CONDENSED IMIDAZOLES

This is the forty-sixth 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

CONDENSED IMIDAZOLES

5-5 Ring Systems

P. N. Preston

DEPARTMENT OF CHEMISTRY
HERIOT-WATT UNIVERSITY
EDINBURGH, SCOTLAND

AN INTERSCIENCE® PUBLICATION

JOHN WILEY & SONS
NEW YORK CHICHESTER BRISBANE TORONTO SINGAPORE

An Interscience® Publication

Library of Congress Cataloging in Publication Data:

Preston, P. N.
Condensed imidazoles.

(The Chemistry of heterocyclic compounds, ISSN 0069-3154; v. 46)
"An Interscience publication."
Includes indexes.
1. Imidazole. I. Title. II. Series.
QD401.P93 1986 547'.593 85-20344
ISBN 0-471-88384-0

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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.

Research Laboratories
Eastman Kodak Company
Rochester, New York

ARNOLD WEISSBERGER

Princeton University
Princeton, New Jersey

EDWARD C. TAYLOR

Preface

The imidazole ring occurs in the essential amino acid histidine and in the closely related hormone histamine but, more importantly, is a constituent of nucleic acids. Accordingly, a massive research effort has been expended on the chemistry of this ring system and also on condensed derivatives including purines, benzimidazoles, and related compounds.

Coverage of the literature in this series has reflected the importance of this field and includes the early volume *Imidazole and Its Derivatives* by Klaus Hofmann; *Fused Pyrimidines, Part II, Purines* by J. H. Lister; and *Benzimidazoles and Congeneric Tricyclic Compounds,* edited by the present author. A variety of condensed imidazoles are also covered in W. L. Mosby's treatise *Heterocyclic Systems with Bridgehead Nitrogen Atoms.*

During the preparation of the volume on benzimidazoles and related compounds it became clear that a more extensive, systematic coverage of the literature on condensed imidazoles was required. This volume contains a survey of 51 ring systems in which an imidazole ring is fused to an additional five-membered ring system. The synthesis, physicochemical properties, and reactions of compounds in each ring system are covered; reactions are organized on a mechanistic basis and the survey includes compounds that are both partially and fully saturated. A number of the ring systems covered have been extensively studied, either because of their inherent biological interest (e.g., the chemistry of biotin is considered in the section on thieno[3,4-*d*]imidazoles) or because they contain commercially important compounds (e.g., the anthelmintic agent tetramisole is discussed in the section on imidazo[2,1-*b*]thiazoles). I hope that this volume will encourage further studies on the chemistry of bicyclic condensed imidazoles and related compounds containing three or more rings, and I believe this volume should be the first of a series devoted to such condensed heterocycles.

I have received much help and advice from friends and colleagues during preparation of the manuscript. I am especially grateful to Alan R. Edgar, for chemical advice, particularly where expert knowledge of carbohydrate chemistry became valuable. I also thank Janet M. Evans for providing information on condensed imidazoles of commercial importance and Wade A. Freeman for generously donating photographic plates illustrating the detailed molecular structure of the unusual imidazo[4,5-*d*]imidazole derivative, curcurbituril. The collection of data for the volume and organization of the manuscript required a considerable team effort, and it is a pleasure to acknowledge the assistance of Anne Smith and Julie Gill of Heriot-Watt University Library and also Elizabeth Jones, Nancy Brown, and Jennifer Daniels for their diligence in preparing the typescript. Last, but certainly not least,

I thank Veronica and my daughters Helen, Jane, and Joanne for assistance in checking the manuscript and for their patience and understanding when I became engrossed in this venture.

P. N. PRESTON

Edinburgh, Scotland
January 1986

Contents

CONDENSED IMIDAZOLES

This is the forty-sixth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

Chemistry of Heterocyclic Compounds, Volume 46
P. N. Preston

INTRODUCTION

Literature Coverage and Organization of the Volume

Previous volumes in this series, *The Chemistry of Heterocyclic Compounds*, that have been devoted to imidazole and related condensed compounds, but excluding purines, are *Imidazole and Its Derivatives* by Klaus Hofmann and *Benzimidazoles and Congeneric Tricyclic Compounds*, edited by the present author; condensed derivatives are also covered as part of Mosby's wider treatise entitled *Compounds with Bridgehead Nitrogen*.

Condensed imidazoles in which the imidazole ring is fused to an additional five-membered ring are described in this volume. Ring systems included are those appearing in the *Chemical Abstracts Index of Ring Systems* under the two-ring 5-5 citation and including a C_3N_2 fragment. The material is subsequently subdivided into chapters based on the number and types of hetero atoms in the additional five-membered ring. The 51 ring systems and chapter delineations in the volume are as follows:

Chapter 1 (No Additional Heteroatoms)

C_3N_2–C_5	Cyclopentimidazole
C_3N_2–C_4N	Pyrrolo[1,2-*a*] imidazole
	Pyrrolo[1,2-*c*] imidazole

Chapter 2 (One Additional Heteroatom)

C_3N_2–C_4N	Pyrrolo[3,4-*d*] imidazole
	Pyrrolo[2,3-*d*] imidazole
C_3N_2–C_3N_2	Imidazo[1,2-*a*] imidazole
	Imidazo[1,5-*a*] imidazole
	Imidazo[1,5-*c*] imidazole
	Imidazo[1,2-*b*] pyrazole
	Imidazo[1,5-*b*] pyrazole
C_3N_2–C_4O	Furo[2,3-*d*] imidazole
	Furo[3,4-*d*] imidazole
C_3N_2–C_3NO	Imidazo[2,1-*b*] oxazole

	Imidazo[5,1-*b*] oxazole
	Imidazo[1,5-*c*] oxazole
	Imidazo[1,5-*b*] isoxazole
$C_3N_2-C_4S$	Thieno[2,3-*d*] imidazole
	Thieno[3,4-*d*] imidazole
$C_3N_2-C_3NS$	Imidazo[1,2-*b*] isothiazole
	Imidazo[2,1-*b*] thiazole
	Imidazo[5,1-*b*] thiazole
	Imidazo[1,5-*c*] thiazole
	Imidazo[1,2-*c*] thiazole and imidazo[1,2-*c*] thiazole-6-*S* (IV)
$C_3N_2-C_4Se$	Selenolo[2,3-*d*] imidazole
	Selenolo[3,4-*d*] imidazole
$C_3N_2-C_3NSe$	Imidazo[2,1-*b*] selenazole

Chapter 3 (Two Additional Heteroatoms)

$C_3N_2-C_3N_2$	Imidazo[4,5-*d*] imidazole
	Imidazo[4,5-*c*] pyrazole
$C_3N_2-C_2N_3$	Imidazo[2,1-*c*] [1,2,4] triazole
	Imidazo[1,2-*b*] [1,2,4] triazole
	Imidazo[1,5-*b*] [1,2,4] triazole
	Imidazo[5,1-*c*] [1,2,4] triazole
	Imidazo[1,5-*c*] [1,2,3] triazole
	Imidazo[1,2-*c*] [1,2,3] triazole
$C_3N_2-C_3NO$	Imidazo[4,5-*d*] oxazole
	Imidazo[4,5-*d*] isoxazole
$C_3N_2-C_2N_2O$	Imidazo[1,2-*d*] [1,2,4] oxadiazole
	Imidazo[2,1-*b*] [1,3,4] oxadiazole
	Imidazo[1,5-*b*] [1,2,4] oxadiazole
$C_3N_2-C_3NS$	Imidazo[4,5-*d*] thiazole
$C_3N_2-C_2N_2S$	Imidazo[1,2-*d*] [1,2,4] thiadiazole
	Imidazo[1,2-*b*] [1,2,4] thiadiazole
	Imidazo[2,1-*b*] [1,3,4] thiadiazole
$C_3N_2-C_2N_2Se$	Imidazo[2,1-*b*] [1,3,4] selenadiazole
$C_3N_2-C_2NS_2$	Imidazo[2,1-*c*] [1,2,4] dithiazole
	Imidazo[1,2-*b*] [1,4,2] dithiazole
$C_3N_2-C_2NSSi$	Imidazo[1,2-*d*] [1,4,2] thiazasilole

Chapter 4 (Three Additional Heteroatoms)

C_3N_2–C_2N_3	Imidazo[4,5-*d*] [1,2,3] triazole
C_3N_2–CN_4	1*H*- and 4*H*-Imidazo[1,2-*d*] tetrazole
C_3N_2–CN_3S	Imidazo[1,2-*c*] [1,2,3,5] thiatriazole-2-*S*(IV)
C_3N_2–CN_3Se	Imidazo[1,2-*c*] [1,2,3,5] selenatriazole-2-*Se* (IV)

The text within each ring system is organized consecutively in terms of synthesis, physicochemical studies, and reactions, and subdivisions within each section are delineated on the basis of increasing saturation of the system.

The literature on some of the compounds is covered in the volume by Mosby up to 1959, and treatment is this volume includes material from Volumes 53–97 of *Chemical Abstracts*. Bicyclic condensed imidazoles without a bridgehead nitrogen atom are covered from the origin of such studies also through Volume 97 of *Chemical Abstracts.*

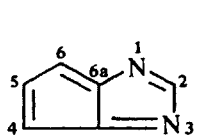
Chemistry of Heterocyclic Compounds, Volume 46
P. N. Preston

CHAPTER 1

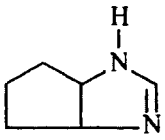
Condensed Imidazoles of Type 5-5 with No Additional Heteroatom

1.1. RING SYSTEM C_3N_2–C_5: CYCLOPENTIMIDAZOLE

Results of molecular orbital calculations provide a value of the resonance energy per π electron (REPE) for the fully unsaturated, parent cyclopentimidazole molecule (**1.1**) of -0.037β, and the system is thus strongly antiaromatic.[1,2] Compounds in this class are unknown, and this section is concerned almost entirely with hexahydro derivatives in which the imidazole fragment is condensed with a cyclopentane ring (cf. **1.2**)



(**1.1**)



(**1.2**)

1.1.1. Synthesis

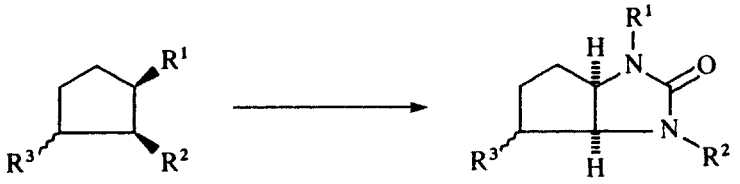
1.1.1.1. From Amido and Acylhydrazido Derivatives of Cyclopentane

Condensed imidazolones (cf. **1.4**) can be prepared with Curtius (e.g., **1.3a** → **1.4a**) and Hofmann (e.g., **1.3g** → **1.4b**) degradation products from appropriately substituted hydrazido and amido derivatives of cyclopentane. In an alternative approach to the unsubstituted imidazolone derivative (**1.4e**), cyclopentane-*cis*-1,2-dicarboxylic acid (**1.3e**) is first transformed by hydrazoic acid into *cis*-1,2-diaminocyclopentane (K. F. Schmidt degradation), and this product is treated with phosgene. Reactions

TABLE 1.1. SYNTHESIS OF CONDENSED IMIDAZOLONES (1.4) FROM ACYL DERIVATIVES OF CYCLOPENTANE

Starting Material	Product	Yield (%)	mp (°C)	Solvent for Recrystallization	Reaction Conditions	Reference
1.3a[a]	**1.4a**	31	175–176[3] 172–173[4]	EtOAc–petroleum	1. 2 *M* HCl, $NaNO_2$ 2. EtOH, reflux	3,4
1.3b	**1.4b**	31	156–157	Aqueous MeOH	1. 2 *M* HCl, $NaNO_2$ 2. MeOH, reflux	3
1.3c	**1.4c**	89	162–163	EtOAc	1. $NaNO_2$, H_2O 2. EtOAc, reflux	4
1.3d	**1.4d**[b]	57	190–192	$CHCl_3$–petroleum	1. $NaNO_2$, H_2O 2. EtOAc, reflux	4
1.3e	**1.4e**		204–205	95% EtOH	1. HN_3, conc. H_2SO_4 2. $COCl_2$	3
1.3f	**1.4f**[c,d]	49	116–118	EtOAc–petroleum	1. 2 *M* HCl, $NaNO_2$ 2. C_6H_6, reflux	5
1.3g	**1.4b**	22	156–157	Aqueous MeOH	1. NaOMe, MeOH 2. Br_2, reflux	3

[a] Contaminated by *trans* isomer.
[b] Stereochemistry is all *cis*.
[c] Undefined stereochemistry at C-4.
[d] Spectral data: uv $\lambda_{max}^{EtOH} = 271$ nm; ϵ, 1774; ir $\nu_{max} = 3448, 1724, 1618$ cm^{-1}.



(1.3) (1.4)

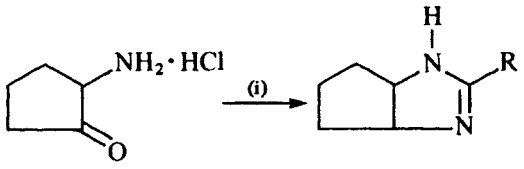
	R^1	R^2	R^3
a,	$CONHNH_2$	NHCOPh	H
b,	$CONHNH_2$	$CONHNH_2$	H
c,	$CONHNH_2$	$NHCONH_2$	H
d,	$CONHNH_2$	$NHCONH_2$	Me
e,	CO_2H	CO_2H	H
f,	$CONHNH_2$	NHCOMe	$(CH_2)_4OPh$
g,	$CONH_2$	$NHCO_2Me$	H

	R^1	R^2	R^3
a,	H	COPh	H
b,	H	CO_2Me	H
c,	H	$CONH_2$	H
d,	H	$CONH_2$	Me
e,	H	H	H
f,	H	COMe	$(CH_2)_4OPh$

in the three categories are summarized in Table 1.1, and hydrolytic reactions on substituted derivatives of type **1.4** are described in Section 1.1.2.

1.1.1.2. From Cyclopentanone and Cyclopentanone Oxime Derivatives

2-Aminocyclopentanone hydrochloride (**1.5**) is converted by potassium thiocyanate in moderate yield into the condensed (tautomeric) mercaptoimidazoline derivative (**1.6a**),[6] and this can be desulfurized by Raney nickel in ethanol to give the unsubstituted compound (**1.6b**) in 50% yield.[6]

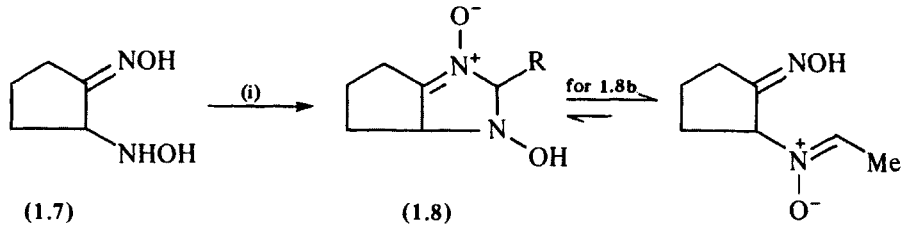


(1.5) (1.6)

	R	mp (°C)
a,	SH	275–280 (EtOH)
b,	H	150–151

(i) KNCS, H_2O, reflux (50% yield to **1.6a**)

The products (**1.8a,b**) of reactions of α-hydroxylamino cyclopentanone oxime (**1.7**) with formaldehyde and acetaldehyde are formulated (cf. **1.8**) as cyclic nitrones, but in dimethyl sulfoxide (DMSO) solution it is apparent (^1H nmr analysis) that there is a tautomeric equilibrium with an acyclic form (e.g., **1.8c**).[7]



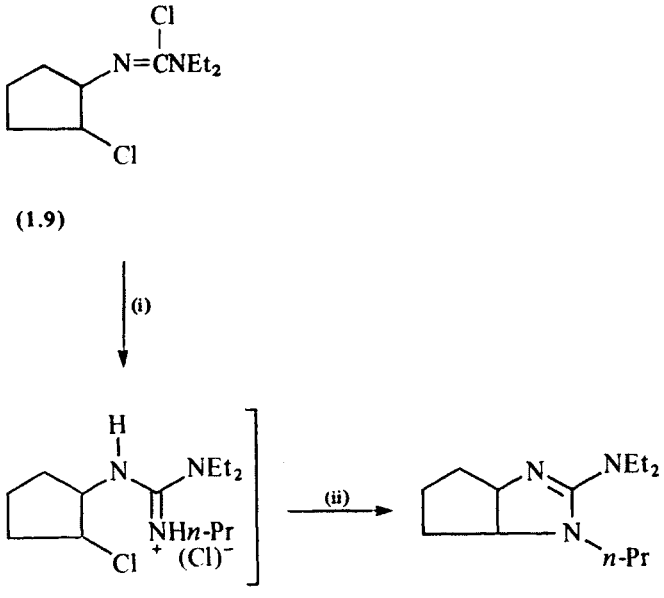
(1.7) (1.8) (1.8c)

