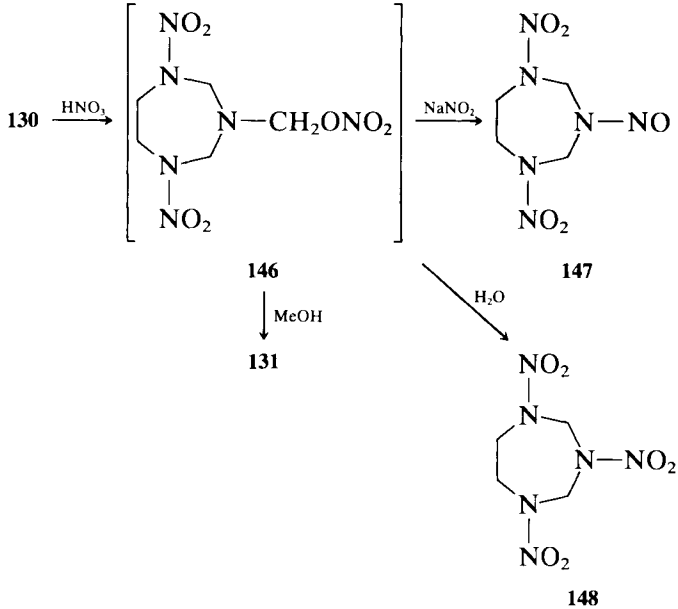


**140**, $n = 1$
**141**, $n = 2$
**142**, $n = 3$

(20)



**143**, $n = 1$
**144**, $n = 2$
**145**, $n = 3$



(21)

yield (38%) of **148** than that reported (21%) by Bell and Dunstan (38). Bell and Dunstan (41) in yet another report invoked **129** (R = $CH_2$) as an intermediate in the formation of **148** from the nitrolysis of hexamethylenetetra-

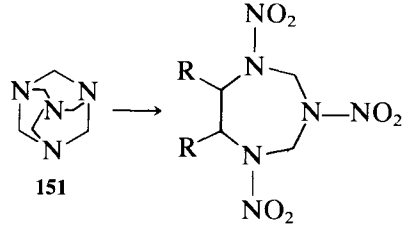
mine. Spectral data for **148** have been reported by Bell and Dunstan (42) and by Tamura and Sim (43). Interest in **148** and the related dinitrotriazepines stems from their structural similarity to hexahydro-1,3,5-trinitro-*s*-triazine, or cyclonite (44,45), which is a high explosive. Differential thermal analysis data for **148** have been recorded (46). Cyclonite has been shown to act as a nitrating agent in sulfuric acid, its effectiveness as a nitrating agent being comparable to that of **129** (R = $CH_2$) and **148** (47).

Acyclic nitramines have also been used (Eq. 22) in the preparation of hexahydro-1,3,5-trinitro-1H-[1,3,5]triazepine (**148**). Nitration of ethylenebis(morpholinomethylnitroamine) (**149**) (48) with nitric acid, acetic anhydride, and ammonium nitrate was found by Chapman (49) to give **148** and 4-nitromorpholine, and a similar preparation of **148** from **150** was reported earlier by Franchimont (50).

$$\mathrm{RCH_2N(NO_2)CH_2CH_2N(NO_2)CH_2R} \xrightarrow[\substack{\mathrm{Ac_2O,\ NH_4NO_3} \\ 55\text{–}60^\circ\mathrm{C}}]{\mathrm{HNO_3}} \mathbf{148} + \mathrm{RNO_2} \qquad (22)$$

**149**, R = 4-morpholino
**150**, R = 1-piperidino

6,7-Disubstituted derivatives of **148** have been prepared by Chute and coworkers (51). Treatment of hexamethylenetetramine (**151**) with nitrogen pentoxide and nitric acid (Eq. 23) led to dinitroxy derivative **152**, whereas treatment of **151** in acetic acid with acetic anhydride and nitric acid produced diacetoxy derivative **153**. Other 6,7-disubstituted derivatives of **148** were also reported (51). Compound **153** has been the subject of a crystallographic study (52). Physical constants for the 3,3′-alkylenebis(1,5-dinitrohexahydro-1H-[1,3,5]triazepines) and hexahydro-1H-1,3,5-trinitro[1,3,5]triazepines are listed in Tables 5 and 6, respectively.



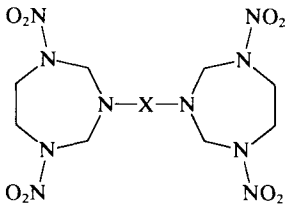
**151** (23)

**152**, R = $ONO_2$
**153**, R = OAc

## b. HEXAHYDRO-1,5-BIS(ALKYL- AND ARYLSULFONYL)-1H-[1,3,5]TRIAZEPINES

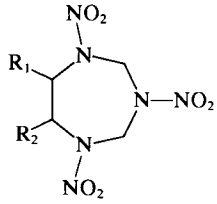
Hexahydro-1H-[1,3,5]triazepines with electron-withdrawing substituents on nitrogen other than nitro groups have been disclosed by Strycker (28,53).

TABLE 5. 3,3′-ALKYLENEBIS(1,5-DINITROHEXAHYDRO-1H-[1,3,5]TRIAZEPINES)



| X | mp (°C) | Refs. |
|---|---|---|
| $CH_2$ | — | 26 |
| $CH_2$ | 128.5–130 | 36 |
| $CH_2$ | 132.6–132.8 | 51 |
| $(CH_2)_2$ | — | 26 |
| $(CH_2)_2$ | 205–207 (dec.) | 29 |
| $(CH_2)_2$ | 187–189 | 37 |
| $(CH_2)_4$ | 188–190 | 35 |
| $(CH_2)_6$ | 170–171 | 35 |
| $(CH_2)_3O(CH_2)_3$ | 130–132 | 35 |
| $(CH_2)_3O(CH_2)_2O(CH_2)_3$ | 78–80 | 35 |
| $(CH_2)_2C(NO_2)_2CH_2CH_2$ | 200 (dec.) | 35 |
| $(CH_2)_2N(NO_2)CH_2CH_2N(NO_2)CH_2CH_2$ | 180 (dec.) | 35 |
| $(CH_2)_3$ | 150–155 | 37 |
| $CH(Me)CH_2$ | 158–160 | 37 |
| $CH_2N(NO_2)CH_2N(NO_2)CH_2$ | 183–185 (dec.) | 36 |
| $CH_2N(NO_2)CH_2CH_2N(NO_2)CH_2$ | — | 36 |
| $CH_2N(NO_2)CH_2CH_2CH_2N(NO_2)CH_2$ | 168–174 (dec.) | 36 |

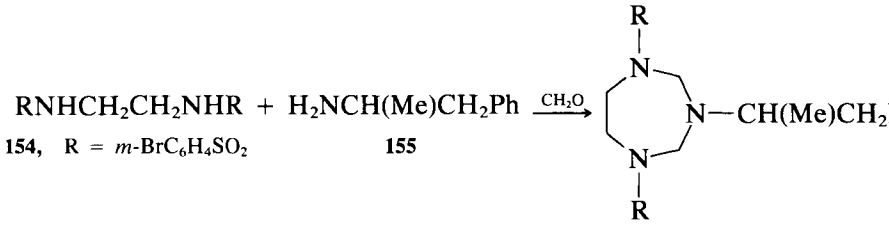
TABLE 6. 6,7-DISUBSTITUTED HEXAHYDRO-1H-1,3,5-TRINITRO[1,3,5]TRIAZEPINES[a]



| $R_1$ | $R_2$ | mp (°C) |
|---|---|---|
| AcO | AcO | 155–156 |
| MeO | MeO | 104–105 |
| EtO | EtO | 79–80.5 |
| AcO | EtO | 135–138 |
| $O_2NO$ | $O_2NO$ | 153–154 |

[a]Ref. 51.

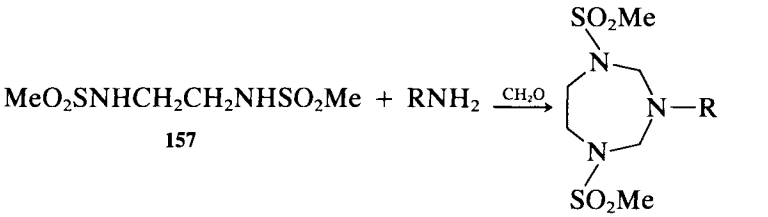
Reaction of the disubstituted ethylenediamine **154** with amphetamine (**155**) in aqueous formaldehyde (Eq. 24) produced triazepine **156** (28). In similar fashion, ethylenebis(methanesulfonamide) (**157**) was treated with aqueous formaldehyde and various amines (Eq. 25) to yield triazepines **158–163** (53). Table 7 lists physical constants for these compounds.



$RNHCH_2CH_2NHR + H_2NCH(Me)CH_2Ph \xrightarrow{CH_2O}$ (24)

**154**, R = *m*-$BrC_6H_4SO_2$ **155**

**156**, R = *m*-$BrC_6H_4SO_2$

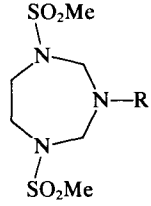


$MeO_2SNHCH_2CH_2NHSO_2Me + RNH_2 \xrightarrow{CH_2O}$ (25)

**157**

**158**, R = Me
**159**, R = *i*-Pr
**160**, R = Hexyl
**161**, R = $HOCH(Me)CH_2$
**162**, R = $MeOCH_2CH_2$
**163**, R = $NaOSO_2(CH_2)_3$

TABLE 7. 3-SUBSTITUTED HEXAHYDRO-1,5-BIS(METHYLSULFONYL)-1H-[1,3,5]TRIAZEPINES[a]

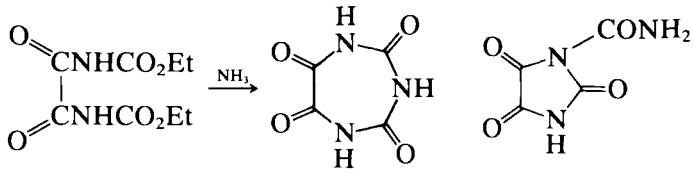


| R | mp (°C) |
|---|---|
| Me | 182–183 |
| *i*-Pr | 159–161 |
| $Me(CH_2)_5$ | 150–151 |
| $HOCH(Me)CH_2$ | 150–152 |
| $MeOCH_2CH_2$ | 165–168 |
| $NaOSO_2(CH_2)_3$ | 255–256 (dec.) |

[a]Ref. 47.

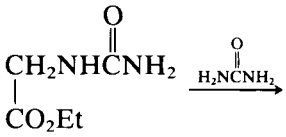
## c. HEXAHYDRO-1H-[1,3,5]TRIAZEPINONES AND -THIONES

The early chemical literature contains two reports citing the formation of oxygenated [1,3,5]triazepine systems. Guha and Ramaswami (54) treated oxalyldiurethane (**164**) with ammonia (Eq. 26) and assigned triazepinetetrone

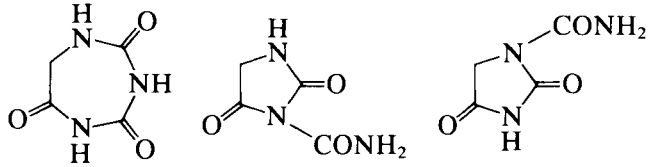


**164** **165** **166** (26)

structure **165** to the reaction product on the basis of a nitrogen combustion analysis. In the same article, the authors claimed that the product of reaction of the urea derivative **167** with urea was triazepinetrione **168** (Eq. 27). The



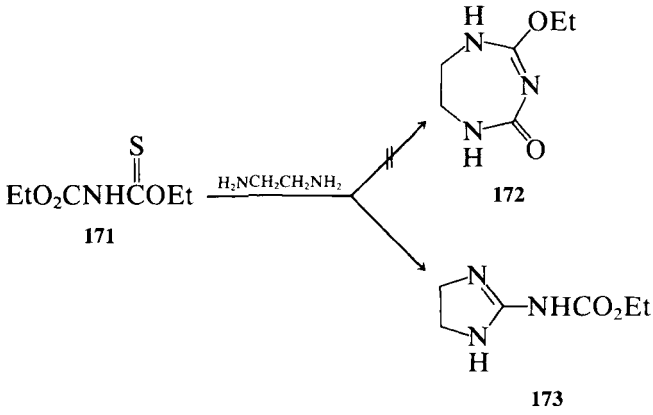
**167**



**168** **169** **170** (27)

evidence for these structural assignments is meager at best. Alternative structures—**166** for the product of **164** with ammonia and either **169** or **170** (or a mixture of the two) for the product of **167** with urea—are much more likely, considering the ease with which five- or six-membered rings form in comparison with seven-membered rings. A literature search for compounds **166, 169,** and **170** yielded physical constants only for **170** (55) (mp 255°C (dec.)). The melting point reported by Guha and Ramaswami (54) for **168** was 220–221°C.

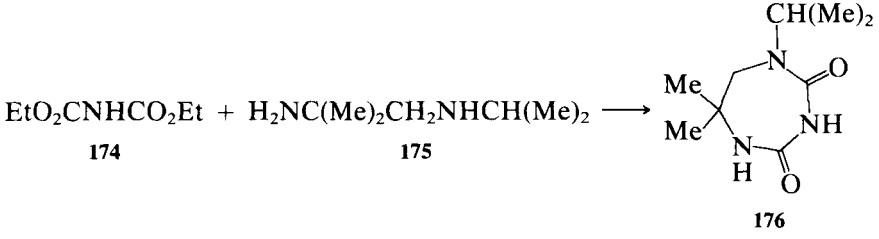
In a subsequent article Guha and co-workers (56) reported a triazepinone whose structural assignment likewise seems questionable. These authors treated thiocarbamate **171** with ethylenediamine (Eq. 28) and obtained a




(28)

product which they formulated as ethoxytriazepinone **172,** again solely on the basis of elemental analysis for nitrogen. This work was recently reinvestigated by Peet and Sunder (57), who showed that the reaction product is in fact (4,5-dihydro-1-H-imidazol-2-yl)carbamic acid ethyl ester (**173**).

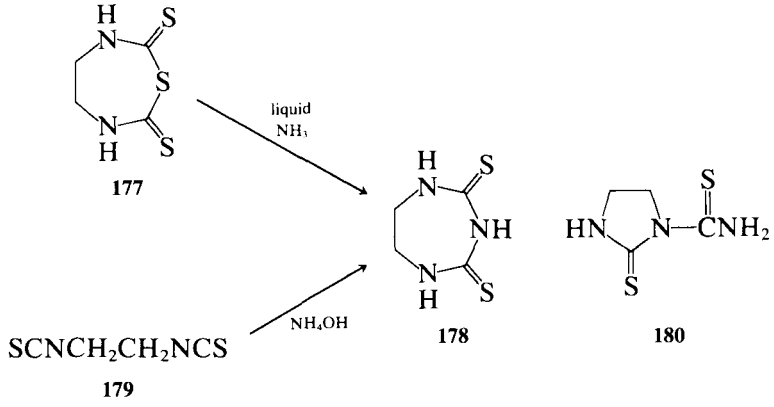
More recently other workers have reported oxygenated [1,3,5]triazepine systems. For example, Pachter and Riebsomer (58) treated *N*-(2-aminoisobutyl)isopropylamine (**175**) with diethyl imidodicarboxylate (**174**) and obtained triazepinedione **176** (Eq. 29).




(29)

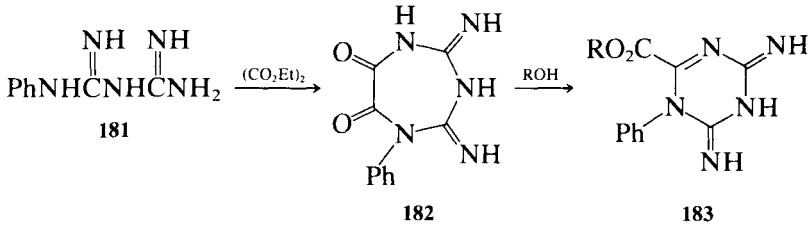
Thorn and Ludwig (59) allowed a compound they believed to be hexahydro-1H-[1,3,6]thiadiazepine-2,7-dithione (**177**) to react with liquid ammonia (Eq. 30) and obtained a crystalline, monomeric material to which they assigned structure **178.** The same material was prepared from ethylenebisisothiocyanate (**179**) and ammonium hydroxide. Other evidence cited in support of structure **178** included elemental analysis and the observation that the fingerprint region in the infrared spectrum of **178** was very similar to that of ethyldithiobiuret. Alternative structure **180,** which cannot be ruled out on the basis of the available evidence, was not considered (59).

The product from the reaction of 1-phenylbiguanide (**181**) and diethyl




(30)

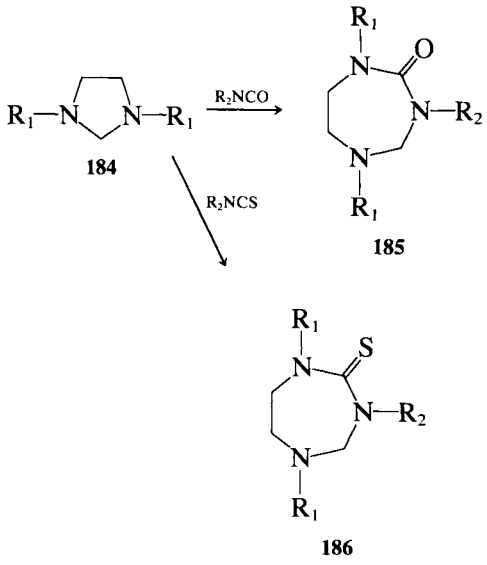
oxalate (Eq. 31) was postulated by Checchi and co-workers (60) to be triazepinedione **182** on the basis of its reaction with alcohols to yield triazines of general structure **183.** This is weak evidence for the structural assignment, however, since alternative structures for **182** that could also yield triazines on alcoholysis can be envisioned.



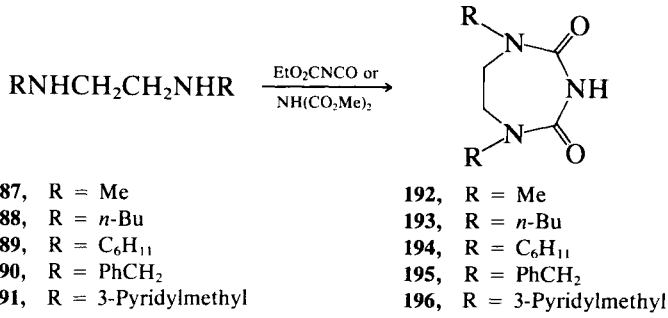

(31)

A large number of 3-substituted 1,5-dialkylhexahydro-1H-[1,3,5]triazepin-2-ones of general structure **185** were prepared by Boehme and Pasche (61) from isocyanates and 1,3-dialkylimidazolidines (**184**), as shown in Eq. 32. 1,3-Diphenylimidazolidine and 1-phenyl-3-alkylimidazolidines failed to react. A variety of isocyanates were employed successfully, including alkyl, aryl, and aroyl isocyanates. Aryl and aroyl isothiocyanates were also treated with imidazolidines **184** to produce [1,3,5]triazepin-2-thiones of general structure **186.** Physical constants for these products are given in Tables 8 and 9.

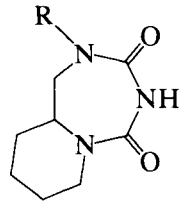
A series of hexahydro-1H-[1,3,5]triazepine-2,4-diones was obtained by Hagemann (62). These compounds (Table 10), reportedly useful in the manufacture of plant-protective agents, were prepared from ethylenediamines and carbethoxy isocyanate or dimethyl iminodicarboxylate. Thus the ethylenediamines **187–191** yielded triazepinediones **192–196** (Eq. 33). In the same fashion, bridged triazepinediones **197** and **198** were synthesized from the appropriate 2-aminomethylpiperidines.




(32)

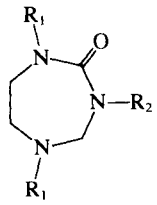



(33)




Kubik and Reimschuesel (63) recently described a group of three hexahydro-1H-[1,3,5]triazepine-2,4-diones (**202–204**). These compounds were prepared by heating ethylenediamines **199–201** with urea (Eq. 34).

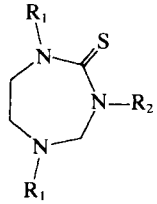
TABLE 8. 3-SUBSTITUTED 1,5-DIALKYLHEXAHYDRO-1H-[1,3,5]TRIAZEPIN-2-ONES[a]



| $R_1$ | $R_2$ | mp (°C) or bp (°C/torr) | Yield (%) |
|---|---|---|---|
| *n*-Bu | *n*-Bu | 114–115/0.01 | 42 |
| $C_6H_{11}$ | *p*-$MeC_6H_4SO_2$ | 138–141 | 48 |
| Ph | *n*-Bu | 62–64/0.01 | 58 |
| Ph | $C_6H_{11}$ | 110–111 | 85 |
| Ph | $PhCH_2$ | 113 | 86 |
| 3,4-$Cl_2C_6H_3$ | *n*-Bu | 150/0.01 | 50 |
| 3,4-$Cl_2C_6H_3$ | $C_6H_{11}$ | 134–136 | 82 |
| 3,4-$Cl_2C_6H_3$ | $PhCH_2$ | 84–86 | 51 |
| PhCO | $C_6H_{11}$ | 155–157 | 75 |
| PhCO | $PhCH_2$ | 90 | 90 |
| *p*-$MeC_6H_4CO$ | $C_6H_{11}$ | 167 | 63 |
| *p*-$MeC_6H_4CO$ | $PhCH_2$ | 143 | 92 |
| *p*-$ClC_6H_4CO$ | $C_6H_{11}$ | 206 (dec.) | 66 |
| *p*-$ClC_6H_4CO$ | $PhCH_2$ | 128 | 59 |

[a]Ref. 54.

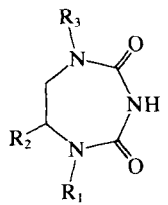
TABLE 9. 3-SUBSTITUTED 1,5-DIALKYLHEXAHYDRO-1H-[1,3,5]TRIAZEPINE-2-THIONES[a]

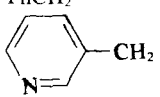
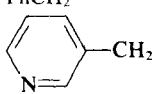


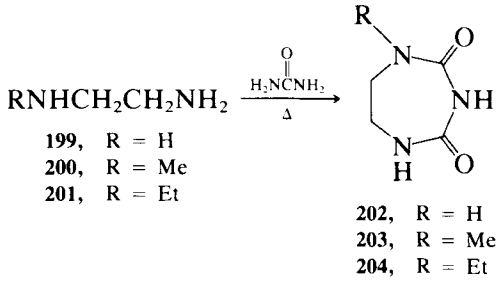
| $R_1$ | $R_2$ | mp (°C) | Yield (%) |
|---|---|---|---|
| *n*-Bu | Ph | 77–78 | 92 |
| $C_6H_{11}$ | Ph | 230–232 (dec.) | 56 |
| $PhCH_2$ | Ph | 151 | 55 |
| $PhCH_2$ | PhCO | 155–156 | 96 |
| $PhCH_2$ | *p*-$MeC_6H_4CO$ | 148–150 | 65 |

[a]Ref. 54.

TABLE 10. HEXAHYDRO-1H-[1,3,5]TRIAZEPINE-2,4-DIONES

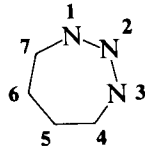


| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|
| H | H | H | — | 23 | 63 |
| H | H | Me | — | — | 63 |
| H | H | Et | — | — | 63 |
| Me | H | Me | 202–204 | 72–83 | 62 |
| *n*-Bu | H | *n*-Bu | 140–142 | — | 62 |
| $C_6H_{11}$ | H | $C_6H_{11}$ | 218–220 | — | 62 |
| $PhCH_2$ | H | $PhCH_2$ | 206–208 | — | 62 |
|  | H |  | 152–154 | — | 62 |
| —$(CH_2)_4$— | | H | 218–220 | — | 62 |
| —$(CH_2)_4$— | | $PhCH_2$ | 194 | — | 62 |

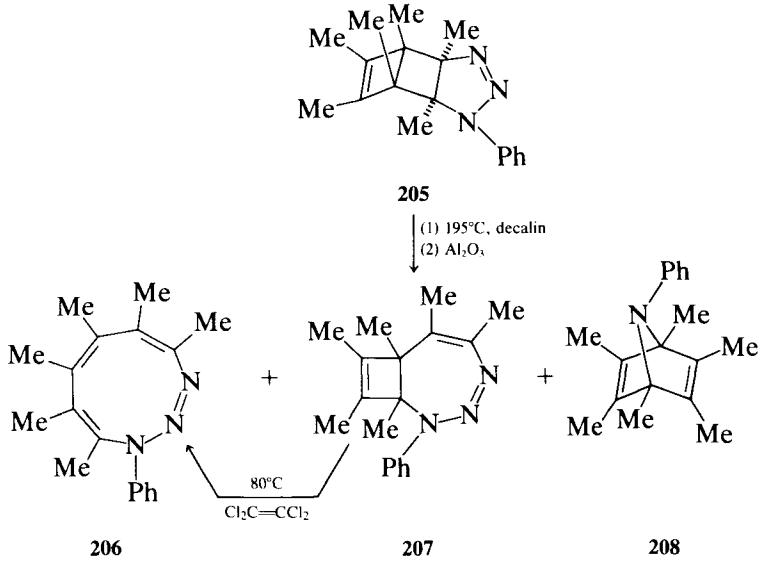



(34)

## D. [1,2,3]*Triazepines*




Only one member of the [1,2,3]triazepine system has been reported (Eq. 35). Paquette and co-workers (64) described the preparation of 1,2,3,4,5,6-hexamethyl-7-phenyl-7,8,9-triazatricyclo[4.3.0.$0^{2,5}$]nona-3,8-diene (**205**). In an accompanying article, Paquette and Haluska (65) reported the thermolysis of **205** as part of a study designed to determine the importance of ring strain

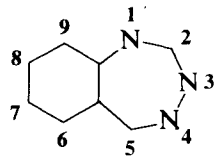



(35)

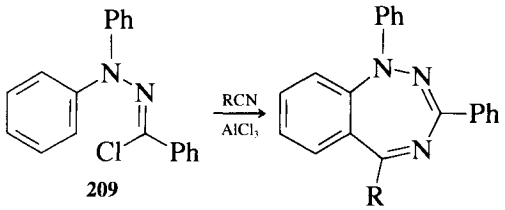
on various modes of thermally induced triazoline decomposition. This work inadvertently led to the preparation of [1,2,3]triazepine **207.** Triazepine **207** was shown to be a secondary product of the thermolysis, resulting only after the reaction mixture was chromatographed on alumina. The isomeric products **208** and **206** were primary thermolysis products. Proof of structure for **207** was based on its spectral data and clean conversion to **206** in tetrachloroethylene at 80°C.

## 3. Benzotriazepine Ring Systems

### A. *[1,2,4]Benzotriazepines*

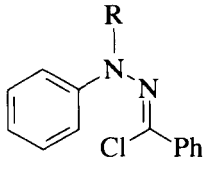



A series of 1H-[1,2,4]benzotriazepines that was recently described by Conde and co-workers (66) is the only literature report dealing with [1,2,4]benzotriazepine systems (see Table 11). These authors prepared *N,N*-diphenylbenzhydrazidoyl chloride (**209**) and examined its reaction with various nitriles in the presence of aluminum chloride (Eq. 36). The 5-substituted 1,3-diphenyl-2H-[1,2,4]benzotriazepines **210–221** were produced in uniformly good yields (50–85%) by this route, which bears analogy to a reported (67) quinazoline synthesis. Interestingly, efforts to prepare 1H-[1,2,4]benzotriazepines from *N*-methyl-*N*-phenylbenzhydrazide (**222**), nitriles, and aluminum chloride led to [1,2,4]triazoles via *N*-demethylation. An attempt to produce benzhydrazidoyl chloride **223** from *N*-phenyl-*N*-carbethoxybenzhydrazide led instead to 2,4-diphenyl[1,3,4]oxadiazol-5-one (**224**).

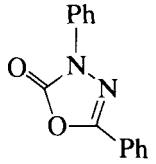



**209** (36)

| | | | |
|---|---|---|---|
| **210,** | R = EtS | **216,** | R = *p*-$MeOC_6H_4$ |
| **211,** | R = PhS | **217,** | R = *o*-$ClC_6H_4$ |
| **212,** | R = *n*-Pr | **218,** | R = *m*-$ClC_6H_4$ |
| **213,** | R = *n*-Bu | **219,** | R = *p*-$ClC_6H_4$ |
| **214,** | R = Ph | **220,** | R = *m*-$O_2NC_6H_4$ |
| **215,** | R = *p*-$MeC_6H_4$ | **221,** | R = $EtO_2CCH_2$ |

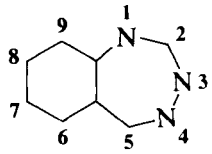


**222**, R = Me
**223**, R = $EtO_2C$



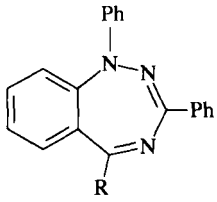
**224**

## B. *[1,2,5]Benzotriazepines*



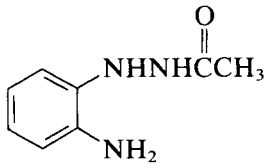
A potential synthetic route to [1,2,5]benzotriazepines from 2-(*o*-aminophenyl)-1-acetylhydrazine (**225**) was devised by Sparatore (68). However, an attempt to generate *o*-aminophenylhydrazine from **225** in the presence of 1,2-dicarbonyl compounds failed to yield [1,2,5]benzotriazepines as condensation products, giving quinoxalines instead.

TABLE 11. 5-SUBSTITUTED 1,3-DIPHENYL-1H-[1,2,4]BENZOTRIAZEPINES[a]



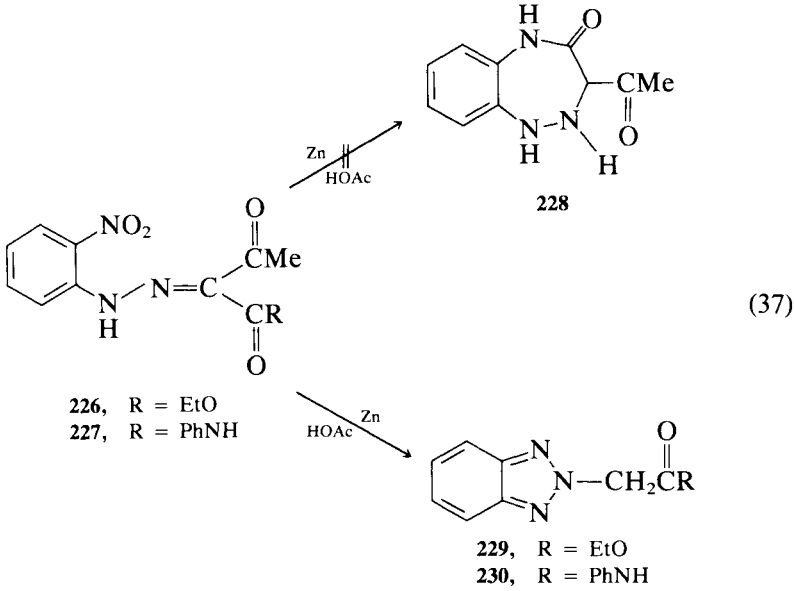
| R | mp (°C) | Yield (%) |
|---|---|---|
| EtS | 116–117 | 80 |
| PhS | 149 | 55 |
| *n*-Pr | 100 | 80 |
| *n*-Bu | 125 | 50 |
| Ph | 214 | 70 |
| *p*-$MeC_6H_4$ | 219–220 | 85 |
| *p*-$MeOC_6H_4$ | 155–156 | 57 |
| *o*-$ClC_6H_4$ | 195 | 62 |
| *m*-$ClC_6H_4$ | 140 | 55 |
| *p*-$ClC_6H_4$ | 224–225 | 60 |
| *m*-$O_2NC_6H_4$ | 214 | 60 |
| $EtO_2CCH_2$ | 139 | 75 |

[a]Ref. 66.



225

A later report by Sparatore and Pagani (69) described the reduction of *o*-nitrophenylhydrazones **226** and **227** (70) with zinc and acetic acid (Eq. 37). Although it was recognized that the [1,2,5]benzotriazepine **228** might be formed, the products actually obtained from these reductions were benzotriazoles **229** and **230.** Convincing evidence offered for these latter structural assignments included alternative syntheses. A review article on attempted syntheses of [1,2,5]benzotriazepines has been written by Sparatore (71).



**226,** R = EtO
**227,** R = PhNH

**228**

**229,** R = EtO
**230,** R = PhNH

(37)

The chemistry of 1,5-dihydro-4H-[1,2,5]benzotriazepin-4-ones (Fig. 1) has been studied by Rossi and co-workers (72–79). *In situ* preparation of the acid chloride of monoethyl malonate (**232**) in the presence of *N*-monosubstituted *o*-nitroanilines (**231**) yielded the acylated *o*-nitroanilines **233,** which on catalytic or chemical (zinc and hydrochloric acid) reduction gave the substituted *o*-phenylenediamines **234.** Treatment with nitrous acid resulted in the formation of diazonium intermediates, which underwent direct intramolecular cyclization to the 3-carbethoxy-1,5-dihydro-4H-[1,2,5]benzotriazepin-4-ones **235.** Hydrolysis produced the corresponding 3-carboxy derivatives **236,** which could be thermally decarboxylated to benzotriazepines of general structure **237.** Various substituents were then reintroduced at the

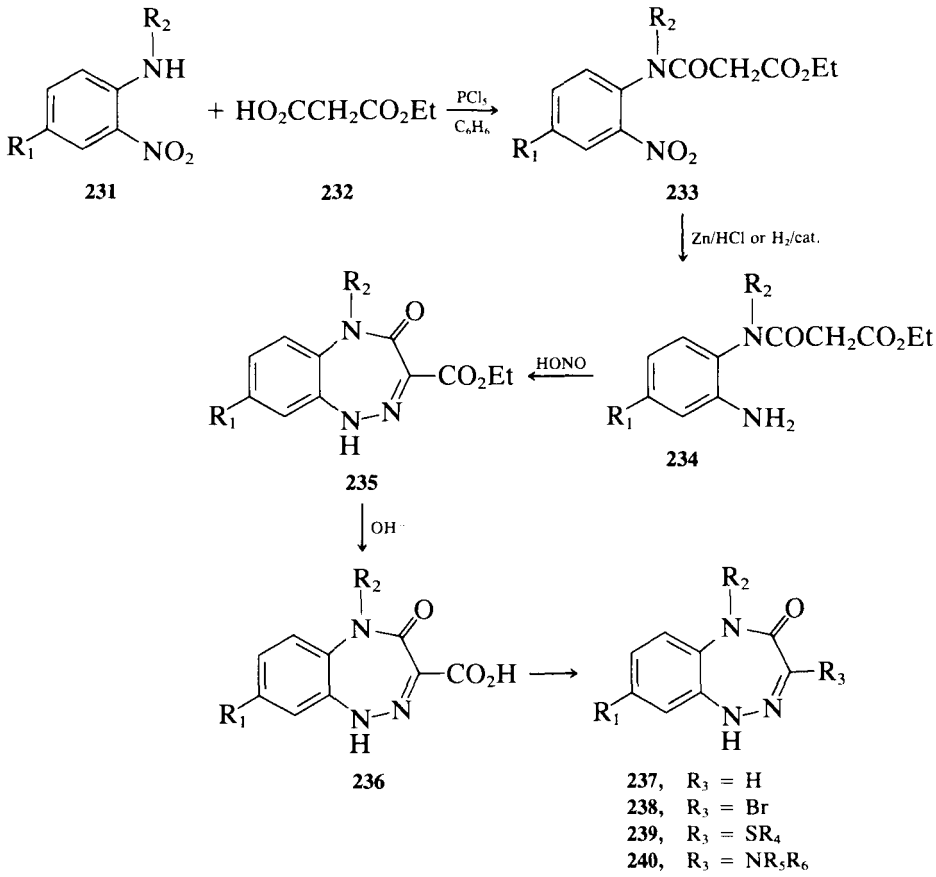


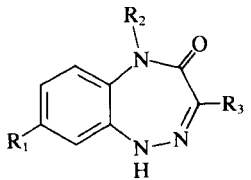

**Figure 1**

3-position. Bromination of **237** produced 3-bromo derivatives (**238**), which on treatment with mercaptans and amines yielded the sulfides **239** and the 3-amino derivatives **240,** respectively. The 3-cyano derivatives **241** were prepared in the same manner as the 3-carbethoxy derivatives **235,** except that cyanoacetic acid was used in place of **232.** Treatment of **241** with hydroxylamine hydrochloride (Eq. 38) afforded compounds of general structure **242.**

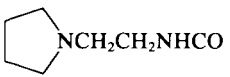
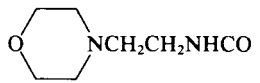
Benzotriazepines of general structures **235–241** were reported by Rossi to have central nervous system depressant activity. Compounds of general structure **242** were patented (78) as antidepressant and thymoanaleptic agents. In addition, 3-carboxamido derivatives of general structure **244,** which were prepared by the reaction of the corresponding esters (**235**) with amines **243** (Eq. 39) were described by Rossi (80) as vasodilator agents.

A recent report by Bianchi and co-workers (81) dealt with the mechanism of the reactions of benzotriazepines **245–247** with aqueous base. All of these compounds suffered cleavage of the seven-membered ring, with compound

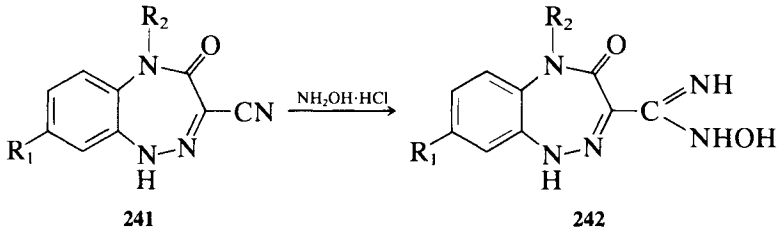
TABLE 12. 1,5-DIHYDRO-4H-[1,2,5]BENZOTRIAZEPIN-4-ONES



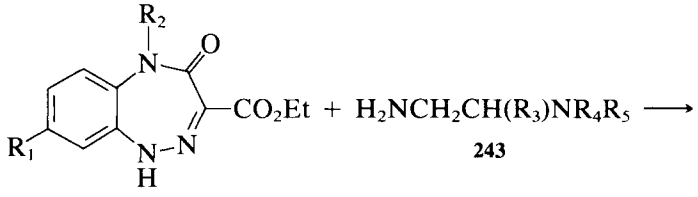
| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Refs. |
|---|---|---|---|---|
| H | Me | $EtO_2CNH$ | 204–205 | 77 |
| H | Me | $H_2N$ | — | 77 |
| Cl | Me | $H_2N$ | — | 77 |
| H | Me | H | 119–121 | 72,74 |
| H | $C_6H_{11}$ | H | 135–137 | 72,74 |
| Cl | Me | H | 128–130 | 72,74 |
| H | Ph | H | 158–160 | 72,74 |
| H | $PhCH_2$ | H | 148–150 | 72,74 |
| H | Me | $PhCH_2S$ | 124–125 | 76 |
| H | Me | $EtO_2CCH_2S$ | 135–138 | 76 |
| H | Me | $Me_2NCH_2CH_2S$ | — | 76 |
| H | Me | $HO_2CCH_2S$ | 173–175 | 76 |
| H | Me | Br | 166–168 | 75 |
| Cl | Me | Br | — | 75 |
| H | Me | $EtO_2C$ | 182–183 | 72,73 |
| H | Me | $MeO_2C$ | 195–196 | 72 |
| Cl | Me | $EtO_2C$ | 204–206 | 72 |
| H | $C_6H_{11}$ | H | 181–183 | 72 |
| H | Ph | H | 185–187 | 72 |
| H | $PhCH_2$ | H | 160–161 | 72 |
| H | Me | $HO_2C$ | 158–159 (dec.) | 72 |
| Cl | Me | H | 157–159 (dec.) | 72 |

| | | | | |
|---|---|---|---|---|
| H | $C_6H_{11}$ | H | 160–161 (dec.) | 72 |
| H | $PhCH_2$ | H | 140–142 | 72 |
| H | Ph | H | 160–161 | 72 |
| H | *p*-$ClC_6H_4CH_2$ | HONHC=NH | — | 78 |
| H | *p*-$ClC_6H_4CH_2$ | NC | — | 78,79 |
| H | $C_6H_{11}CH_2$ | HONHC=NH | — | 78 |
| H | $PhCH_2$ | $HO_2CCH_2CH_2CO_2NHC{=}NH$ | — | 78 |
| H | Me | $Me_2NCH_2CH_2NHCO$ | — | 80 |
| Cl | Me | $Et_2NCH_2CH_2NHCO$ | — | 80 |
| Cl | Me | $Me_2NCH(Me)CH_2NHCO$ | — | 80 |
| H | Me |  | — | 80 |
| H | Me |  | — | 80 |
| H | Me | NC | 165–166 | 81 |
| H | Me | HONHC=NH | 186–188 (dec.) | 81 |
| H | Me | $H_2NNHC{=}O$ | 186–188 (dec.) | 81 |

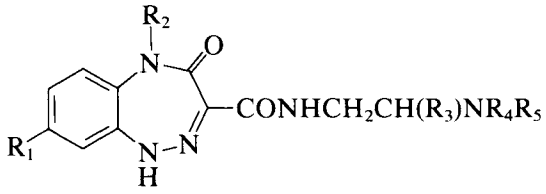
**245** yielding a ring-contraction product as well. Known members of the 1,5-dihydro-4H-[1,2,5]benzotriazepin-4-one family are listed in Table 12.



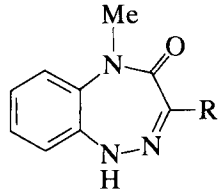

**241** **242** (38)




**235** **243**

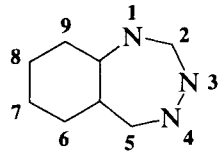



**244** (39)




**245**, R = H
**246**, R = HONHC=NH
**247**, R = $H_2NNHC{=}O$

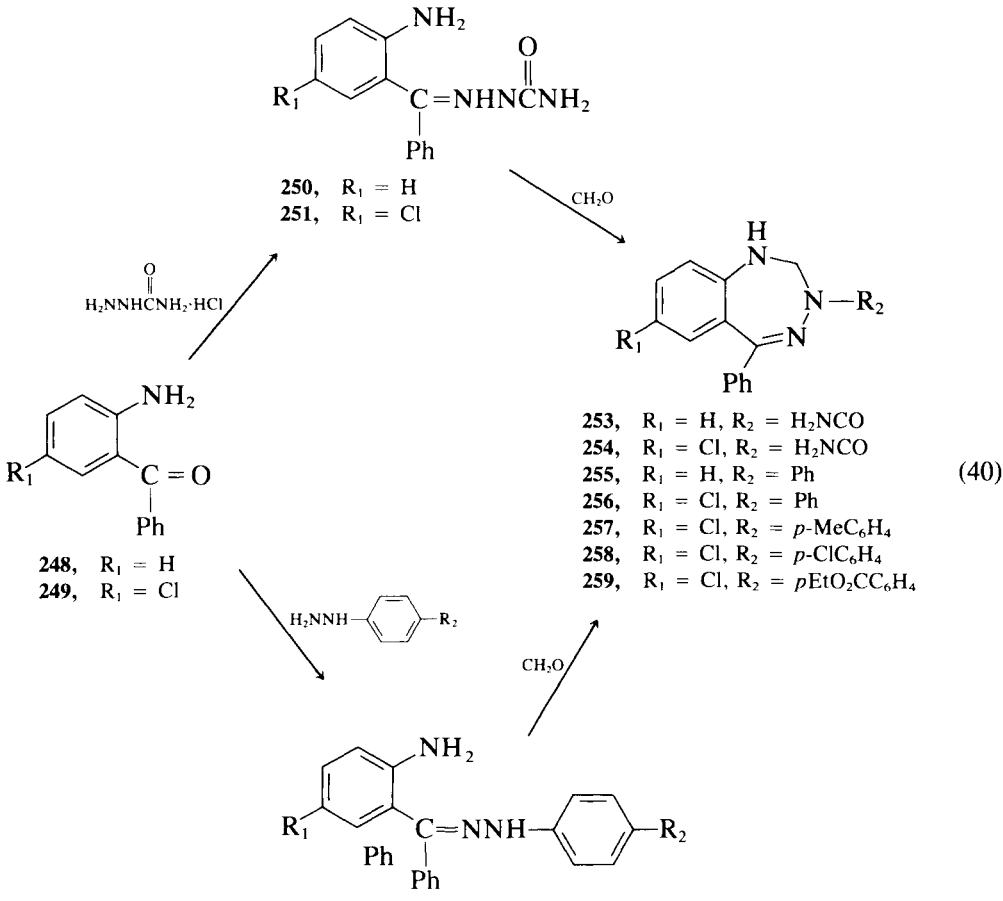
## C. *[1,3,4]Benzotriazepines*



## a. NONOXYGENATED AND NONCONDENSED [1,3,4]BENZOTRIAZEPINES

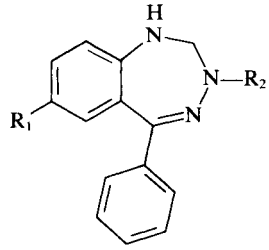
Syntheses of 2,3-dihydro-5-phenyl-1H-[1,3,4]benzotriazepines have been reported by Ishiwaka and co-workers (82). The common starting materials for these syntheses (Eq. 40) were 2-aminobenzophenone (**248**) and 2-amino-5-chlorobenzophenone (**249**). Treatment of **248** and **249** with semicarbazide hydrochloride gave the respective semicarbazones **250** and **251,** whereas treatment of **248** and **249** with arylhydrazines led to arylhydrazones of general structure **252.** Cyclization of intermediates **250–252** with paraformaldehyde in xylene at reflux gave the 3-substituted 2,3-dihydro-5-phenyl-1H-[1,3,4]benzotriazepines **253–259.** Physical constants for these compounds are given in Table 13.

Leiby and Heindel (83) have prepared a series of 2-amino-1,4-dihydro-5H-[1,3,4]benzotriazepin-5-ones (**261–267**). Anthraniloylhydrazines of gen-




(40)

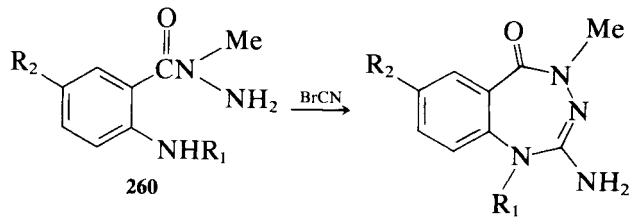
TABLE 13. 2,3-DIHYDRO-5-PHENYL-1H-[1,3,4]BENZOTRIAZEPINES[a]



| $R_1$ | $R_2$ | mp (°C) | Yield (%) |
|---|---|---|---|
| H | $H_2NCO$ | 209–210 | 15 |
| Cl | $H_2NCO$ | 217–218 | 13 |
| H | Ph | 180–181 | 27 |
| Cl | Ph | 168–169 | 24 |
| Cl | *p*-$MeC_6H_4$ | 141–142 | 22 |
| Cl | *p*-$ClC_6H_4$ | 137–138 | 34 |
| Cl | *p*-$EtO_2CC_6H_4$ | 181–182 | 23 |

[a]Ref. 82.

eral structure **260,** which were prepared by opening the appropriate isatoic anhydrides with methylhydrazine (84), were treated with cyanogen bromide to yield benzotriazepinones **261–267** directly (Eq. 41). Physical constants for these products are shown in Table 14.



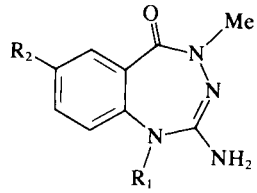
**260**

(41)

**261,** $R_1 = R_2 = H$
**262,** $R_1 = H$, $R_2 = Cl$
**263,** $R_1 = H$, $R_2 = Br$
**264,** $R_1 = H$, $R_2 = O_2N$
**265,** $R_1 = Me$, $R_2 = H$
**266,** $R_1 = Me$, $R_2 = Cl$
**267,** $R_1 = Me$, $R_2 = O_2N$

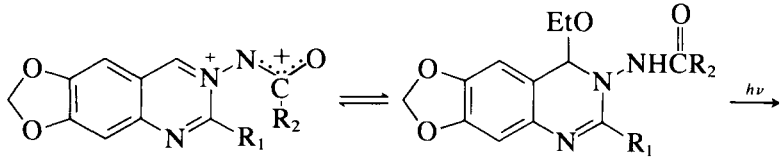
The photolysis of quinazolinoamidates **268,** which exist in equilibrium with their alcohol adducts **269** in ethanol solution (85) (Eq. 42), was shown recently to produce 3,5-dihydro-4H-[1,3]dioxolo[4,5-*h*][1,3,4]benzotriazepines **270–273** by Fetter and co-workers (86). Irradiation of these electron-deficient heteroaromatic systems was carried out with a high-pressure mercury lamp through Pyrex and produced other products as well. Physical constants for these compounds are shown in Table 15.

TABLE 14. 2-AMINO-1,4-DIHYDRO-5H-[1,3,4]BENZOTRIAZEPIN-5-ONES[a]

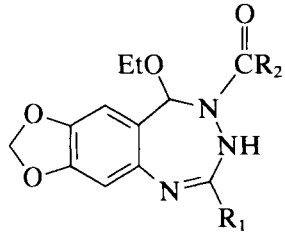


| $R_1$ | $R_2$ | mp (°C) | Yield (%) |
|---|---|---|---|
| H | H | 226–226.5 | 80 |
| H | Cl | 218–219 | 72 |
| H | Br | 177–179 | 36 |
| H | $O_2N$ | 212–212.5 | 69 |
| Me | H | 212–212.5 | 76 |
| Me | Cl | 240–240.5 | 85 |
| Me | $O_2N$ | 246–247 | 79 |

[a]Ref. 83.



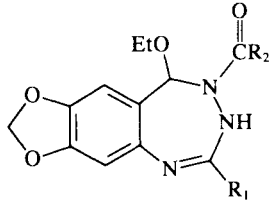
**268** **269**



(42)

**270,** $R_1$ = Me, $R_2$ = EtO
**271,** $R_1$ = Me, $R_2$ = $PhCH_2O$
**272,** $R_1$ = Me, $R_2$ = Ph
**273,** $R_1$ = H, $R_2$ = EtO

TABLE 15. 5-ETHOXY-3,5-DIHYDRO-2-ALKYL-4H-[1,3]DIOXOLO[4,5-*h*][1,3,4]BENZOTRIAZEPINES[a]



*(continued)*

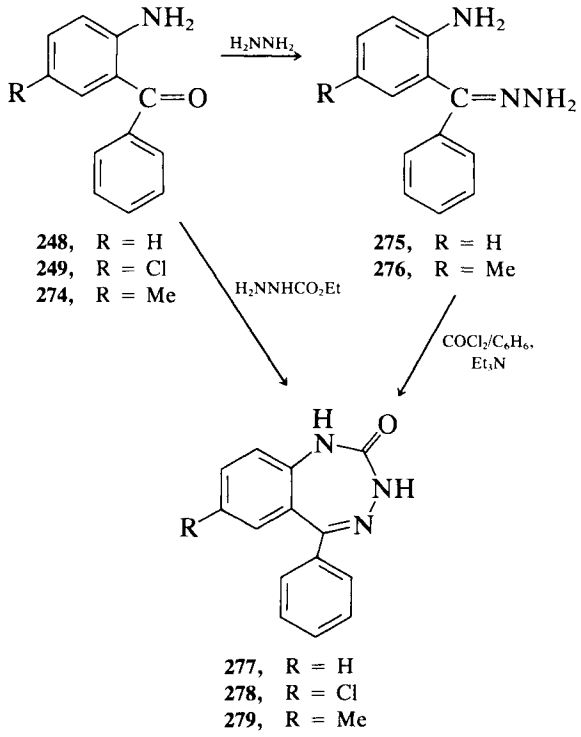
TABLE 15. *(Continued)*

| $R_1$ | $R_2$ | mp (°C) | Yield (%) |
|---|---|---|---|
| Me | EtO | 174–175 | 26 |
| Me | $PhCH_2O$ | 176 | 23 |
| Me | Ph | 197 | 26 |
| H | EtO | 122–124 | 11 |

[a]Ref. 86.

## b. [1,3,4]BENZOTRIAZEPIN-2-ONES

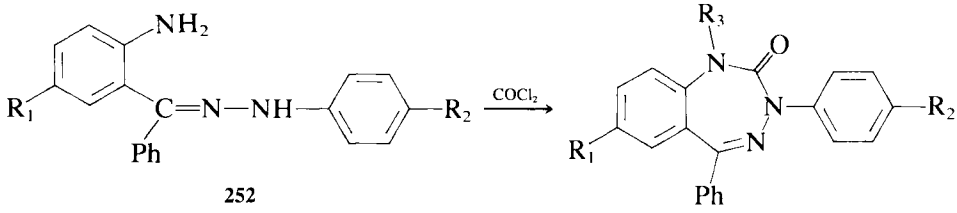
Methods for the preparation of 1,3-dihydro-5-phenyl-2H-[1,3,4]-benzotriazepin-2-ones have been described by Sulkowski and Childress (87) (Eq. 43). Reaction of 2-amino-5-chlorobenzophenone (**249**) with ethyl carbazate (neat at 190°C for 1 hr) produced benzotriazepinone **278** directly. Alternatively, the *o*-aminobenzophenone hydrazones **275** and **276** could be prepared and subsequently cyclized with phosgene to yield benzotriazepinones **277** and **279**, respectively. Compounds **277–279** and related 5-aryl-1,3-




(43)

dihydro-2H-[1,3,4]benzotriazepin-2-ones (Table 16) are reported to possess anticonvulsant activity (88).

Ishiwaka and co-workers (82) have prepared 3,5-diaryl-1,3-dihydro-2H-[1,3,4]benzotriazepin-2-ones from the previously mentioned intermediates **252.** Cyclization with phosgene (Eq. 44), using the procedure employed by Sulkowski and Childress (87), afforded triazepinones **280–283.**

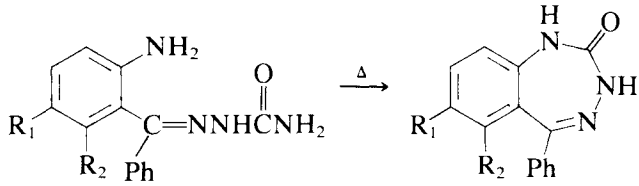


**252**

**280,** $R_1 = R_2 = R_3 = H$
**281,** $R_1 = Cl, R_2 = R_3 = H$
**282,** $R_1 = R_2 = H, R_3 = HO_2C$
**283,** $R_1 = Cl, R_2 = H, R_3 = HO_2C$

(44)

The intermediates **250** and **251** of Ishiwaka and co-workers (82) and the analogous semicarbazones **284** and **285** (89) have been thermally cyclized (Eq. 45) to benzotriazepinones **277–279** and **286,** which possess antispasmodic activity (89). Toyoshima and co-workers (90) also synthesized benzotriazepinones **287–292** from the appropriately substituted 2-methylaminobenzophenones. These compounds were claimed as analgesics, antispasmodics, and muscle relaxants.



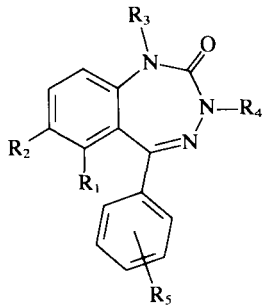
**250,** $R_1 = R_2 = H$
**251,** $R_1 = Cl, R_2 = H$
**284,** $R_1 = Me, R_2 = H$
**285,** $R_1 = Cl, R_2 = Me$

**277,** $R_1 = R_2 = H$
**278,** $R_1 = Cl, R_2 = H$
**279,** $R_1 = Me, R_2 = H$
**286,** $R_1 = Cl, R_2 = Me$

(45)

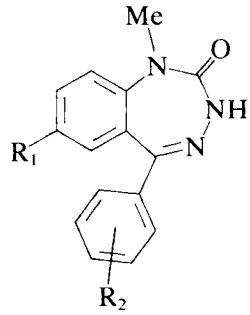
Kohl and co-workers (91) recently prepared several new 3-substituted 7-chloro-1,3-dihydro-5-phenyl-2H-[1,3,4]benzotriazepin-2-ones (**294–297**) (Fig. 2), using the procedures of Sulkowski and Childress (87) and Ishiwaka and co-workers (82). In addition, alkylation of **294** with methyl bromide and dimethylchloromethylphosphine oxide in xylene, with sodium hydride as the

TABLE 16. 5-ARYL-1,3-DIHYDRO-2H-[1,3,4]BENZOTRIAZEPIN-2-ONES




| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|---|
| H | H | H | H | H | 238 | 36 | 87 |
| H | H | H | H | H | 238–239.5 | — | 88 |
| H | H | H | H | H | 230–231 | 20 | 82 |
| H | H | H | H | H | 234.5–235.5 | — | 89 |
| H | Me | H | H | H | 253–255 | 50 | 87 |
| H | Me | H | H | H | 253–254.5 | — | 88 |
| H | Me | H | H | H | 239 | 40 | 89 |
| H | Cl | H | H | H | 246–248 | 27 | 87 |
| H | Cl | H | H | H | 246–248 | — | 88 |
| H | Cl | H | H | H | 235–237 | 25 | 82 |
| H | Cl | H | H | H | 255–258 | 53 | 89 |
| H | Cl | H | H | H | 242–243 | 75 | 91 |
| H | $F_3C$ | H | H | H | — | — | 88 |
| H | Br | H | H | H | — | — | 88 |
| H | Cl | H | H | *o*-Cl | — | — | 88 |
| H | $O_2N$ | H | H | H | — | — | 88 |
| H | H | H | Ph | H | 207–208 | 14 | 82 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| H | Cl | H | Ph | H | 243–244 | 40 | 82 |
| H | Cl | H | Ph | H | 237–238 (dec.) | 82 | 91 |
| H | H | $HO_2C$ | Ph | H | 141–142 | 16 | 82 |
| H | Cl | $HO_2C$ | Ph | H | 172–173 | 30 | 82 |
| H | H | Me | H | H | 154.5–155 | — | 90 |
| H | Cl | Me | H | H | 188 | — | 90 |
| H | Cl | Me | H | *p*-Me | 221 | — | 90 |
| H | Cl | Me | H | *m*-Me | 146 | — | 90 |
| H | Me | Me | H | H | 164 | — | 90 |
| H | Cl | Me | H | *p*-Cl | 160–162 | — | 90 |
| Me | Cl | H | H | H | 240 | 38 | 89 |
| H | Cl | H | Me | H | 215–218 | 80 | 91 |
| H | Cl | H | *i*-Pr | H | 226 | 78 | 91 |
| H | Cl | H | *p*-$ClC_6H_4$ | H | 235–236 | 76 | 91 |
| H | Cl | H | *p*-$MeOC_6H_4$ | H | 246 | 78 | 91 |
| H | Cl | Me | Me | H | 226–228 | 85 | 91 |
| H | Cl | $Me_2POCH_2$ | Me | H | 196–198 | 90 | 91 |
| H | Cl | $Me_2POCH_2$ | Ph | H | 245 | 87 | 91 |



**287,** $R_1 = R_2 = H$
**288,** $R_1 = Cl$, $R_2 = H$
**289,** $R_1 = Cl$, $R_2 = p$-Me
**290,** $R_1 = Cl$, $R_2 = m$-Me
**291,** $R_1 = Me$, $R_2 = H$
**292,** $R_1 = Cl$, $R_2 = p$-Cl

base, produced the 1-alkyl derivatives **298** and **299,** respectively. In similar fashion, **300** was produced from **281.** Compounds **278, 281,** and **294–300** were found to possess mild sedative and anticonvulsant activity.

Alternative modes of cyclization employed with hydrazones of general structure **293** produced some interesting results. Treatment of **293** ($R_1$ = H) with an alkyl chloroformate yielded carbalkoxyhydrazone **301** ($R_1$ = H), which was then thermally cyclized to **278.** On the other hand, treatment of **293** ($R_1$ = aryl) with an alkyl chloroformate yielded, exclusively, urethanes of general structure **302,** which thermally cyclized to quinazolinone **303.** Treatment of **293** ($R_1$ = alkyl) with an alkyl chloroformate yielded a mixture of carbalkoxyhydrazones **301** ($R_1$ = alkyl) and urethanes **302** ($R_1$ = alkyl). Thermal cyclization of the former produced exclusively the benzotriazepinones **294** or **295,** whereas the latter produced mixtures of the benzotriazepinones (**294** or **295**) and quinazolinone **303.**

### c. [1,3,4]BENZOTRIAZEPIN-5-ONES

Hromatka and co-workers (92) were the first to report the preparation of [1,3,4]benzotriazepin-5-ones (Table 17). Their synthesis involved the cyclization of (2-aminobenzoyl)hydrazines with aldehydes or ketones (Eq. 46). Thus treatment of hydrazides of general structure **305,** which were prepared by reaction of the appropriately substituted isatoic anhydrides (**304**) with 1,2-dimethylhydrazine (93), with aldehydes—or, in the case of **305** ($R_1$ = H, $R_2$ = Me), benzaldehyde diethyl acetal—and ketones produced the 1,2,3,4-tetrahydro-5H-[1,3,4]benzotriazepin-5-ones **306–315.** It is interesting to note that **305** ($R_1$ = H, $R_2$ = Me) could not be cyclized to **312** with benzaldehyde in ethanol at reflux. The formation of this crowded molecule required treatment of **305** ($R_1$ = H, $R_2$ = Me) with benzaldehyde diethyl acetal at an elevated temperature.

1,2,3,4-Tetrahydro-2-methyl-5H-[1,3,4]benzotriazepine-5-one (**317**) was

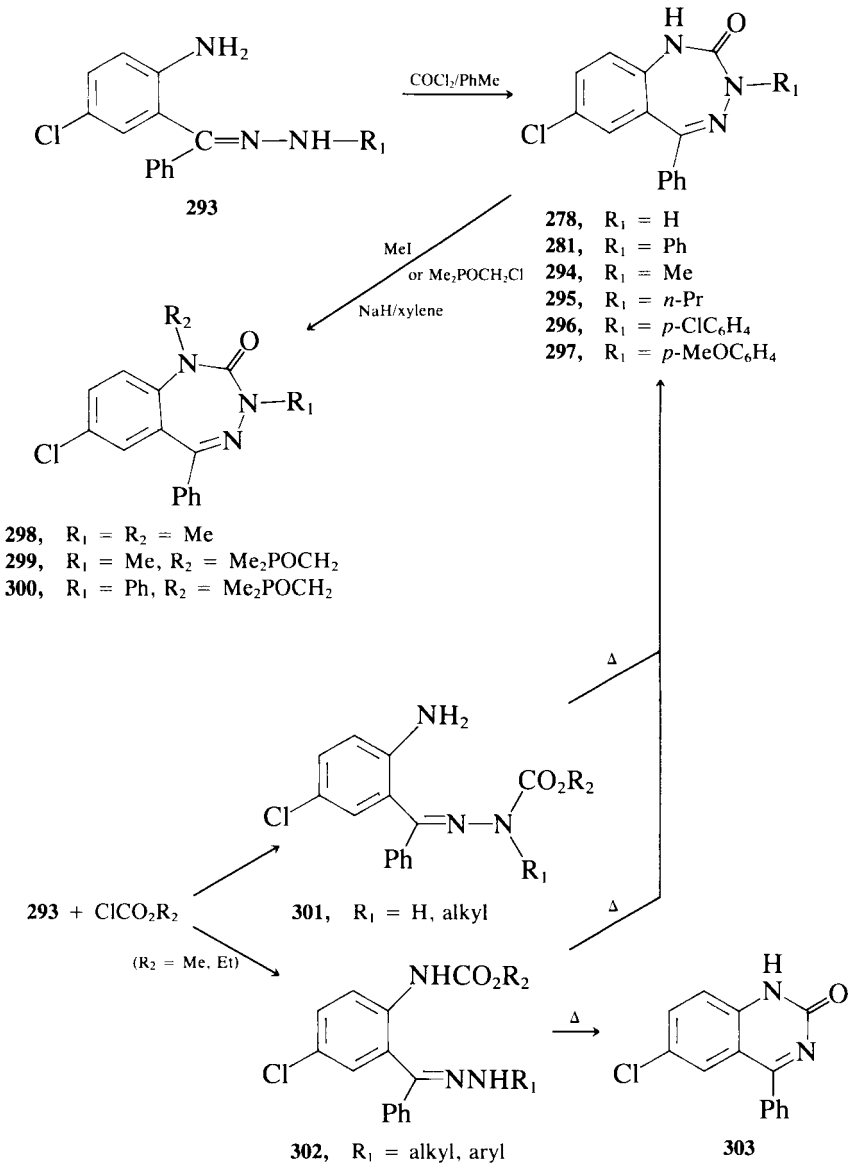
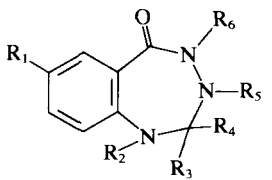



**Figure 2**

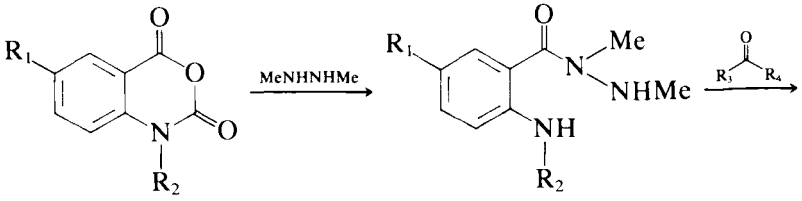
synthesized by Ninomiya and Yamamoto (94). Compound **317** was prepared by irradiation of (2-aminobenzoyl)hydrazine (**316**) in ethanol (Eq. 47).