	R	mp (°C)
a,	H	133–135
b,	Me	141–142

(i) RCHO, EtOH, heat

1.1.1.3. By Intramolecular Cyclization of Urea, Thiourea, and Formamidine Derivatives

Reactions in this group occur by intramolecular nucleophilic addition or substitution processes at a preformed carbocyclic ring and lead to products containing either a condensed cyclopentane or a cyclopentene ring. For example, cyclization of the *N*(2-chlorocylopentyl)-*N'*,*N'*-diethylformamidine derivative (**1.10**) is caused by aqueous base and gives the condensed imidazole (**1.11**), albeit in poor yield.[8]



(1.9)

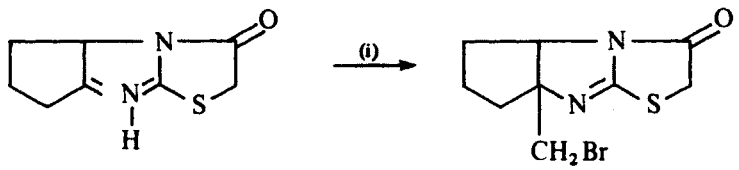
(1.10)

(1.11)

bp 92°C/1.3 torr
n_D^{20} = 1.4849
17% yield

(i) *n*-PrNH$_2$ (ii) NaOH

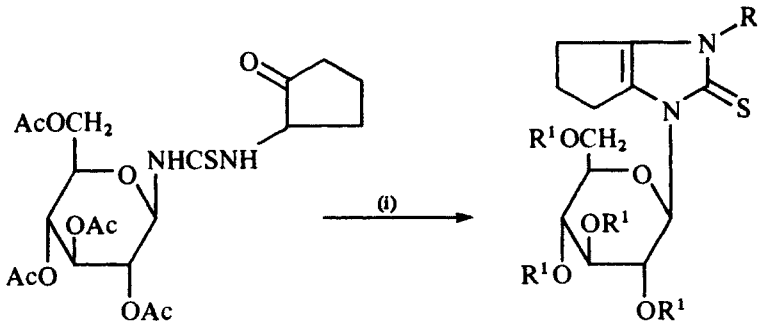
An analogous intramolecular displacement of halogen occurs in the transformation (**1.12** → **1.13**) in which a bromocyclopentane is generated *in situ* from a methylene cyclopentane derivative (**1.12**).[9]



(**1.12**) (**1.13**)

(i) Br_2, CH_3CO_2K mp 103°C

The nucleoside (**1.14a**) has been synthesized in two steps from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate and represents the isolated example of a cyclopentimidazole prepared by intramolecular nucleophilic addition in a cyclopentanone derivative.[10] Reacetylation of the deprotected compound (**1.14a**) can be effected by acetic anhydride in pyridine to give a pentaacetyl derivative (**1.14b**).[10]

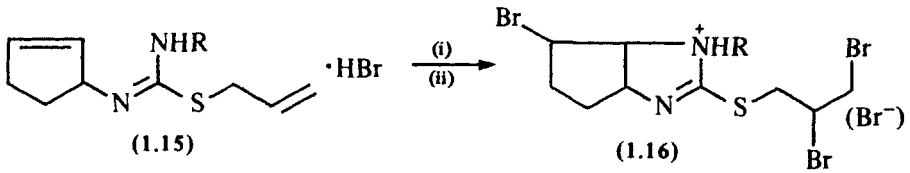


(**1.14**)

	R	R^1	mp (°C)	MeOH λ_{max}	log ε
a,	H	H	not quoted	277	4.18
b,	Ac	Ac	182–185	282	4.10

(i) 0.1 *M* NaOMe, room temp. (35% yield to **1.14a**)

Two approaches have been used for the synthesis of cyclopentimidazoles from cyclopentenes. For example, condensed imidazolium bromides (**1.16a,b**) are formed from S-allylthioureas (**1.15**) in processes presumably involving intramolecular attack at an intermediate bicyclic bromonium ion.[11]

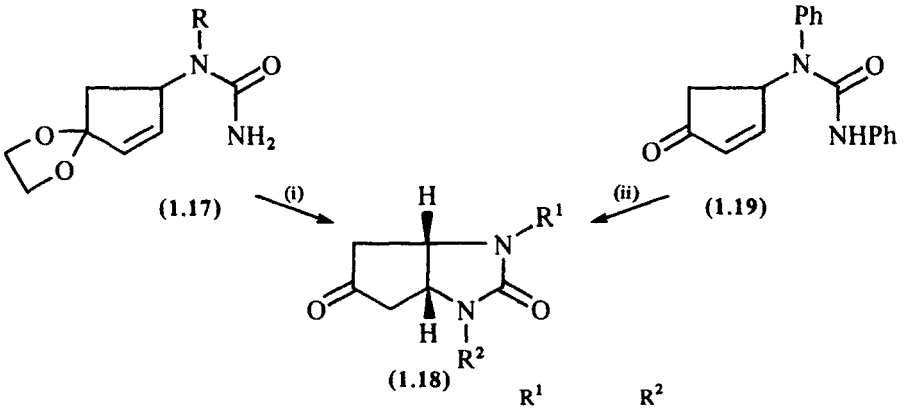


(1.15) (1.16)

(i) CH_3CO_2K, MeOH (ii) Br_2, CCl_4

	R	Yield (%)	mp (°C)
a,	H	51	46
b,	Me	81	52

Secondly, intramolecular nucleophilic addition in conjugated cyclopentenones can be effected either *in situ* (see **1.17** → **1.18a, b**) or directly (**1.19** → **1.18c**) and provide valuable methods for the synthesis of condensed imidazolones (**1.18a–c**) (see Table 1.2).[12]



(1.17) (1.19) (1.18)

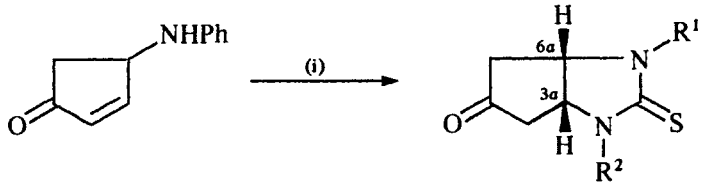
(i) 2 *M* HCl, tetrahydrofuran (to **1.18a, b**)
(ii) trace HCl, $CHCl_3$ (to **1.18c**)

	R^1	R^2
a,	CH_2Ph	H
b,	n-C_8H_{17}	H
c,	Ph	Ph

TABLE 1.2 PREPARATION OF CONDENSED IMIDAZOLONES (1.18) FROM CYCLIZATION REACTIONS OF PROTECTED CYCLOPENTENONES (1.17) AND A CYCLOPENTENONE DERIVATIVE (1.19)[12]

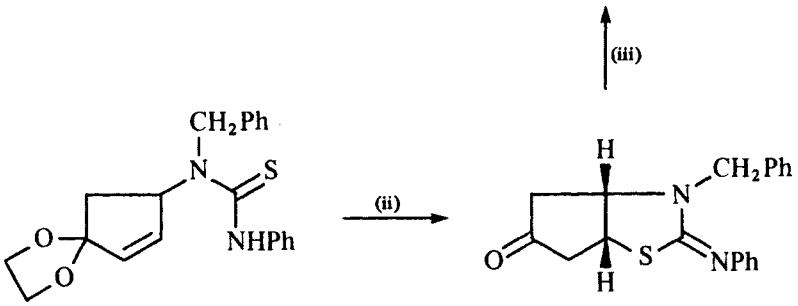
Starting Material	Product	Yield (%)	mp (°C)	ir, Ketone CO (cm^{-1})	ir, Cyclic Urea CO (cm^{-1})
1.17 (R = CH_2Ph)	**1.18a**[a]	98	135–136	1735	1705
1.17 (R = n-C_8H_{17})	**1.18b**	75	54–56	1740	1695
1.19	**1.18c**	100	171–173 (dec.)	1740	1700

[a]Nuclear magnetic resonance: $\delta = 2.2$–2.7 (m, 4H, 4- and 6-CH_2), 4.02 (1H, d, $J = 15$ Hz, C*H*Ph), 4.0–4.6 (2H, m, 3*a*- and 6*a*-H), 4.76 (1H, d, $J = 15$ Hz, C*H*Ph), 5.94 (br, 1H, NH), 7.29 (5H, m, Ar–H).



(1.20) (1.21)

	R^1	R^2	Yield (%)	mp (°C)
a,	Ph	Ph	40	267–268
b,	CH_2Ph	Ph	50	134–135



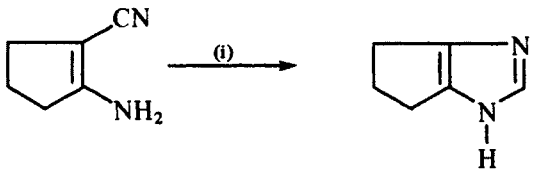
(1.22)

(i) $PhNCS$, $CHCl_3$, Et_3N (to **1.21a**)
(ii) 2 *M* HCl, tetrahydrofuran
(iii) Et_3N, $(CH_3)_2SO$, 60°C (to **1.21b**)

A cyclization (**1.20** → **1.21a**) analogous to **1.19** → **1.18c** can be used[12] to provide the cyclic thiourea analog of **1.18c**, but elaboration of the process illustrated in **1.17** → **1.18** leads to a condensed thiazolidine derivative (**1.22**); the latter can be isomerized to the appropriate condensed imidazoline thione (**1.21b**) in a process with precedent in the acyclic thioamide–thioimidate system. Evidently the cyclic thioamide structure (**1.21b**) is thermodynamically preferred, and the *cis* ring fusion is apparent from ^1H nmr analysis ($J_{3aH-6aH}$ = 8.2 Hz).[13]

1.1.1.4. From Photolysis of 2-Amino-1-cyclopentene-1-carbonitrile

Ultraviolet irradiation of 2-amino-1-cyclopentene-1-carbonitrile (**1.23**) in tetrahydrofuran gives the condensed imidazole (**1.24**) in excellent yield based on consumed starting material.[14] Compound **1.24** is characterized by the following spectral properties: uv λ_{max}^{EtOH} = 224 nm; mass spectrum *m/z* 108 (89%) [$M^{\cdot+}$] and 107 (100%); and nmr ($CDCl_3$) δ = 2.6 (m, 6H, H-4, -5 and -6), 7.5 (s, H-2), and 10.2 ppm (s, N*H*).



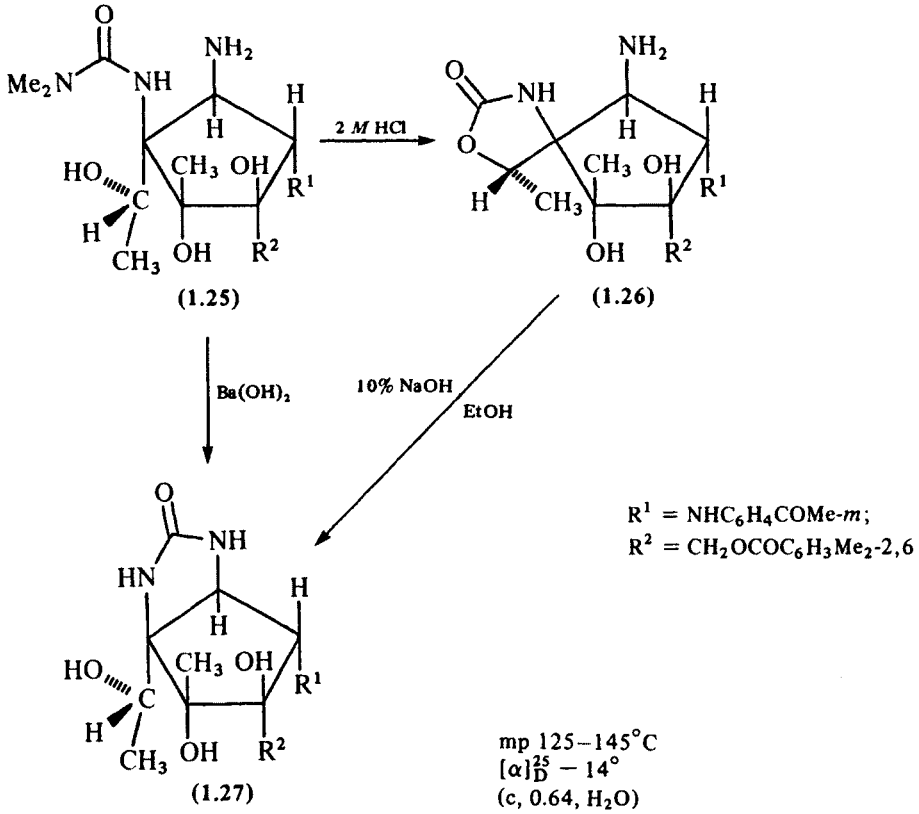
(1.23) (1.24)

(i) uv light (254 nm), tetrahydrofuran, 90% yield based on (1.23) consumed.

mp 145.5–147°C
picrate, mp 175–177°C

1.1.1.5. From Degradation of Pactamycin

The highly functionalized condensed imidazolone derivative (1.27) can be obtained directly from the antibiotic pactamycin (1.25) or its degradation product pactamycate (1.26);[15a] it may be noted that the absolute stereochemistry[15b] and the biosynthesis[15c] of pactamycin have been elucidated. Compound 1.27 is characterized by the following spectral properties: $\lambda_{max}^{H_2O} = 238$ nm (ϵ, 26,550), 350 (1700); $\lambda_{sh}^{H_2O}$ 264 nm ir, $\nu_{max} = 3300$, 1705, 1680, 1600, 1583, 1510, and 1100 cm^{-1}.



(1.25) (1.26) (1.27)

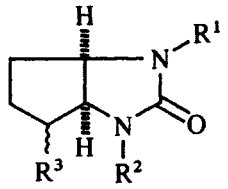
$R^1 = NHC_6H_4COMe\text{-}m$;
$R^2 = CH_2OCOC_6H_3Me_2\text{-}2,6$

mp 125–145°C
$[\alpha]_D^{25} - 14°$
(c, 0.64, H_2O)

1.1.2. Reactions

1.1.2.1. With Nucleophiles

Routine reactions of side chains of reduced cyclopentimidazoles with nucleophiles are summarized in Table 1.3. A notable product listed in Table 1.3 is the diastereomeric mixture **1.28g**, which is closely related to biotin (see Section 2.15.5). Biological evaluation of this material (carbobiotin) indicates that it possesses approximately 15% of the potency of *d*-biotin as a growth factor for *d*-biotin-requiring microorganisms.[5]



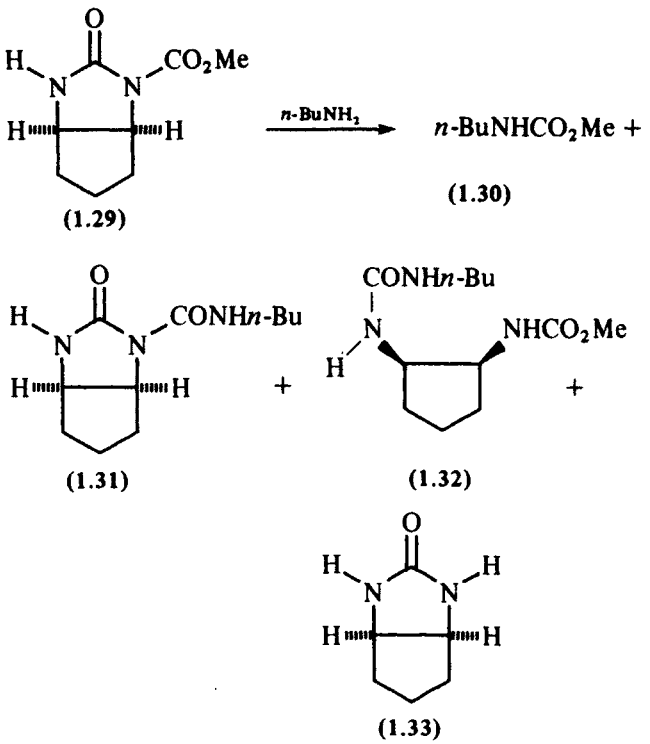
(1.28)

	R^1	R^2	R^3
a	H	COPh	H
b	H	H	H
c	H	COMe	$(CH_2)_4OPh$
d	H	H	$(CH_2)_4OPh$
e	H	H	$(CH_2)_4Br$
f	H	H	$(CH_2)_4CN$
g	H	H	$(CH_2)_4CO_2H$

TABLE 1.3. FORMATION OF CONDENSED IMIDAZOLONES (1.28) BY ROUTINE SIDE-CHAIN TRANSFORMATIONS

Starting Material	Product	Reaction Conditions	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reference
1.28a	**1.28b**	10% aqueous $Ba(OH)_2$	87	205–206 (95% EtOH)	3
1.28c	**1.28d**[a]	Aqueous $Ba(OH)_2$	46	103–106	5
1.28c	**1.28e**[b]	HBr, AcOH	82	(Oil)	5
1.28e	**1.28f**[c]	Aqueous NaCN	94	(Oil)	5
1.28f	**1.28g**[d]	KOH/aqueous MeOH	95	211–213	5

[a]Spectral data: λ_{max}^{EtOH} = 278 nm (*e*, 1894); ir ν_{max} = 3448 and 1695 cm^{-1}.
[b]Spectral data. ir ν_{max} = 3472, 3333, and 1681 cm^{-1}.
[c]Spectral data: ir ν_{max} = 3472, 3247, 2247, and 1681 cm^{-1}.
[d]Spectral data: ir ν_{max} = 3257 and 1695 cm^{-1}.