A highly substituted tetrahydro[1,3,4]benzotriazepin-5-one has been reported by Nair (95). Treatment of (2-aminobenzoyl)hydrazine (**316**) with dimethyl acetylenedicarboxylate (Eq. 48) yielded the 1 : 1 adduct **318.** The structure of **318** was established on the basis of spectral evidence, an alter-

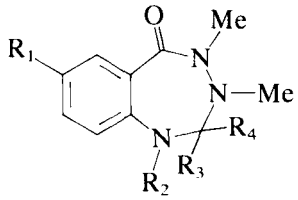
TABLE 17. 1,2,3,4-TETRAHYDRO-5H-[1,3,4]BENZOTRIAZEPIN-5-ONES




| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | mp (°C) | Yield(%) | Refs. |
|---|---|---|---|---|---|---|---|---|
| H | H | H | Me | H | H | — | — | 94 |
| H | H | H | H | Me | Me | 195–197 | 94 | 92 |
| Cl | H | H | H | Me | Me | 185–187 | 78 | 92 |
| H | Me | H | H | Me | Me | 76–78 | 89 | 92 |
| Cl | Me | H | H | Me | Me | 95–96 | 85 | 92 |
| H | H | H | Ph | Me | Me | 218–220 | 91 | 92 |
| Cl | H | H | Ph | Me | Me | 225–226 | 86 | 92 |
| H | Me | H | Ph | Me | Me | 124–126 | 86 | 92 |
| H | H | Me | Me | Me | Me | 179–181 | 84 | 92 |
| Cl | H | Me | Me | Me | Me | 173–175 | 90 | 92 |
| H | H | —$(CH_2)_4$— | | Me | Me | 160–162 | 89 | 92 |
| H | Ac | Ac | $MeO_2CCH_2$ | Ac | H | 137–138 | 60 | 95 |

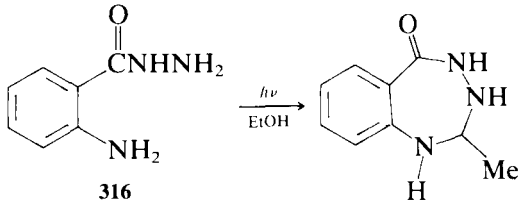



304 305



(46)

**306,** $R_1 = R_2 = R_3 = R_4 = H$
**307,** $R_1 = Cl, R_2 = R_3 = R_4 = H$
**308,** $R_1 = R_3 = R_4 = H, R_2 = Me$
**309,** $R_1 = Cl, R_2 = Me, R_3 = R_4 = H$
**310,** $R_1 = R_2 = R_3 = H, R_4 = Ph$
**311,** $R_1 = Cl, R_2 = R_3 = H, R_4 = Ph$
**312,** $R_1 = R_3 = H, R_2 = Me, R_4 = Ph$
**313,** $R_1 = R_2 = H, R_3 = R_4 = Me$
**314,** $R_1 = Cl, R_2 = H, R_3 = R_4 = Me$
**315,** $R_1 = R_2 = H, R_3 R_4 = (CH_2)_4$

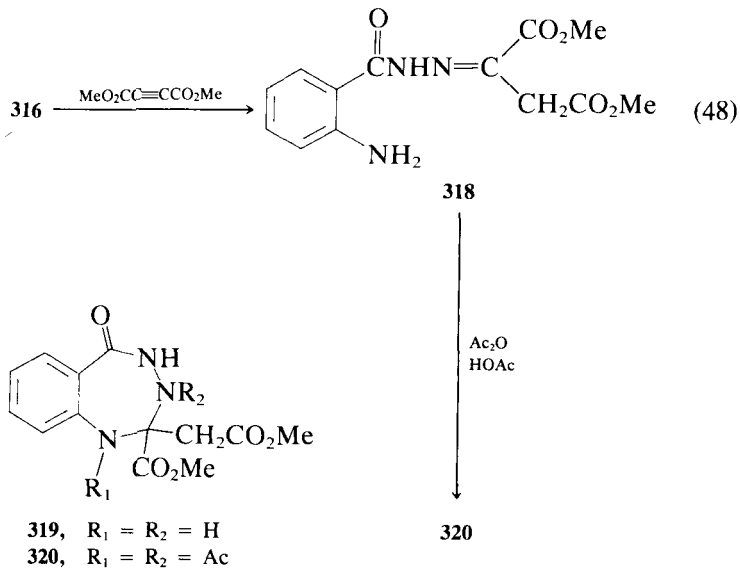



316 317

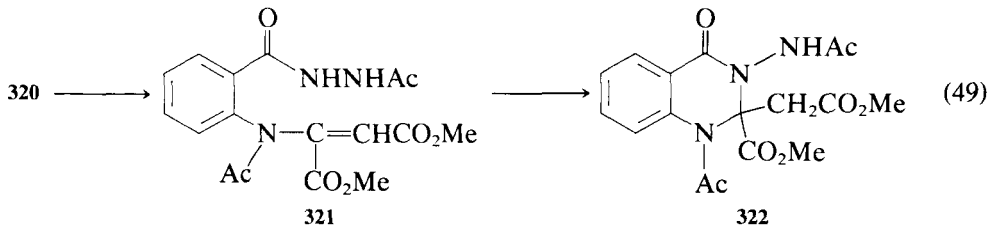
(47)

nate synthesis, and additional chemical evidence. Benzotriazepinone **319** was thus ruled out as a structural possibility for this reaction product. However, the product isolated on reaction of **318** with acetic anhydride in acetic acid was formulated as the diacylbenzotriazepinone **320.** Notwithstanding the spectral evidence presented in support of structure **320,** it seems quite possible that under the reaction conditions the initially formed **320** might rearrange to dihydroquinazolinone **322** via intermediate **321,** as depicted in Eq. 49.

The formation of tetrahydro[1,3,4]benzotriazepin-5-one **324** was suggested recently by Peet and co-workers (96) as an intermediate step in the conversion of 2-(*o*-aminobenzoyl)-1-acetyl-1-methylhydrazine (**323**) to *N*-



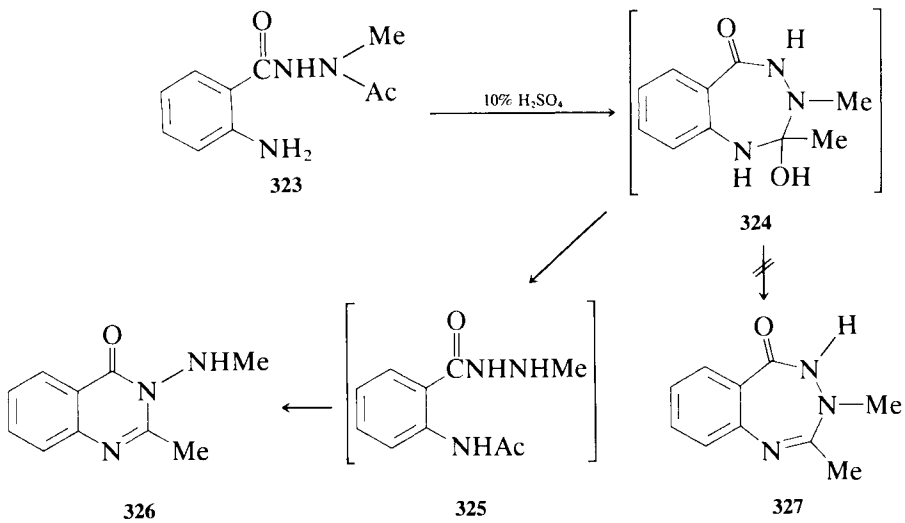

(48)




(49)

methyl-*N*-[2-methyl-4-oxo-3(4H)-quinazolinyl]acetamide (**326**) on treatment with sulfuric acid (Eq. 50). The isomeric benzotriazepinone **327** was not produced in this reaction.

3,4-Dihydro-5H-[1,3,4]benzotriazepin-5-ones were first mentioned in the literature by Langis (97). Isatoic anhydride (**328**) was treated with isonicotinic acid hydrazide (Fig. 3) to produce diaroylhydrazine **331,** which Langis claimed could be cyclized with polyphosphoric acid (PPA) to benzotriazepinone **332.** Fourteen additional diacylhydrazines similar to **331** were likewise prepared and treated with polyphosphoric acid. Later studies by Takahashi and coworkers (98), however, indicated that polyphosphoric acid resulted in the formation of [1,3,4]oxadiazoles rather than benzotriazepinones. Condensation of isatoic anhydrides **328** and **329** with 2-pyridylamidrazone yielded aroylamidrazones **338** and **339,** respectively (98), and the latter compounds were converted to benzotriazepinones **333** and **334** with methanolic sulfuric acid. Also prepared (by the Langis method) was 1-(2-aminobenzoyl)-2-(2-




(50)

pyridyl)hydrazine (**330**), which underwent cyclization to oxadiazole **336** in polyphosphoric acid. Structural assignments for **333** and **336** were deduced on the basis of the spectral data for these compounds and the corresponding isomeric monoacetates of **336** and **333** (**335**). Thus it was shown that the product claimed to be **332** by Langis (97) was actually oxadiazole **337.** The work of Takahashi and co-workers (98) again demonstrates the need to consider possible alternative structures when designing syntheses of benzotriazepine systems.

A report by Panse and Kamat (99) describing the synthesis of 3,4-dihydro-5H-[1,3,4]benzotriazepin-5-one (**340**) has also been shown to be in error. These authors reported the preparation of **340** from (2-aminobenzoyl)-hydrazine (**316**) using the following sets of reagents: triethyl orthoformate in the presence of *p*-toluenesulfonic acid, ethyl formate, and diethyl oxalate, to yield the 2-carbethoxy derivative **342,** followed by methanolic sodium hydroxide (Eq. 51). It has since been shown by Peet and co-workers (100) that the product of these reactions is 3-amino-4(3H)-quinazolinone (**341**) rather than benzotriazepinone **340.** The authors showed that the product (**341**) obtained from these reactions formed, under mild conditions, a salt with picric acid and Schiff bases with benzaldehyde and *p*-nitrobenzaldehyde. In addition, the product was identical with the one obtained by other unequivocal routes to **341** (101–104). The compound claimed to be **342** by Panse and Kamat has to be 2-carbethoxy-3-amino-4(3H)-quinazolinone (**343**), which was in fact described earlier by George and co-workers (105).

A straightforward route to 3,4-dihydro-5H-[1,3,4]benzotriazepin-5-ones has been reported by Sunder, Peet, and Trepanier (106). These authors treated isatoic anhydride (**328**), obtained in high purity from the reaction of methyl anthranilate with phosgene (107), with methylhydrazine in dime-

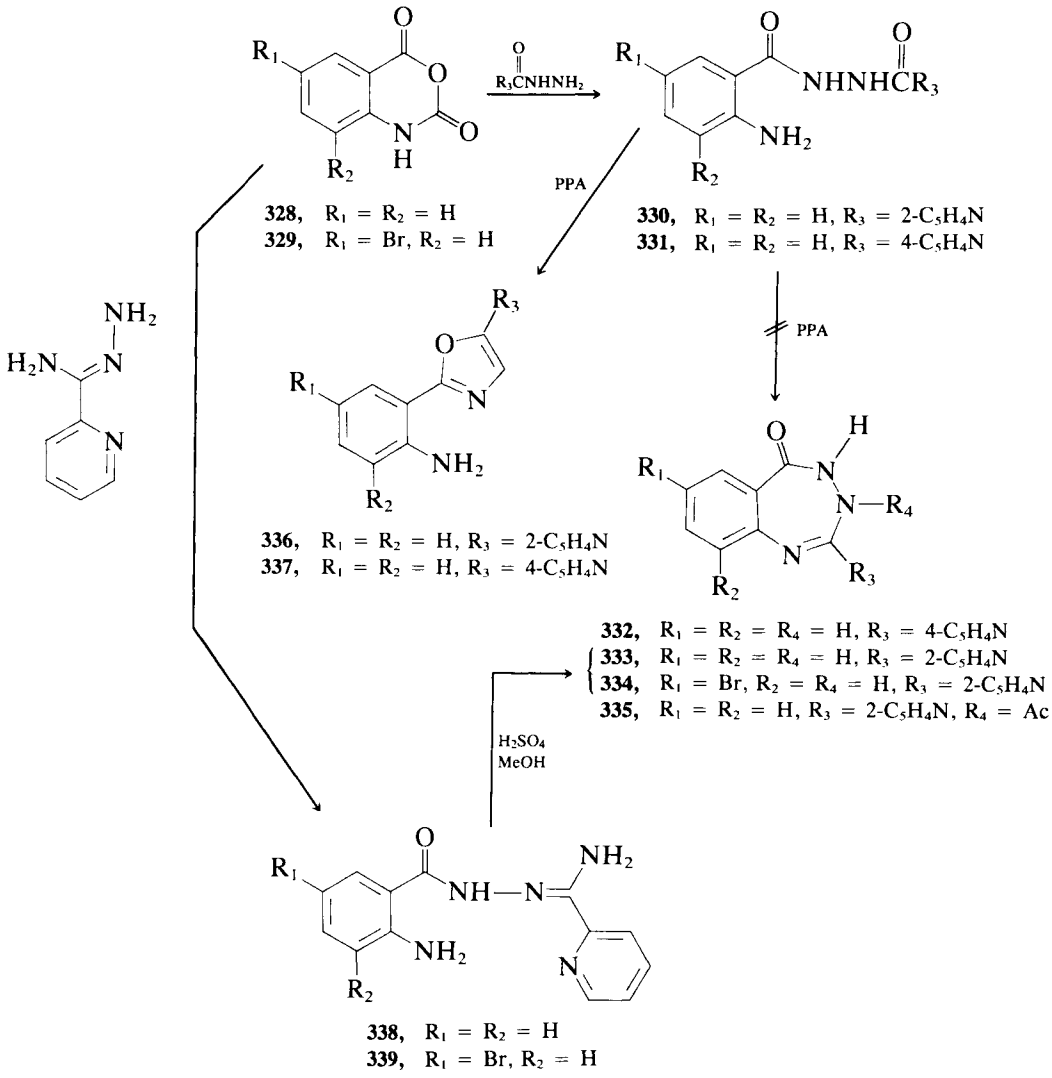
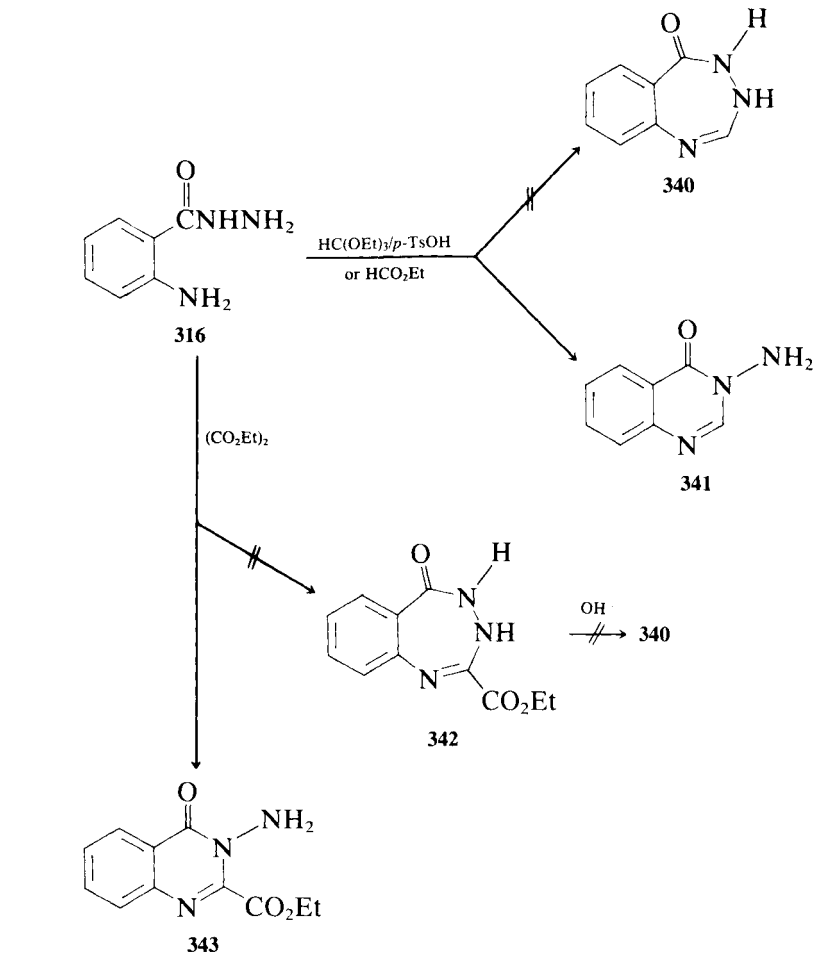


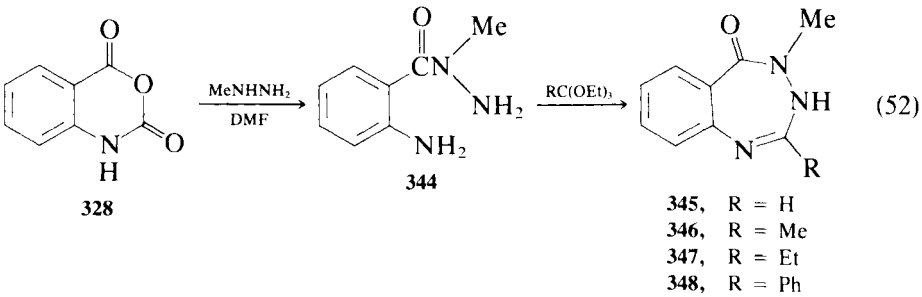

**Figure 3**

thylformamide (Eq. 52). The resulting 2-(2-aminobenzoyl)-1-methylhydrazine (**344**) was then treated with orthoesters to yield benzotriazepinones **345–348.** A simultaneous report by Leiby and Heindel (108) also described the synthesis of **345, 346,** and **348** from **344,** as well as twelve additional 3,4-dihydro-5H-[1,3,4]benzotriazepin-5-ones (**349–360**). These authors treated isatoic anhydrides with methylhydrazine in ethanol to produce the hydrazide intermediates corresponding to **344** (84). Physical constants for the known members of the 3,4-dihydro-5H-[1,3,4]benzotriazepin-5-one family are listed in Table 18.

Also reported by Leiby and Heindel (108) were 1,4-dihydro-5H-



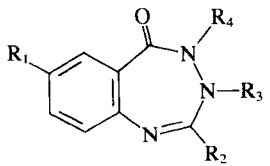

(51)



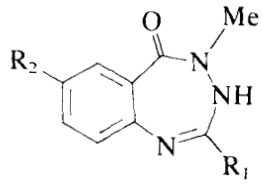

(52)

[1,3,4]benzotriazepin-5-ones **363–370,** which were prepared (Eq. 53) from *N*-methylisatoic anhydrides (**361**). Physical constants for these compounds are given in Table 19. Heindel and Leiby (109) later reported that benzotriazepines **363–368** underwent base-induced (sodium ethoxide) ring-contrac-

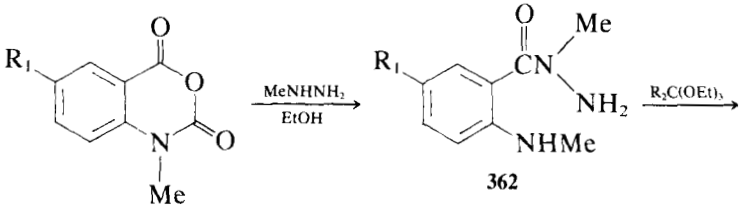
TABLE 18. 3,4-DIHYDRO-5H-[1,3,4]BENZOTRIAZEPIN-5-ONES



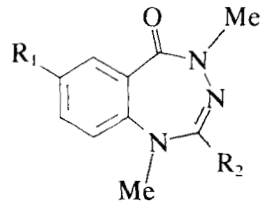
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| H | H | H | Me | 159–161 | 46 | 106 |
| H | H | H | Me | 162–162.5 | 89 | 108 |
| Cl | H | H | Me | 222–223.5 | 72 | 108 |
| Br | H | H | Me | 256.5–257 | 73 | 108 |
| $O_2N$ | H | H | Me | 270.5–271 | 71 | 108 |
| H | Me | H | Me | 132–133 | 57 | 106 |
| H | Me | H | Me | 133–133.5 | 58 | 108 |
| Cl | Me | H | Me | 227–228 | 61 | 108 |
| Br | Me | H | Me | 226–227 | 58 | 108 |
| $O_2N$ | Me | H | Me | 277–278 | 84 | 108 |
| H | Et | H | Me | 103–104.5 | 58 | 106 |
| Cl | Et | H | Me | 167–168 | 68 | 108 |
| Br | Et | H | Me | 176–176.5 | 46 | 108 |
| $O_2N$ | Et | H | Me | 203–205 | 85 | 108 |
| H | Ph | H | Me | 162–163.5 | 63 | 106 |
| H | Ph | H | Me | 165–166 | 68 | 108 |
| Cl | Ph | H | Me | 240–241 | 64 | 108 |
| Br | Ph | H | Me | 247–248 | 51 | 108 |
| $O_2N$ | Ph | H | Me | 295–296 | 69 | 108 |
| H | 2-$C_5H_4N$ | H | H | 247–248 | 59 | 98 |
| Br | 2-$C_5H_4N$ | H | H | 249–250 | 74 | 98 |
| H | 2-$C_5H_4N$ | Ac | H | 193–196 | 42 | 98 |
| H | 1-Pyrrolidino | Me | Et | 71–72 | — | 118 |



**349,** $R_1$ = H, $R_2$ = Cl
**350,** $R_1$ = H, $R_2$ = Br
**351,** $R_1$ = H, $R_2$ = $O_2N$
**352,** $R_1$ = Me, $R_2$ = Cl
**353,** $R_1$ = Me, $R_2$ = Br
**354,** $R_1$ = Me, $R_2$ = $O_2N$
**355,** $R_1$ = Et, $R_2$ = Cl
**356,** $R_1$ = Et, $R_2$ = Br
**357,** $R_1$ = Et, $R_2$ = $O_2N$
**358,** $R_1$ = Ph, $R_2$ = Cl
**359,** $R_1$ = Ph, $R_2$ = Br
**360,** $R_1$ = Ph, $R_2$ = $O_2N$




**361** **362**



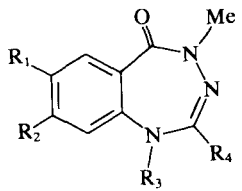
(53)

**363,** $R_1$ = $R_2$ = H
**364,** $R_1$ = Cl, $R_2$ = H
**365,** $R_1$ = $O_2N$, $R_2$ = H
**366,** $R_1$ = H, $R_2$ = Me
**367,** $R_1$ = Cl, $R_2$ = Me
**368,** $R_1$ = Cl, $R_2$ = Ph
**369,** $R_1$ = $O_2N$, $R_2$ = Me
**370,** $R_1$ = $O_2N$, $R_2$ = Et

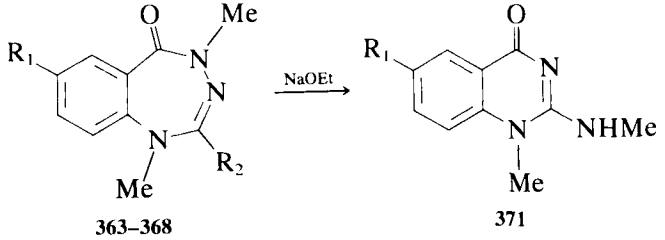
tion reactions (Eq. 54) to produce the quinazolinones represented by general structure **371.**

Much of the synthetic work in the benzotriazepine area has been stimulated by the remarkable range of psychotherapeutic activities of the analogous benzodiazepines. For example, syntheses of 1,4-dihydro-4-methyl-1-phenyl-5H-[1,3,4]benzotriazepin-5-one (**379**) and its 8-chloro analog (**380**), compounds which bear structural similarity to 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-[1,4]benzodiazepin-2-one (**382,** diazepam), have been carried out by Peet and Sunder (110), as outlined in Fig. 4.

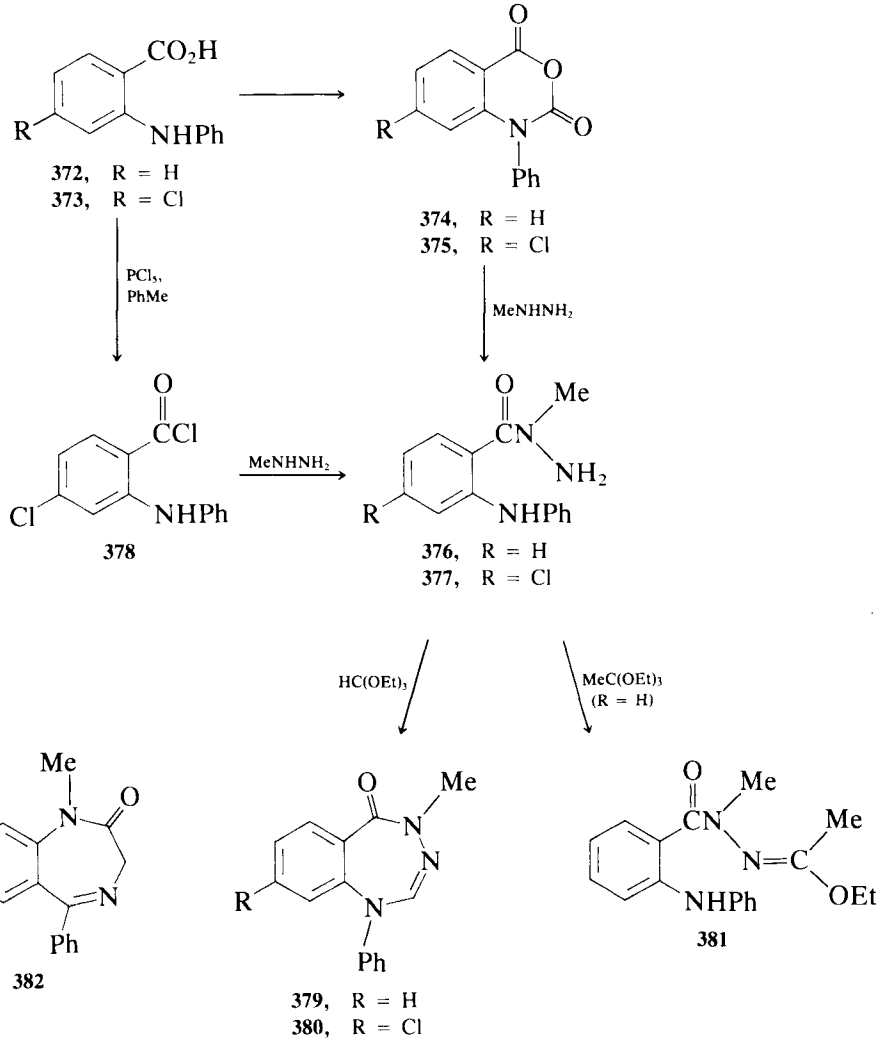
TABLE 19. 1,4-DIHYDRO-5H-[1,3,4]BENZOTRIAZEPIN-5-ONES




| $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| H | H | Me | H | 102.5–103.5 | 53 | 108 |
| Cl | H | Me | H | 166–166.5 | 61 | 108 |
| $O_2N$ | H | Me | H | 225–227 | 57 | 108 |
| H | H | Me | Me | 150.5–151.5 | 77 | 108 |
| Cl | H | Me | Me | 131–132 | 64 | 108 |
| $O_2N$ | H | Me | Me | 185.5–186 | 44 | 108 |
| $O_2N$ | H | Me | Et | 149.5–150 | 42 | 108 |
| Cl | H | Me | Ph | 104–105.5 | 27 | 108 |
| H | H | Ph | H | 108–109 | 50 | 110 |
| H | Cl | Ph | H | 160–161 | 60 | 110 |
| MeO | H | *p*-$MeOC_6H_4$ | H | 126–127 | 74 | 111 |




363–368 371 (54)




372, R = H
373, R = Cl

374, R = H
375, R = Cl

378

376, R = H
377, R = Cl

382

379, R = H
380, R = Cl

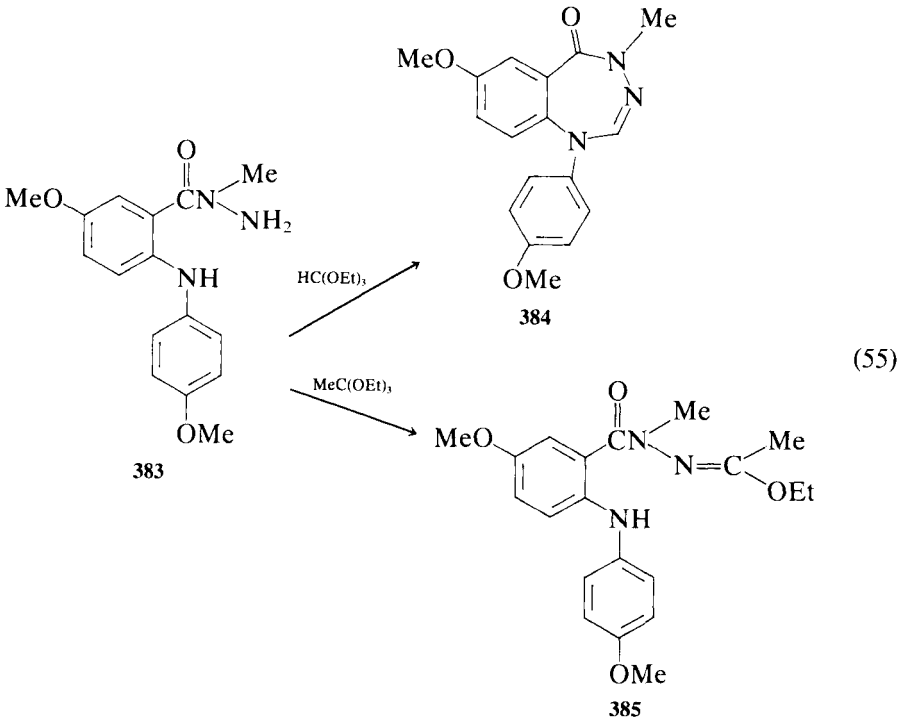
381

**Figure 4**

Treatment of 2-(phenylamino)benzoic acid (**372**) with ethyl cloroformate produced *N*-phenylisatoic anhydride (**374**), which yielded the hydrazide **376** upon treatment with methylhydrazine. Although 4-chloro-2-(phenylamino)benzoic acid (**373**) could be converted to the isatoic anhydride **375** with phosgene, it failed to react with ethyl chloroformate. Hydrazide **377** was therefore prepared from 4-chloro-2-(phenylamino)benzoyl chloride (**378**), which was prepared from **373** by treatment with phosphorous pentachloride. Hydrazides **376** and **377** were converted to benzotriazepinones **379** and **380,** respectively, with triethyl orthoformate.

It is interesting to note that treatment of hydrazide **376** with triethyl orthoacetate did not result in benzotriazepinone formation. The product of this reaction was the imino ether **381,** which could not be induced to cyclize under a variety of conditions.