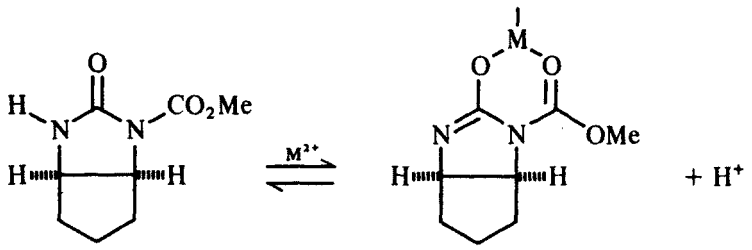


The reaction of *n*-butylamine with the methoxycarbonyl derivative (**1.29**) has been studied in some detail.[16] Four products (**1.30–1.33**) are formed in this reaction, with the amide (**1.31**) predominant. The course of the reaction is markedly modified by the addition of equimolar amounts of magnesium chloride or manganese chloride, and the carbamate derivative (**1.30**) becomes the predominant product (see Table 1.4). It is suggested[16] that the electrophilic reactivity of the methoxycarbonyl group is accentuated by the formation of coordination complexes in the manner depicted in **1.34** ⇌ **1.35**. The results (Table 1.4) indicate that the formation of such chelates is favored by association of the imidazolone

TABLE 1.4. EFFECT OF ADDED SALTS ON REACTION[a] OF ESTER (**1.29**) WITH *n*-BUTYLAMINE[16]

Added Metal Chloride	Reaction Products (%)			
	1.30	**1.31**	**1.32**	**1.33**
None	7	55	15	13
AgCl	8	51	20	7
$CuCl_2$	10	52	17	15
$MgCl_2$	66	28	–	38
$MnCl_2$	68	22	–	44

[a]Reaction conditions: (**1.29**), *n*-$BuNH_2$, equimolar metal chloride.



(1.34) (1.35)

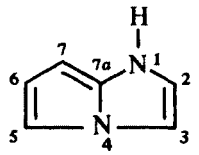
ring with hard[17] metal ions such as Mg^{2+} and Mn^{2+}. In contrast, bivalent ions belonging to the borderline class[17] (e.g., Cu^{2+}) and monovalent ions do not form stabilized chelate rings.

1.1.3. Practical Applications

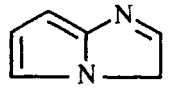
The biotin analog described earlier (see **1.28g** in Section 1.1.2) has been shown to inhibit the growth of roots and stems of tomato and flax seedlings.[18]

1.2. RING SYSTEM $C_3N_2-C_4N$: PYRROLO[1,2-*a*]IMIDAZOLE

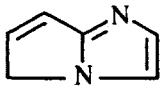
Fusion of a three-carbon fragment across the N-1–C-2 bond of an imidazole ring gives rise to the pyrrolo[1,2-*a*]imidazole ring system. In principle, compounds in this group can belong to either the 1*H* (**1.36**), 3*H* (**1.37**), 5*H* (**1.38**), or 7*H* (**1.39**) categories; compounds in the 1*H* and 5*H* groups are well documented, but few 7*H* derivatives are described in this section, and 3*H* derivatives are not cited during the literature period covered. The present section is subdivided to cover compounds in the 1*H*, 5*H*, and 7*H* categories, and included within each section are compounds that are partially reduced (e.g., 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazoles, **1.40**, and 2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazoles, **1.41**).



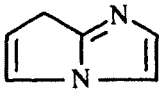
(1.36)



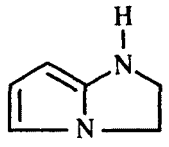
(1.37)



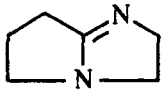
(1.38)



(1.39)



(1.40)

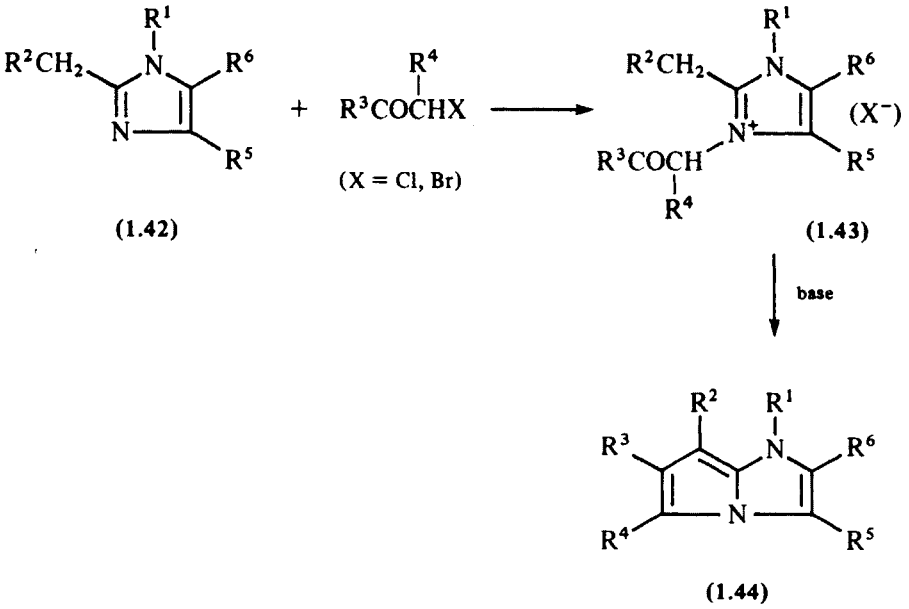


(1.41)

1.2.1. 1*H*-Pyrrolo[1,2-*a*]imidazoles

1.2.1.1. Synthesis

Compounds in the fully unsaturated 1*H*-pyrrolo[1,2-*a*]imidazole system (cf. **1.44** and Table 1.5) are synthesized in high yield by the base-promoted cyclization of 1,2-dialkyl-3[β-ketoalkyl]imidazolium halides (cf. **1.43**); the latter are readily available by treating 1,2-disubstituted imidazoles (**1.42**) with the appropriate halogeno ketone derivative.[19–21]



Reactions of this type can be effected[19] in either water, alcohols, dimethylformamide, or acetic anhydride with a variety of basic catalysts, such as sodium hydrogen carbonate, sodium carbonate, sodium acetate, sodium hydroxide, or sodium ethoxide. The cyclization step in this versatile synthesis is usually achieved by simply heating the isolated imidazolium salt (cf. **1.43**) with aqueous sodium hydrogen carbonate (Table 1.5, reaction condition A). It is also possible to proceed directly from the imidazole derivative (cf. **1.42**) without isolation of the intermediate salt (**1.43**) (Table 1.5, reaction conditions B and E), although yields achieved by this route are generally lower. A detailed study[20] of the efficiency of a variety of bases on the cyclization of **1.43** (R^1 = Et, R^2 = H, R^3 = Ph, R^4 = R^5 = H, R^6 = Cl) to 2-chloro-1-ethyl-6-phenylpyrrolo[1,2-*a*]imidazole indicates (Table 1.6) that weak bases such as ammonium hydroxide or pyridine either do not cause cyclization or give very low yields of cyclized product. The mechanism of the transformation **1.43** → **1.44** almost certainly involves intermediate imidazolium betaines

TABLE 1.5. SYNTHESIS OF 1*H*-PYRROLO[1,2-*a*]IMIDAZOLES (1.44) BY RING CLOSURE REACTIONS OF IMIDAZOLIUM SALTS (1.43)

Substituents in (1.44)										
R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	mp (°C) (Solvent for Recrystallization)	mp (°C) Picrate	Reaction Conditions[a]	References
Me	H	*p*-BrC_6H_4	H	H	H	46	135–136[b]	238–240[b]	A	19
Et	H	Ph	H	H	Cl	84	84–85	236–238[b]	A	19
Et	H	*p*-BrC_6H_4	H	H	Cl	74	148–150[b]		A	19
Et	H	Ph	Me	H	Cl			162–164	A	19
Et	H	*p*-C_6H_5–C_6H_4	Me	H	Cl	91	128–130		A	19
Pr	Me	H	H	H	Cl			167–168	A	19
Pr	Me	*p*-BrC_6H_4	H	H	Cl	23	99–100		A	19
Pr	Me	*p*-BrC_6H_4	H	Cl	H			186–188[b]	A	19
Et	H	*p*-BrC_6H_4	H	Ph	Ph	92	182–184		A	19
Ph	H	*p*-BrC_6H_4	H	Ph	Ph	90	199–201	204–205	A	19
Et	H	*p*-$MeOC_6H_4$	H	Cl	H	54	165–167		A	20
Et	H	Ph	H	Ph	Ph	53	158–159 (C_6H_6)		A	20
Ph	H	Ph	H	Ph	Ph	84	218–220 (C_6H_6)		A	20
Ph	H	*m*-$O_2NC_6H_4$	H	Ph	Ph	91	182–184 (EtOH–DMF)		A	20
Ph	H	*p*-$O_2NC_6H_4$	H	Ph	Ph	61	235–237[b] (EtOH–DMF)		A	20
$PhCH_2$	H	*p*-BrC_6H_4	H	Ph	Ph	92	180–181 (C_6H_6)		A	20
Me	H	Ph	H	Ph	Ph	36	148–150 (EtOH)		B	20
Me	H	*p*-BrC_6H_4	H	Ph	Ph	39	173–175 (C_6H_6)		B	20
Et	H	Me	H	Ph	Ph	35	95–96 (EtOH)		B	20
Et	H	Me	Me	Ph	Ph	26	99–100 (EtOH)		B	20
Et	H	Ph	Me	Ph	Ph	33	162–165 (EtOAc)		B	20
Ph	H	Me	H	Ph	Ph	40	186–188 (C_6H_6)		B	20
Ph	H	Me	Me	Ph	Ph	36	177–179 (EtOH)		B	20
$PhCH_2$	H	Me	H	Ph	Ph	53	124.5–126 (EtOH)		B	20
$PhCH_2$	H	Ph	H	Ph	Ph	89	174–176.5[b] (C_6H_6)		B	20
Me	CN	Ph	H	H	H	79	135–137 (EtOH)		C	21
Me	CN	Me	Me	H	Cl	74	138–140 (EtOH)		D	21
Me	CN	Me	H	H	H	20	114–116 (EtOH)		E	21

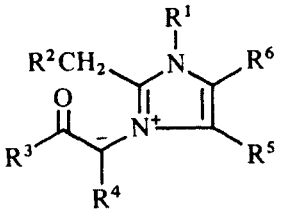
[a]Reaction conditions: (A) aqueous $NaHCO_3$, reflux, 2–5 h, (B) (i) imidazole derivative, α-bromoketone, Me_2CO, reflux; (ii) imidazolium compound (not isolated)/NaOEt, EtOH, reflux; (C) H_2O, reflux; (D) NaOEt, EtOH, 18–20°C, 0.5 h; (E) imidazole derivative, $BrCH_2COCH_3$, reflux, 2 h.
[b]Melting with decomposition.

TABLE 1.6. EFFECT OF NATURE OF BASIC CATALYST ON CYCLIZATION OF IMIDAZOLIUM SALT (**1.43**, R^1 = Et, R^2 = H, R^3 = Ph, R^4 = R^5 = H, R^6 = Cl) TO 2-CHLORO-1-ETHYL-6-PHENYLPYRROLO[1,2-*a*]IMIDAZOLE (**1.44**, R^1 = Et, R^3 = Ph, R^6 = Cl)[20]

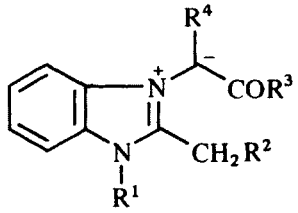
Basic Catalyst[a]	Reaction Time (h)	Yield of Cyclized Product (%)
EtONa[b]	5	79
NaOH	2	79
$Ca(OH)_2$	10	79
$Ba(OH)_2$	5	47
Na_2CO_3	5	63
$NaHCO_3$	5	63–84
$CaCO_3$	10	Trace
Ch_3CO_2Na	20	Trace
NH_4OH	20	Trace
i-$BuNH_2$	10	15
Piperidine	10	55
Pyridine	10	8

[a] Reaction conditions: reflux in water.
[b] Reaction conditions: reflux in ethanol.

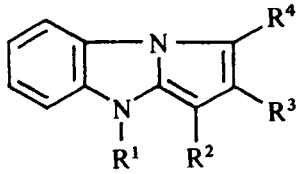
(cf. **1.45**), and it is relevant that benzimidazolium betaines (cf. **1.46**) can be isolated in reactions of benzo analogs, and that these can be cyclized to 4*H*-pyrrolo[1,2-*a*]-benzimidazoles (**1.47**) by warming in water or on attempted recrystallization from organic solvents.[22,23]



(1.45)



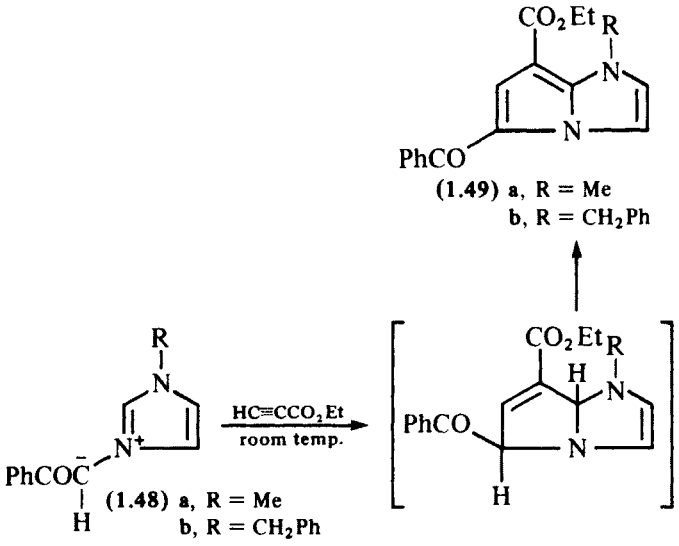
(1.46)

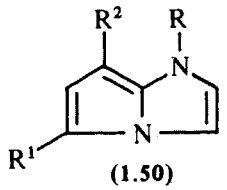


(1.47)

From a synthetic viewpoint the last three entries in Table 1.5 are notable. In these examples the 2-alkyl group of the imidazolium salt (cf. R^2 in **1.43**) is activated by a cyano substituent. Cyclization is relatively easy and the products (cf. **1.44**, R^2 = CN) allow synthetic access to acyl derivatives in the series (cf. preparation of analogous 3-cyano-4*H*-pyrrolo[1,2-*a*]benzimidazoles; **1.47**, R^2 = CN).[21]

In a different approach, imidazolium betaines (**1.48**) have been cyclized to 5,7-disubstituted acyl derivatives of 1*H*-pyrrolo[1,2-*a*]imidazoles (**1.49**) in processes of 1,3-dipolar cycloaddition (see Table 1.7).[24] Although the initial products (**1.49a,b**) are formed in poor yield, they can be used to prepare carboxylic acid derivatives (**1.50a,b**) and their products of decarboxylation (**1.50c,d**) in good yields. An interesting feature noted during the synthesis of the 5-benzyl-1*H*-pyrrolo[1,2-*a*]imidazole (**1.50e**) by reduction of the 5-benzoyl analog (**1.50c**) is the relative instability fo the former in solution; thus the uv spectrum of **1.50e** in ethanol shows a band at 283 nm, but this is gradually replaced by an absorption peak at 360 nm. A similar instability of compounds in this ring system was noted[24] during attempts to synthesize 1-methyl and 1-benzyl-2,3,5,6,7-unsubstituted derivatives by treating 5-benzoyl derivatives (**1.50c,d**) with concentrated hydrochloric acid under reflux. The free base corresponding to debenzoylation of **1.50c** could not be isolated, and the colorless product (**1.50f**) from **1.50d** was obtained in poor yield, turned red on standing, and was necessarily characterized spectroscopically (see footnote *g* in Table 1.7).





(1.50)

a, R = Me, R^1 = COPh, R^2 = CO_2H
b, R = CH_2Ph, R^1 = COPh, R^2 = CO_2H
c, R = Me, R^1 = COPh, R^2 = H
d, R = CH_2Ph, R^1 = COPh, R^2 = H
e, R = Me, R^1 = CH_2Ph, R^2 = H
f, R = CH_2Ph, R^1 = R^2 = H

TABLE 1.7. 1*H*-PYRROLO[1,2-*a*] DERIVATIVES (**1.49**) DERIVED FROM IMIDAZOLIUM BETAINES (**1.48**) AND ENSUING REACTIONS LEADING TO **1.50**[24]

Starting Material	Reaction Conditions	Product	Yield (%)	mp (°C)	Solvent for Recrystallization
1.48a	$HC{\equiv}CCO_2Et$, room temp.	**1.49a**[a]	14	126–127	EtOH
1.48b	$HC{\equiv}CCO_2Et$, room temp.	**1.49b**	–	103–104	Et_2O–S[b]
1.49a	10% aq KOH, MeOH	**1.50a**[c]	85	206–207	Me_2CO
1.49b	10% aq KOH, MeOH	**1.50b**	82	181–182	
1.50a	Sublime at 200°C, 10 torr	**1.50c**[d]	67	113–115	Et_2O–S[b]
1.50b	Heat to 220°C	**1.50d**	–	101–103	Et_2O–S[b]
1.50c	$LiAlH_4$, Et_2O, room temp.	**1.50e**[e]	–	116–118	Et_2O
1.50d	Concentrated HCl, reflux	**1.50f**[f,g]	–	–[h]	–

[a] Spectral data: uv λ_{max}^{EtOH} = 357 nm (ϵ, 23,680), 267 (16,200), 251 (sh, 12,600), ir λ_{Nujol} = 5.92 μm (ester CO), 6.25 (aryl CO), 6.3 (aryl C=C); nmr (δ, CCl_4), 8.00 (1 H, d, J = 2 Hz), 7.76 (2 H, *m*), 7.33 (4 H, *m*), 6.70 (1 H, br, s), 4.04 (2 H, q, J = 7 Hz), 4.04 (s, 3H), 1.29 (3 H, t, J = 7 Hz).

[b] S = Skellysolve.

[c] Spectral data: uv λ_{max}^{EtOH} = 362 nm (ϵ, 22,530), 260 (14,740), 249 (16,080).

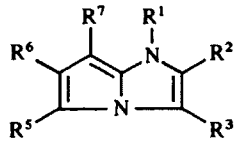
[d] Spectral data: uv λ_{max}^{EtOH} = 363 nm (ϵ, 23,555), 241 (8615), ir λ_{Nujol} = 6.24 μm (CO), 6.3 (aryl C=C); ^{1}H nmr (CCl_4) δ = 7.93 (1 H, d, J = 2 Hz), 7.70 (2 H, m), 7.30 (3 H, m), 6.88 (1 H, d, J = 4 Hz), 6.59 (1 H, d, J = 2 Hz), 5.42 (1 H, d, J = 4 Hz), 3.49 (3 H, s).

[e] Spectral data: uv λ_{max}^{EtOH} = 283 nm (accurate determination of extinction coefficient impossible because of instability of material in solution); nmr (CCl_4) δ = 7.08 (5 H, s), 6.31 (1 H, d, J = 5 Hz), 6.29 (1 H, d, J = 5 Hz), 6.02 (1 H, d, J = 4 Hz), 5.02 (1 H, d, J = 4 Hz), 4.05 (2 H, s), 3.38 (3 H, s).

[f] Benzoic acid also formed.

[g] Spectral data: uv λ_{max} = 285 nm (accurate determination of extinction coefficient impossible because of instability of material in solution); nmr (CCl_4) δ = 7.22 (5H, s, Ar–H), 6.83 (1 H, J = 2 Hz, H-2), 6.45 (2 H, m, H-3 and -5), 6.22 (1 H, t, J = 3.5 Hz, H-6), 5.15 (2 H, s, PhCH_2), 5.08 (1 H, d, J = 3.5 Hz, H-7).

TABLE 1.8. ^{1}H NMR SPECTRA OF 1*H*-PYRROLO[1,2-*a*]IMIDAZOLES IN NEUTRAL AND ACIDIC MEDIA[26]

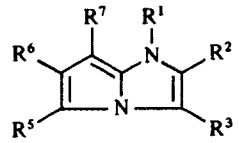


(1.51)

	Chemical Shifts (ppm)									
	Base[a]			C-5 Protonation			C-7 Protonation		Percent of Protonated Forms[b]	
Compound 1.51	5-H	7-H	R^1	5-CH_2	7-CH	R^1	7-CH_2	R^1	C-5	C-7
R^1 = Me, R^2 = R^3 = R^5 = R^7 = H, R^6 = *p*-ClC_6H_4	6.64	5.33	3.40	5.30	7.10	3.99	4.62	4.05	78	22
R^1 = Et, R^2 = Cl, R^3 = R^7 = H, R^5 = Me, R^6 = *p*-$C_6H_5C_6H_4$	2.43[c]	5.38	1.40 3.94	1.79[c] 5.63	7.09	4.40	4.24	4.40	5	95
R^1 = C_3H_7, R^2 = Cl, R^3 = R^5 = H, R^6 = *p*-BrC_6H_4, R^7 = Me	6.52	2.26[d]	0.99 1.77 3.94	5.19	2.53[d]	1.17 2.05 4.43	–	–	100	0

[a] Measured in CCl_4 or $CDCl_3$.
[b] Measured in CF_3CO_2H.
[c] Corresponds to δ value of Me at C-5.
[d] Corresponds to δ value of Me at C-7.

TABLE 1.9. SYNTHESIS OF DERIVATIVES OF 1*H*-PYRROLO[1,2-*a*]IMIDAZOLES BY ELECTROPHILIC SUBSTITUTION PROCESSES



(1.52)

Entry	Product (1.52)	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reaction Conditions[a]	Reference
1	$R^1 = n\text{-}C_3H_7$, $R^2 = Cl$, $R^3 = H$, $R^5 = CHO$, $R^6 = p\text{-}BrC_6H_4$, $R^7 = CH_3$	57	138–140	A[b]	28
2	$R^1 = PhCH_2$, $R^2 = R^3 = H$, $R^5 = COMe$, $R^6 = p\text{-}MeC_6H_4$, $R^7 = H$	87	111–113	B[c]	28
3	$R = PhCH_2$, $R^2 = R^3 = H$, $R^5 = R^7 = COMe$, $R^6 = p\text{-}MeC_6H_4$	86	157–159	B	28
4	$R^1 = Me$, $R^2 = R^3 = H$, $R^5 = R^7 = COMe$, $R^6 = p\text{-}ClC_6H_4$	58	218–219	B	28
5	$R^1 = C_3H_7$, $R^2 = Cl$, $R^3 = H$, $R^5 = CH_2OH$, $R^6 = p\text{-}BrC_6H_4$, $R^7 = Me$	54	165–167	C[d]	28
6	$R^1 = R^2 = R^3 = Ph$, $R^5 = N_2C_6H_4Br\text{-}p$, $R^6 = Ph$, $R^7 = H$	87	202–204	D	28

7	$R^1 = PhCH_2$, $R^2 = R^3 = H$, $R^5 = R^7 = N_2C_6H_4Br$-*p*, $R^6 = p$-MeC_6H_4	35	252–253	D	28
8	$R^1 = Et$, $R^2 = OH$,[e] $R^3 = H$, $R^5 = R^6 = Ph$, $R^7 = N_2C_6H_4CO_2H$-*o*	98	233–235 (aqueous EtOH)	E	29
9	$R^1 = CH_2Ph$, $R^2 = R^3 = H$, $R^5 = N_2C_6H_4CO_2H$-*o*, $R^6 = R^7 = Ph$	55	242–243 (dec.) (EtOH)	E	29
10	$R^1 = C_3H_7$, $R^2 = Cl$, $R^3 = H$, $R^5 = NO$, $R^6 = p$-BrC_6H_4, $R^7 = Me$	92	167–168	F	28
11	$R^1 = PhCH_2$, $R^2 = R^3 = H$, $R^5 = NO$, $R^6 = R^7 = Ph$	40	193–195 (EtOH)	F	29
12	$R^1 = Me$, $R^2 = R^3 = H$, $R^5 = NO_2$, $R^6 = p$-ClC_6H_4, $R^7 = NO_2$	50	232.5–233.5	G	28
13	$R^1 = C_2H_5$, $R^2 = R^3 = Ph$, $R^5 = R^6 = Me$, $R^7 = HgCl$	71	135–137	H	28
14	$R^1 = PhCH_2$, $R^2 = R^3 = H$, $R^5 = HgCl$, $R^6 = p$-MeC_6H_4, $R^7 = H$	80	133–135	H	28

[a] Reaction conditions: (A) $POCl_3$, dimethylformamide, 18–20°C, 1 h; (B) sodium acetate, acetic anhydride, reflux; (C) CH_2O, dimethylformamide, room temperature; (D) $ArN_2^+ BF_4^-$, MeOH, AcOH, room temperature; (E) *o*-$HO_2CC_6H_4N_2^+Cl^-$, 18–20°C; (F) $NaNO_2$, AcOH, 18–20°C; (G) 98% HNO_3, AcOH, 18–20°C; (H) $HgCl_2$, EtOH, reflux.

[b] Spectral data: ir (Nujol) $\nu_{max} = 1615\ cm^{-1}$ (CO); nmr $\delta = 2.17$ (Me), 9.1 (C*H*O), 7.94 (H-3), 0.98, 1.78, and 3.97 (*n*-C_3H_7), 7.0–7.5 (Ar–H).

[c] Spectral data: ir (Nujol) $\nu_{max} = 1610\ cm^{-1}$ (CO); nmr $\delta = 1.96$ (COMe), 2.36 ($C_6H_4CH_3$), 5.01 (CH_2Ph), 6.82 (H-2), 8.13 (H-3), 7.0–7.5 (Ar–H), 5.48 (H-7).

[d] Spectral data: ir (Nujol) $3150\ cm^{-1}$ (OH); nmr $\delta = 0.86$, 1.66, 3.85 (*n*-Pr), 2.10 (Me), 4.00 (CH_2OH), 7.38 (CH_2OH).

[e] Exists as the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-one tautomer.

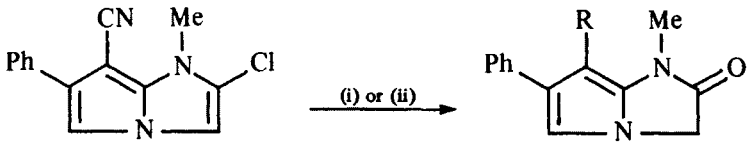
1.2.1.2. Physicochemical Studies

Calculation[25] of π-electron density distributions in the parent 1*H*-pyrrolo[1,2-*a*]-imidazole ring system (see **1.36**) by molecular orbital methods [linear combination of atomic orbitals (LCAO) with self-consistent field (SCF) approximation] leads to the prediction[25] that compounds of this type will be susceptible to electrophilic attack at C-5 and to a lesser extent at C-7; these predictions have been borne out in studies of the reactivity of this ring system (see Section 1.2.1.3). It has also been demonstrated by ^{1}H nmr spectroscopy that protonation of 5,7-unsubstituted derivatives in trifluoroacetic acid gives rise to a mixture of two forms of cations from electrophilic attack at C-5 and C-7 with predominant attack at C-5.[26] Introduction of a methyl group at C-5 changes the direction of protonation to favor C-7 predominantly, whereas 7-methyl derivatives are protonated exclusively at C-5. (See examples in Table 1.8 and ref. 27 for a more detailed kinetic study of the protonation of 1*H*-pyrrolo[1,2-*a*] imidazoles in hydrochloric acid and trifluoroacetic acid.)

1.2.1.3. Reactions

The most extensively studied class of reactions of 1*H*-pyrrolo[1,2-*a*] imidazoles is that of electrophilic aromatic substitution. In general, and in agreement with predictions from molecular orbital calculations[25] (see previous section), electrophilic substitution occurs at C-5 with a lesser propensity for substitution at C-7. Examples (cf. **1.52**) of such reactions are collected in Table 1.9 and include products of Vilsmeier formylation (Table 1.9, entry 1), acetylation (entries 2–4), methylolation (entry 5), diazonium coupling (entries 6–9), nitrosation (entries 10 and 11), nitration (entry 12), and chloromercuration (entries 13 and 14); the products (**1.54**) of Mannich reactions (cf. **1.53** → **1.54**) are shown separately in Table 1.10.[30]

A number of products resulting from the electrophilic substitution reactions described above have been subjected to routine functional group transformations, and these are listed in Table 1.11. A notable feature of the reactions given in Table 1.11 is the reluctance of the 7-cyano function to undergo hydrolysis. For example, when the nitrile derivative (**1.55**) is heated in a sealed tube with sulfuric



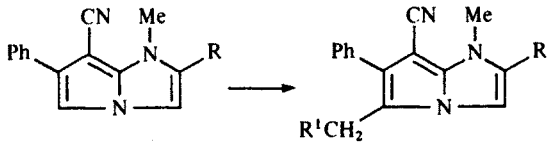
(1.55)

(i) H_2SO_4, EtOH, 140°C (to **1.56a**)
(ii) 90% H_3PO_4, 160°C (to **1.56b**)

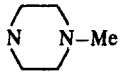
(1.56)

a, R = CN
b, R = H

TABLE 1.10. SYNTHESIS OF 5-(DIALKYLAMINO)METHYL AND RELATED DERIVATIVES OF 1*H*-PYRROLO[1,2-*a*]IMIDAZOLES (1.54) BY MANNICH REACTIONS[a] OF 1.53[30]

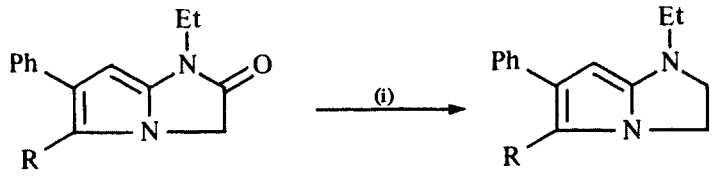


(1.53) (1.54)

Product (1.54)		mp (°C) (Solvent for	
R	R^1	Recrystallization)	Yield (%)
H	NMe_2	95–97 (EtOH)	90
H	1-Pyrrolidinyl	92–94 (EtOH)	82
H	1-Piperidinyl	163–164.5 (EtOH)	83
H	1-Morpholinyl	161–162 (Me_2CO)	47
H		140–141.5 (EtOH)	91
Cl	NMe_2	97–99 (EtOH)	97
Cl	NEt_2	88–89 (EtOH)	83
Cl	1-Piperidinyl	128–130	82
Cl	1-Morpholinyl	181–183	85

[a]Reaction conditions: secondary amine, formaldehyde, dimethylformamide, 20°C, 3 h.

acid in ethanol at 140°C, the cyano group remains unchanged but the 2-chloro function is hydrolytically displaced (**1.55** → **1.56a**);[31] in 90% phosphoric acid at 160°C the latter reaction occurs in addition to hydrolysis of the nitrile and ensuing decarboxylation (**1.55** → **1.56b**).[31] It may be noted that 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones (**1.57**) can be converted by lithium aluminum hydride into 2,3-dihydro derivatives (**1.58**) in reactions in which the pyrrole ring is not further reduced.[29,32]



(1.57) (1.58)

R	mp (°C)	yield (%)
Ph	116–118 (EtOH)	91
H	119–201 ($MeNO_2$)	20

(i) $LiAlH_4$, Et_2O, reflux

TABLE 1.11. SIMPLE FUNCTIONAL GROUP INTERCONVERSIONS IN 1*H*-PYRROLO[1,2-*a*]IMIDAZOLES

Functional Group Transformed	Other Substituents	Functional Group in Product	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reaction Conditions	Reference
5-NO	1-CH_2Ph–6,7-Ph_2	5-NH_2	63	211–213 (MeOH)	Zn, AcOH, 30°C, 2 h	29
5-$N_2C_6H_4CO_2H$-*o*	1-CH_2Ph–6,7-Ph_2	5-NH_2	55	211–213	Zn, AcOH, room temp.	29
7-$N_2C_6H_4CO_2H$-*o*	1-Et–2-OH[a]–5,6-Ph_2	7-NH_2[b]	37	117–119	Zn, AcOH, 100°C	29
7-CN	1-Me–2-Cl–5-Ph	7-$CONH_2$[c]	72	154–155	90% H_2SO_4, 100°C	31
7-CN	1-Me–5-Ph	7-H	27	90–92	90% H_3PO_4, 160–165°C	31
7-CN	1,5,6-Me_3	7-H	6	120–122	90% H_3PO_4, 160–165°C	31
7-CN	1-Me–2-Cl–6-Ph	2-OH–7-H[a]	84	138–140[d]	90% H_3PO_4 160°C	31
7-$CONH_2$	1-Me–2-Cl–5-Ph	7-H	16	201–202[e]	$NaNO_2$, 50% H_2SO_4, 100°C	31

[a] Exists as the tautomeric 2,3-dihydropyrrolo[1,2-*a*]imidazol-2-one derivative.
[b] Spectral data: ir ν_{max} = 3400, 3280 (NH_2), 1680 cm^{-1} (CO).
[c] Spectral data: ir ν_{max} = 3460, 3140 (NH_2), 1740 cm^{-1} (CO).
[d] Spectral data: ir ν_{max} = 1728 (CO).
[e] Melting point of sulfate quoted.