The dimethoxy derivative of **376** (**383**) was also prepared by Peet and Sunder (111) in an attempt to produce a derivative of **376** that would cyclize to a benzotriazepinone with triethyl orthoacetate. The dimethoxy substitution pattern was chosen to increase the nucleophilicity and basicity of the diphenylamino nitrogen. Cyclization of **383** with triethyl orthoformate (Eq. 55) proceeded smoothly to yield 1,4-dihydro-7-methoxy-1-(4-methoxyphenyl)-4-methyl-5H-[1,3,4]benzotriazepin-5-one (**384**). However, pro-



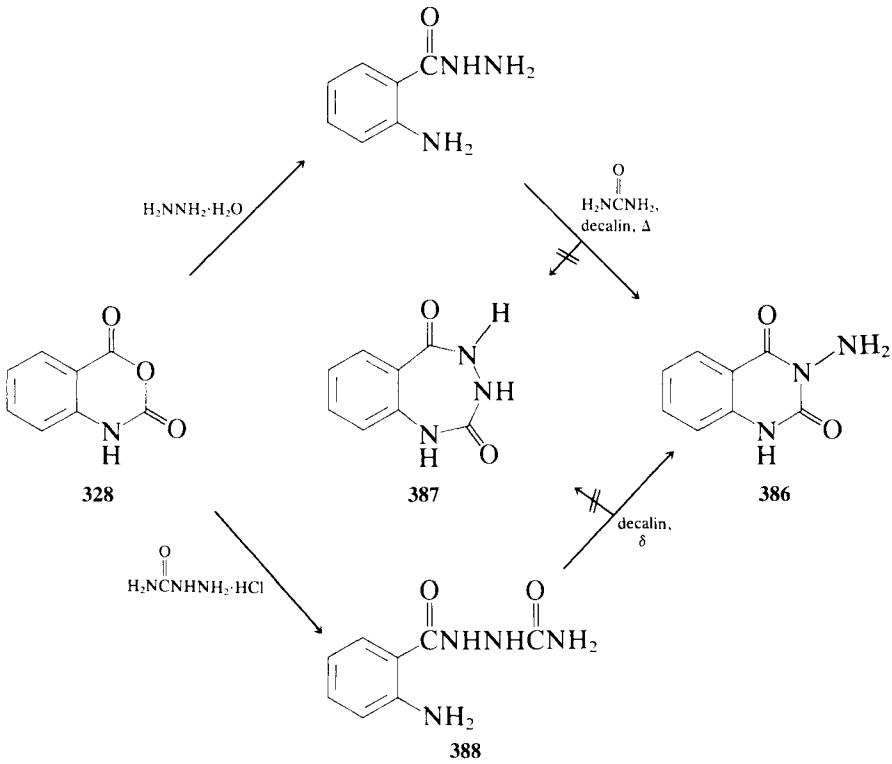

383 384 385 (55)

longed treatment of **383** with triethyl orthoacetate led only to imino ether **385.** Hydrazide **383** was prepared in the same general fashion as was hydrazide **377.**

### d. [1,3,4]BENZOTRIAZEPINE-2,5-DIONES

Of the many [1,3,4]benzotriazepine-2,5-diones that have been reported in the literature only a few are authentic. The reported synthetic routes to [1,3,4]benzotriazepine-2,5-diones that are in error lead, instead, to six-membered rings.

Langis and Charest (112) have reported two routes to 3,4-dihydro-1H-[1,3,4]benzotriazepine-2,5-dione (**387**). One of their synthetic methods (Eq. 56) involved the treatment of 2-aminobenzoylhydrazine (**316**), which was prepared from isatoic anhydride (**328**) and hydrazine hydrate, with urea in decalin at reflux. The other method utilized 1-(2-aminobenzoyl)semicarbazide (**388**), which was also prepared from isatoic anhydride (**328**) by treatment with semicarbazide hydrochloride. Cyclization of **388** in decalin at reflux led to the same product, which was reported to be **387** by Langis and Charest (112). In a reexamination of this work, however, Peet and Sunder (113) found that the product of these reactions was 3-amino-

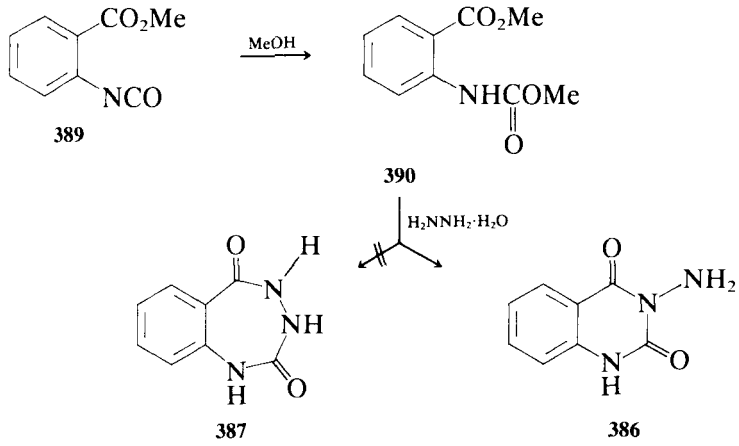



(56)

2,4(1H,3H)-quinazolinedione (**386**) rather than benzotriazepinedione **387.** This finding indicated that most of the additional compounds (19 out of 21) reported by Langis and Charest (112) as benzotriazepinediones were actually aminoquinazolinediones.

Although it is easy to mechanistically visualize the transformation of **316** to **386,** the conversion of **388** to **386** is less obvious. Possible mechanisms for the latter transformation were offered by Peet and Sunder (113).

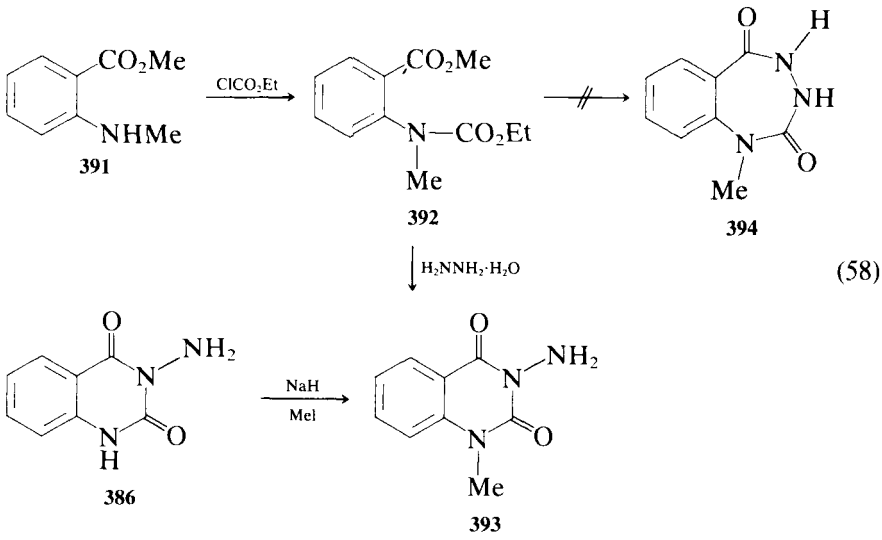
3,4-Dihydro-1H-[1,3,4]benzotriazepine-2,5-diones have also been reported by Bailey (114). The general method of preparation involved the condensation of alkyl *N*-carboxyanthranilates with hydrazines. For example, benzotriazepinediones **387** and **394** were the structures assigned to the compounds obtained by treating methyl 2-[(methoxycarbonyl)amino]benzoate (**390**) and its *N*-methyl analog **392,** respectively, with hydrazine hydrate (Eqs. 57 and 58). In a reinvestigation of this work, Peet and Sunder (113) prepared




389 390 387 386 (57)

**390** from 2-carbomethoxyphenyl isocyanate (**389**) and found that the product resulting from treatment with hydrazine hydrate was 3-amino-2,4(1H,3H)-quinazolinedione (**386**), rather than **387.** Likewise, it was found that 1-methyl-3-amino-2,4(1H,3H)-quinazolinedione (**393**), rather than **394**, was the product resulting from the treatment of **392** with hydrazine hydrate. An authentic sample of **393** was generated for comparison by methylation of **386.** Thus these results indicated that at least 70 and perhaps all of the 77 compounds claimed by Bailey (114) to be benzotriazepinediones were actually aminoquinazolinediones.

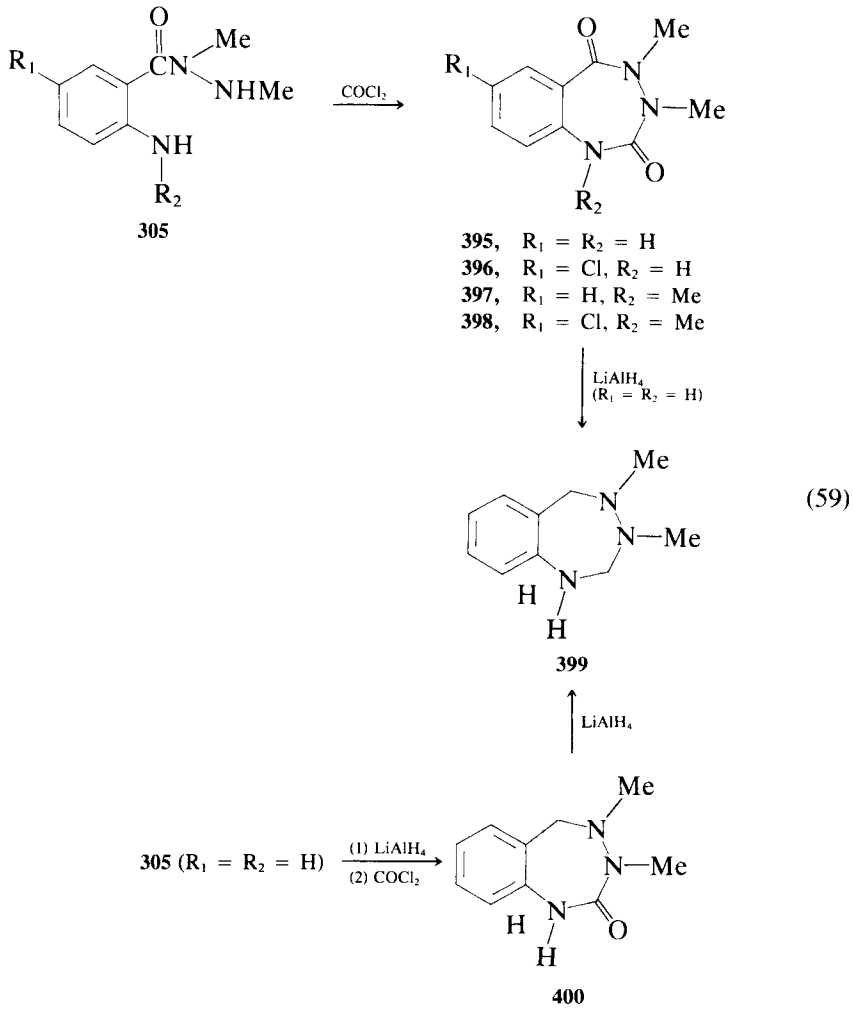
Authentic 3,4-dihydro-1H-[1,3,4]benzotriazepine-2,5-diones have been reported by Hromatka and co-workers (93). Treatment of hydrazides of general structure **305** with phosgene (Eq. 59) yielded compounds **395–398.** The methyl groups on the hydrazides (**305**) employed in these syntheses precluded the formation of six-membered rings. Also reported was the re-




(58)

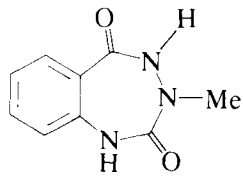
duction of **395** with lithium aluminum hydride to yield 2,3,4,5-tetrahydro-3,4-dimethyl-1H-[1,3,4]benzotriazepine (**399**). Treatment of hydrazide **305** ($R_1 = R_2 = H$) with lithium aluminum hydride and then phosgene yielded 1,3,4,5-tetrahydro[3,4]benzotriazepin-2-one (**400**), which also afforded **399** upon further reduction.

Benzotriazepinedione **395** was also prepared from two different precursors by Peet and Sunder (113), as shown in Eq. 60. Methylation of either 3,4-dihydro-3-methyl-1H-[1,3,4]benzotriazepine-2,5-dione (**401**) or the 4-methyl isomer (**402**) produced **395.** These alkylations served to relate **401** and **402** to each other and to the known literature compound **395.** Syntheses of **401** and **402** were also reported by Peet and Sunder (113). Treatment of 2-carbomethoxyphenyl isocyanate (**389**) with methylhydrazine (Eq. 61) produced hydrazide **403,** which could be cyclized with base under anhydrous conditions to **401.** A co-product of this cyclization was the acylated benzotriazepinedione **404.** The 4-methyl isomer of **401** (**402**) was prepared directly from methylhydrazine and 2-isocyanatobenzoyl chloride (**406**), whose synthesis from isatoic anhydride (**328**) and thionyl chloride (Eq. 62) has been reported (115,116). It is noteworthy that **402** was the only monomeric material produced in this reaction. The 5-chloro derivative of **406** (**407**) was also prepared (from **405**) and similarly treated with methylhydrazine to produce benzotriazepinedione **408.** In contrast to the preparation of **406,** which was prepared in 82% yield, the yield of **407** obtained under similar reaction conditions was only 31%. Accounting for most of the remaining mass balance in the latter reaction was the interesting quinazolinobenzoxazine **409** (117). An alternate preparation of benzotriazepinedione **402** from hydrazide **344** and ethyl chloroformate was also reported by Sunder, Peet, and Trepanier (106).

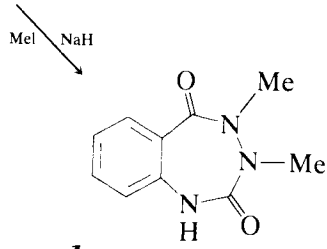



(59)

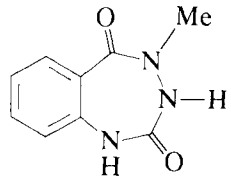
Further alkylation studies on benzotriazepinediones **401** and **402** were performed by Sunder and Peet (118). The preparation of **395** from both **401** and **402** indicated that selective monoalkylations of **401** at the 4-position and of **402** at the 3-position were feasible. This supposition was confirmed by the efficient preparation of several other 3,4-dialkylbenzotriazepinediones, i.e., **410** and **412** from **401** (Eq. 63) and **414, 416,** and **417** from **402** (Eq. 64). Trialkyl derivatives were also prepared, either by direct dialkylation (as in the preparation of **411** and **413** from **401** and of **415** from **402**) or by successive monoalkylations. The latter method was demonstrated by the efficient preparation of **418,** a benzotriazepinedione bearing three different *N*-alkyl groups, from **402.** Substitution at carbon could also be accomplished with an appropriate starting material. Thus the imino ether of benzotriazepinedione **410**



401

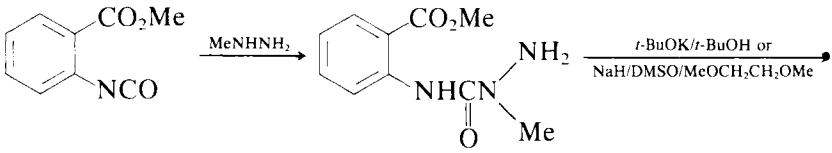


395

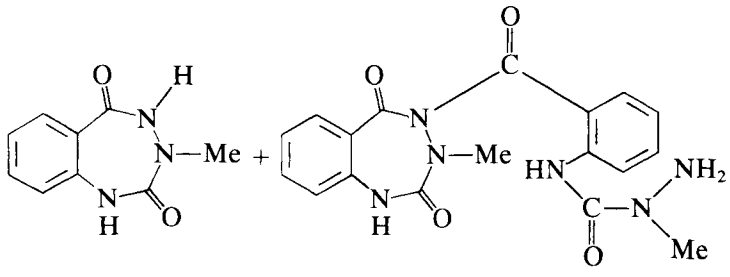


402

(60)



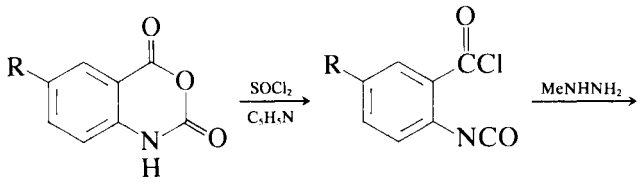
389 403



401 404

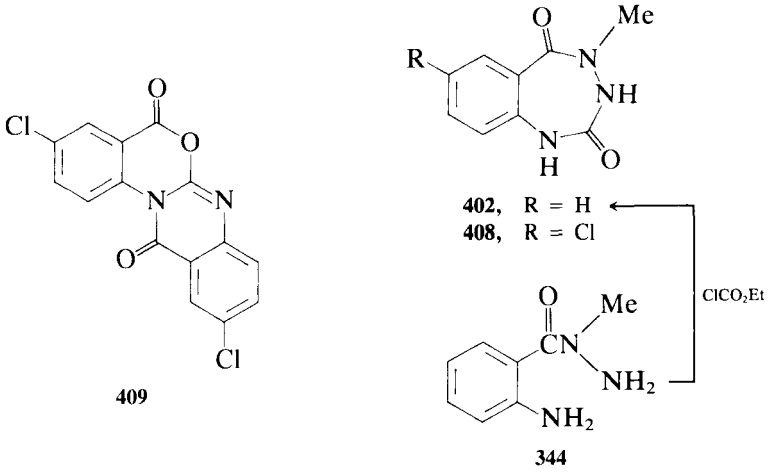
(61)

was generated *in situ* and quenched with pyrrolidine (Eq. 65) to yield the 2-substituted derivative **419.**

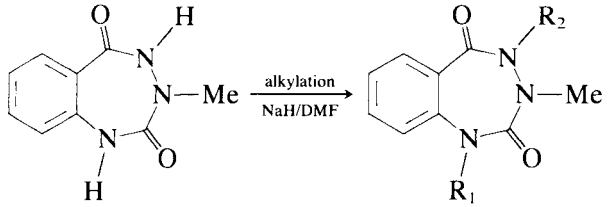



**328**, R = H
**405**, R = Cl

**406**, R = H
**407**, R = Cl




(62)

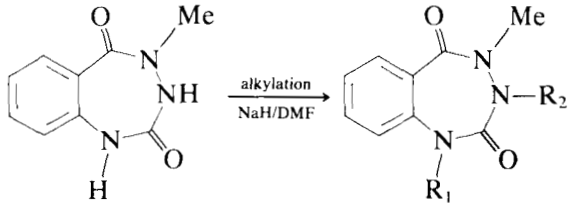



**401**

**410**, $R_1$ = H, $R_2$ = Et
**411**, $R_1$ = $R_2$ = Et
**412**, $R_1$ = H, $R_2$ = $PhCH_2$
**413**, $R_1$ = $R_2$ = $PhCH_2$

(63)

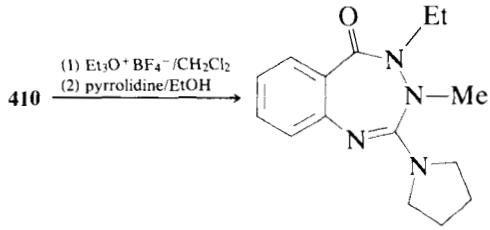
Acylated benzotriazepinedione **404** could be efficiently dialkylated with methyl or ethyl iodide. In each of these dialkyl derivatives spectral data confirmed that one alkyl group was present on the amino group, but it could




(64)

**402**

**414**, $R_1 = H$, $R_2 = Et$
**415**, $R_1 = R_2 = Et$
**416**, $R_1 = H$, $R_2 = PhCH_2$
**417**, $R_1 = H$, $R_2 = (Me)_2NCH_2CH_2$
**418**, $R_1 = PhCH_2$, $R_2 = Et$

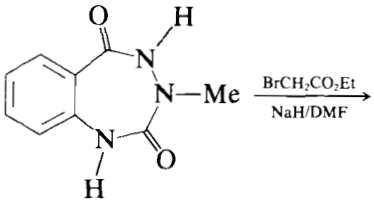



(65)

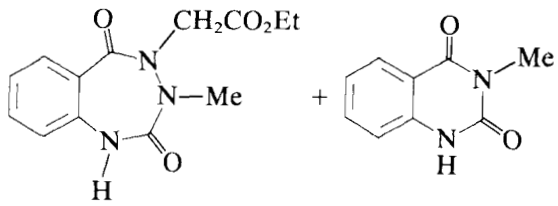
**419**

not be ascertained at which of the other two possible sites alkylation had occurred (119).

Alkylations of **401** and **402** with ethyl bromoacetate produced the most interesting results (Eqs. 66 and 67). When the reaction temperature was not controlled, mixtures of products resulted. Thus compound **401** yielded the

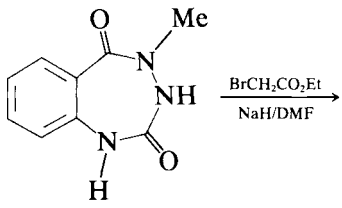



**401**



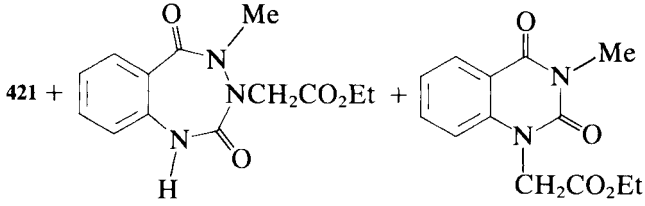

(66)

**420** **421**




**402**

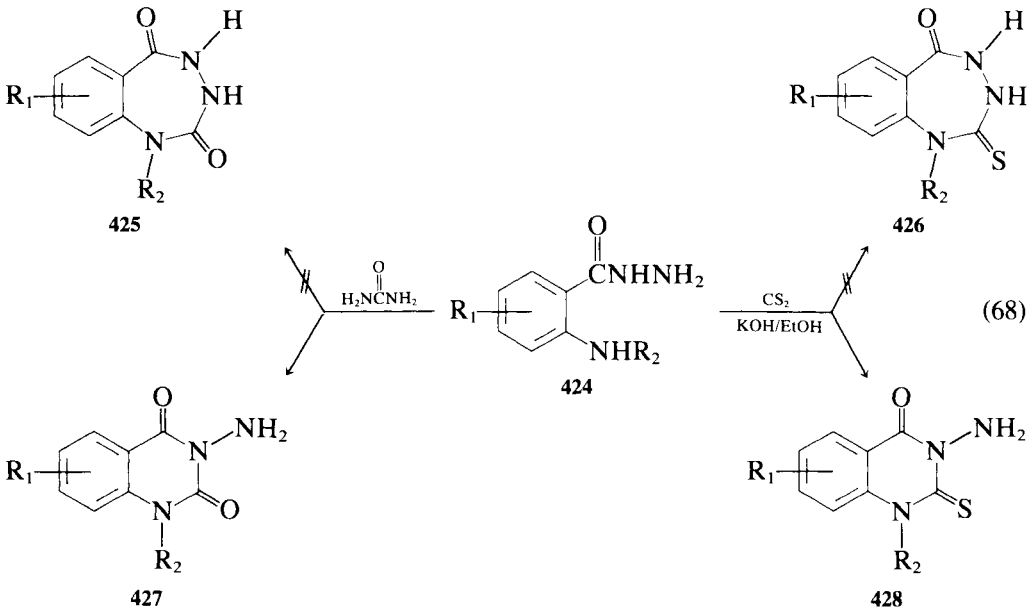
(67)




**422** **423**

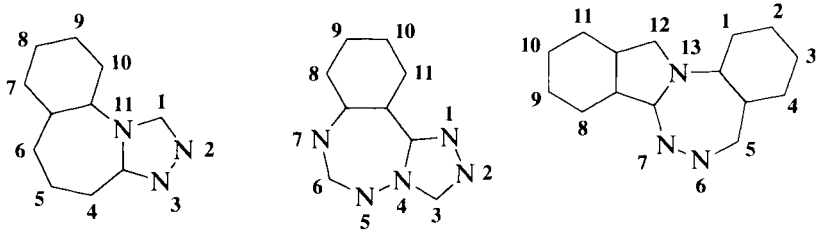
expected 4-alkyl derivative **420** and a product resulting from ring contraction, which was shown to be 3-methyl-2,4(1H,3H)-quinazolinedione (**421**). Alkylation of **402** under the same conditions produced some of the anticipated 3-alkyl derivative **422,** isomeric with **420.** However, quinazolinedione **421** was also isolated from the product mixture, along with quinazolinedione **423,** which was apparently derived from **421** by further alkylation. When the reaction temperature of these alkylations was controlled at ca. 10°C, compounds **420** and **422** became the major reaction products (69 and 64% yields, respectively). It was then shown that quinazolinedione **421** was being produced from **420** and **422.** Treatment of these benzotriazepinones with equivalent amounts of sodium hydride in dimethylformamide at 90–100°C for 2 hr produced **421** in isolated yields of 82 and 88%, respectively. It seems remarkable that **421** is efficiently produced from either **420** or **422.** Mechanisms for these ring-contraction reactions were postulated by Sunder and Peet (118). Physical constants for 3,4-dihydro-1H-[1,3,4]benzotriazepine-2,5-diones are presented in Table 20.

Two patent disclosures have dealt with substituted 3,4-dihydro-1H-[1,3,4]benzotriazepine-2,5-diones (120) of general structure **425** and with the corresponding 2-thione derivatives (121) of general structure **426.** A variety of pharmacologic properties were claimed for these compounds. The common starting materials for both series were hydrazides of general structure **424.** These hydrazides, when treated with urea or carbon disulfide under basic conditions (Eq. 68), reportedly gave compounds **425** and **426,** respectively. However, the previously described work of Peet and Sunder (113) casts serious doubt on these structural assignments. The compounds claimed to be **425** and **426** are undoubtedly 3-amino-2,4(1H,3H)-quinazolinediones **427** and their 2-thione analogs **428,** respectively.



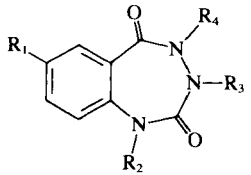

(68)

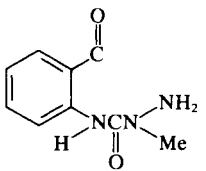
## e. CONDENSED [1,3,4]BENZOTRIAZEPINES

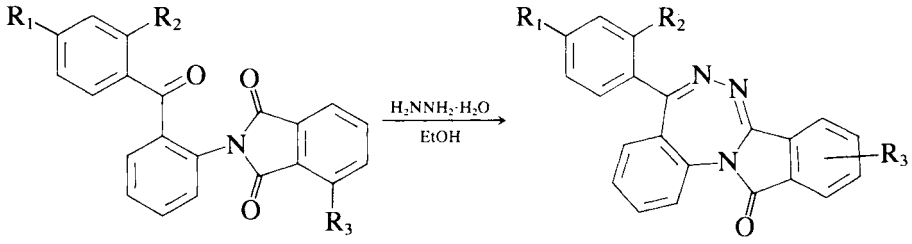


In performing a Friedel–Crafts condensation with *N*-phthaloylanthranilic acid and dimethylresorcinol, Engels and co-workers (122,123) obtained 4-methoxy-2′-phthalimidobenzophenone (**429**). Subsequent attempts to remove the phthaloyl group using the conditions of Ing and Manske (124) led to 5-(2,4-dimethoxyphenyl)-12H-isoindolo[2,1-*a*][1,3,4]benzotriazepin-12-one (**434**) (Eq. 69). Similarly, benzophenone **430** was converted to triazepine **435.** However, unsubstituted phthalimidobenzophenone **431** underwent a normal deprotection without giving a triazepine product. This result indicated the possible necessity of electron-donating substituents on the phthalimidobenzophenones for triazepine formation. Confirmation of this hypothesis was provided in a later study by Lamchen and Wicken (125,126), who found that the presence of an electron-donating substituent at the 4′-position of the phthalimidobenzophenones was necessary for carbonyl activation and the production of triazepines. From an extensive series of phthalimido-

TABLE 20. 3,4-DIHYDRO-1H-[1,3,4]BENZOTRIAZEPINE-2,5-DIONES



| $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| H | H | Me | H | 242–245 | 35 | 113 |
| H | H | H | Me | 266–267 | 14 | 113 |
| H | H | H | Me | 266–267 | 26 | 106 |
| Cl | H | H | Me | 280–284 | 14 | 113 |
| H | H | Me | Me | 189–190 | 35 | 93 |
| H | H | Me | Me | 185–188 | 62 | 113 |
| Cl | H | Me | Me | 222 | 30 | 93 |
| Cl | H | Me | Me | 218–220 | 55 | 113 |
| H | Me | Me | Me | 97–99 | 28 | 93 |
| Cl | Me | Me | Me | 149–150 | 32 | 93 |
| H | H | H | Ph | 223–225 | 12 | 112 |
| Cl | H | H | Ph | 274–276 | 9 | 112 |
| H | H | Me | Et | 129–130 | 65 | 118 |
| H | Et | Me | Et | 98–99 | 52 | 118 |
| H | H | Me | $PhCH_2$ | 150–151 | 66 | 118 |
| H | $PhCH_2$ | Me | $PhCH_2$ | 173–174 | 24 | 118 |
| H | H | Et | Me | 186–188 | 76 | 118 |
| H | Et | Et | Me | 77–79 | 73 | 118 |
| H | $PhCH_2$ | $PhCH_2$ | Me | 183–184 | 68 | 118 |
| H | H | $(Me)_2NCH_2CH_2$ | Me | 158–159 | — | 118 |
| H | $PhCH_2$ | Et | Me | — | 100 | 118 |
| H | H | $EtO_2CCH_2$ | Me | 146–148 | 64 | 118 |
| H | H | Me | $EtO_2CCH_2$ | 138–140 | 69 | 118 |
| H | H | Me |  | 237–239 | 17 | 113 |




(69)

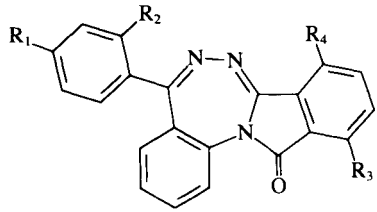
**429,** $R_1 = R_2 = MeO, R_3 = H$
**430,** $R_1 = MeO, R_2 = R_3 = H$
**431,** $R_1 = R_2 = R_3 = H$
**432,** $R_1 = MeS, R_2 = R_3 = H$
**433,** $R_1 = R_2 = MeO, R_3 = O_2N$

**434,** $R_1 = R_2 = MeO, R_3 = H$
**435,** $R_1 = MeO, R_2 = R_3 = H$
**436,** $R_1 = MeS, R_2 = R_3 = H$
**437,** $R_1 = R_2 = MeO, R_3 = O_2N$

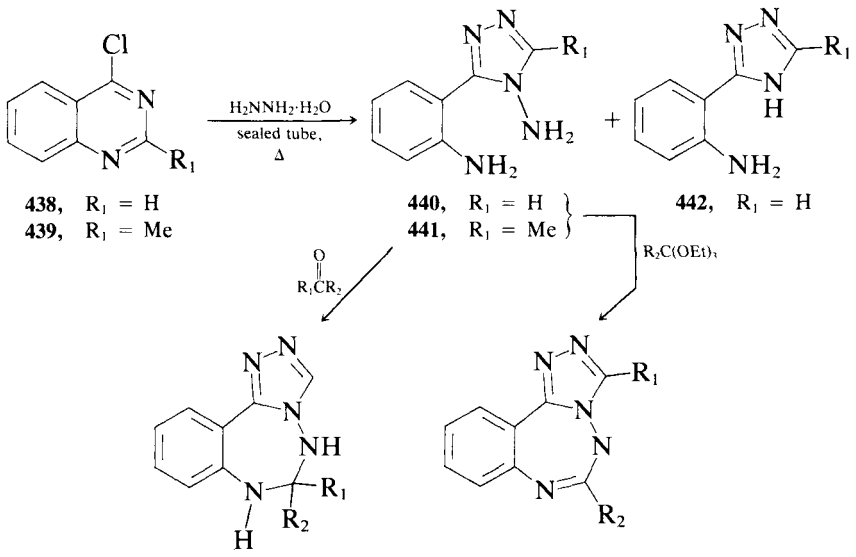
benzophenones that were subsequently prepared (125), Lamchen and Wicken (126) found that only two, **432** and **433,** produced triazepines (**436** and **437,** respectively) on treatment with ethanolic hydrazine hydrate. Physical constants for members of this series are given in Table 21.