1.2.2. 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]imidazoles

Elaboration of the method described earlier (see Section 1.2.1.1, and **1.42** → **1.44**) for the preparation of 1*H*-pyrrolo[1,2-*a*]imidazoles provides the method of choice for the synthesis of 2,3-dihydro derivatives in the 1*H*-pyrrolo[1,2-*a*]-imidazole series (see **1.48A** → **1.51A** and Table 1.12).[33] Cyclization of the salt (**1.49A** → **1.51A**) can be effected by aqueous sodium hydrogen carbonate under reflux, almost certainly by way of intermediate imidazolinium betaines (cf. **1.50A**). Significantly, under certain basic conditions (e.g., aqueous NaOH, room temperature) betaines (e.g., **1.50A**; R = H, R^1 = Ph; 88% yield) can be isolated in such processes and can be transformed into the 2,3-dihydro derivative (**1.51A**, R = H, R^1 = Ph) by heating the betaine in water.[33a]

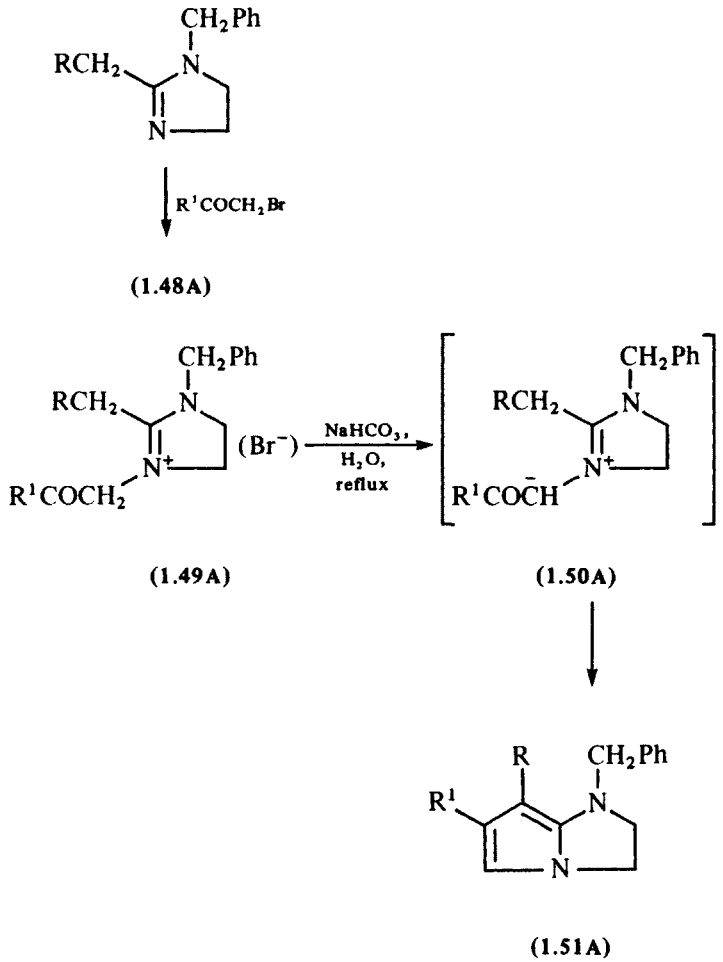
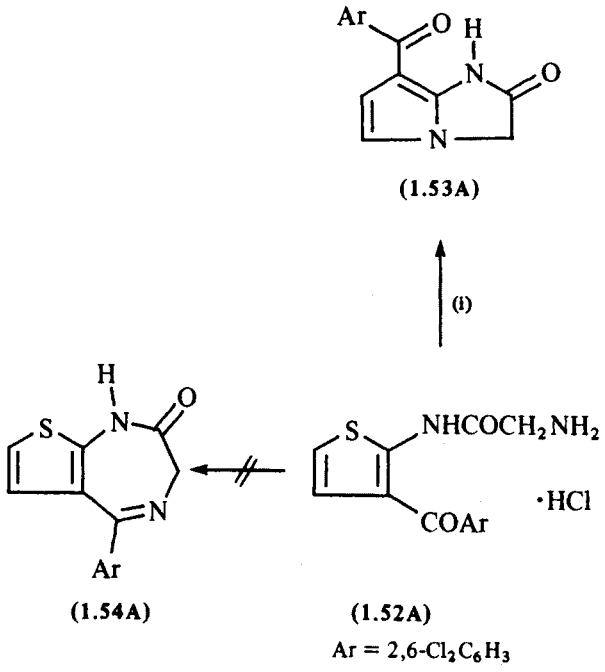


TABLE 1.12. SYNTHESIS[a] OF 2,3-DIHYDRO-1*H*-PYRROLO[1,2-*a*]IMIDAZOLES (1.51A) FROM 1-BENZYL-3-PHENACYL IMIDAZOLINIUM SALTS (1.49A)[33a]

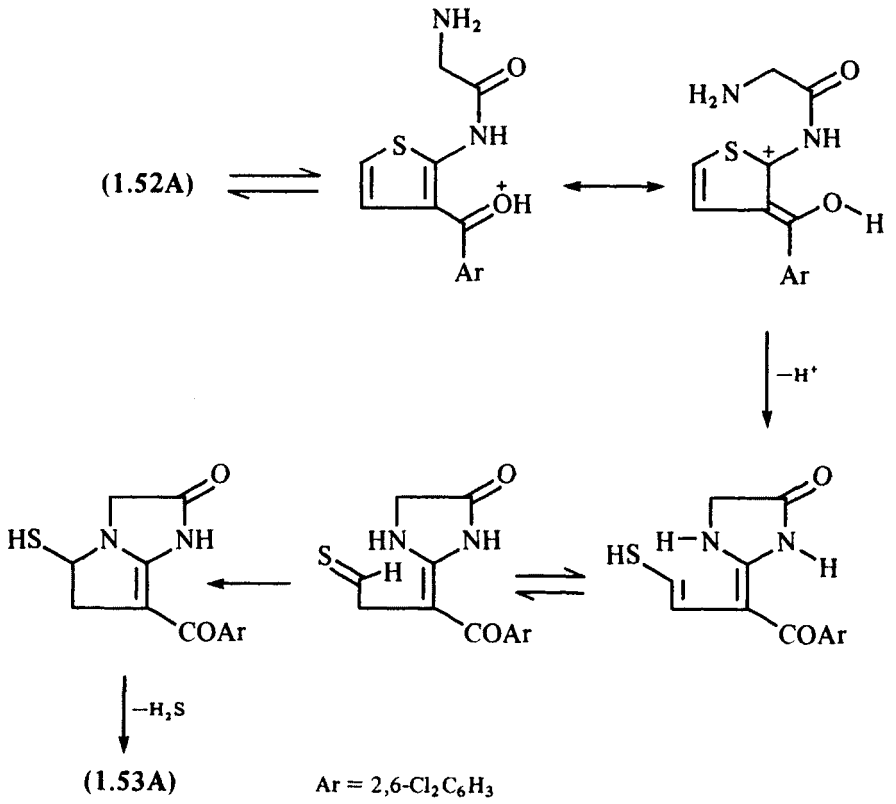
Product (1.51A)			
R	R^1	Yield (%)	mp (°C)[b]
H	*p*-MeC_6H_4	45	90–91 (dec.)
H	*p*-BrC_6H_4	64	126–127
Ph	*p*-MeC_6H_4	64	113–115 (dec.)
Ph	*p*-BrC_6H_4	89	129 (dec.)
Ph	*p*-$O_2NC_6H_4$	87	145–147

[a] Reaction conditions: $NaHCO_3$, H_2O, reflux, 2 h.
[b] From EtOH in each case.

A 2,3-dihydro derivative (**1.53A**) has also been isolated in modest yield in a serendipitous route from the thiophene derivative (**1.52A**) during an attempted synthesis of 5-(2,6-dichlorophenyl-1*H*-thieno[2,3-*e*][1,4]diazepin-2(3*H*)-one (**1.54A**).[34] (See the mechanism outlined in Scheme 1.1.) Compound **1.53A** is characterized by the following spectral parameters: nmr (DMSO-d_6), $\delta = 4.56$ (2*H*, s, NCH_2CO), 5.81 (H-6), 6.58 (H-5) [AB system J_{AB}, 3.6 Hz] 7.48 (s, 3H, Ar–H), and 11.75 (s, 1H, br, NH); ir (KBr) = 3220, 1760, 1625,, 1565, 1150, 1095, 900, and 760 cm^{-1}.[34]



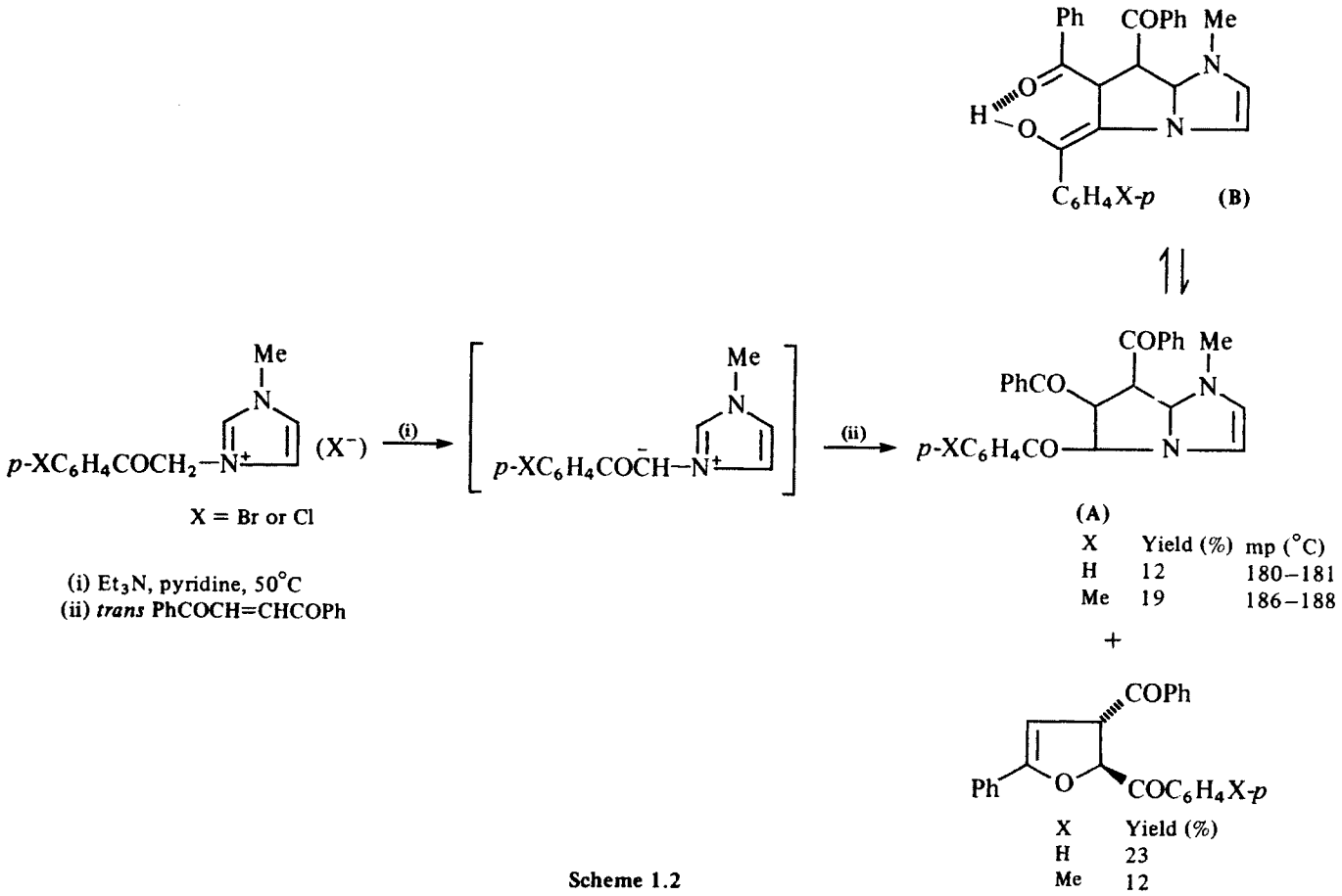
(i) Pyridine, reflux, 20 h (22% yield)



Scheme 1.1

1.2.3. 5,6,7,7*a*-Tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazoles

Compounds in this category have been obtained from 1,3-dipolar cycloaddition reactions of imidazolium betaines (see Scheme 1.2).[35] Unfortunately, yields are poor and the formation of 2,3-diaroyl-2,3-dihydrofurans is a competing process. The course of the reaction is markedly sensitive to the nature of the substituent (X) in the aryl ring of the imidazolium salt; thus Michael addition and ensuing cyclization leading to a dihydrofuran derivative is favored when X = Cl or NO_2 and no reaction is observed for X = MeO. An interesting feature in the ir spectra of the triaroyl derivative (Formula **A** in Scheme 1.2; X = H and Me) is the appearance of a concentration-independent band at 3370 cm^{-1}. This is ascribed[35] to the presence of an enolic function and is attributed specifically to a tautomeric equilibrium of the 5-aroyl group such that conjugation is enhanced by the bridgehead nitrogen (see **A** ⇌ **B** in Scheme 1.2).



(i) Et_3N, pyridine, 50°C
(ii) *trans* PhCOCH=CHCOPh

Scheme 1.2

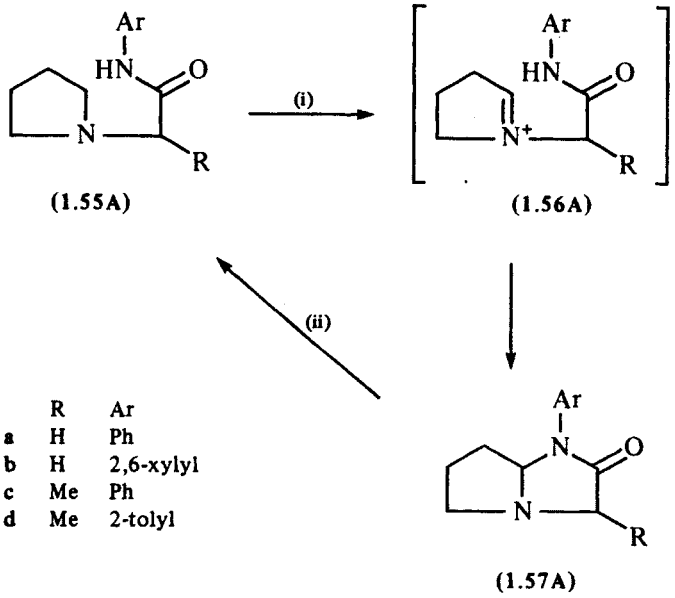
TABLE 1.13. SYNTHESIS[a] OF 2,3,5,6,7,7*a*-HEXAHYDRO-1*H*-PYRROLO[1,2-*a*]IMIDAZOLES (**1.57A**) FROM PYRROLIDINE DERIVATIVES (**1.55A**): PHYSICAL AND SPECTRAL CHARACTERISTICS[36]

	nmr ($CDCl_3$) δ (ppm)					Coupling Constant *J* (Hz)				IR (KBr) ν_{CO}		
Product	H-3 (*cis*)	H-3 (*trans*)	3-Me (*cis*)	3-Me (*trans*)	7*a*-H	$J_{H\text{-}3(cis)\text{-}H\text{-}3(trans)}$	$J_{H\text{-}7a\text{-}H\text{-}7(cis)}$	$J_{H\text{-}7a\text{-}H\text{-}7(trans)}$	$J_{H\text{-}7a\text{-}H\text{-}3(cis)}$	(cm^{-1})	mp (°C)	Yield (%)
1.57Aa	3.70 (d)	3.48d	–	–	5.30–5.50 (m)	16.4	4.0	2.4	0.5	1705	55–58	67
1.57Ab	3.79 (d)	3.46d	–	–	5.15–5.33 (m)	16.6	5.6	2.0	1.0	1710	81–82	85
1.57Ac (*cis*)[d]	3.76 (q)	–	–	1.48d	5.25–5.42	7.2	5.0	2.0	0.7	1698	106–108	77
1.57Ac (*trans*)[d]	–	3.48q	1.37d	–	5.28–5.47 (m)	6.4	6.0	2.0	–	1702[c]	Oil	–[b]
1.57Ad (*cis*)	3.85 (q)	–	–	1.46d	5.16–5.32 (m)	7.0	4.0	–	0.6	1703	106–109	86
1.57Ad (*trans*)	–	3.44q	1.42d	–	5.10–5.30 (m)	6.6	3.0	–	–	1703[c]	Oil	–[b]

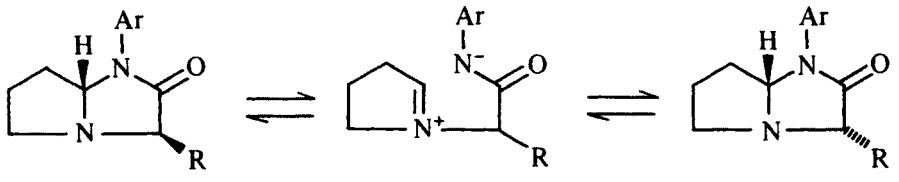
[a] Reaction conditions: $K_3[Fe(CN)_6]$, 2 *M*. KOH, MeOH, room temperature, pH = 12.
[b] Isolated as an approximately 5 : 1 mixture of *trans*:*cis* isomers.
[c] Liquid film.
[d] The terms *cis* and *trans* here refer to the stereochemical relationship of the 3H to the 7*a*-H.

1.2.4. Perhydro Derivatives of 1*H*-Pyrrolo[1,2-*a*]imidazoles

Fully reduced derivatives (**1.57A**) in the 1*H*-pyrrolo[1,2-*a*]imidazole ring system have been synthesised,[36] probably through iminium salts (cf. **1.56A**) by the oxidative cyclization of readily available pyrrolidines (**1.55A**) of interest as local anesthetics (see Table 1.13); the starting materials (**1.55A**) are regenerated by treating the cyclized products (**1.57A**) with sodium borohydride. Syntheses leading to disubstituted derivatives (**1.57Ac,d**) give rise to approximately 5:1 separable *trans*:*cis* mixtures. The separate *cis* or *trans* isomers of (**1.57Ac** or **d**) epimerize rapidly in protic solvents to the 5:1 equilibrium mixture, perhaps[36] by a mechanism depicted in Scheme 1.3.

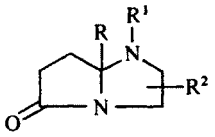


(i) $K_3[Fe(CN)_6]$, KOH, MeOH
(ii) $NaBH_4$, MeOH, H_2O, room temperature (55–60% yield)



Scheme 1.3

TABLE 1.14. SYNTHESIS OF 7*a*-SUBSTITUTED DERIVATIVES OF 2,3,5,6,7,7*a*-HEXAHYDRO-1*H*-PYRROLO[1,2-*a*]IMIDAZOLES (1.59A) BY CYCLIZATIONS OF TYPE 1.58A → 1.59[37,38]

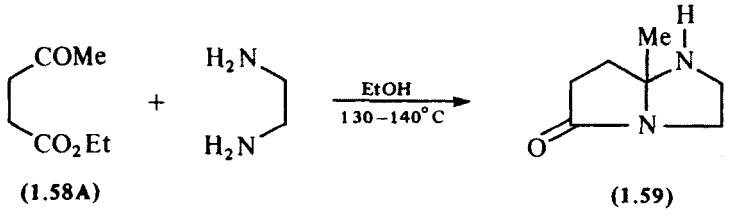


(1.59A)

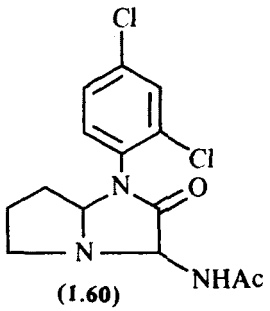
Product (1.59A)					
R	R^1	R^2	mp (°C) or bp (°C/torr)	Yield (%)	Reference
Me	H	H	108–109/0.4	82	37
Me	H	Me	90–92/0.3[a]	90	37
Me	Ph	H	60–64/5	76	37
Me	Ph $(CH_2)_2$	H	165–170/0.3	78	37
Ph	H	H	128–129	81	37
Ph	H	H	129–130[b]	–	38

[a] Product is a mixture of structural isomers with Me at C-2 or C-3.
[b] Starting material is PhCO $(CH_2)_2CO_2H$. Product is recrystallized from *i*-PrOH.

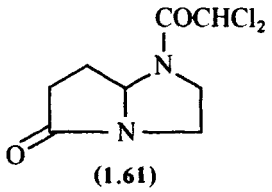
The synthesis of fully reduced compounds in the 1*H*-pyrrolo[1,2-*a*] imidazole system has also been achieved in excellent yield by condensation of ethylene diamines with simple keto acids or esters (e.g., **1.58A** → **1.59**[37] and Table 1.14).[37,38] Compounds of type **1.59** and also hexahydro derivatives with a 2-carbonyl group (e.g., **1.60**)[39] are of interest as central nervous system active compounds (depressant, sedative, anticonvulsant), and **1.61** has been prepared for use as an antagonist for acetanilide-type herbicides.[40]



(1.58A) (1.59)



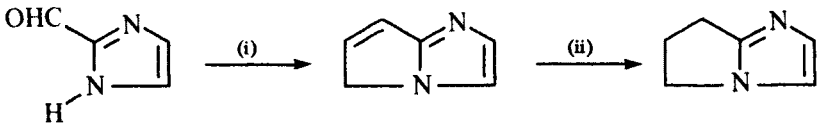
(1.60)



(1.61)

1.2.5. 5*H*-Pyrrolo[1,2-*a*]imidazoles

Compounds in the 5*H*-pyrrolo[1,2-*a*]imidazole ring system belong almost entirely to the dihydro (Section 1.2.6) and related classes (Section 1.2.7), and the fully unsaturated derivative (**1.63**)[41] represents the isolated example of a compound in the parent ring system; it may be noted that the procedure **1.62** → **1.63** can be modified by means of 4-formylimidazoles to provide synthetic entry into the 5*H*-pyrrolo[1,2-*c*]imidazole ring system (see Section 1.3.10). Compound **1.63** has been characterized spectroscopically [uv λ_{max}^{EtOH} = 267 nm, ϵ, 7350; nmr ($CDCl_3$) δ = 4.25 (2H, H-5), 6.06 (2H, H-6 and -7), and 7.03 (2H, H-2 and -3)] but rapidly decomposes to an unidentified product on standing in air. Its structure has been confirmed from results of catalytic hydrogenation in which it is transformed into 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole (**1.64**).[41]



(**1.62**) (**1.63**) (**1.64**)

bp. 85°C/0.5 torr
mp 28–29°C

(i) $CH_2{=}CH\overset{+}{P}Ph_3(Br^-)$, NaH, tetrahydrofuran (35% yield)
(ii) 5% Rh on charcoal, H_2, atmospheric pressure.

1.2.6. 6,7-Dihydro-5*H*-pyrrolo[1,2-*a*]imidazoles

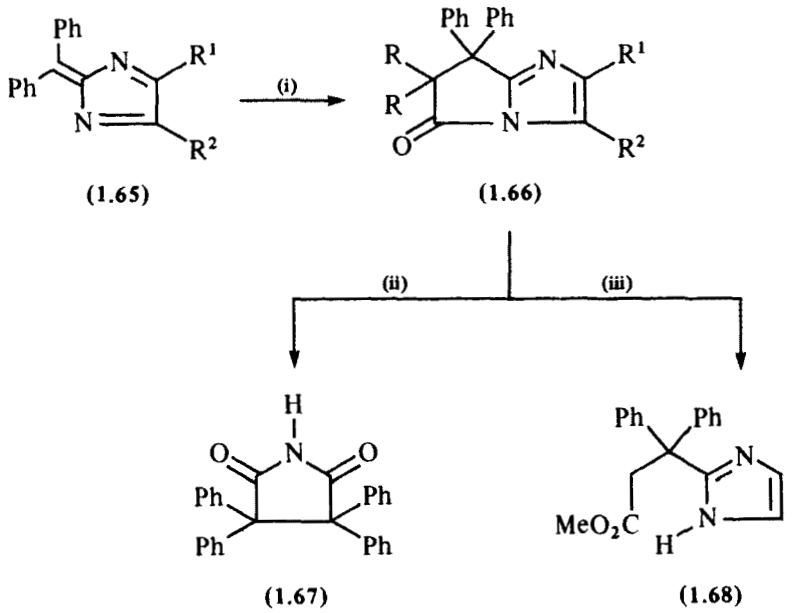
1.2.6.1. Synthesis from Imidazoles

6,6,7,7-Tetraphenyl- (**1.66**, R = Ph) and 7,7-diphenyl-6,7-dihydro-5*H*-pyrrolo-[1,2-*a*]imidazol-5-ones (**1.66**, R = H) can be prepared in excellent yield by treating diazafulvene derivatives (**1.65**) with diphenylketene or ketene (Table 1.15).[42]

TABLE 1.15. SYNTHESIS OF SUBSTITUTED 6,7-DIHYDRO-5*H*-PYRROLO[1,2-*a*]-IMIDAZOL-5-ONES (**1.66**)

Product (**1.66**)					
R	R^1	R^2	mp (°C)	Solvent for Recrystallization	Yield (%)
H	H	H	113–114	C_6H_6	72
Ph	H	H	236–237	C_6H_6	100
Ph	Ph	Ph	256–257	C_6H_6-THF	100
Ph	Ph	H	215–216	C_6H_{12}	100

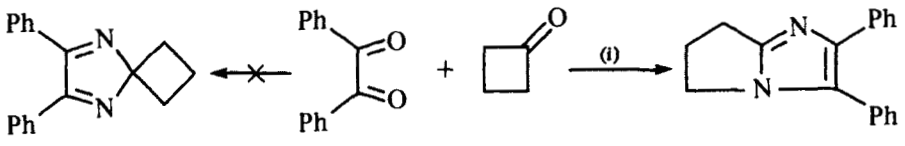
The bicyclic system (**1.66**) can be cleaved either by ozonolysis to give tetraphenylsuccinimide (**1.67**) or by methanol to yield 3,3-diphenyl-3-[imidazol-2-yl] propionic acid methyl ester (**1.68**).



(**1.65**) (**1.66**) (**1.67**) (**1.68**)

(i) CH_2=C=O or Ph_2C=C=O in tetrahydrofuran or benzene
(ii) O_3, CH_2Cl_2, −48°C (R = R^1 = Ph; R^2 = H)
(iii) reflux, MeOH (R = R^1 = R^2 = H)

An additional example of a procedure leading to a 6,7-dihydro compound (**1.70**) in the 5*H*-pyrrolo[1,2-*a*]imidazole category emerged during an attempt to prepare the 4,5-diphenyl-2*H*-imidazole derivative (**1.69**) from the reaction of benzil and cyclobutanone;[43] the latter (**1.69**) is presumably an intermediate but is considerably strained and undergoes a thermal rearrangement to **1.70**.



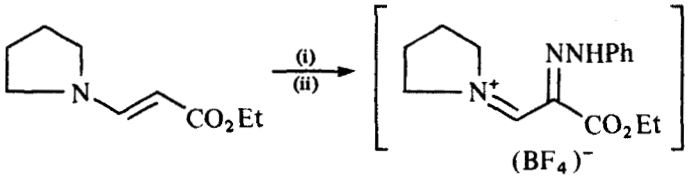
(**1.69**) (**1.70**)

(i) $CH_3CO_2NH_4$, AcOH or $HCONMe_2$

mp. 154–155°C

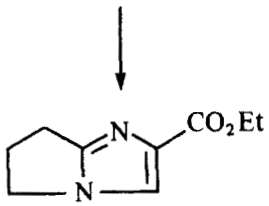
1.2.6.2. Synthesis from Pyrrole Derivatives

Treatment of the pyrrolidine derivative (**1.71**) with phenyldiazonium tetrafluoroborate followed by triethylamine provides a one-step synthesis of the 2-ethoxycarbonyl derivative (**1.73**), but the scope of this simple method has not been evaluated.[44] Compound **1.73** is characterized by the following spectral data:



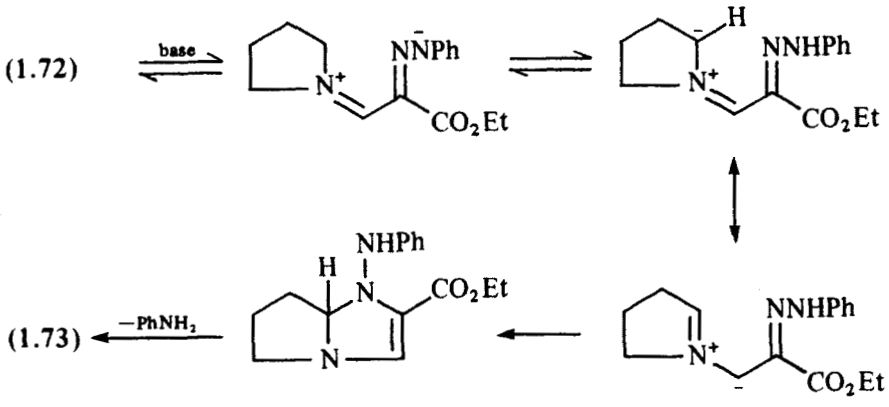
(1.71) **(1.72)**

(i) $PhN_2^+BF_4^-$ (ii) Et_3N, reflux



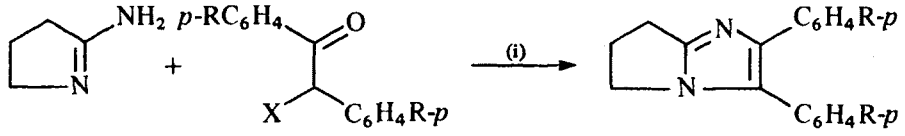
(1.73) mp 88–89° (EtOAc-*i*-Pr_2O) 40% yield

ir $\nu_{max} = 1705\,cm^{-1}$ (CO); ^1H nmr ($CDCl_3$) $\delta = 1.38$ (t, 3H, Me), 2.65 (m, 2H, H-6), 2.89 (t, 2H, H-7, $J = 7$ Hz), 4.03 (t, 2H, H-5, $J = 7$ Hz), 4.35 (q, 2H, CH_2O), and 7.57 (s, 1H, H-3). A suggested[44] mechanism for this useful process is depicted in Scheme 1.4.



Scheme 1.4

2,3-Disubstituted-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazoles (**1.74**) are also formed in the more straightforward condensation of 2-amino-4,5-dihydro-3*H*-pyrrole with 2-halogeno-1,2-disubstituted ethanones;[45] the latter are readily available by treating benzoins with thionyl chloride, and this route is obviously more versatile than the previously described method from diazafulvenes (see **1.69** → **1.70**).[43] The dimethoxyphenyl derivative (**1.74a**) can be transformed (BBr_3, CH_2Cl_2, − 75°C) into a dihydroxy compound (**1.74d**), and this can be realkylated (NaH, DMF, alkyl iodide) to give new alkoxyaryl derivatives (e.g., **1.74e, f**). Compounds **1.74** have been patented[43] as antiarthritic agents and as regulators of cell-mediated immunity.

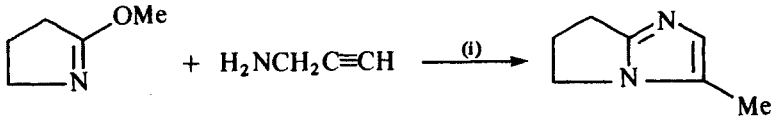


(X = Cl, Br) **(1.74)**

(i) $HCONMe_2$, 3 days, 25°C

	R	mp (°C)
a	MeO	146–147.5
b	Cl	189–192
c	MeS	127–128
d	OH	
e	*i*-PrO	259–262 (hydrochloride)
f	EtO	135–137.5

The preparation of 3-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole (**1.76**) by condensation of the cyclic imidate (**1.75**) with propargylamine represents an isolated example of this type of reaction, and its scope has not been evaluated.[46]



(1.75) **(1.76)**

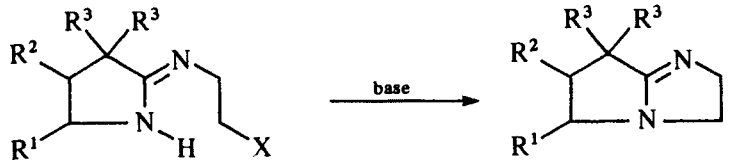
(i) C_6H_5Me, reflux 5 h (48% yield) bp 90°C/1 torr

1.2.7. 2,3,6,7-Tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazoles

1.2.7.1. Synthesis from Reduced Pyrrole Derivatives

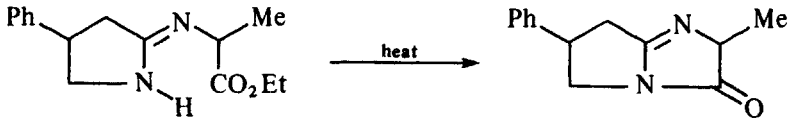
The base-promoted cyclization of β-haloalkylimino derivatives of pyrrolidine (**1.77**) provides an efficient general synthesis of substituted derivatives in the

2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazole group (see **1.78** and Table 1.16);[47,48] the starting materials (**1.77**) are readily prepared by treating halo-, alkoxy-, or alkylthiopyrrolines with β-halogenoalkylamines, and the method can be adapted to provide bicyclic derivatives (**1.78**) with substituents in the imidazole ring.