Triazolobenzotriazepines were reported first by Bowie and Thomason (127). The starting materials for these fused benzotriazepines were 4-amino-3-(2-aminophenyl)-4H-[1,2,4]triazole (**440**) and the 5-methyl derivative **441.** Triazoles **440** and **441** were the major products from the reactions of 4-chloroquinazolines **438** and **439,** respectively, with hydrazine hydrate in a sealed tube (Eq. 70). Mechanisms for these remarkable transformations were presented. In the preparation of **440,** the deaminated triazole **442** was a co-product. Treatment of **440** with aldehydes and ketones produced the 6,7-dihydro-5H-[1,2,4]triazolo[4,3-*d*][1,3,4]benzotriazepines **443–448.** When treated with triethyl orthoesters, **440** and **441** yielded the 5H-[1,2,4]triazolo[4,3-

TABLE 21. 5-ARYL-12H-ISOINDOLO[2,1-*a*][1,3,4]BENZOTRIAZEPIN-12-ONES




| $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| MeO | MeO | H | H | 271–272 | 95 | 123 |
| MeO | H | H | H | 241–242 | 91 | 123 |
| MeS | H | H | H | 242–244 | 91 | 126 |
| MeO | MeO | H($O_2$N) | $O_2$N(H) | 293–296 | 98 | 126 |




**438**, $R_1$ = H
**439**, $R_1$ = Me

**440**, $R_1$ = H
**441**, $R_1$ = Me

**442**, $R_1$ = H

(70)

**443**, $R_1$ = H, $R_2$ = Ph
**444**, $R_1$ = H, $R_2$ = *p*-$ClC_6H_4$
**445**, $R_1$ = H, $R_2$ = *p*-$O_2NC_6H_4$
**446**, $R_1$ = H, $R_2$ = 5-nitro-2-furyl
**447**, $R_1$ = $R_2$ = Me
**448**, $R_1R_2$ = $(CH_2)_5$

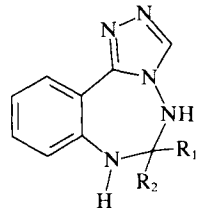
**449**, $R_1$ = $R_2$ = H
**450**, $R_1$ = H, $R_2$ = Me
**451**, $R_1$ = H, $R_2$ = Et
**452**, $R_1$ = H, $R_2$ = Ph
**453**, $R_1$ = Me, $R_2$ = H
**454**, $R_1$ = $R_2$ = Me

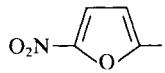
*d*][1,3,4]benzotriazepines **449–454.** Physical constants for these compounds are listed in Tables 22 and 23.

A longer synthetic route to a triazolobenzotriazepine system (Fig. 5) has recently been disclosed by Hester (128). 2-Benzyl-4-chloroaniline (**456**) was prepared from 2-amino-5-chlorobenzophenone (**249**) by Wolff–Kishner reduction and subsequently treated with triethyl orthoformate and acetylhydrazine to produce hydrazide **457.** Cyclization of **457** in pyridine and diglyme yielded the [1,2,4]triazole **458.** Reintroduction of the carbonyl group by chromic acid oxidation gave 5-chloro-2-(3-methyl-4H-[1,2,4]triazol-4-yl)benzophenone (**459**), which was brominated with *N*-bromosuccinimide to the 5-bromo derivative **460.** Cyclization of **460** with hydrazine gave 8-chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-*a*][1,3,4]benzotriazepine (**461**). Alkylation of **461** with methyl iodide and sodium hydride in dimethylformamide produced the 4-methyl derivative **462.** The overall yield of **462** from **249** was approximately 4%. Triazolobenzotriazepines **461** and **462** were shown to have sedative, tranquilizing, and muscle relaxant properties in mice.

In a related patent (Eq. 71), Hester (129) described the synthesis of the 1-(dimethylamino)methyl derivative of **461** (**467**). Since the synthetic route to **461** was not amenable to aminoalkyl substitution at the 3-position of the triazole ring, a different pathway, starting with 3-amino-6-chloro-3,4-dihy-

TABLE 22. 6,7-DIHYDRO-5H-[1,2,4]TRIAZOLO[4,3-*d*][1,3,4]BENZOTRIAZEPINES[a]

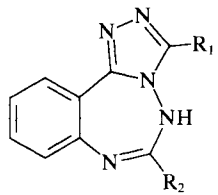


| $R_1$ | $R_2$ | mp (°C) | Yield (%) |
|---|---|---|---|
| H | Ph | 176–178 | 80 |
| H | *p*-$ClC_6H_4$ | 204 | 90 |
| H | *p*-$O_2NC_6H_4$ | 227–229 | 90 |
| H |  | 215–216 | 80 |
| Me | Me | 170–172 | 80 |
| —$(CH_2)_5$— | | 210–212 | 90 |

[a]Ref. 127.

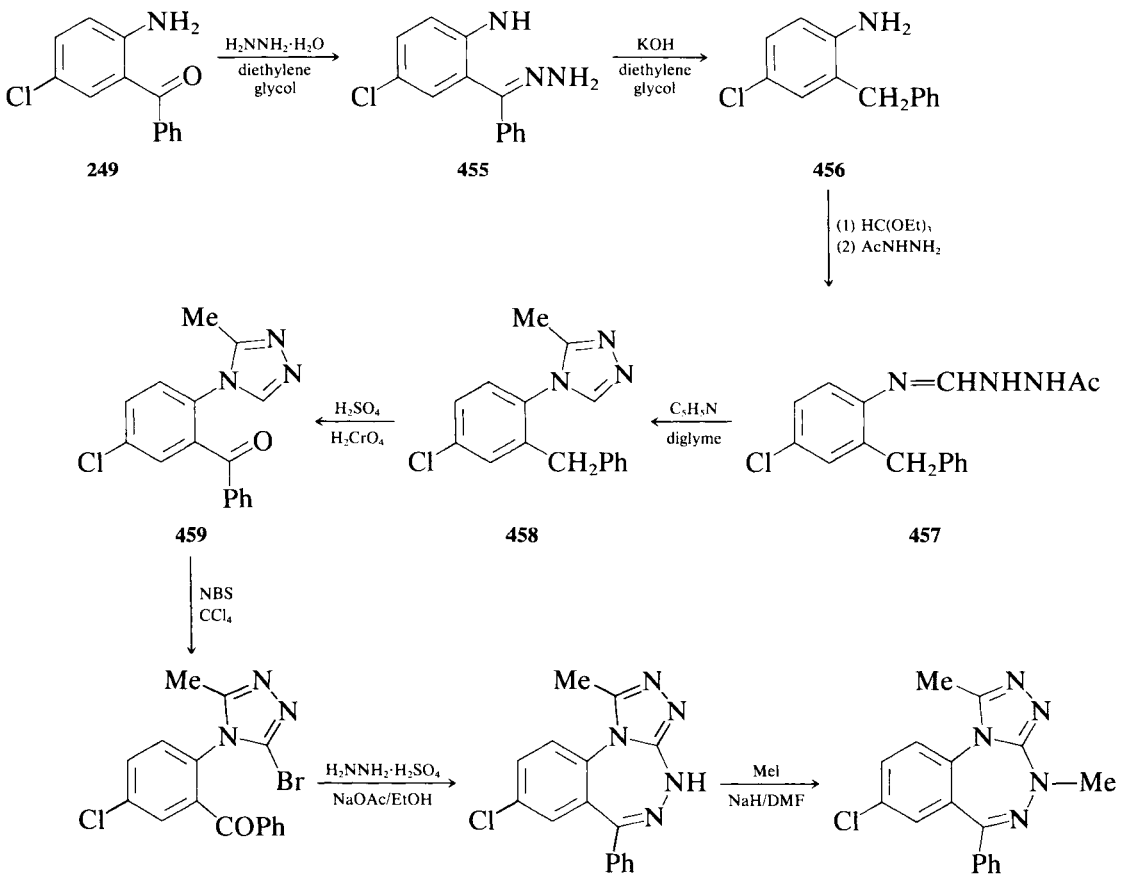
dro-4-hydroxy-4-phenylquinazoline (**463**), was employed. Compound **463** was first prepared by Derieg and co-workers (130). Interestingly, they showed it to be identical with a compound that had been prepared in a different manner by Podesva and co-workers (131) and formulated as 4,5-dihydro-5-hydroxy-5-phenyl-3H-[1,3,4]benzotriazepine. Conversion of **463** to 5-chloro-2-[3-(chloromethyl)-4H-[1,2,4]triazol-4-yl]benzophenone (**464**) was accomplished with chloroacetyl chloride. Treatment of **464** with *N*-bromosucci-

TABLE 23. 5H-[1,2,4]TRIAZOLO[4,3-*d*][1,3,4]BENZOTRIAZEPINES[a]



| $R_1$ | $R_2$ | mp (°C) | Yield (%) |
|---|---|---|---|
| H | H | 176–178 | 80 |
| H | Me | 339–341 | 80 |
| H | Et | 284–285 | 80 |
| H | Ph | 261–262 | 50 |
| Me | H | 313–316 | 50 |
| Me | Me | 315–317 | 60 |

[a]Ref. 127.

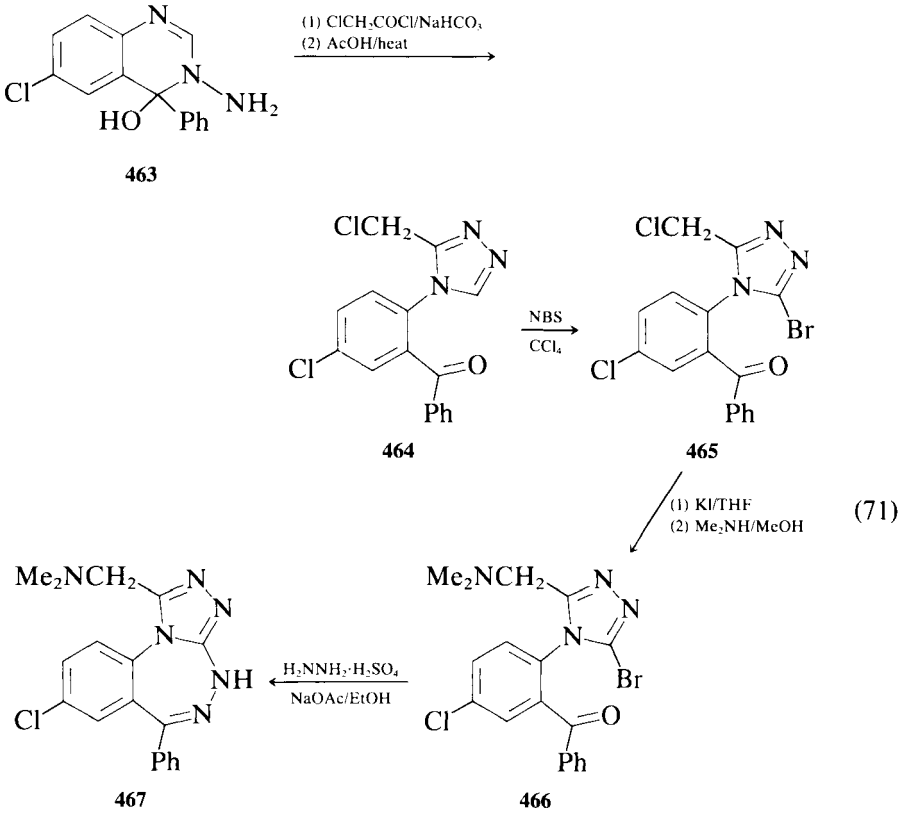



249 455 456

459 458 457

460 461 462

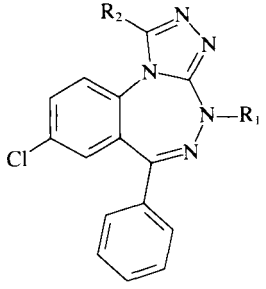
**Figure 5**




463 464 465 466 467 (71)

nimide led to the 5-bromo derivative (**465**), which was then treated with dimethylamine to afford the 3-(dimethylamino)methyl derivative **466.** Subsequent cyclization of **466** with hydrazine gave triazolobenzotriazepine **467.** Compound **467** was shown to possess anticonvulsant and muscle relaxant properties in mice. Members of this ring system are listed in Table 24.

TABLE 24. 8-CHLORO-6-PHENYL-4H-[1,2,4]TRIAZOLO[4,3-*a*]-[1,3,4]BENZOTRIAZEPINES



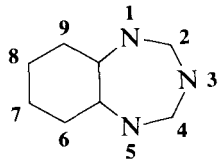
*(continued)*

TABLE 24. (*Continued*)

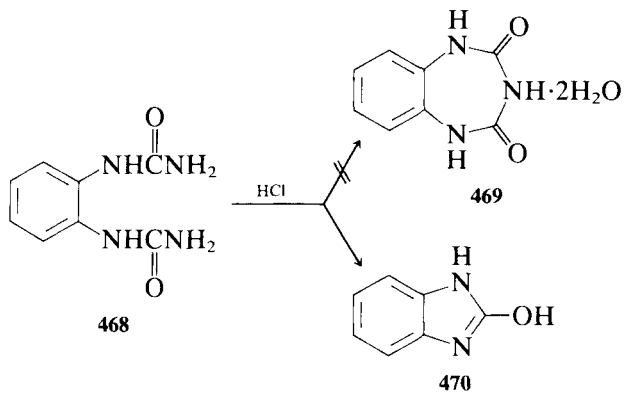
| $R_1$ | $R_2$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|
| H | Me | 241–245 | 45 | 128 |
| Me | Me | 227–230 | 68 | 128 |
| H | $Me_2NCH_2$ | 226–228.5 | 23 | 129 |

## D. [*1,3,5*]*Benzotriazepines*

### a. OXYGENATED [1,3,5]BENZOTRIAZEPINES



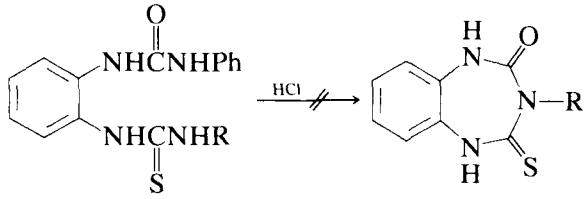

In 1929 Ghosh and Guha (132) reported benzotriazepinedione dihydrate **469,** which they assigned as the product resulting from the treatment of *N,N*″-1,2-phenylenebisurea (**468**) with hydrochloric acid (Eq. 72). In a rein-




(72)

vestigation of this work, Peet and Sunder (57) found that this structural assignment was incorrect and that the correct structure was 2-hydroxybenzimidazole (**470**). Ghosh and Guha (132) had based their structural assignment on elemental analysis for nitrogen, which is similar for compounds **469** (19.71%) and **470** (20.89%). Similar reactions reported by these authors included preparations of thioxobenzotriazepinones **473** and **474** from **471** and **472,** respectively (Eq. 73). It follows that these structural assignments, which were also made solely on the basis of elemental analysis for nitrogen, are

probably incorrect. Lempert and co-workers (133, 134) have stated that the benzotriazepine structures reported by Ghosh and Guha (132) are apparently misassigned.

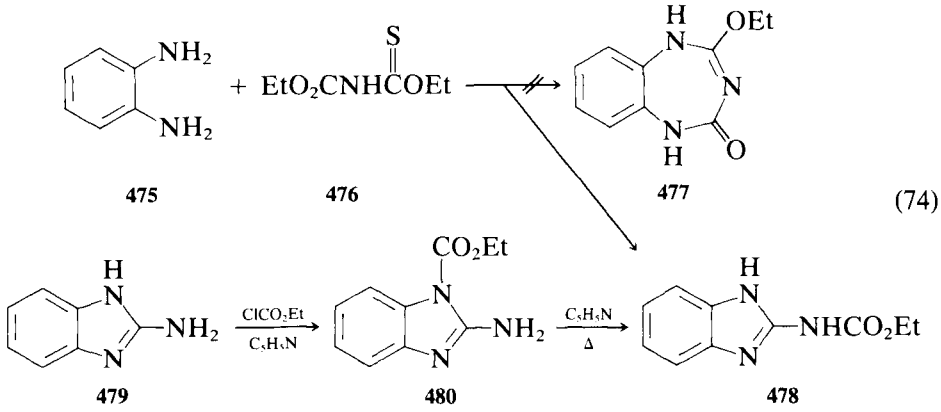


(73)

**471**, R = Ph
**472**, R = *p*-$MeC_6H_4$

**473**, R = Ph
**474**, R = *p*-$MeC_6H_4$

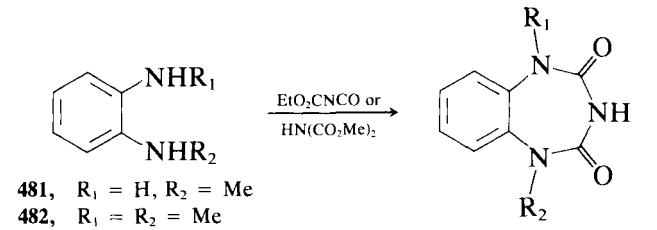
In a subsequent article, Guha and co-workers (56) reported the reactions of ethyl carbethoxythiocarbamate (**476**) with diamines, including *o*-phenylenediamine (**475**). Benzotriazepinone **477** was claimed to be the reaction product (Eq. 74). However, this reaction was reinvestigated by Peet and Sunder (57), who found that the reaction product was not **477,** but rather the isomeric 2-benzimidazolylcarbamic acid ethyl ester **478.** The correct structural assignment was supported by an alternative synthesis. Treatment of 2-aminobenzimidazole with ethyl chloroformate according to the procedure of Stedman (135) yielded 2-amino-1H-benzimidazole-1-carboxylic acid ethyl ester (**480**), which was then isomerized to **478** in pyridine at reflux. It is interesting to note that Ridi and Checchi (136) had earlier prepared **480,** but misassigned its structure as **478.**



(74)

**475** **476** **477** **479** **480** **478**

Hagemann (62) recently disclosed the preparation of benzotriazepinediones **483** and **484** from *o*-phenylenediamines (Eq. 75). These compounds were cited as plant-protective agents and were prepared by treatment of substituted *o*-phenylenediamines **481** and **482** with carbethoxy isocyanate or



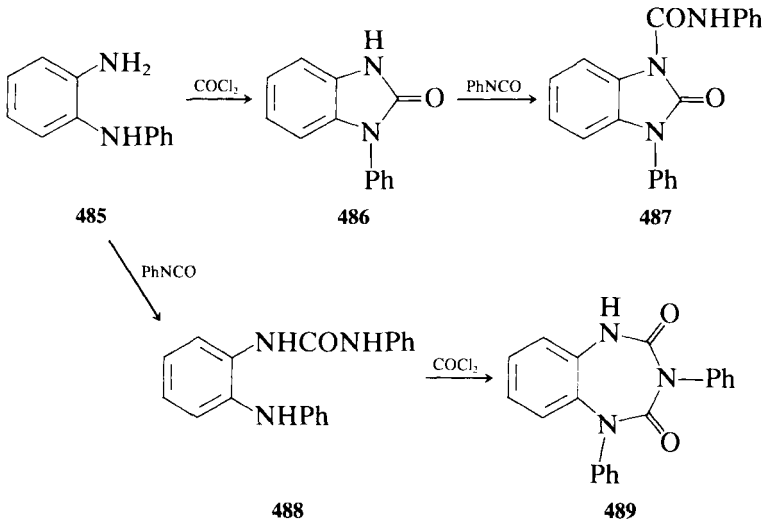

**481**, $R_1$ = H, $R_2$ = Me
**482**, $R_1$ = $R_2$ = Me

**483**, $R_1$ = H, $R_2$ = Me
**484**, $R_1$ = $R_2$ = Me

(75)

dimethyl iminodicarboxylate, respectively. However, Lempert and co-workers (133, 134) have cautioned that these structural assignments may be in error.

3,5-Dihydro-1,3-diphenyl-1H-[1,3,5]benzotriazepine-2,4-dione (**489**) has been synthesized by Weigert (137) and appropriately distinguished from the isomeric benzimidazolinone (**487**). Treatment of *N*-phenyl-*o*-phenylenediamine (**485**) with phosgene (Eq. 76) yielded 1-phenylbenzimidazolin-2-one (**486**), which then gave **487** upon treatment with phenyl isocyanate. However, when the order of treatment with these reagents was reversed, **489** was produced via the carbanilide **488.** Actually, in this study benzotriazepinone **489** was prepared for the purpose of establishing the structure of benzimidazolinone **487** (138).

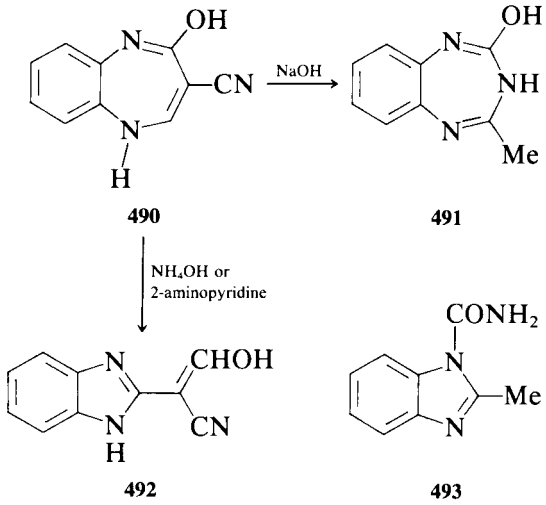



**485** **486** **487**

**488** **489**

(76)

Okamoto and Ueda (139,140) reported the formation of benzotriazepinone **491** in 38% yield from 4-amino-1H-[1,5]benzodiazepine-3-carbonitrile (**490**) upon treatment with sodium hydroxide (Eq. 77). In contrast to this finding, benzimidazole **492** was produced from **490** in 36% yield by treatment with ammonium hydroxide or 2-aminopyridine. The authors did not mention the

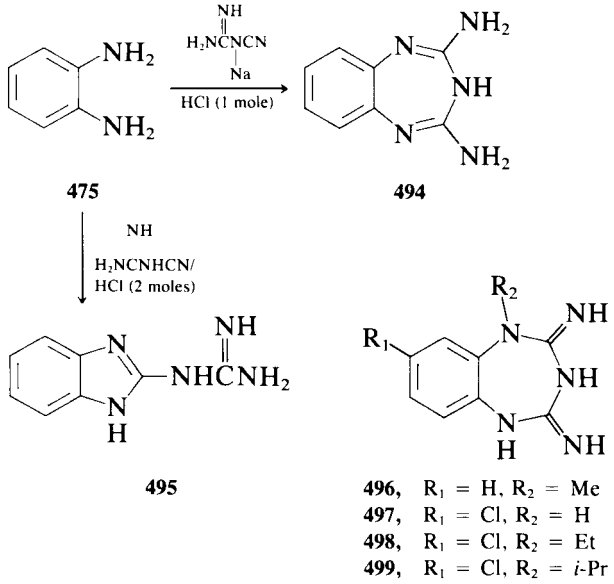



(77)

isomeric benzimidazole **493** as an alternative structural possibility for **491.** The formation of **493** from **490** seems plausible and can be envisioned by a simple variation of the mechanism depicted by the authors for the formation of **491.**

b. 2,4-DIAMINO-2,5-DIHYDRO-1H-[1,3,5]BENZOTRIAZEPINES

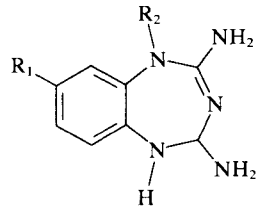
King, Acheson, and Spensley (141) reported in 1949 that the reaction of sodium dicyanodiamide with *o*-phenylenediamine (**475**) in water containing 1 mole of concentrated hydrochloric acid (Eq. 78) produced the diamino-




(78)

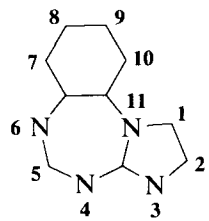
benzotriazepine **494.** This result was contrasted with that of Pellizarri (142,143), who treated **475** with dicyanodiamide in water containing 2 moles of concentrated hydrochloric acid and obtained benzimidazole **495.** The benzotriazepine structure **494** was assigned on the basis of its failure to react with nitrous acid. In a subsequent article Acheson and Taylor (144) reported benzotriazepines **496–499,** which were prepared in similar fashion to **494** from substituted *o*-phenylenediamines. Compounds **494** and **496–499** were isolated as salts (Table 25).

TABLE 25. 2,4-DIAMINO-2,5-DIHYDRO-1H-[1,3,5]BENZOTRIAZEPINES



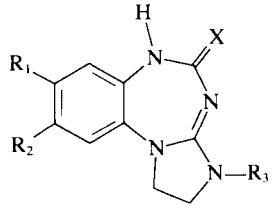
| $R_1$ | $R_2$ | Adducts | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|
| H | H | Nitrate | 269 (dec.) | 77 | 141 |
| H | H | Picrate | 268 (dec.) | — | 141 |
| H | H | ¼ Hydrate | 191 (dec.) | — | 141 |
| H | Me | Dipicrate | 216–217 (dec.) | 68 | 144 |
| H | Me | Sulfate dihydrate | 252 (dec.) | — | 144 |
| Cl | H | Picrate | 263–264 | 79 | 144 |
| Cl | H | Hemisulfate, hemihydrate | 274 (dec.) | — | 144 |
| Cl | Et | Dipicrate | 195–196 (dec.) | 58 | 144 |
| Cl | Et | Sulfate, 2.5 hydrate | 170–180 (dec.) | — | 144 |
| Cl | *i*-Pr | Dipicrate | 208–210 (dec.) | 81 | 144 |
| Cl | *i*-Pr | Sulfate | 175–177 (dec.) | 86 | 144 |

## c. IMIDAZO[1,2-*a*][1,3,5]BENZOTRIAZEPINES



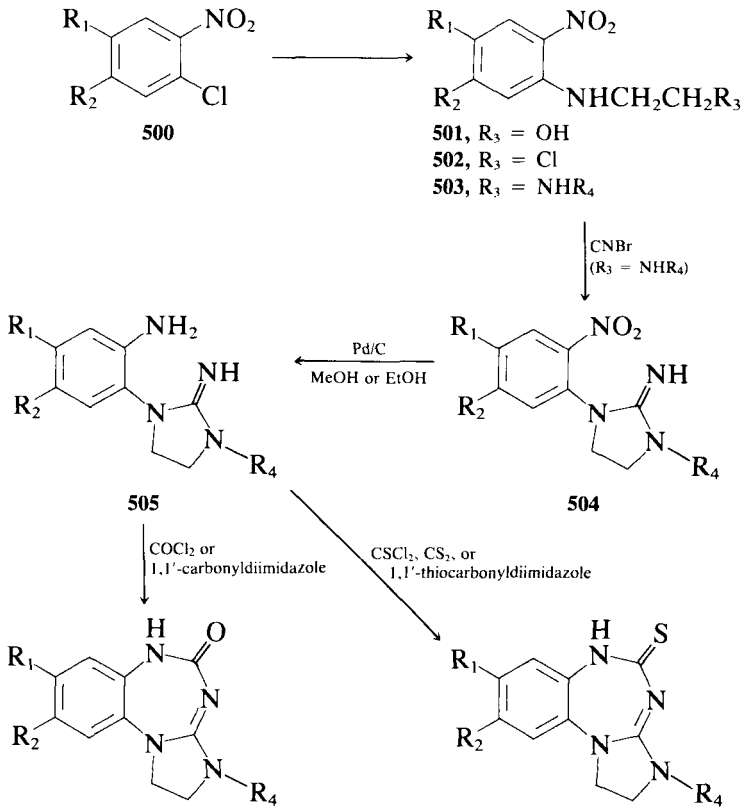
In several papers dealing with [1,3,5]benzotriazepines Lempert and coworkers (133,134,145) have called attention to the pitfalls present in designing syntheses of this ring system. These authors devised routes to 2,3-dihydro-1H-imidazo[1,2-*a*][1,3,5]benzotriazepine-5(6H)-ones **506–511** and the corresponding thiones **512–520** (Table 26) which precluded the formation of benzimidazoles as ring contraction products, either directly or subsequent to the formation of the [1,3,5]benzotriazepine systems. 2-Chloronitrobenzenes (**500**) were converted to amino alchohols of general structure **501** with 2-aminoethanol (Fig. 6). Treatment of **501** with thionyl chloride gave 2-chloroethylanilines **502,** which, when treated with *n*-butylamine led to ethylenediamines **503** ($R_4$ = *n*-Bu). Compounds **503** ($R_4$ = H) could be prepared directly from **500** and ethylenediamine. Cyclization of **503** with cyanogen bromide yielded iminoimidazolines **504,** which were catalytically reduced to the corresponding anilines **505.** Phosgenation of **505** or treatment of **505** with 1,1′-carbonyldiimidazole yielded the benzotriazepinones **506–511.** Benzotriazepinethiones **512–520** were produced by treatment of **505** with thiophosgene, carbon disulfide, or 1,1′-thiocarbonyldiimidazole.

TABLE 26. 2,3-DIHYDRO-1H-IMIDAZO[1,2-*a*][1,3,5]BENZOTRIAZEPIN-5(6H)-ONES AND -THIONES[a]




| $R_1$ | $R_2$ | $R_3$ | X | mp (°C) | Yield (%) |
|---|---|---|---|---|---|
| H | H | H | O | 255–257 | 30–90 |
| H | H | *n*-Bu | O | 205–207 | 41 |
| Cl | H | *n*-Bu | O | 220 | 27 |
| H | Cl | *n*-Bu | O | 197–198 | 12 |
| $MeO_2C$ | H | H | O | 272 (dec.) | 27 |
| *n*-BuNHCO | H | *n*-Bu | O | 244–245 | 21 |
| H | H | H | S | 264–265 (dec.) | 46–82 |
| H | H | *n*-Bu | S | 187–188 | 95 |
| Cl | H | H | S | 257–258 (dec.) | 60 |
| Cl | H | *n*-Bu | S | 214–216 | 16–90 |
| H | Cl | *n*-Bu | S | 217–218 | 20–70 |
| MeO | H | H | S | 260–261 | 95 |
| $MeO_2C$ | H | H | S | >300 (dec.) | 89 |
| *n*-BuNHCO | H | H | S | 248–249 | 73 |
| *n*-BuNHCO | H | *n*-Bu | S | 207–208 | 20–92 |

[a]Refs. 133 and 134.



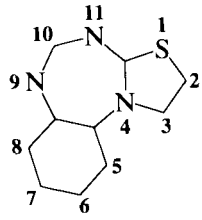

**506,** $R_1 = R_2 = R_4 = H$
**507,** $R_1 = R_2 = H$, $R_4 = n$-Bu
**508,** $R_1 = Cl$, $R_2 = H$, $R_4 = n$-Bu
**509,** $R_1 = H$, $R_2 = Cl$, $R_4 = n$-Bu
**510,** $R_1 = MeO_2C$, $R_2 = R_4 = H$
**511,** $R_1 = n$-$BuO_2C$, $R_2 = H$, $R_4 = n$-Bu

**512,** $R_1 = R_2 = R_4 = H$
**513,** $R_1 = R_2 = H$, $R_4 = n$-Bu
**514,** $R_1 = Cl$, $R_2 = R_4 = H$
**515,** $R_1 = Cl$, $R_2 = H$, $R_4 = n$-Bu
**516,** $R_1 = H$, $R_2 = Cl$, $R_4 = n$-Bu

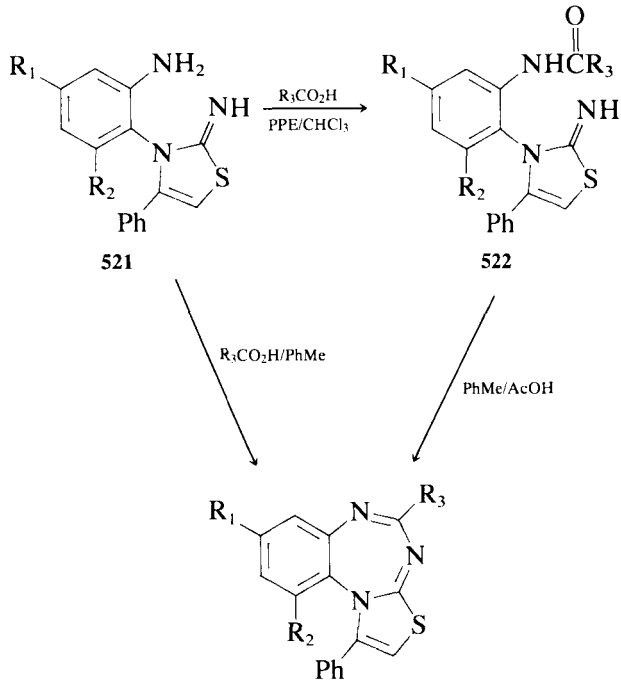
**517,** $R_1 = MeO$, $R_2 = R_4 = H$
**518,** $R_1 = MeO_2C$, $R_2 = R_4 = H$
**519,** $n$-$BuO_2C$, $R_2 = H$, $R_4 = H$
**520,** $R_1 = n$-$BuO_2C$, $R_2 = H$, $R_4 = n$-Bu

**Figure 6**

## d. 3-PHENYLBENZO[1,2-*f*]THIAZOLO[2,3-*d*][1,3,5]TRIAZEPINES



The synthesis of intermediates similar to **505,** namely 2-imino-3-(*o*-aminoaryl)-4-phenylthiazolines of general structure **521,** was reported by Vasudeva, Mahajan, and Ralhan (146). In a subsequent report, Mahajan, Sondhi, and Ralhan (147) described the conversion of **521** to 3-phenylbenzo[1,2-*f*]thiazolo[2,3-*d*][1,3,5]benzotriazepines **523–534.** Treatment of **521** with stoichiometric amounts of carboxylic acids and polyphosphate ester (PPE) in chloroform (Eq. 79) produced amides **522.** Excess carboxylic acid and acetic

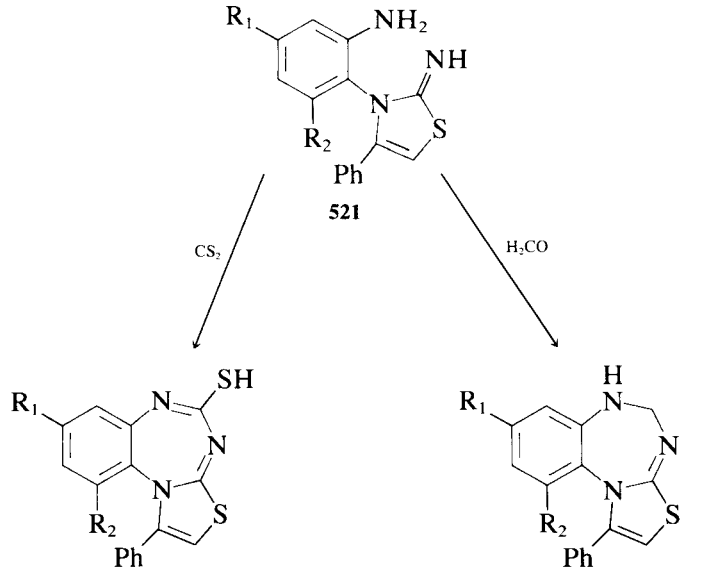



(79)

**523,** $R_1 = R_2 = R_3 = H$
**524,** $R_1 = R_2 = H, R_3 = Me$
**525,** $R_1 = R_2 = H, R_3 = Et$
**526,** $R_1 = R_3 = H, R_2 = Me$
**527,** $R_1 = H, R_2 = R_3 = Me$
**528,** $R_1 = H, R_2 = Me, R_3 = Et$
**529,** $R_1 = Me, R_2 = R_3 = H$
**530,** $R_1 = R_3 = Me, R_2 = H$
**531,** $R_1 = Me, R_2 = H, R_3 = Et$
**532,** $R_1 = MeO, R_2 = R_3 = H$
**533,** $R_1 = MeO, R_2 = H, R_3 = Me$
**534,** $R_1 = MeO, R_2 = H, R_3 = Et$

anhydride afforded diacyl derivatives of **521.** When compounds **522** were heated in toluene containing a catalytic amount of acetic acid, benzotriazepines **523–534** resulted. Alternatively, benzotriazepines **523–534** could be produced directly from **521** by treatment with stoichiometric quantities of carboxylic acids in toluene at reflux.

Sondhi, Mahajan, and Ralhan (148) also used intermediates of general structure **521** for the synthesis of 3-phenylbenzo[1,2-*f*]thiazolo[2,3-*d*]-[1,3,5]triazepine-10-thiols **535–538** and 9,10-dihydro-3-phenylbenzo[1,2,-*f*]thiazolo[2,3-*d*][1,3,5]triazepines **539–542.** Thus treatment of **521** with carbon disulfide gave thiols **535–538,** while compounds **539–542** were obtained by treating **521** with paraformaldehyde (Eq. 80). Physical constants for members of this ring system are given in Tables 27 and 28.

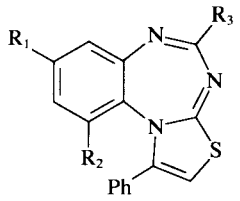



(80)

**535,** $R_1 = R_2 = H$
**536,** $R_1 = H$, $R_2 = Me$
**537,** $R_1 = Me$, $R_2 = H$
**538,** $R_1 = MeO$, $R_2 = H$

**539,** $R_1 = R_2 = H$
**540,** $R_1 = H$, $R_2 = Me$
**541,** $R_1 = Me$, $R_2 = H$
**542,** $R_1 = MeO$, $R_2 = H$

TABLE 27. 3-PHENYLBENZO[1,2-*f*]THIAZOLO[2,3-*d*][1,3,5]TRIAZEPINES

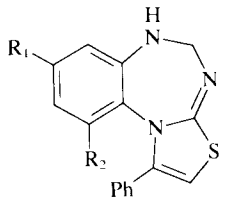



*(continued)*

TABLE 27. (*Continued*)

| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|
| H | H | H | 245 | 73 | 147 |
| H | H | Me | 241 | 74 | 147 |
| H | H | Et | 238 | 80 | 147 |
| H | Me | H | 176 | 62 | 147 |
| H | Me | Me | 175 | 62 | 147 |
| H | Me | Et | 172 | 68 | 147 |
| Me | H | H | 236 | 65 | 147 |
| Me | H | Me | 234 | 68 | 147 |
| Me | H | Et | 230 | 72 | 147 |
| MeO | H | H | 214 | 60 | 147 |
| MeO | H | Me | 216 | 58 | 147 |
| MeO | H | Et | 212 | 76 | 147 |
| H | H | HS | 195 | 60–85 | 148 |
| H | Me | HS | 193 | 60–85 | 148 |
| Me | H | HS | 199 | 60–85 | 148 |
| MeO | H | HS | 190 | 60–85 | 148 |

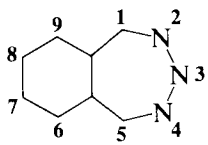
TABLE 28. 9,10-DIHYDRO-3-PHENYLBENZO[1,2-*f*]THIAZOLO[2,3-*d*]-[1,3,5]TRIAZEPINES[a]



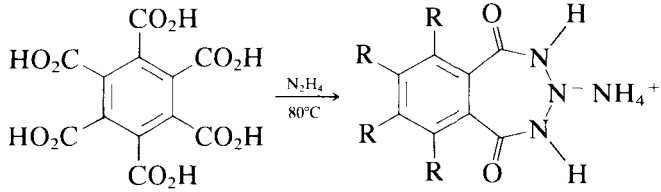

| $R_1$ | $R_2$ | mp (°C) | Yield (%) |
|---|---|---|---|
| H | H | 216 | 60–85 |
| H | Me | 211 | 60–85 |
| Me | H | 201 | 60–85 |
| MeO | H | 208 | 60–85 |

[a]Ref. 148.

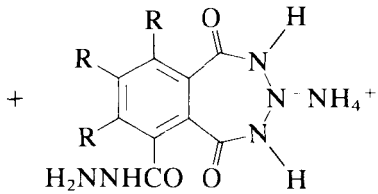
## E. [2,3,4]Benzotriazepines



There is one report concerning [2,3,4]benzotriazepines in the older chemical literature, by Luria (149). When heated with hydrazine at 80°C, mellitic acid (**543**) yielded two colored products (Eq. 81). A yellow-colored material was formulated as the 3,4-dihydro-2H-[2,3,4]benzotriazepine-1,5-dione-6,7,8,9-tetracarboxylic acid salt **544.** An intensely red-colored material was assigned as the corresponding 6-hydrazide **545.** These assignments were made on the basis of elemental analyses of these compounds and their silver salts and titration with potassium hydroxide. The transformation of **543** into **544** and **545** is completely without precedent, and there is little reason to believe that these product assignments are correct.



**543** **544,** R = $CO_2^- N_2H_5^+$

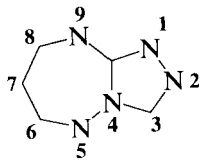


**545,** R = $CO_2^- N_2H_5^+$ (81)

## 4. Other Fused-Ring Triazepine Ring Systems

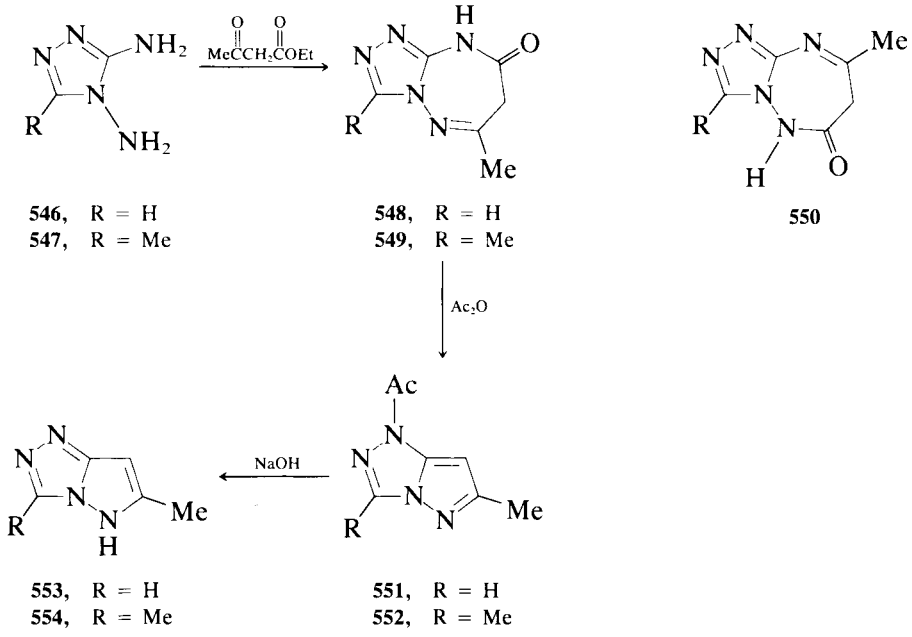
### A. *[1,2,4]Triazepine Fused Systems*

#### a. TRIAZOLO- AND TRIAZINO[1,2,4]TRIAZEPINES



Condensation reactions of ethyl acetoacetate with 3,4-diamino-[1,2,4]triazoles have been investigated by several groups. Claramunt and co-

workers (150) assigned structures **548** and **549** to the products they obtained, respectively, from the condensation of 3,4-diamino[1,2,4]triazole (**546**) and 3,4-diamino-5-methyl[1,2,4]triazole (**547**) with ethyl acetoacetate (Eq. 82). The basis for their assignments emerged from subsequent transformations of **548** and **549.** Treatment of these compounds with acetic anhydride followed by base hydrolysis led to pyrazolotriazoles **553** and **554,** respectively. The authors argued that these structures could not have arisen from triazolotriazepines of general structure **550,** which had earlier been assigned to the reaction products by Gehlen and Drohla (151). These authors evidently had also produced **553** and **554** by the acetylation–hydrolysis sequence but misassigned their structures. The structure of **549** has been confirmed by Leroy and co-workers (152) from crystallographic studies.




**546,** R = H
**547,** R = Me

**548,** R = H
**549,** R = Me

**550**

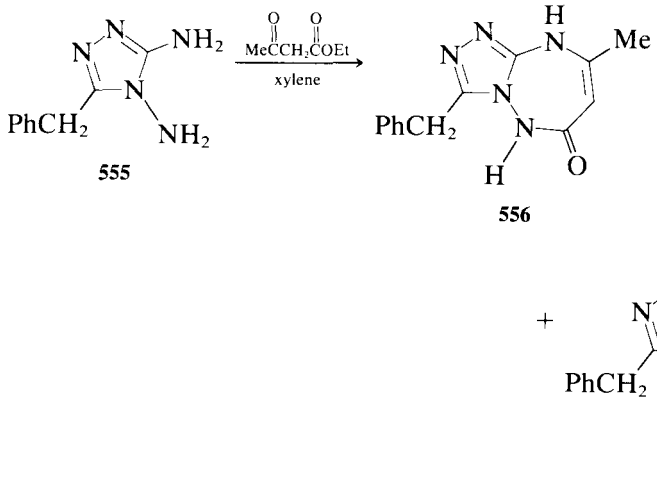
(82)

**553,** R = H
**554,** R = Me

**551,** R = H
**552,** R = Me

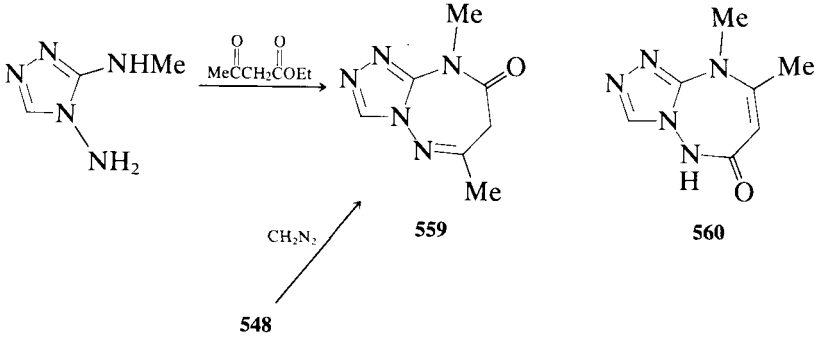
Kochbar (153) reported that the condensation of 3,4-diamino-5-benzyl[1,2,4]triazole (**555**) with ethyl acetoacetate yielded the two isomeric triazolotriazepines **556** and **557** in yields of 24 and 1%, respectively (Eq. 83). Structural assignments were made largely on the basis of nmr spectra.

The condensation of ethyl acetoacetate with **546** was recently reinvestigated by Essassi and co-workers (154), who confirmed that the reaction product was **548.** The triazolotriazepine that resulted from the condensation was treated with diazomethane (Eq. 84), and the resulting methylated material was found to be identical to the sole product obtained by condensation of 3-methylamino-4-amino[1,2,4]triazole (**558**) with ethyl acetoacetate. The latter reaction could have produced either **559** or **560.** However, nmr spec-




(83)

trometry indicated the absence of an olefinic proton and the presence of a methylene group, which clearly showed the product to be **559.**




(84)

In a subsequent report, Essassi and co-workers (155) converted **548** to its thione analog (**561**) with phosphorous pentasulfide. The thione served as the starting material for the attachment of a second fused triazole ring to the triazepine nucleus (Fig. 7). The hydrazino derivative of **561** (**563**) was prepared directly from **561** by treatment with hydrazine as well as through the methylthio derivative **562.** Subsequent reaction of **563** with formic and acetic acids led to the fused triazepines **566** and **565,** respectively. Alternatively, **565** was produced from **561** by treatment with acetylhydrazine to yield hydrazide **564,** which was then cyclized with acetic acid. The phenyl-substituted triazolotriazepine **568** was prepared in similar fashion via hydrazide **567.** Members of this ring system are listed in Tables 29 and 30.

Lavergne and co-workers (156) also investigated the reactions of 3,4-

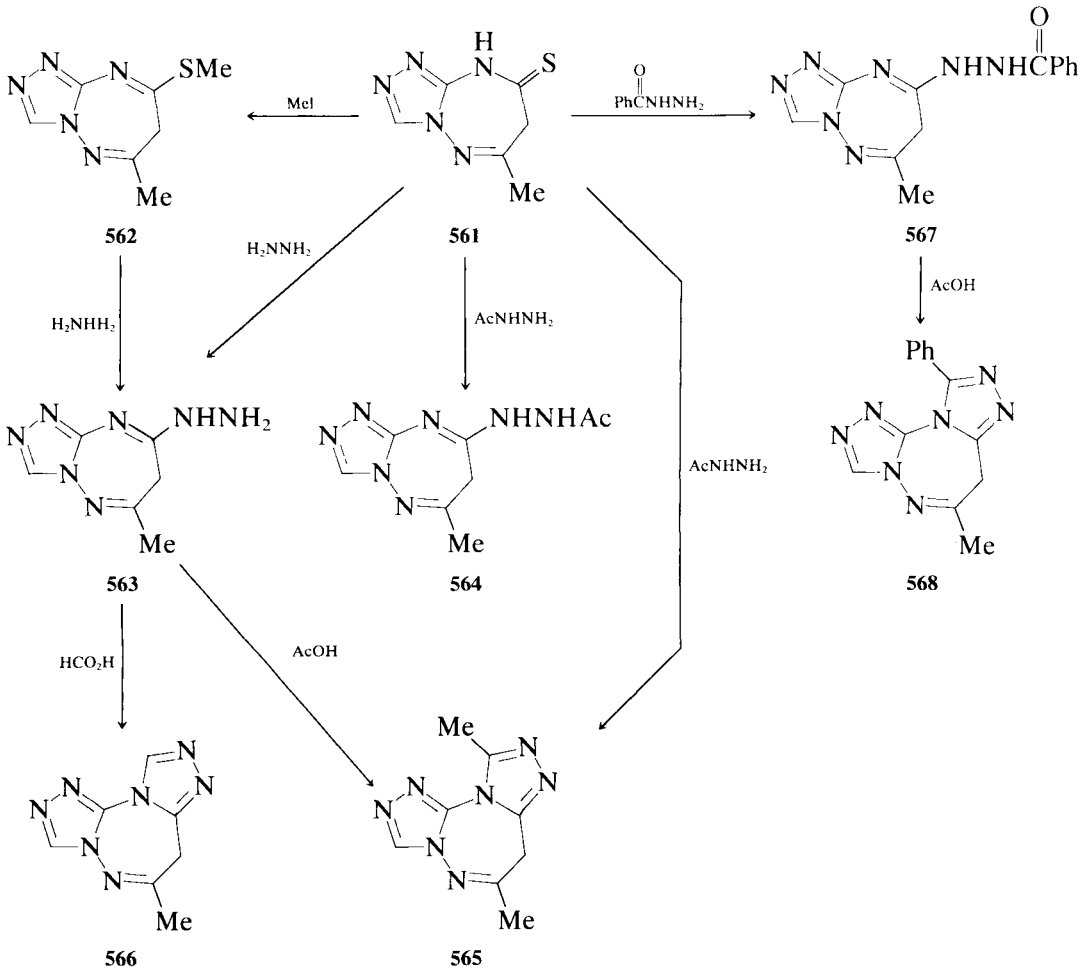
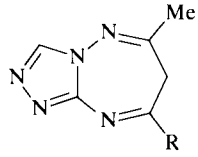

SMe
MeI
H
S
PhCNHNHCO
NHNHCPh
O
Me
562
561
567
H2NNH2
AcOH
Ph
NHNH2
AcNHNH2
NHNHAc
AcNHNH2
563
564
568
HCO2H
AcOH
566
565

Figure 7

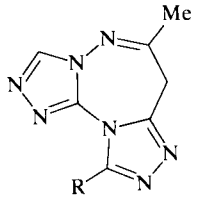
TABLE 29. 8,9-DIHYDRO-6-METHYL-7H-[1,2,4]TRIAZOLO[4,3-*b*][1,2,4]TRIAZEPINES



| R | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|
| HO | 253–255 | 76 | 150 |
| HO | 255–257 | 30–75 | 154 |
| HS | 221–223 | 70 | 155 |
| MeS | 174–175 | 60 | 155 |
| $H_2NNH$ | 175–177 | 70 | 155 |
| AcNHNH | 235–236 | 60 | 155 |
| PhCONHNH | 232–234 | 80 | 155 |

diamino-4,5-dihydrotriazine-5-ones of general structures **569** and **578** with ethyl acetoacetate. With triazines **569,** 1,8-dihydro-7-methyl[1,2,4]triazino[4,3-*b*][1,2,4]triazepine-4,9-diones **570–572** (Table 31) and smaller amounts of the isomeric 1,6-dihydro-9-methyl[1,2,4]triazino[4,3-*b*][1,2,4]triazepine-4,7-diones **573–575** resulted (Eq. 85). Also produced in two of these reactions were triazolotriazines **576** and **577.** Structural assignments were made on the basis of spectral data and methylation studies. Triazinotriazepines **579** and **580** and smaller amounts of triazinotriazepines **581** and **582** were similarly produced from the reaction of triazines of general structure **578** with ethyl acetoacetate (Eq. 86). These structural assignments were made on the basis of nmr spectrometry.

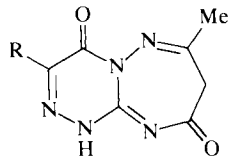
TABLE 30. 6-METHYL-7H-BIS[1,2,4]TRIAZOLO[4,3-*b*:4,3-*d*][1,2,4]TRIAZEPINES[a]



| R | mp (°C) | Yield (%) |
|---|---|---|
| H | 240–241 | 80 |
| Me | 232–234 | 80 |
| Ph | 230–232 | 70 |

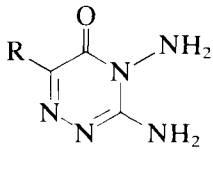
[a]Ref. 155.

TABLE 31. 1,8-DIHYDRO-7-METHYL[1,2,4]TRIAZINO[4,3-*b*][1,2,4]TRIAZEPINE-4,9-DIONES[a]

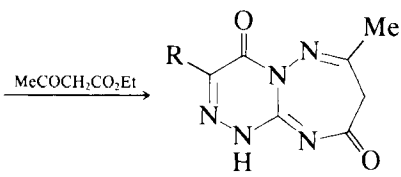


| R | mp (°C | Yield (%) |
|---|---|---|
| H | — | 5 |
| Me | 183–184 | 12–15 |
| Ph | 253–254 | 17–27 |

[a]Ref. 156.

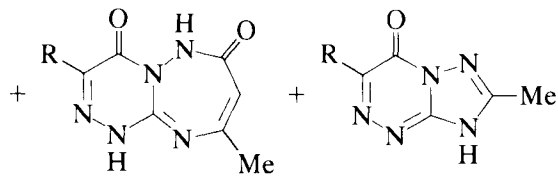


**569**



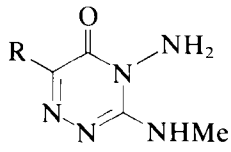
**570**, R = H
**571**, R = Me
**572**, R = Ph

(85)

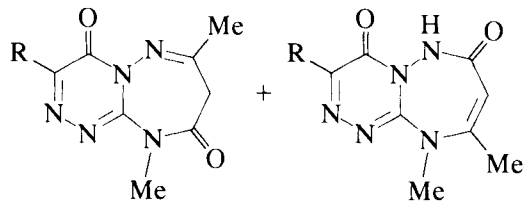


**573**, R = H
**574**, R = Me
**575**, R = Ph

**576**, R = Me
**577**, R = Ph



**578**



**579**, R = Me
**580**, R = Ph

**581**, R = Me
**582**, R = Ph

(86)

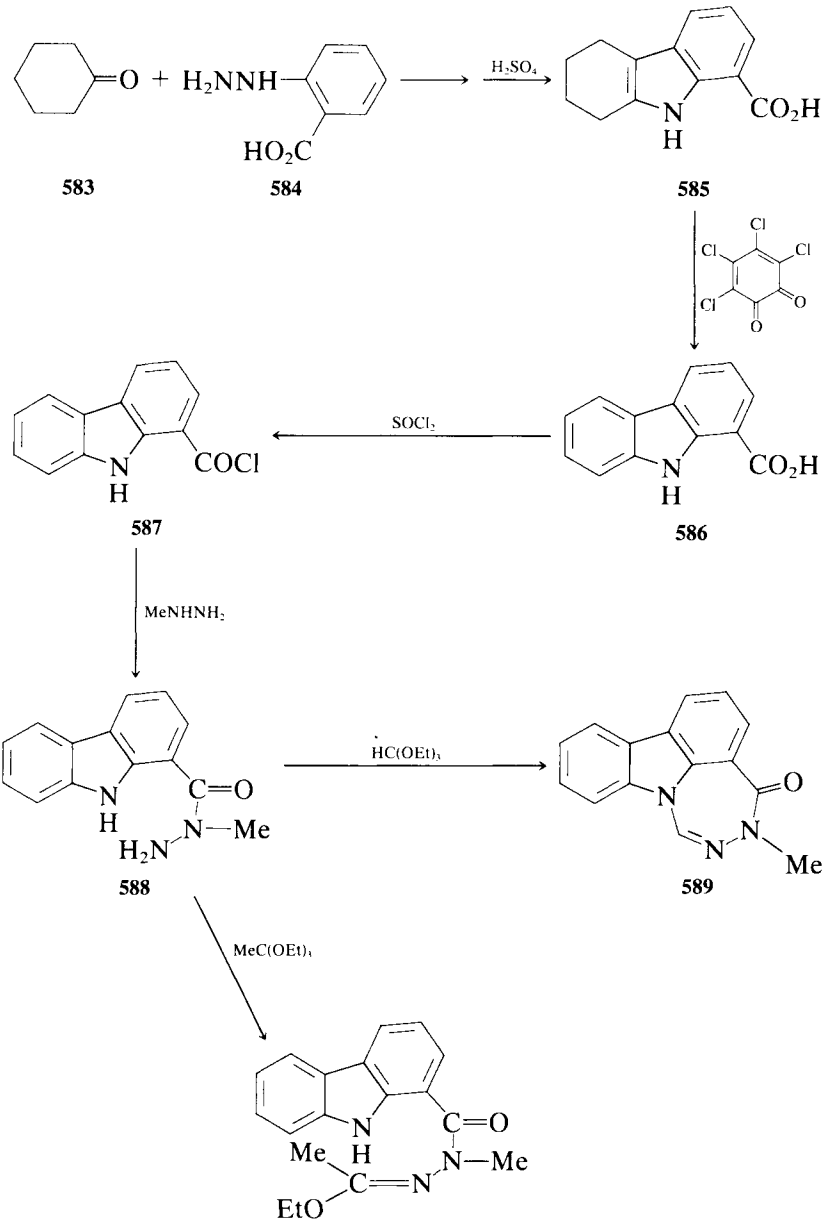
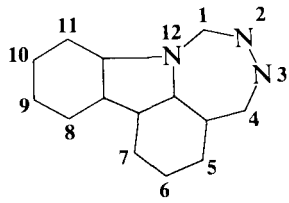

H2SO4
583
584
585
586
587
588
589
590
SOCl2
MeNHNH2
HC(OEt)3
MeC(OEt)3

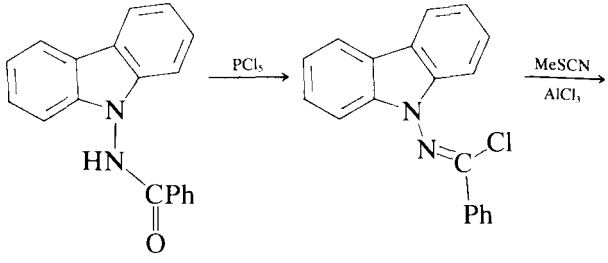
**Figure 8**

## b. [1,2,4]TRIAZEPINOCARBAZOLES

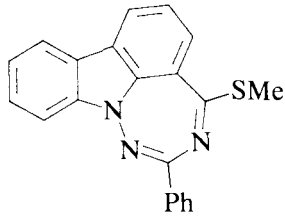



Another fused [1,2,4]triazepine compound, 3-methyl[1,2,4]triazepino[6,5,4-*jk*]carbazol-4(3H)-one (**589**), was prepared by Peet and Sunder (157). The Fischer indole synthesis (Fig. 8) was employed in the preparation of the tetrahydrocarbazole **585** from cyclohexanone (**583**) and 2-carboxyphenylhydrazine (**584**). Dehydrogenation of **585** with *o*-chloranil produced 1-carboxycarbazole (**586**), which was converted with thionyl chloride to the known (158) 1-carbazolecarboxylic acid chloride (**587**). Treatment of **587** with methylhydrazine yielded the hydrazide **588,** which was cyclized with triethyl orthoformate to **589.** Treatment of **588** with triethyl orthoacetate led only to the Schiff base **590,** which could not be subsequently cyclized to the methyl analog of **589.**

A carbazolotriazepine was also prepared by Conde and co-workers (66) from *N*-benzoylaminocarbazole (**591**). Treatment of **591** with phosphorous pentachloride (Eq. 87) gave benzhydrazidoyl chloride **592,** which was converted with aluminum chloride and methyl thiocyanate to 4-(methylthio)-2-phenyl[1,2,4]triazepino[6,7,1-*jk*]carbazole (**593**).

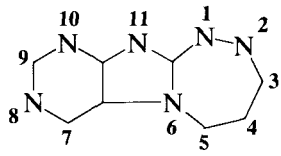



**591** **592** (87)

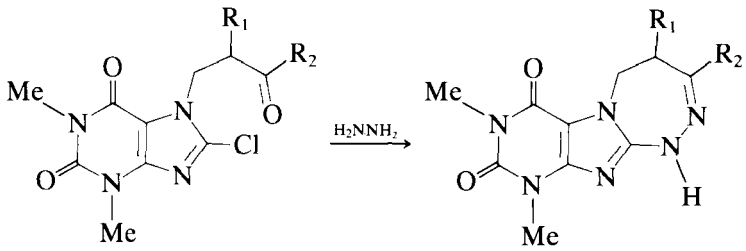



**593**

## c. 4,5-DIHYDRO-8,10-DIMETHYL-1H-[1,2,4]TRIAZEPINO-[3,4-*f*]PURINE-7,9(8H,10H)-DIONES



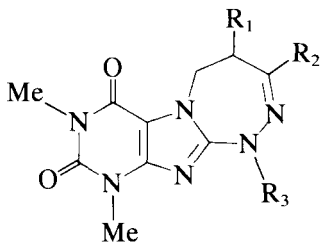
Two reports have dealt with the preparation of 1H-[1,2,4]triazepino[3,4-*f*]-purines from 7-alkyl-8-chlorotheophyllines **594–596,** which are obtainable by alkylation of 8-chlorotheophylline. Eckstein and Zajaczkowska (159) treated **594** and **595** with hydrazine to produce the triazepinoxanthines **597** and **598,** respectively (Eq. 88). Subsequent acylations and alkylations led to deriva-



**594,** $R_1$ = H, $R_2$ = Me
**595,** $R_1$ = H, $R_2$ = Et
**596,** $R_1$ = $R_2$ = Ph

**597,** $R_1$ = H, $R_2$ = Me
**598,** $R_1$ = H, $R_2$ = Et
**599,** $R_1$ = $R_2$ = Ph

(88)

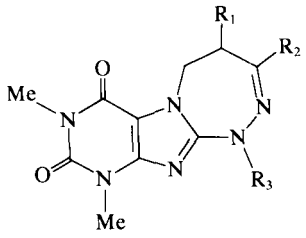


**600,** $R_1$ = H, $R_2$ = Me, $R_3$ = Ac
**601,** $R_1$ = H, $R_2$ = Me, $R_3$ = EtCO
**602,** $R_1$ = H, $R_2$ = Me, $R_3$ = $NCCH_2CH_2$

**603,** $R_1$ = H, $R_2$ = Et, $R_3$ = Ac
**604,** $R_1$ = H, $R_2$ = Et, $R_3$ = EtCO
**605,** $R_1$ = H, $R_2$ = Et, $R_3$ = $NCCH_2CH_2$

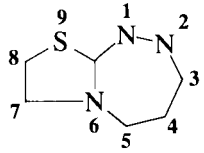
tives **600–605.** Earlier, Pazdro and Eckstein (160) had reported the diphenyl derivative **599,** which was prepared from the theophylline derivative **596.** Table 32 lists physical constants for these compounds.