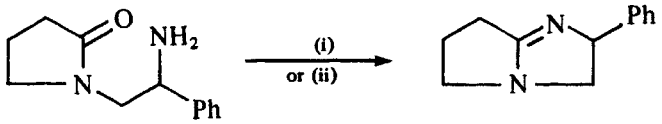


(**1.77**) X = Cl, Br (**1.78**)

Pyrrolidine starting materials (**1.79** and **1.81**) have also been used to synthesize substituted 2,3,6,7-tetrahydro compounds **1.80**[49] and **1.82**,[50] respectively, and the oxidative intramolecular cyclization of aminoalkylpyrrolidines (**1.83** → **1.84**) provides a valuable route to 2- and 3-substituted derivatives in this class.[51] The



(**1.79**) (**1.80**)



(**1.81**) (**1.82**) bp. 212–215°C/16 torr
mp. perchlorate 118.5–119.5°C

(i) *p*-$MeC_6H_4SO_3H$, vacuum distillation, bath temperature 250°C (51% yield)
(ii) *p*-$MeC_6H_4SO_3H$, C_6H_5Me, heat.

susceptibility to hydrolysis of derivatives of type **1.84** is demonstrated during preparation of their perchlorates in which partial conversion to pyrrolidones (**1.85** and **1.86**) is observed.[51]

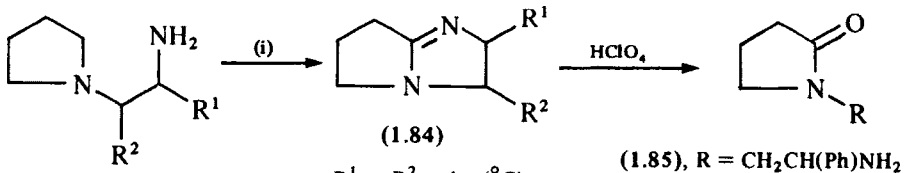
TABLE 1.16. SYNTHESIS OF 2,3,6,7-TETRAHYDRO-5*H*-PYRROLO[1,2-*a*]IMIDAZOLES (1.78) FROM PYRROLIDINES (1.77)

Product (1.78)			Reaction	mp	Solvent for	
R^1	R^2	R^3	Conditions[a]	(°C)	Recrystallization	Reference
Me	H	Ph	A	103[b]	aqueous MeOH	47
H	2,6-$Cl_2C_6H_3$	H	B	287–288[c]	EtOH	48
H	2,6-$Me_2C_6H_3$	H	C	226–227	EtOH	48
H	2-ClC_6H_4	H	C	169–171	*i*-PrOH–EtOAc	48
H	2-Br–6-ClC_6H_3	H	C	308–310 (dec.)	EtOH–*i*-PrOH	48
H	2-Cl–6-$CF_3C_6H_3$	H	C	305 (dec.)	EtOH–EtOAc	48
H	2,4,6-$Cl_3C_6H_2$	H	C	273–274	*i*-PrOH–Et_2O	48
H	2-Cl–6-$MeOC_6H_3$	H	C	204–206	*i*-PrOH	48
H	2-F–6-$CF_3C_6H_3$	H	C	223–226	*i*-PrOH	48
H	2,6-Cl_2–3-$O_2NC_6H_2$	H	C	290–292	EtOH	48
H	2,6-Cl_2–3-MeC_6H_2	H	C	280–281	*i*-PrOH	48
H	2,6-Cl_2–3-$MeOC_6H_2$	H	C	237–238	*i*-PrOH	48
H	2-Me–naphth-1-yl	H	C	276–277	EtOH–*i*-PrOH	48
H	2-Cl–naphth-1-yl	H	C	288–290	EtOH	48
H	4-Br–2,5–Me_2-thien-1-yl	H	C	267–268	*i*-PrOH	48
H	2,5-Me_2-thien-3-yl	H	C	234–235	*i*-PrOH–EtOAc	48

[a]Reaction conditions: (A) 5 *M* NaOH, room temperature on **1.77** (X = Cl); (B) Na_2CO_3, *i*-PrOH, reflux on **1.77** (X = Br, hydrobromide); (C) Na_2CO_3, *i*-PrOH, reflux on **1.77** (X = Br, hydrochloride).

[b]Yield = 84%.

[c]Melting point of hydrochloride.



(1.83) (1.84)

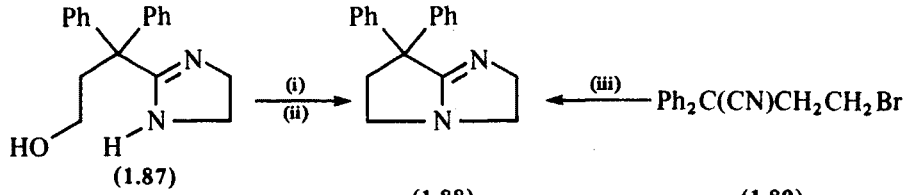
	R^1	R^2	bp (°C)
a	Ph	H	–
b	H	Ph	140–150

(1.85), R = $CH_2CH(Ph)NH_2$
(1.86), R = $CH(Ph)CH_2NH_2$

(i) HgO + EDTA [providing Hg(II)ethylenediamine tetraacetate]

1.2.7.2. Synthesis from Imidazolines

7,7-Diphenyl-2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazole (**1.88**) has been obtained by intramolecular cyclization of the imidazoline derivative (**1.87**) as well as from condensation of the nitrile (**1.89**) with ethylene diamine.[52]

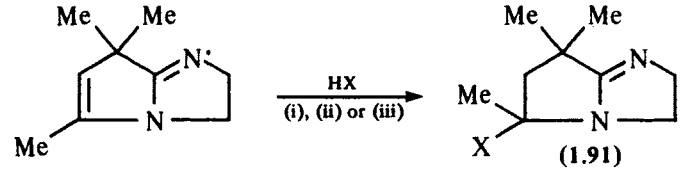


(1.87) (1.88) (1.89)

(i) $SOCl_2$, room temperature
(ii) KOH, EtOH, reflux
(iii) $H_2N(CH_2)_2NH_2$, 150°C, 1.5 h

1.2.7.3. Synthesis from 2,3-Dihydro-7H-pyrrolo[1,2-a]imidazoles

Carefully controlled addition across the 5,6-double bond of the title compounds (**1.90**) provides a useful synthetic entry into 5,5,7,7-tetrasubstituted derivatives (**1.91**) of 2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazoles.[53a–c] Conversions of the type **1.90** → **1.91** (X = OH) are characterized by a hypsochromic shift in the uv absorption spectrum [$\lambda_{max}^{isooctane}$ 244 (ε, 16,900) for **1.90** to $\lambda_{max}^{H_2O}$ 220 (ε, 6400) for **1.91** (X = OH).



(1.90) (1.91)

X	Yield (%)	mp (°C) or bp
OH	100	108–109
OMe	–	liquid, n_D^{25} = 1.4861
CN	85	66–69 (0.15 torr), n_D^{25} = 1.4811

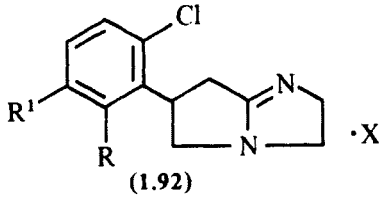
(i) H_2O, 6 h, room temperature
(ii) MeOH, pyridine HCl, reflux, 22 h
(iii) HCN, <80°C

1.2.7.4. Reactions

The susceptibility of derivatives in the 2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-a] imidazole class to ring opening has been illustrated in the previous section (see **1.84** → **1.85** and **1.86**). In contrast, the internal double bond of **1.91** (X = CN) is resistant to catalytic hydrogenation, and a conventional CN → CH_2NH_2 transformation is observed [**1.91** (X = CN) → **1.91** (X = CH_2NH_2); Raney nickel, 130–140°C].[53b,c]

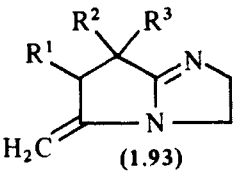
1.2.7.5. Practical Applications

Compounds of type **1.78** are claimed[48] as antihypertensive and sedative agents, and the condensed imidazolone (**1.80**) is reported to possess an ED_{50} against reserpine-induced ptosis in mice of 33 mg/kg orally.[49] Compounds of type **1.91** are claimed[53b] as antihypertensive and fungicidal agents with particular utility ascribed to **1.91**, (X = CN). 6-Halogenoaryl derivatives in this group (**1.92**) are α-adrenoceptor antagonists,[54] and the exo methylene derivatives (**1.93**) form copolymers with methyl methacrylate that are useful for molding purposes.[55]



(**1.92**)

e.g. R = F, R^1 = H; X = HBr



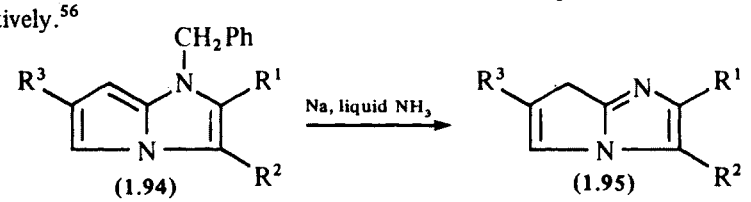
(**1.93**)

R^1 = H or C_{1-5} alkyl

R^2, R^3 = H or C_{1-10} hydrocarbon groups

1.2.8. 7*H*-Pyrrolo[1,2-*a*]imidazoles

Compounds in this category are rare and can be prepared by the reductive debenzylation of 1-benzyl-1*H*-pyrrolo[1,2-*a*]imidazoles with sodium in liquid ammonia (see **1.94** → **1.95**).[56] An unusual hydrogen shift occurs in this transformation to give products that lack an ir N–H stretching absorption and exhibit ^{1}H nmr resonances at δ = 4.70 and 4.64 for the H-7 protons of **1.95a** and **b**, respectively.[56]

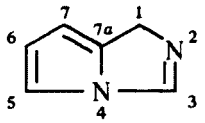


(**1.94**) (**1.95**)

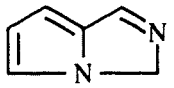
	R^1	R^2	R^3	mp (°C)	Yield (%)
a,	H	H	*p*-MeC_6H_4	152–153 (EtOH)	58
b,	Ph	Ph	Ph	247–249 (EtOH)	36

1.3. RING SYSTEM C_3N_2–C_4N: PYRROLO[1,2-*c*]IMIDAZOLE

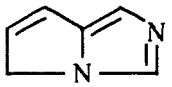
Fusion of a three-carbon fragment across the N-1–C-5 bond of an imidazole ring gives rise to the pyrrolo[1,2-*c*]imidazole ring system. In this section the compounds described belong to either 1*H*- (**1.97**), 3*H*- (**1.98**), or 5*H*-pyrrolo[1,2-*c*]-imidazole (**1.99**) ring systems; compounds in the 7*H*-pyrrolo[1,2-*c*]imidazole class (**1.100**) are also possible but are not cited in the literature period covered. The material in this section is subdivided in the order described above (1*H*, 3*H*, 5*H*), and compounds within each group are discussed in terms of increasing saturation of the ring system. For example, compounds in the 1*H*-pyrrolo[1,2-*c*]-imidazole group can exist in 2,3-dihydro-(**1.101**), 2,3,5,6-tetrahydro-(**1.102**), and 2,3,5,6,7,7*a*-hexahydro-(**1.103**) forms.



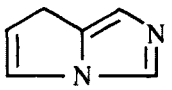
(1.97)



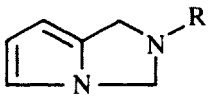
(1.98)



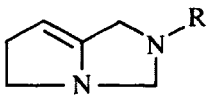
(1.99)



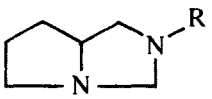
(1.100)



(1.101) R = H, alkyl, etc.



(1.102)



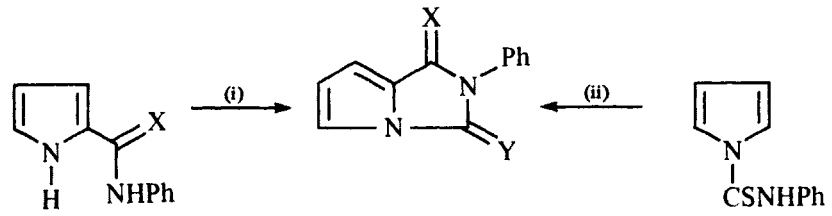
(1.103)

1.3.1. 2,3-Dihydro-1*H*-pyrrolo[1,2-*c*]imidazoles

1.3.1.1. Synthesis

Compounds of this type (cf. **1.101**) are prepared by cyclization of appropriately substituted pyrrole derivatives. For example, 2-carbanilide (**1.104a**) and 2-thiocarbanilide (**1.104b**) derivatives of pyrrole react with two molar equivalents of phenyl isocyanate in the presence of triethylamine to give 2,3-dihydro-1*H*-pyrrolo [1,2-*c*]imidazol-1,3-dione (**1.105a**)[57] and the mono thione analog (**1.105b**),[58] respectively, in high yield. Synthesis of the closely related derivatives (**1.105c, d**) is achieved by treatment of the thiocarbanilide (**1.106**) with a base followed by phosgene and thiophosgene, respectively.[58]

Cyclizative condensations of pyrroles with isocyanates have also been used to synthesize carbamate ester derivatives (**1.107a, b**) in the 1-substituted-1*H*-pyrrolo [1,2-*c*]imidazole category.[59]



(1.104) **a**, X = O
b, X = S

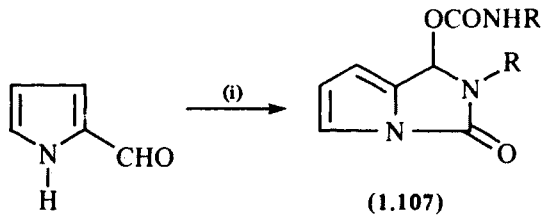
(1.105)

(1.106)

	X	Y	mp (°C)
a,	O	O	226–227
b,	S	O	139.5–140.5
c,	O	S	144–144.5
d,	S	S	134–134.5

(i) 2 PhNCO, Et_3N, 60–70°C, 22 h (92% to **1.105a**) or room temperature, 15 min (72% to **1.105b**)
(ii) either (a) NaH, tetrahydrofuran (b) $COCl_2$ (65% to **1.105c**)
or (a) NaH, tetrahydrofuran (b) $CSCl_2$ (24% to **1.105d**)

Cyclization reactions induced in *N*-ethoxycarbonylpyrrole-2-thiocarboxamide (**1.108**) (readily available in high yield from pyrrole and ethoxycarbonylthiocyanate) and a related compound (viz., **1.109**) have provided valuable practicable syntheses of 2,3-dihydro-1*H*-pyrrolo[1,2-*c*]imidazoles (see **1.110–1.112** and Table 1.17).[60] The isomeric *N*-ethoxycarbonyl pyrrole-1-thiocarboxamide (**1.113**) (readily available from the potassium salt of pyrrole and ethoxycarbonylthiocyanate) has also been used for the synthesis of a 2,3-dihydro 1*H*-pyrrolo[1,2-*c*]-imidazole derivative (see **1.114** and Table 1.17) in a transformation related to the previously described route to a 2-phenyl analog (cf. **1.106** → **1.105c**).