TABLE 32. 4,5-DIHYDRO-8,10-DIMETHYL-1H-[1,2,4]TRIAZEPINO[3,4-*f*]PURINE-7,9(8H,10H)-DIONES

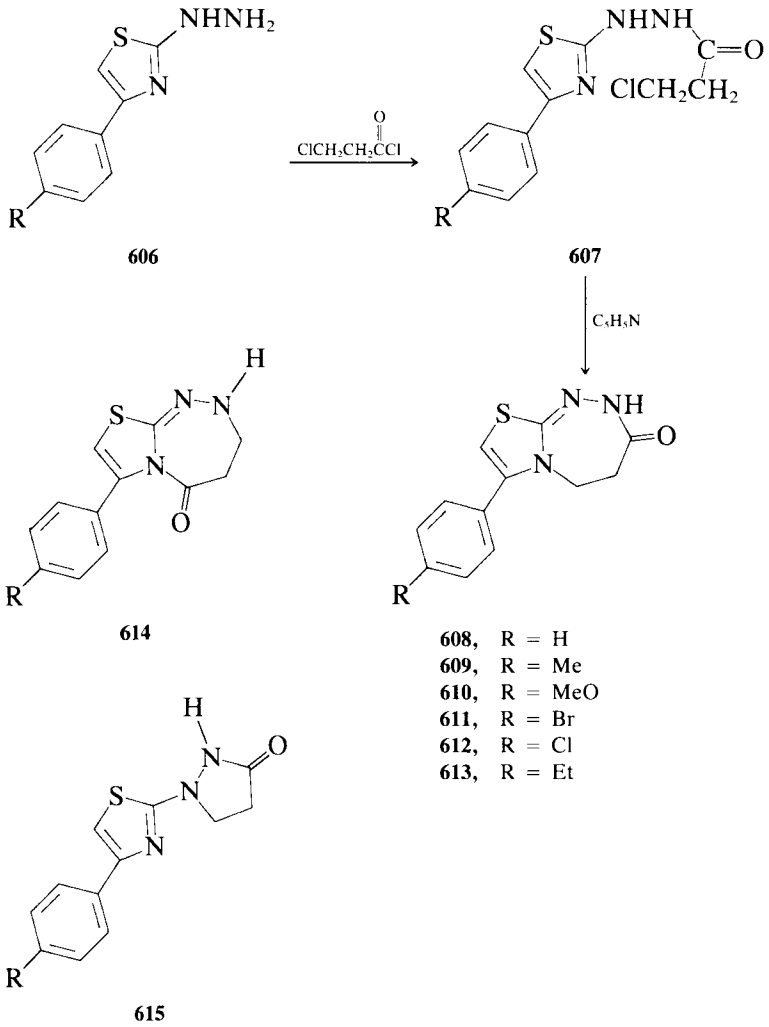


| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|
| H | Me | H | — | — | 159 |
| H | Me | Ac | — | — | 159 |
| H | Me | EtCO | — | — | 159 |
| H | Me | $NCCH_2CH_2$ | — | — | 159 |
| H | Et | H | — | — | 159 |
| H | Et | Ac | — | — | 159 |
| H | Et | EtCO | — | — | 159 |
| H | Et | $NCCH_2CH_2$ | — | — | 159 |
| Ph | Ph | H | 299 | 10 | 160 |

## d. 7-ARYL-4,5-DIHYDROTHIAZOLO[2,3-*c*][1,2,4]TRIAZEPIN-3(2H)-ONES

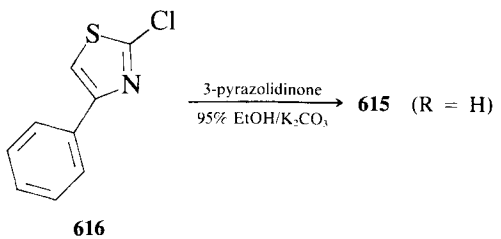


Mahajan and co-workers (161) recently reported a synthesis of thiazolo[2,3-*c*][1,2,4]triazepines (Eq. 89). 4-Aryl-2-hydrazinothiazoles (162) of general structure **606** were treated with 3-chloropropionyl chloride to yield hydrazides **607.** Cyclization of hydrazides **607** in pyridine yielded thiazolotriazepines **608–613.** The authors correctly excluded from consideration the isomeric thiazolotriazepines of general structure **614** as possible reaction products on the basis of the known selectivity of reaction of 3-chloropropionyl chloride with hydrazines. Not considered as alternate structural possibilities were thiazolopyrazolidinones of general structure **615.** However, 1-(4-phenyl-2-thiazolyl)-3-pyrazolidinone (**615,** R = H) has been synthesized by Peet and co-workers (163), as shown in Eq. 90, and its physical properties (mp 113°C) are different from those reported for **608** (mp 173°C). The preparation of **608** from **607** using the conditions described by Mahajan and co-



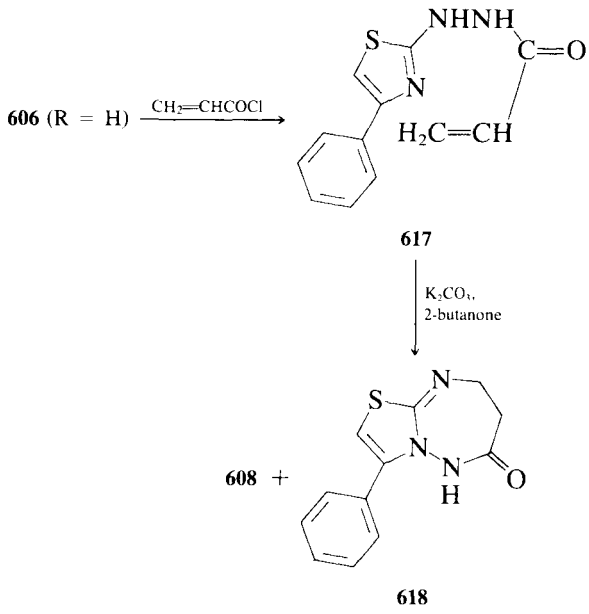

(89)

workers (161), as well as a variety of other conditions, could not be achieved (163). Compound **607**, interestingly, could by cyclized to pyrazolidinone **615**




(90)

(R = H) with potassium carbonate in 2-butanone. When 2-propenoic acid 2-(4-phenyl-2-thiazolyl)hydrazide (**617**), which was prepared by Peet and co-workers (163) from **606** (R = H) and acryloyl chloride, was treated with potassium carbonate in 2-butanone, thiazolotriazepinone **608** resulted. Also obtained was the isomeric 3-phenyl-7,8-dihydrothiazolo[3,2-*b*][1,2,4]triazepin-6(5H)-one (**618**), formed by Dimroth rearrangment from **608** (Eq. 91). Physical constants for the compound reported to be **608** (mp 173°C) by Mahajan and co-workers (161) are different from those found for either authentic **608** (mp 271–272°C) or **618** (mp 288–289°C) by Peet and co-workers (163). It is




(91)

likely that all of the structures (**608–613**) reported to be thiazolotriazepinones (Table 33) by Mahajan and co-workers (161) are incorrectly assigned.

## e. 3,5a,10,10a-TETRAHYDROINDENO[2,1-*e*][1,2,4]TRIAZEPIN-2(1H)-ONES

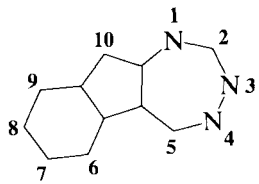
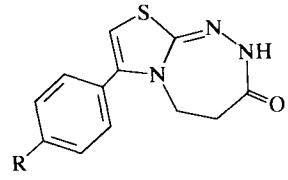
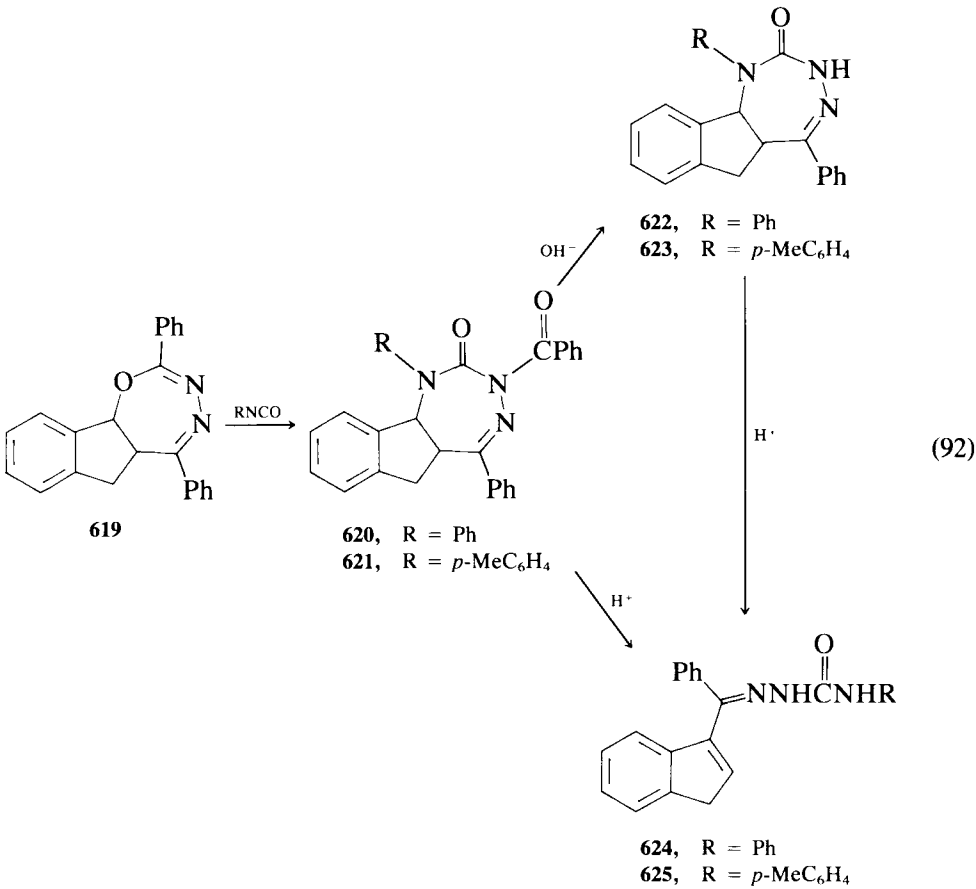


TABLE 33. 7-ARYL-4,5-DIHYDROTHIAZOLO[2,3-*c*][1,2,4]TRIAZEPIN-3(2H)-ONES

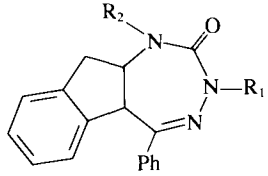


| R | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|
| H | 173 | 75 | 161 |
| H | 271–272 | — | 163 |
| Me | 149 | 70 | 161 |
| MeO | 146 | 72 | 161 |
| Br | 170 | 68 | 161 |
| Cl | 155 | 73 | 161 |
| Et | 162 | 62 | 161 |




(92)

TABLE 34. 3,5a,10,10a-TETRAHYDROINDENO[2,1-*e*][1,2,4]TRIAZEPIN-2(1H)-ONES[a]

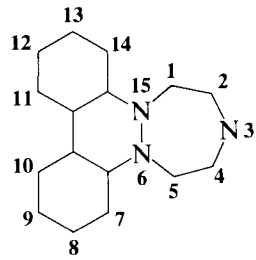


| $R_1$ | $R_2$ | mp (°C) | Yield (%) |
|---|---|---|---|
| Ph | H | 190–192 | 97 |
| *p*-$MeC_6H_4$ | H | 193–194 | 80 |
| Ph | PhCO | 208–209 | 98 |
| *p*-$MeC_6H_4$ | PhCO | 217–218 | 90 |

[a]Ref. 164.

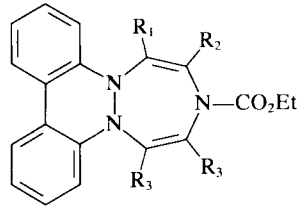
Oe and Tsuge (164) treated [1,3,4]oxadiazepine **619,** which they obtained from the photolysis of 2,5-diphenyl[1,3,4]oxadiazole and indene, with phenyl and 4-methylphenyl isocyanates (Eq. 92). The resulting products (Table 34) were assigned the structures **620** and **621,** respectively, on the basis of spectral data and chemical conversions. Hydrolysis of **620** and **621** led to the [1,3,4]triazepines **622** and **623** plus benzoic acid. Treatment of **620** and **621** with hydrochloric acid in methanol gave the semicarbazones **624** and **625.** Alternatively, **624** and **625** were prepared from **622** and **623** with methanolic hydrochloric acid. Mechanisms for these intriguing reactions were postulated.

## B. [*1,2,5*]*Triazepine Fused Systems*



Rees and co-workers (165,166) prepared 3H-benzo[*c*][1,2,5]triazepino[1,2-*a*]cinnolines **627–630** from azomethine imines (167,168) of general structure **626.** Thus treatment of the azomethine imines with dialkyl acetylenedicarboxylates led to products (Table 35) resulting from 1,5- rather than 1,3-dipolar

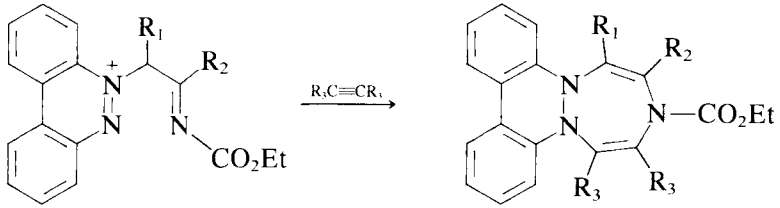
TABLE 35. 3H-BENZO[*c*][1,2,5]TRIAZEPINO[1,2-*a*]CINNOLINES[a]



| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) |
|---|---|---|---|---|
| $MeO_2C$ | $MeO_2C$ | $MeO_2C$ | 85–90 | 47 |
| $EtO_2C$ | $EtO_2C$ | $MeO_2C$ | — | — |
| $MeO_2C$ | H | $MeO_2C$ | 157–159 | 41 |
| $MeO_2C$ | H | $EtO_2C$ | 145–146 | 17 |

[a]Ref. 166.

cycloaddition (Eq. 93). The structure of **629** has been confirmed by Cameron and Freer (169) from crystallographic studies.



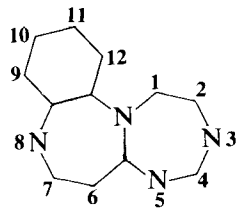
**626**

**627**, $R_1 = R_2 = R_3 = MeO_2C$
**628**, $R_1 = R_2 = MeO_2C$, $R_3 = EtO_2C$
**629**, $R_1 = R_3 = MeO_2C$, $R_2 = H$
**630**, $R_1 = MeO_2C$, $R_2 = H$, $R_3 = EtO_2C$

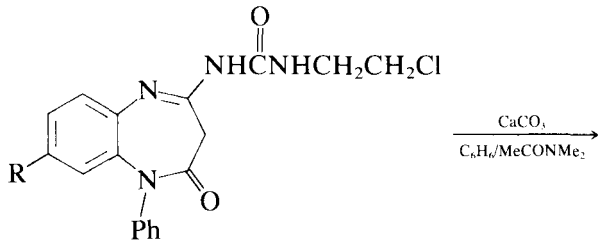
(93)

## C. [*1,3,5*]*Triazepine Fused Systems*

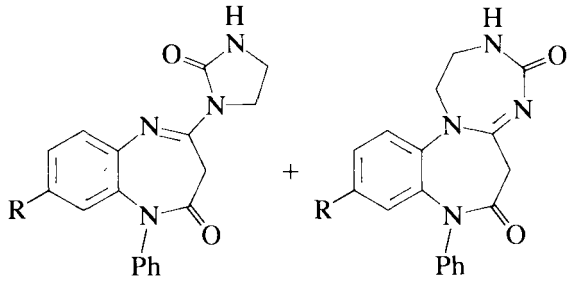
### a. 2,3-DIHYDRO-1H-[1,3,5]TRIAZEPINO[1,2-*a*]-[1,5]BENZODIAZEPINE-4,7(6H,8H)-DIONES



In the course of preparing benzodiazepine derivatives as potential psychotropic agents, Bauer and co-workers (170) cyclized chloroethylureas **631–633** with calcium carbonate in benzene–dimethylacetamide (Eq. 94). The major products were imidazolidinones **634–636,** but smaller amounts of the triazepinobenzodiazepines **637–639** were formed as well (Table 36).




**631,** R = Br
**632,** R = $O_2N$
**633,** R = $F_3C$

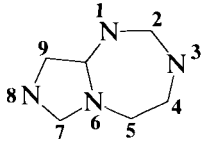


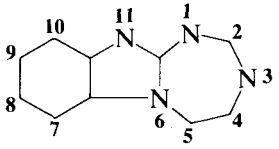

(94)

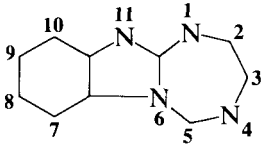
**634,** R = Br
**635,** R = $O_2N$
**636,** R = $F_3C$

**637,** R = Br
**638,** R = $O_2N$
**639,** R = $F_3C$

## b. [1,3,5]TRIAZEPINOIMIDAZOLES AND -BENZIMIDAZOLES

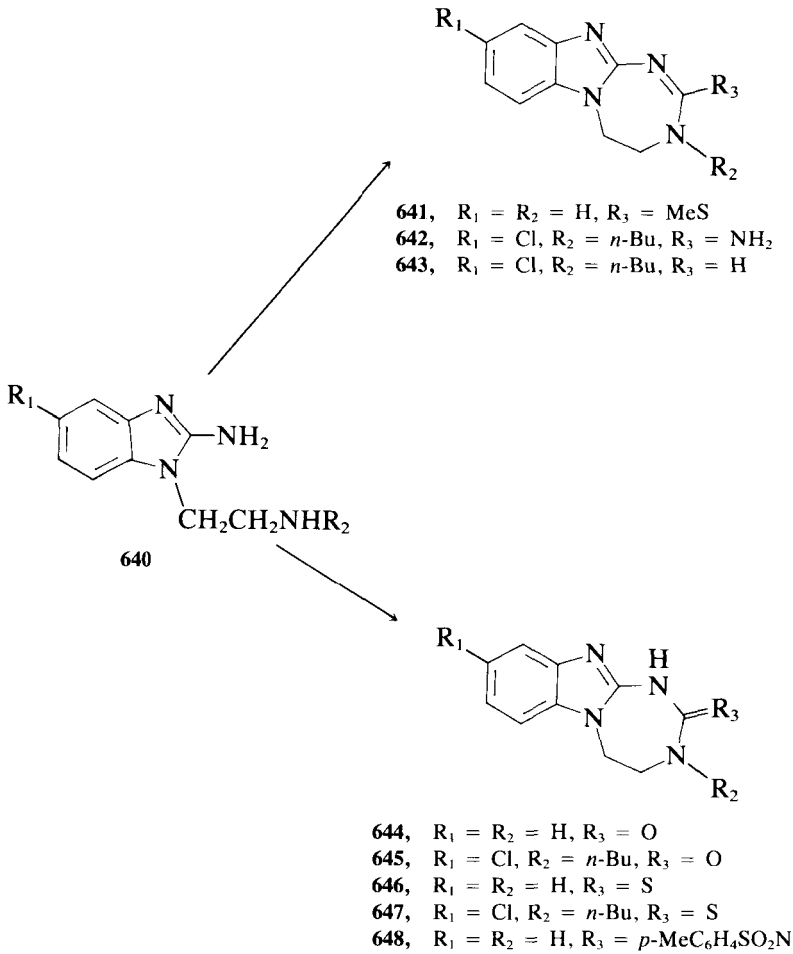


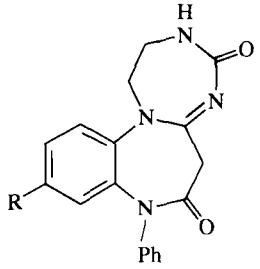

Lempert and co-workers (171) reported the synthesis of benzimidazotriazepines. Employing synthetic sequences similar to those used earlier (133,134,145) for the preparation of benzotriazepine precursors, the authors prepared the diamino compound **640.** Treatment of **640** with the appropriate

cyclizing agents (Eq. 95) led to the variously substituted 4,5-dihydro-3H-[1,3,5]triazepino[1,2-*a*]benzimidazoles **641–643** (Table 37) and the corresponding 2,3,4,5-tetrahydro-1H compounds **644–648** (Table 38).



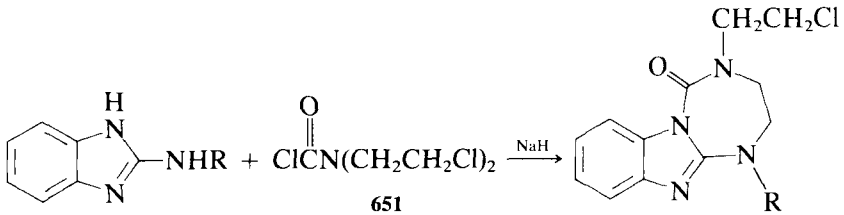

Acylation–displacement reactions of the 2-aminobenzimidazoles **649** and **650** with *N,N*-bis(2-chloroethyl)carbamoyl chloride (**651**) were reported by Schulze and Letsch (172) to yield 4-(2-chloroethyl)-1,2,3,4-tetrahydro-5H-[1,3,5]triazepino[3,2-*a*]benzimidazol-5-one (**652**) and the 1-phenyl derivative **653**, respectively (Eq. 96). These compounds were prepared as potential transport forms for the 2-chloroethylamino moiety.

TABLE 36. 2,3-DIHYDRO-1H-[1,3,5]TRIAZEPINO[1,2-*a*][1,5]BENZODIAZEPINE-4,7(6H,8H)-DIONES[a]



| R | mp (°C) |
|---|---|
| Br | 268–270 |
| $O_2N$ | 200–203 |
| $F_3C$ | 208–210 |

[a]Ref. 170.



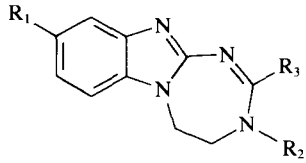
**649**, R = H
**650**, R = Ph

**652**, R = H
**653**, R = Ph

(96)

In a subsequent article, Schulze and co-workers (173) reported the preparation of carbamate **655** from 6-mercaptopurine and **651**, and the subsequent

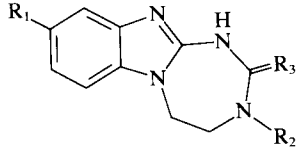
TABLE 37. 4,5-DIHYDRO-3H-[1,3,5]TRIAZEPINO[1,2-*a*]BENZIMIDAZOLES[a]



| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) |
|---|---|---|---|---|
| H | H | MeS | 280–282 | 88 |
| Cl | *n*-Bu | $H_2N$ | 267–268 | 21–52 |
| Cl | *n*-Bu | H | 260–261 | 67 |

[a]Ref. 171.

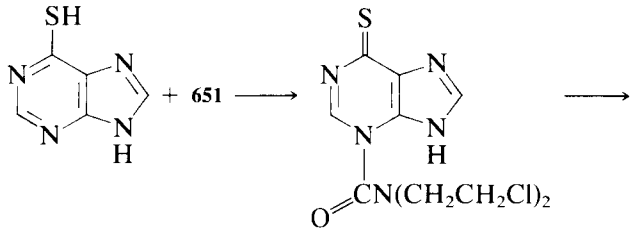
TABLE 38. 2,3,4,5-TETRAHYDRO-1H-[1,3,5]TRIAZEPINO[1,2-*a*]BENZIMIDAZOLES[a]



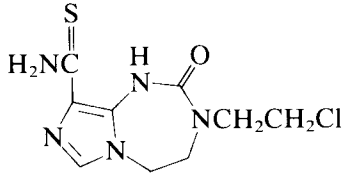
| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) |
|---|---|---|---|---|
| H | H | O | 298–300 | 35 |
| Cl | *n*-Bu | O | 291–294 | 53 |
| H | H | S | 258–260 | 73 |
| Cl | *n*-Bu | S | 264–266 | 46 |
| H | H | *p*-$MeC_6H_4SO_2N$ | 334–335 | 51 |

[a]Ref. 171.

cyclization of **655** to 3-(2-chloroethyl)-2,3,4,5-tetrahydro-2-oxo-1H-imidazo[1,5-*a*][1,3,5]triazepine-9-carbothioamide (**656**), as shown in Eq. 97. A review article on intramolecular cyclization reactions of nitrogen mustard compounds by Schulze (174) has also appeared.

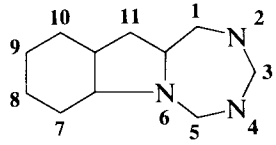


**654** **655** (97)

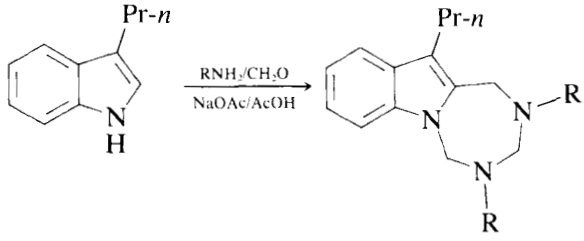


**656**

c. 2,3,4,5-TETRAHYDRO-1H-[1,3,5]TRIAZEPINO[1,7-*a*]INDOLES



Wolinsky and Sundeen (175) have reported the preparation of triazepinoindole fused systems (Eq. 98). 3-Propylindole (**657**) was treated with formalin and primary amines in the presence of acetic acid and sodium acetate to produce triazepinoindoles **658** and **659.** Structural assignments were based on spectral data.

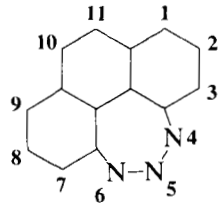



(98)

**657**

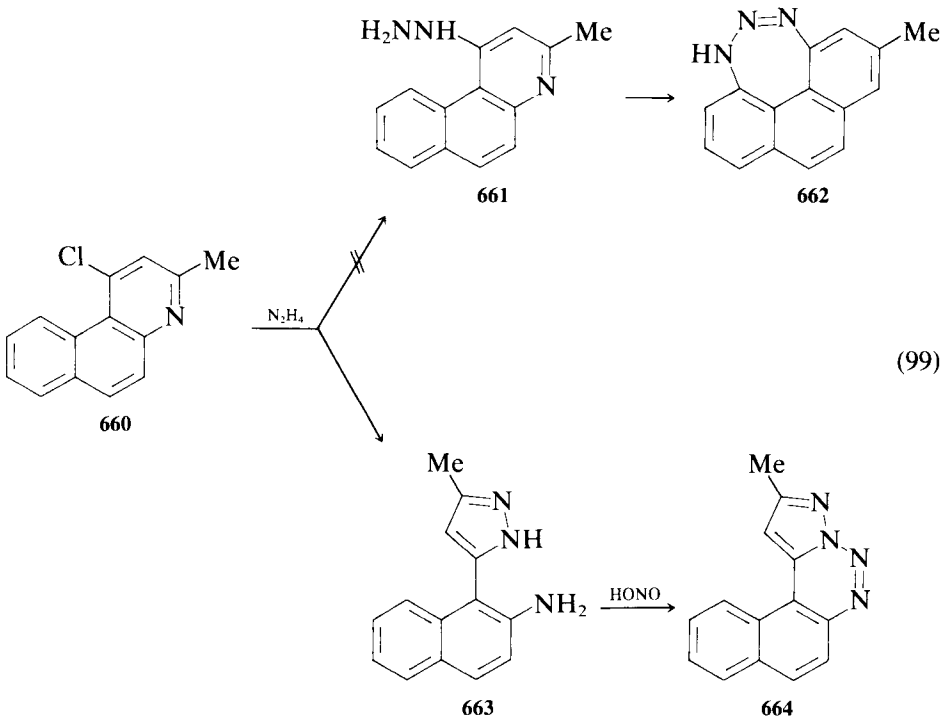
**658,** R = Me
**659,** R = $PhCH_2$

## D. [*1,2,3*]*Triazepine Fused Systems*




The fused [1,2,3]triazepine **662** was reported by Tiagi and Joshi (176) in 1972. These authors treated 1-chloro-3-methylbenzo[*f*]quinoline (**660**) with hydrazine (Eq. 99) to produce a compound to which they assigned structure **661.** Subsequent treatment of **661** with nitrous acid afforded a product which they formulated as the fused [1,2,3]triazepine **662.**

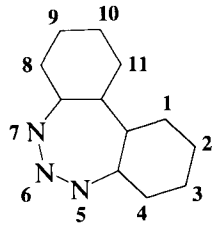
However, a recent reinvestigation of this work by Rees and co-workers (177) has resulted in different structural assignments for compounds **661** and **662.** These authors pointed out the lack of mechanistic precedent for the conversion of **661** to **662.** On the basis of convincing spectroscopic and chemical evidence as well as mechanistic precedent, the authors have reassigned structures **661** and **662** as **663** and **664,** respectively. Related transformations reported by Tiagi and Joshi (176) were also reinvestigated by these authors and found to be in error.




(99)

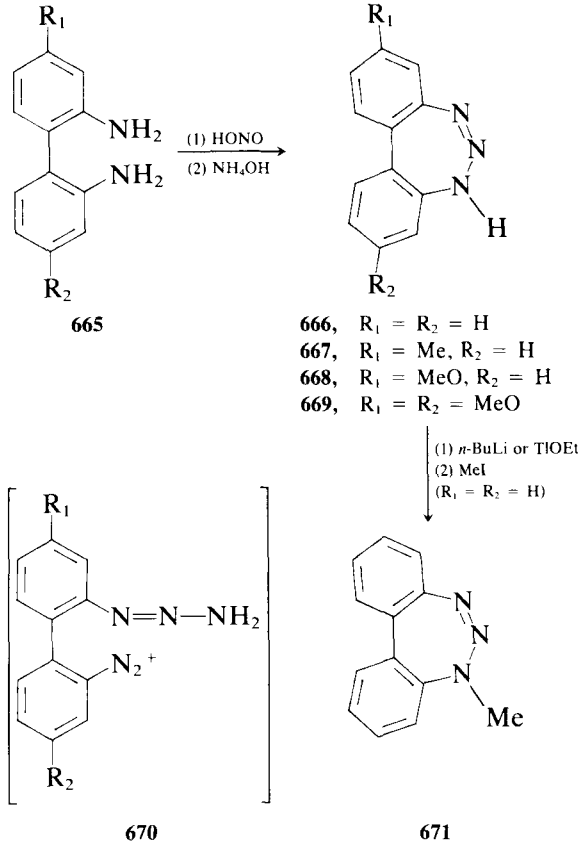
## 5. Dibenzotriazepine Ring Systems

### A. *[1,2,3]Dibenzotriazepines*




A series of 5H-dibenzo[*d,f*][1,2,3]triazepines has been reported by Rees and co-workers (178,179). These authors treated 2,2′-diaminobiphenyls of general formula **665** with nitrous acid followed by aqueous ammonia (Eq. 100) and obtained the dibenzotriazepines **666–669.** The specific reaction conditions were crucial, as several other products were formed using other

diazotization conditions. The intermediacy of a triazeno-diazonium species (**670**) was suggested. Only one of several attempted derivatization reactions was successful. Treatment of the lithium or thallium salt of **666** with methyl iodide produced 5-methyl-5H-dibenzo[*d*,*f*][1,2,3]triazepine (**671**). Members of this ring system are shown in Table 39.




(100)

## B. [*1,2,5*]*Dibenzotriazepines*

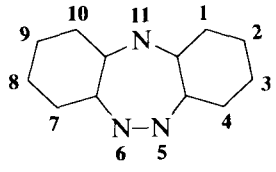
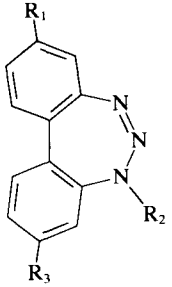
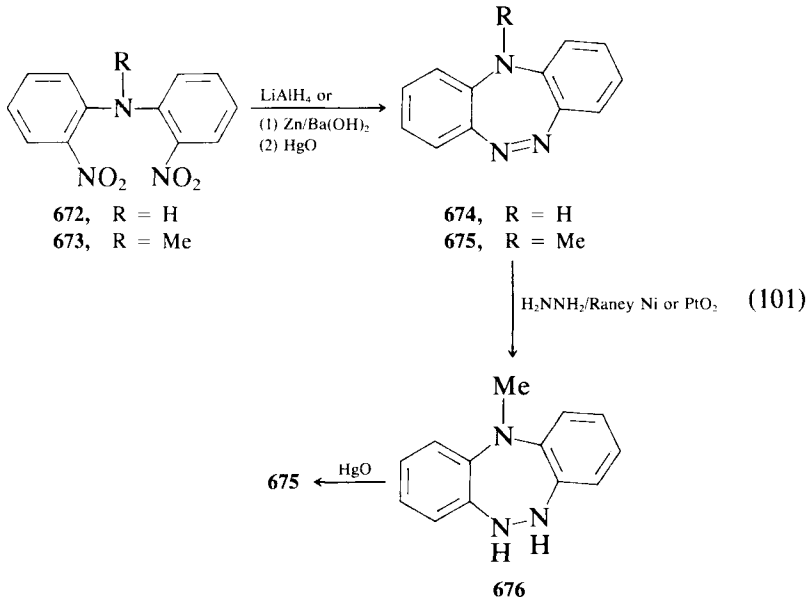


TABLE 39. 5H-DIBENZO[*d*,*f*][1,2,3]TRIAZEPINES



| $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|
| H | H | H | 99–100 | 70 | 178 |
| H | H | H | 98–99 | 60–77 | 179 |
| H | Me | H | 66–67 | 40–67 | 179 |
| Me | H | H | — | 74 | 179 |
| MeO | H | H | — | 62 | 179 |
| MeO | H | MeO | — | 62 | 179 |

Allinger and Youngdale (180,181) explored various methods of reduction of the diphenylamines **672** and **673** and found that lithium aluminum hydride afforded moderate yields of the respective dibenzotriazepines **674** and **675** (Eq. 101). Further reduction of **675** with hydrazine and Raney nickel gave




**672**, R = H
**673**, R = Me

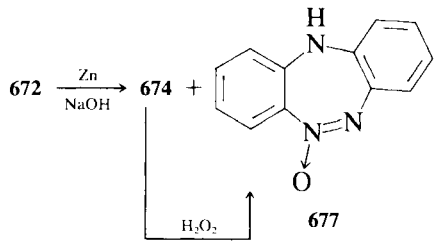
**674**, R = H
**675**, R = Me

**676**

(101)

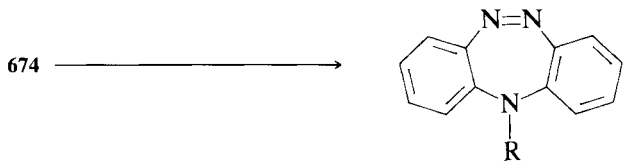
dihydrodibenzotriazepine **676**, a 10 $\pi$-electron system. Oxidation of **676** back to **675** was also reported, using mercuric oxide. In a subsequent report, Lowrie (182) disclosed the preparation of **675** from **672** using zinc reduction followed by oxidation with mercuric oxide. Dihydrodibenzotriazepine **676** was then prepared from **675** by reduction with hydrazine and platinum oxide.

Zinc reduction of **672** has been reported by Grundon and co-workers (183) to follow a different course (Eq. 102). Treatment of **672** with zinc dust and sodium hydroxide produced, after chromatographic purification, dibenzotriazepine **674** (20% yield) and its *N*-oxide, **677** (13% yield). An authentic sample of **677** was generated for comparison by oxidation of **674** with hydrogen peroxide. These authors also prepared **676** from **674** by reduction with hydrazine and Raney nickel, and claimed that **676** rapidly reverted to **674** on air oxidation.

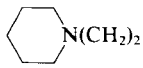
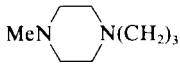



(102)

Two groups have employed **674** as a starting material for the preparation of compounds for biological evaluation. Boissier and Ratouis (184) described the formation of the alkylated derivatives **678, 679, 681, 683,** and **684** from **674** and the appropriate aminoalkyl halide (Eq. 103). Compounds **678** and **679** were cited as anorectic agents in rats. Sparatore and co-workers (185)




(103)

**678**, R = $Me_2N(CH_2)_2$
**679**, R = $Me_2NCH(Me)CH_2$
**680**, R = $Et_2N(CH_2)_2$
**681**, R = $Me_2N(CH_2)_3$
**682**, R = $Et_2N(CH_2)_2$
**683**, R = 
**684**, R = 

also reported the preparation of **678, 681, 683,** and **684,** as well as alkylated derivatives **680** and **682.** A variety of biological activities was cited for these 11-substituted 11H-dibenzo[*c,f*][1,2,5]triazepines. Compound **681** displayed smooth muscle relaxant properties, while **682** was shown to possess anticoagulant and local anesthetic activities. Although compounds **678–684** structurally resemble imipramine, no antidepressent activity was reported. A list of known members of this ring system is given in Table 40.

A different approach to the preparation of a derivative of **674** was reported by Kirchner and Bretschneider (186). 3,4,5-Trimethoxyaniline (**685**) was arylated with either 2-chloro- or 2-fluoronitrobenzene (Eq. 104) to yield diphenylamine **686,** which was then alkylated with 3-dimethylaminopropyl chloride to give **687.** Catalytic reduction of **687** produced the substituted *o*-phenylenediamine **688,** which was treated with nitrous acid to afford 11-(3-dimethylaminopropyl) -2,3,4-trimethoxy-11H-dibenzo [*c,f*] [1,2,5] triazepine (**689**).

Two patents have described the preparation of 2-*n*-butyl-9-methyl-1H,9H-dibenzo[*c,f*]pyrazolo[1,2-*a*][1,2,5]triazepine-1,3(2H)-dione (**690**). Treatment

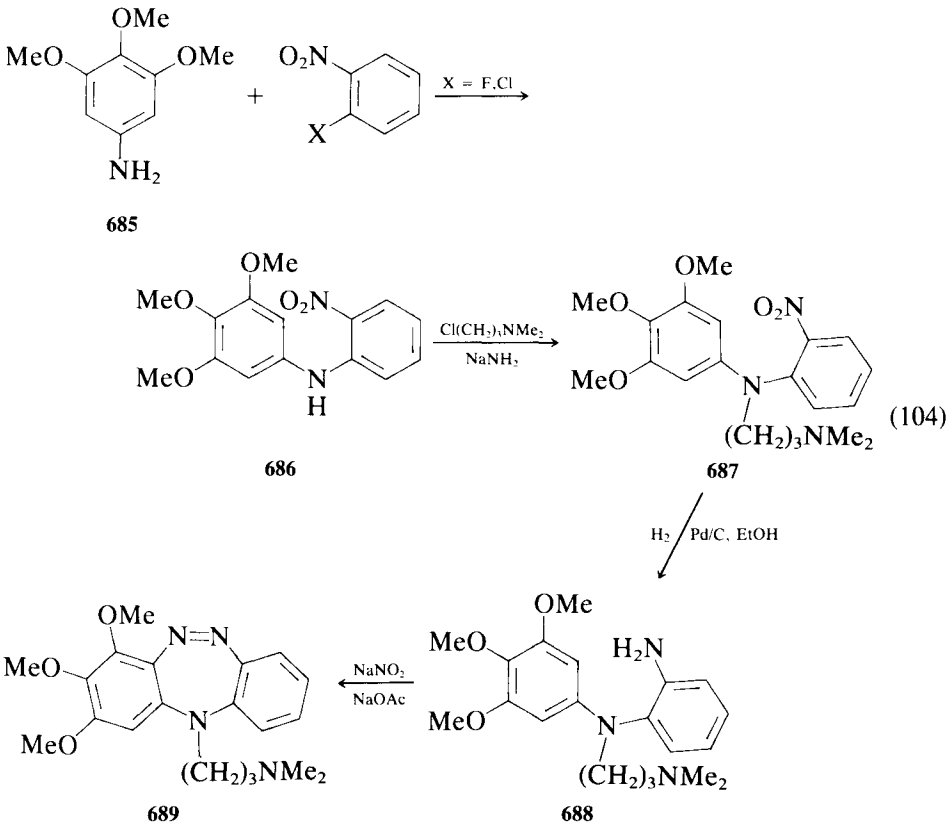
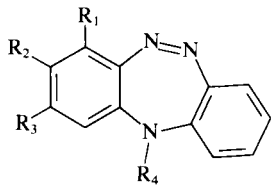
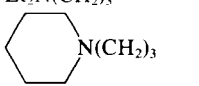
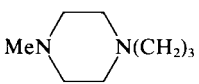
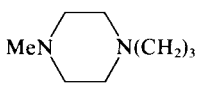
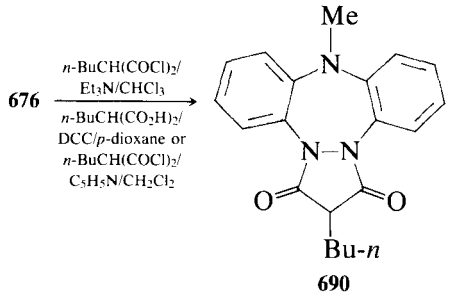


TABLE 40. 11H-DIBENZO[*c*,*f*][1,2,5]TRIAZEPINES



| $R_1$ | $R_2$ | $R_3$ | $R_4$ | mp (°C) | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| H | H | H | H | 166–168 | 6 | 181 |
| H | H | H | H | 191 | 20 | 183 |
| H | H | H | H | — | 20 | 185 |
| H | H | H | Me | — | 21 | 180 |
| H | H | H | Me | 140–140.5 | 21 | 181 |
| H | H | H | $Me_2N(CH_2)_2$ | 129 | 34 | 184 |
| H | H | H | $Me_2N(CH)_2$ | — | (33–59) | 185 |
| H | H | H | $Me_2NCH(Me)CH_2$ | 115–116 | 33 | 184 |
| H | H | H | $Et_2N(CH_2)_2$ | — | (33–59) | 185 |
| H | H | H | $Me_2N(CH_2)_3$ | 107–109 | 62 | 184 |
| H | H | H | $Me_2N(CH_2)_3$ | — | (33–59) | 185 |
| H | H | H | $Et_2N(CH_2)_3$ | — | (33–59) | 185 |
| H | H | H |  | 99–100 | 33 | 184 |
| H | H | H |  | 130 | 35 | 184 |
| H | H | H |  | — | (33–59) | 185 |
| MeO | MeO | MeO | $Me_2N(CH_2)_3$ | 117–120 | 80 | 187 |

of dibenzotriazepine **676** with *n*-butylmalonyl dichloride in chloroform and triethylamine (Eq. 105) gave the fused system **690,** as did coupling of **676** with *n*-butylmalonic acid, using *N,N'*-dicyclohexylcarbodiimide in *p*-dioxane (187). Compound **690** and its analogs were claimed to have anti-inflammatory and antipyretic activities. Lowrie (182,188) prepared **690** from **676** by treatment with *n*-butylmalonyl dichloride in methylene chloride and pyridine. This author also reported anti-inflammatory activity for **690** and related compounds (182), although none was as potent as phenylbutazone (188).

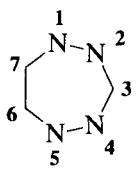


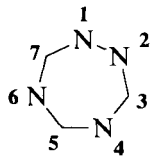

**690** (105)

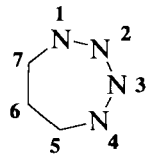
## II. TETRAZEPINES

### 1. Introduction

This section deals with seven-membered heterocyclic compounds containing more than three nitrogen atoms. Since the only existent structural types that fit into this classification are seven-membered heterocyclic compounds containing four nitrogen atoms, the chapter is concise title "Tetrazepines" is used. The known tetrazepines in the literature are [1,2,4,5]tetrazepines, [1,2,4,6]tetrazepines, and a [1,2,3,4]tetrazepine. Some of the literature refers to tetrazepines as cyclic formazans or tetraazacycloheptanes. Since there are only a limited number of references dealing with these ring systems, they will be presented in historical fashion instead of being grouped as monocyclic tetrazepine systems, benzotetrazepine systems, and so on.



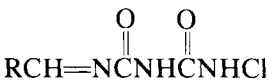



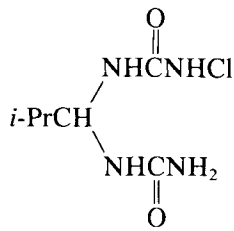
## 2. Historical Presentation of Tetrazepine Systems

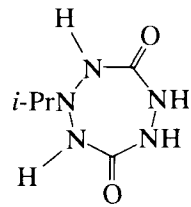
The first reported work on a tetrazepine system was by Ottensooser (189), who studied the reaction of chlorourea with simple aldehydes. An aqueous solution of chlorourea, prepared from chlorine water and urea, was treated with propionaldehyde, butyraldehyde, isobutyraldehyde, and isovaleraldehyde. The products isolated from butyraldehyde and isovaleraldehyde were claimed to be the condensation products **691** and **692,** respectively, while **693** was supposedly produced from chlorobiuret, present in the chlorourea solution, and propionaldehyde. The origin of the compound purported to be **694** was not discussed, although the author probably envisioned its formation from the addition of urea to the condensation product of isobutyraldehyde and chlorourea. Treatment of **694** with potassium hydroxide yielded a compound which was formulated as tetrahydro-5-(1-methylethyl)-4H-[1,2,4,6]-tetrazepine-3,7-dione (**695**). Structures **691–695** should be regarded as suspect and their chemistry reinvestigated, inasmuch as structural assignments were made solely on the basis of combustion analyses.

Henseke and Winter (190) reported that phenylosazones could be partially hydrolyzed to yield, preferentially, osone hydrazones where the hydrazono group was at the terminal position. When either D-fructosone-1-phenylhydrazone (**696**), which was prepared in this fashion, or the corresponding methylphenylhydrazone **697** was treated with thiocarbohydrazide (Eq. 106), the same product was obtained. This product was formulated as 2,4-dihydro-6-D-arabotetrahydroxybutyl-3H-[1,2,4,5]tetrazepine-3-thione (**698**). The structural assignment for tetrazepine **698** was supported by combustion analysis.

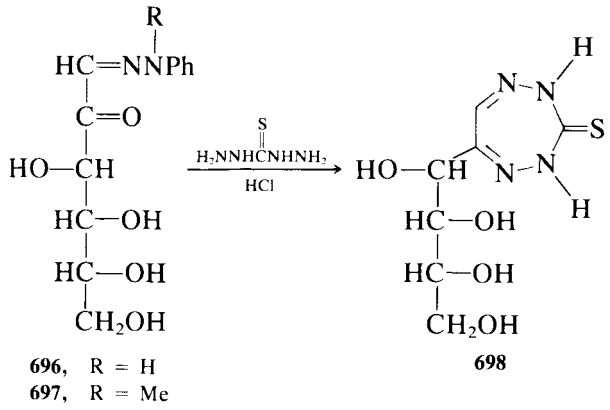


**691,** R = *n*-Pr
**692,** R = *i*-Bu
**693,** R = Et





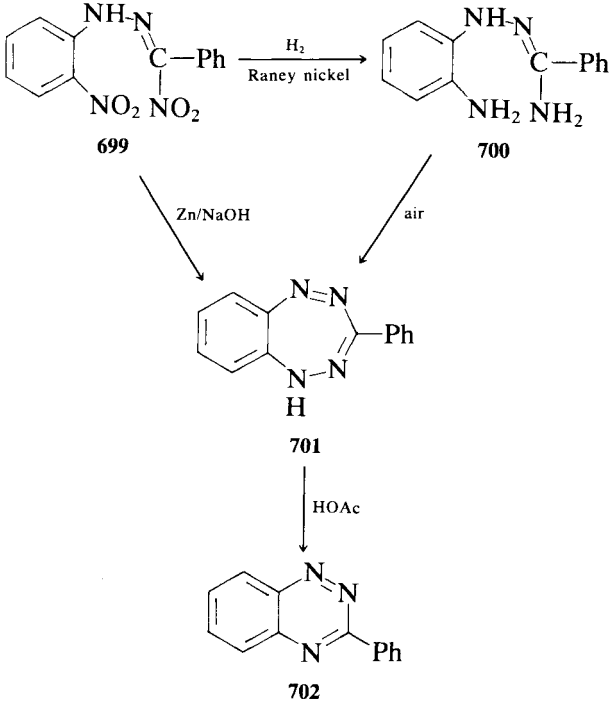
Jerchel and Edler (191) prepared hydrazone **699** by treating phenylnitromethane with diazotized 2-nitroaniline, and found two routes for its conversion to 3-phenyl-1H-[1,2,4,5]benzotetrazepine (**701**). Reduction of **699** with hydrogen and Raney nickel (Eq. 107) led to amidrazone **700,** which was isolated as the dihydrochloride salt. Air oxidation of the free base produced




**696**, R = H
**697**, R = Me

**698**

(106)




**699**

**700**

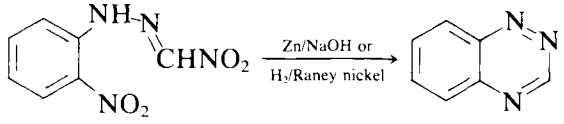
**701**

**702**

(107)

**701.** Alternatively, tetrazepine **701** could be prepared directly from **699** by reduction with zinc in basic solution. Interestingly, **701** was converted to 3-phenyl[1,2,4]benzotriazine (**702**) upon treatment with acetic acid.

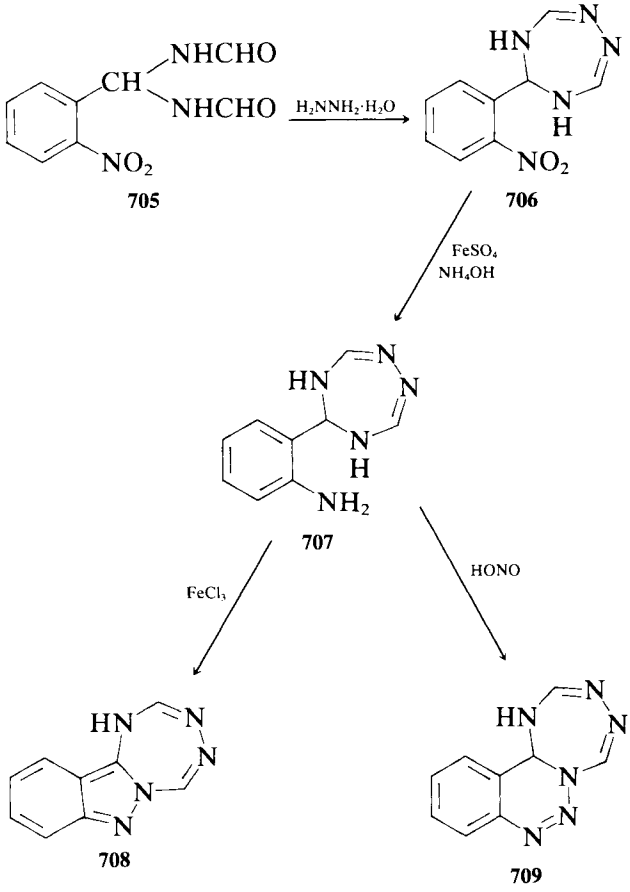
When the authors reduced hydrazone **703** under either of the conditions used to produce **701** from **699**, the product (Eq. 110) was [1,2,4]benzotriazine (**704**). Fusco and Bianchetti (192,193) have reduced several analogs of **699**




703 704 (108)

and **703** directly to benzotriazines, and indicate that the preparation of **701** from **699** is unique.

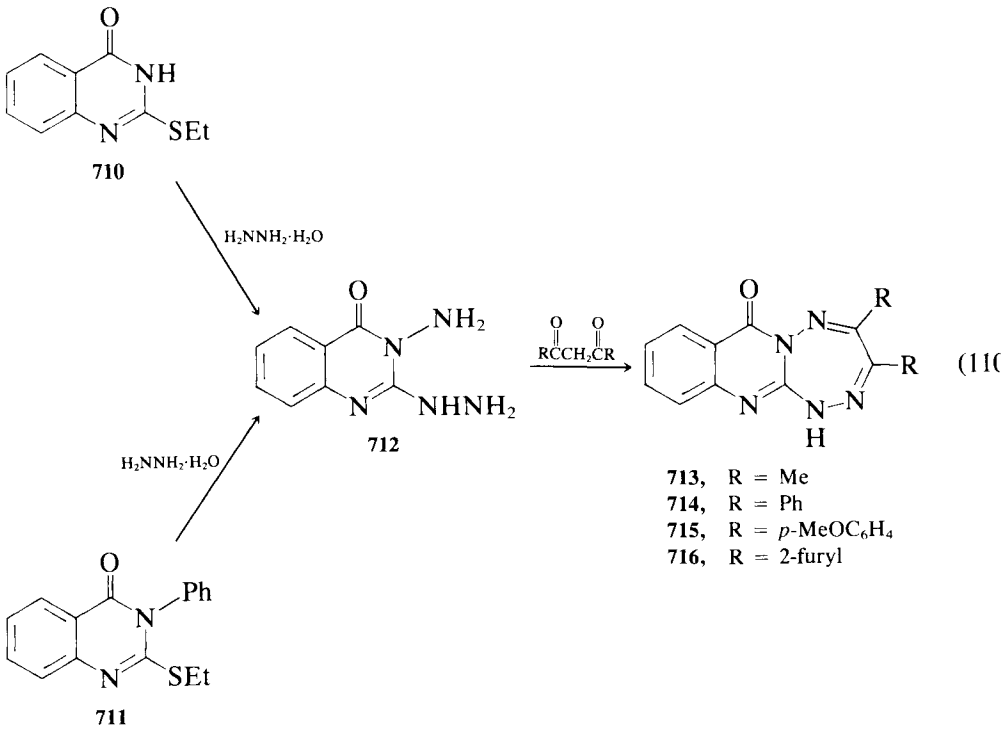
The bisformamido compound **705** was prepared by Sidhu and co-workers (194) in connection with studies on quinazolines. In exploring other possible uses for **705**, the authors treated it with hydrazine hydrate (Eq. 109), which resulted in the formation of 5,6-dihydro-5-(2-nitrophenyl)-4H-[1,2,4,6]-tetrazepine (**706**). Reduction of **706** with ferrous sulfate in aqueous ammonia gave the aminophenyltetrazepine **707**. Oxidation of **707** with ferric chloride




705 706 707 708 709 (109)

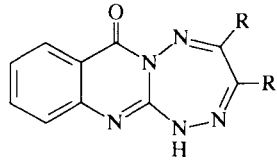
produced 1H-[1,2,4,6]tetrazepino[4,5-*b*]indazole (**708**). Another interesting and novel ring system, [1,2,4,6]tetrazepino[4,5-*c*][1,2,3]benzotriazine (**709**), was obtained by diazotization of **707.**

A group of [1,2,4,5]tetrazepino[3,2-*b*]quinazolin-7(1H)-ones (**713–716**) was prepared by Gupta and co-workers (195) as potential central nervous system depressants, but no activity was found. The preparation of these compounds (Table 41) was accomplished from 2-(ethylthio)-4(3H)-quinazolinone (**710**) or 2-(ethylthio)-3-phenyl-4(3H)-quinazolinone (**711**), each of which afforded 2-hydrazino-3-amino-4(3H)-quinazolinone (**712**) upon treatment with hydrazine hydrate (Eq. 110). Subsequent reaction of **712** with symmetric 1,3-diketones afforded the tetrazepinoquinazolinones **713–716.**



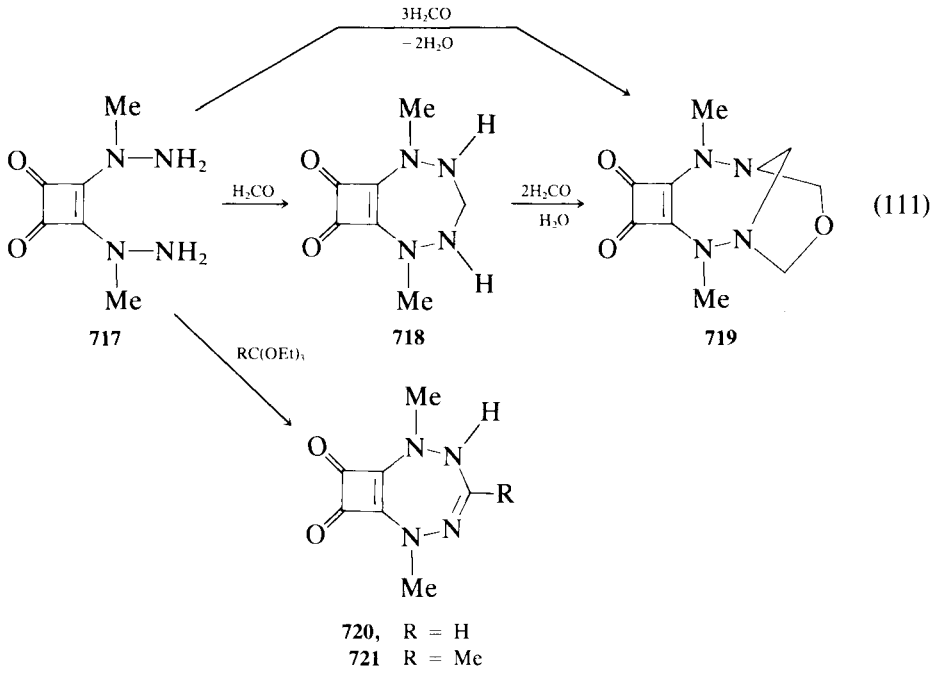

A group of tetrazepinocyclobutenediones has recently been prepared by Morck and Seitz (196). These authors earlier (197) prepared bishydrazide **717** from quadratic acid diethyl ester and methylhydrazine. Treatment of **717** with 1 mole of formaldehyde (Eq. 111) yielded 2,6-dimethyl-2,3,4,5-tetraazabicyclo[5.2.0]non-1(7)-ene-8,9-dione (**718**), and subsequent treatment of **718** with 2 moles of formaldehyde gave compound **719.** Alternatively, **719** could be prepared from **721** and 3 moles of formaldehyde. Treatment of **717**

TABLE 41. [1,2,4,5]TETRAZEPINO[3,2-*b*]QUINAZOLIN-7(1H)-ONES[a]



| R | mp (°C | Yield (%) |
|---|---|---|
| Me | 295–296 (monohydrate) | 23 |
| Ph | 231–232 (monohydrate) | 36 |
| $MeOC_6H_4$ | 205–206 (dihydrate) | 48 |
| 2-Furyl | 223–224 (hemihydrate) | 16 |

[a]Ref. 195.



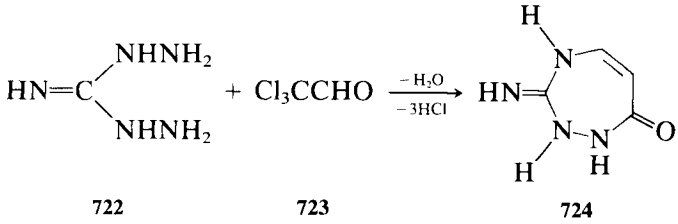
(111)

717 718 719

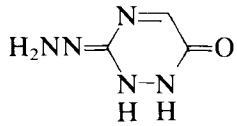
720, R = H
721 R = Me

with triethyl orthoesters yielded tetrazepines **720** and **721.** Ample spectral evidence was provided for all of these novel structures.

Bierowska-Charytonowicz and Konieczny (198) have reported the preparation of 2,3,4,5-tetrahydro-3-imino-6H-[1,2,4,5]tetrazepin-6-one (**724**), a compound with anti-inflammatory activity, from diaminoguanidine (**722**) and chloral (**723**) (Eq. 112). The authors stated that their structural assignment for **724** was in accord with its elemental analysis and infrared and nmr

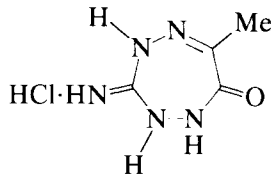


722 723 724 (112)

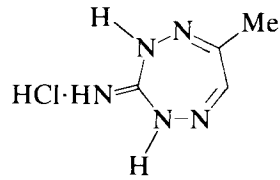


725

spectra, although none of these data were reported. An alternative structural possibility for iminotetrazepinone **724** is triazine **725,** which the authors apparently did not consider.



726



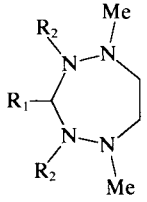
727

Pharmacologic reports on the hydrochloride salts of **724** and related compounds have appeared. Lachowicz and co-workers (199) reported that **724**·HCl displayed mutagenic activity in *Saccharomyces cerevisiae*. Chladzynska (200) described **724**·2HCl and the monohydrochloride salt of 2,3,4,5-tetrahydro-3-imino-7-methyl-6H-[1,2,4,5]tetrazepine-6-one (**726**) as anti-inflammatory agents in animals. The anti-inflammatory and immunosuppressant activities of 2,4-dihydro-6-methyl-3H-[1,2,4,5]tetrazepin-3-imine monohydrochloride (**727**) were reported by Gieldanowski and co-workers (201).

A series of hexahydro-1,5-dimethyl[1,2,4,5]tetrazepines was reported by Gol'din and co-workers (202). These authors condensed substituted 1,2-dihydrazinoethanes of general structure **728** with aldehydes (Eq. 113) to obtain the saturated tetrazepines **729–736.** Spectral data reported for some of these compounds (Table 42) supported the structural assignments.

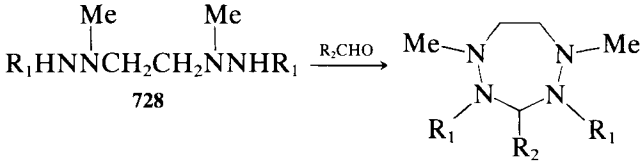
Singh and Joshi (203) have recently reported the preparation of 5H-2,3-diphenyltetrazepino[1,2,4,5][3,2-*b*]-9-fluoroquinazolin-11-one (**737**) from 6-fluoro-2-mercapto-3-phenylquinazolin-4(3H)-one (**738**). Treatment of **738** with ethyl bromide and base gave the ethylthio compound **739** (Eq. 114), which was then converted to 3-amino-6-fluoro-2-hydrazinoquinatolin-4(3H)-one (**740**)

TABLE 42. HEXAHYDRO-1,5-DIMETHYL[1,2,4,5]TETRAZEPINES[a]



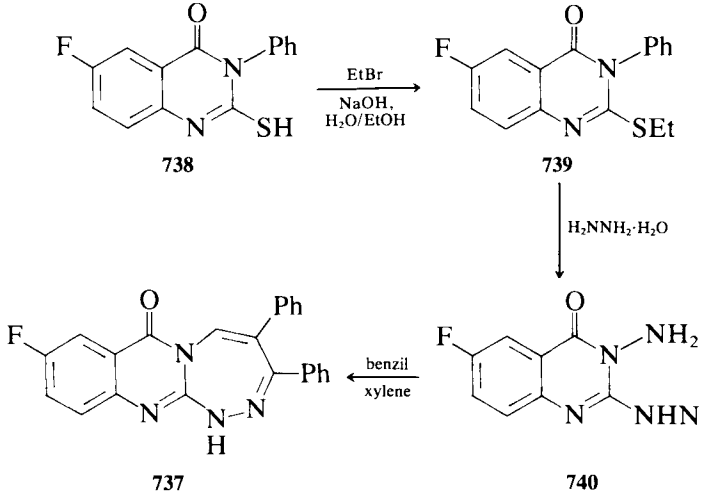
| $R_1$ | $R_2$' | bp (°C/torr) | Yield (%) |
|---|---|---|---|
| H | H | — | 90 |
| H | Et | 83/10 | 37 |
| H | *n*-Pr | 93–94/10 | 65 |
| H | *i*-Oct | 70–72/6 | 68 |
| H | *n*-Bu | 110–111/3 | 70 |
| H | *i*-Bu | 75–80/1 | 75 |
| H | *sec*-Bu | 113–114/5 | 86 |
| Me | H | 71/10 | 28 |

[a]Ref. 202.



(113)

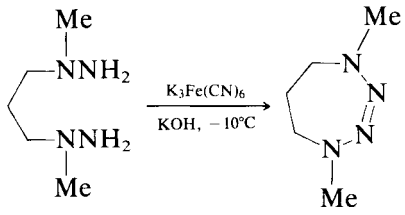
**729**, $R_1 = R_2 = H$ **733**, $R_1 = H$, $R_2 = n$-Bu
**730**, $R_1 = H$, $R_2 = Et$ **734**, $R_1 = H$, $R_2 = i$-Bu
**731**, $R_1 = H$, $R_2 = n$-Pr **735**, $R_1 = H$, $R_2 = sec$-Bu
**732**, $R_1 = H$, $R_2 = i$-Octyl **736**, $R_1 = Me$, $R_2 = H$



(114)

with hydrazine hydrate. Tetrazepine **737** was prepared from **740** by treatment with benzil in xylene. The structural assignment for **737** was supported by combustion analysis.

The only reported [1,2,3,4]tetrazepine is 1,4-dimethyl-1,2,3,4-tetraaza-2-cycloheptene (**741**), which was prepared by Michejda and co-workers (204). Oxidation of dihydrazino compound **742** with potassium ferricyanide (Eq. 115) gave tetrazepine **746.** Kreher and Wissman (205) had earlier employed similar oxidative cyclization conditions for the preparation of the six-membered (triazine) analog of **741.**




**742** **741** (115)

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