(1.107)

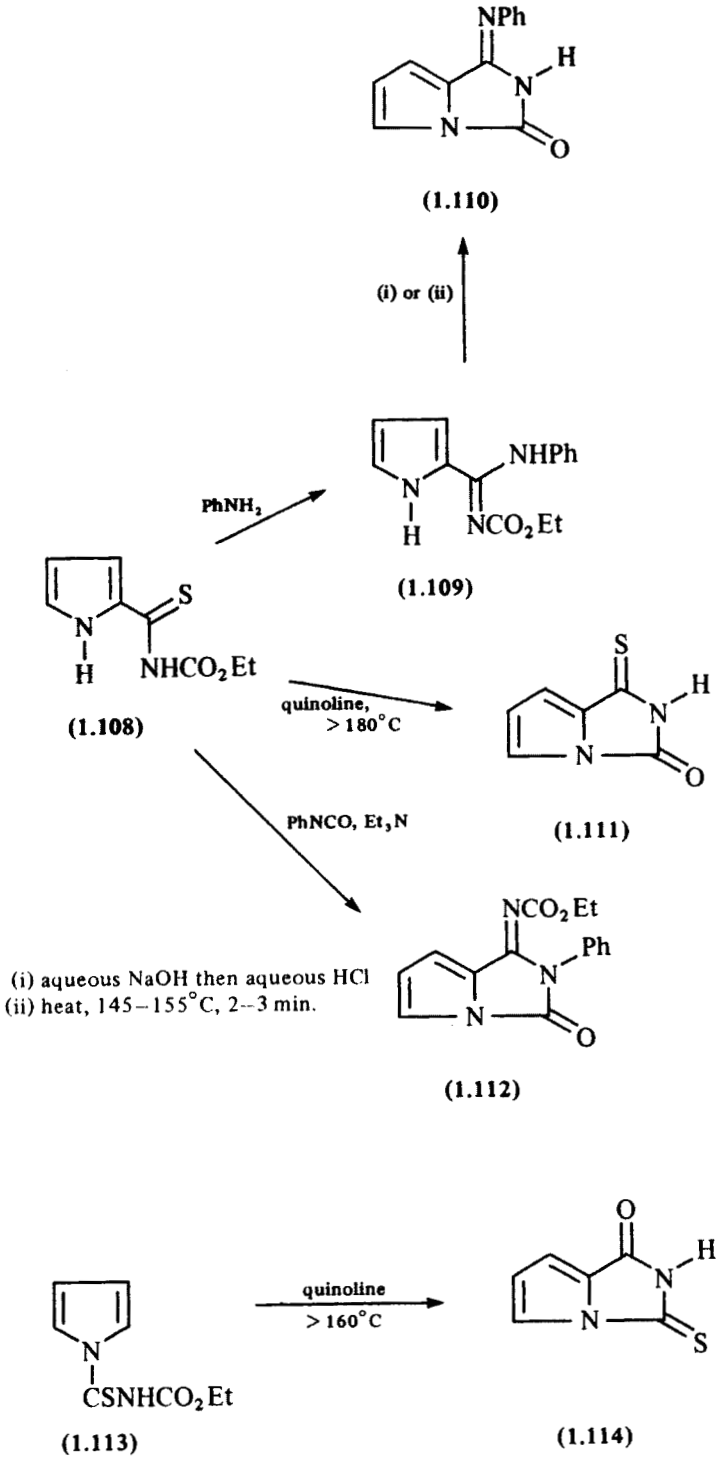
	R	mp (°C)	yield (%)	IR (CO stretch) [cm^{-1}]
a,	Me	104	98	1761, 1712
b,	Ph	128	94	1761, 1739

(i) RNCO, $PhCHN_2$ (catalyst), Et_2O-EtOH (to **1.107a**) or Et_2O (to **1.107b**)

TABLE 1.17. PHYSICAL AND SPECTRAL CHARACTERISTICS OF 2,3-DIHYDROPYRROLO[1,2-*c*]IMIDAZOLE DERIVATIVES (**1.110**, **1.111**, **1.112**, AND **1.114**)

Compound	Yield (%)		mp (°C) (Solvent for Recrystallization)	ir Spectrum (cm^{-1})	^1H nmr Spectrum[a]
1.110	81[b]	85[c]	168–168.5 (C_6H_6)[b]	1780, 1670, 1590, 1430, 1330, 1225, 1180, 1070, 1045, 910, 780, 735, 695, 625, 515, 510	5.6, 6.8 (m, 1H, H-7) 6.4 (m, 1H, H-6), 7.0–7.6 (m, 6H, Ph; H-5), 11.3 (s, 1H, NH)
1.111	87		140–141.5 (aqueous EtOH)	3200, 1760, 1550, 1400, 1300, 1200, 1150, 1060, 1010, 890, 750, 700, 690, 660, 620, 475	6.6 (m, 1H), 7.0 (m, 1H), 7.4 (m, 1H), 12.3 (br, s, 1H, NH)
1.112	–		163–164	1780, 1700, 1650, 1610, 1490, 1280, 1260, 1240, 1165, 1145, 1120, 1010, 830, 795, 750, 700, 690, 640, 620, 610, 580, 500	1.3 (t, 3H, $J = 7$, Me), 4.4 (q, 2H, $J = 7$, CH_2), 6.9 (t, 1H, $J = 3$), 7.2 (d, 1H, $J = 3$), 7.8 (s, 5H, Ph), 8.0 (d, 1H, $J = 3$)
1.114	58		197–198.5 (PhMe)	3150, 1750, 1550, 1300, 1260, 1140, 1055, 1000, 900, 725, 700, 690, 665, 600, 570, 495	6.6 (t, 1H, $J = 3$), 6.9 (d, 1H, $J = 3$), 7.6 (d, 1H, $J = 3$), 12.5 (br, s, 1H, NH)

[a] Measured in $(CD_3)_2SO$ solvent and quoted in ppm from tetramethylsilane as internal standard; J values in hertz.
[b] Method i (see text).
[c] Method ii (see text).


NPh
H
N
N
O
(1.110)
(i) or (ii)
NHPh
N
H
NCO2Et
PhNH2
(1.109)
S
N
H
NHCO2Et
(1.108)
quinoline,
> 180°C
S
H
N
N
O
(1.111)
PhNCO, Et3N
NCO2Et
Ph
N
N
O
(1.112)
(i) aqueous NaOH then aqueous HCl
(ii) heat, 145–155°C, 2–3 min.
N
CSNHCO2Et
(1.113)
quinoline
> 160°C
O
H
N
N
S
(1.114)

1.3.1.2. Spectroscopic Studies

A detailed analysis of the ^{13}C nmr spectra of a series of 2,3-dihydro-1*H*-pyrrolo [1,2-*c*] imidazol-1,3-diones and thiones (**1.115a–h**) has been carried out, and chemical shift data (Table 1.18) provide a valuable method for the assignment of carbonyl and thiocarbonyl groups in such molecules.[61] A number of useful trends are apparent: differences in chemical shifts for the carbonyl and thiocarbonyl groups in equivalent environments are of the order 25–26 ppm. Chemical shifts for C=X groups in amide-type environments are to lower field of those in urea type environments, reflecting the greater delocalization of positive charge from the C=O or C=S carbon in the latter case. These differences are approximately 9–10 ppm and serve to distinguish the isomer pairs **1.115b, c** and **1.115f, g**. Finally it may be noted that substitution of N–H by N–Ph has little effect on the value of the C=S chemical shift values (ca. 2 ppm). This probably indicates that there is little conjugation between the phenyl ring and the imidazole ring in these compounds.

1.3.1.3. Reactions

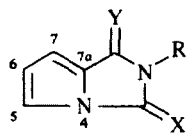
The interconversions of C=S → C=O and C=O → C=S in 2,3-dihydro-1*H*-pyrrolo-[1,2-*c*] imidazolones and -thiones can be achieved oxidatively and by the use of phosphorus pentasulfide, respectively (see structure **1.116** and Table 1.19).[58,60]

The imidazole ring in compounds of type **1.117** is cleaved by nucleophilic reagents, but the mode of attack (at C=S or C=O) is dependent on the type of nucleophile used and the reaction conditions[60] (see Scheme 1.5). Reactions with neat aniline, aqueous ammonia, or aqueous sodium hydroxide occur by attack at the carbonyl carbon with concomitant loss of carbon dioxide in the latter case. In contrast, reactions with primary or secondary amines in ethanol proceed by nucleophilic addition at the thiocarbonyl group and provide a synthetic entry to 1-substituted derivatives (e.g., **1.118**) in the 3*H*-pyrrolo[1,2-*c*] imidazole category.

1.3.2. 5,6-Dihydro-1*H*-pyrrolo[1,2-*c*]imidazoles

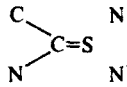
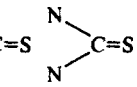
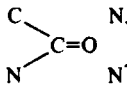
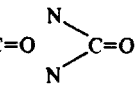
Transformation of the imidazolylidene derivative (**1.119a**) into the 5,6-dihydro-1*H*-pyrrolo[1,2-*c*] imidazole derivative (**1.120**) provides the isolated example of a compound in this group.[62] In contrast to the mode of nucleophilic ring opening observed in analogous 2,3-dihydro-1*H*-pyrrolo[1,2-*c*] imidazoles (see Scheme 1.5), the 5,6-dihydro compound (**1.121**) undergoes attack at the 5-carbonyl group and is transformed by ethanol into the ester (**1.119b**).

TABLE 1.18. ^{13}C CHEMICAL SHIFT DATA[a] FOR 2,3-DIHYDRO-1*H*-PYRROLO[1,2-*c*]IMIDAZOL-1,3-DIONES AND THIONES (**1.115a–h**)[61]



(1.115)

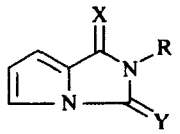
	X	Y	R
a	O	O	H
b	O	S	H
c	S	O	H
d	S	S	H
e	O	O	Ph
f	O	S	Ph
g	S	O	Ph
h	S	S	Ph

	Compound **1.115**				Pyrrole Ring				Phenyl Ring			
					C-7*a*	C-5	C-7	C-6	C-1	C-3,5	C-4	C-2,6
a	–	–	159.3	148.7	126.2	118.9	117.4	112.2				
b	185.3	–	–	149.0	134.9	← 118.3 →		113.2				
c	–	175.5	159.5	–	124.2	119.2	118.1	113.3				
d	183.1	173.5	–	–	134.7	← 116.9 →		112.8				
e	–	–	157.1	147.5	125.0	119.8	117.7	113.5	131.4	128.8	128.2	127.0
f	183.6	–	–	148.0	134.1	119.2	118.3	114.3	132.8	← 128.9 →		
g	–	174.5	157.5	–	122.7	120.3	118.0	114.4	132.5	129.0	128.8	128.7
h	182.5	173.6	–	–	134.4[b]	119.3	118.8	114.7	134.3[b]	← 129.4 →		128.9

[a] Recorded at 25.05 MHz as approximately 0.25 *M* solutions in DMSO containing 20% v/v DMSO-d_6; temperature 30°C. Chemical shift data are quoted in ppm relative to tetramethylsilane.

[b] These assignments may be reversed.

TABLE 1.19. INTERCONVERSIONS IN 2,3-DIHYDRO-1*H*-PYRROLO[1,2-*c*]IMIDAZOLONES AND -THIONES AND IN 1-PHENYLIMINO-PYRROLO[1,2-*c*]IMIDAZOLIN-3(2*H*)-ONE

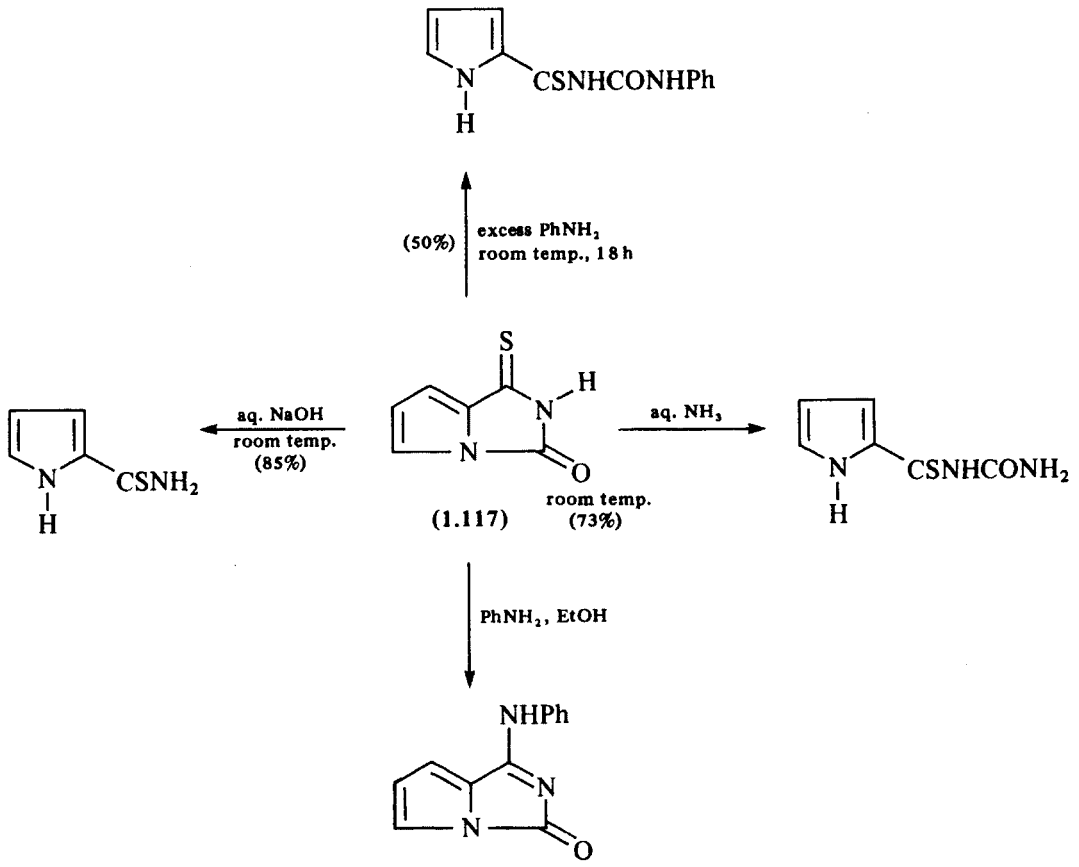


(1.116)

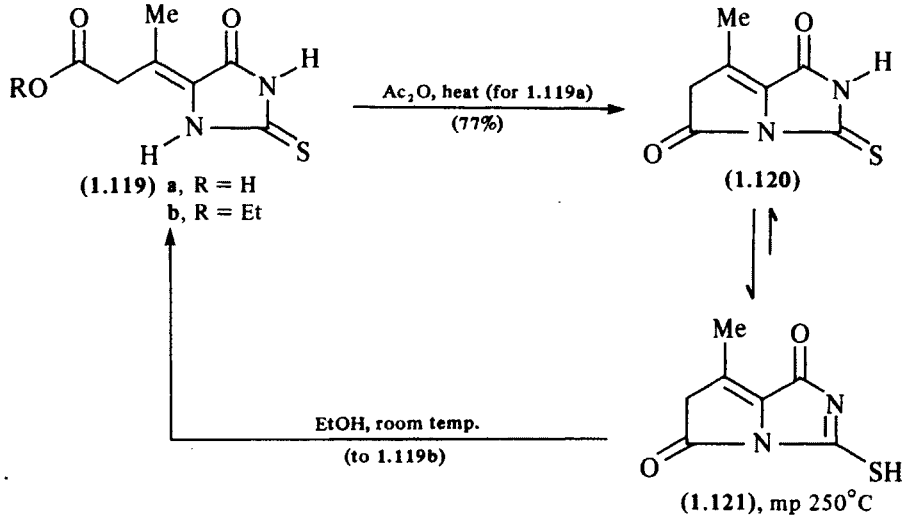
Starting Material (1.116)			Product (1.116)			Reaction Conditions	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reference
X	Y	R	X	Y	R				
S	O	Ph	O	O	Ph	H_2O_2, AcOH, AcONa, room temperature	–[a]	–[a]	58
O	O	Ph	S	O	Ph	P_2S_5, dioxan, reflux	–[a]	–[a]	58
O	S	Ph	S	S	Ph	P_2S_5, dioxan, reflux	–[a]	–[a]	58
S	O	H	S	S	H	P_2S_5, xylene, reflux	55[b]	183–184 (CCl_4)	60
NPh	O	H	O	O	H	Dilute HCl, 100°C, 0.5 h	–	209–211 (EtOH)	60

[a] See data in reactions leading to **1.105** in text.

[b] Spectral data: IR (Nujol mull) 3150, 1550, 1410, 1320, 1240, 1205, 1130, 1040, 1000, 895, 820, 735, 650, 520, 440 cm^{-1}; nmr [$(CD_3)_2SO$] $\delta = 6.6$


CSNHCONHPh
(50%)
excess PhNH2
room temp., 18 h
aq. NaOH
room temp.
(85%)
CSNH2
aq. NH3
CSNHCONH2
room temp.
(73%)
(1.117)
PhNH2, EtOH
NHPh
(1.118)

Scheme 1.5



1.3.3. 2,3,7,7*a*-Tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazoles

Compounds in this group (**1.123**) are obtained together with 5-benzylidene-2-thiohydantoins (**1.124**) when 2-thiohydantoins (**1.122**, R = Ph) are treated with substituted cinnamonitriles under basic conditions (see Table 1.20).[63] Yields are generally high in this versatile synthesis, but the product distribution (**1.123** vs. **1.124**) is sensitive to the nature of substituents in the thiohydantoin (**1.122**). For example, the unsubstituted thiohydantoin (**1.122**, R = H) reacts with cinnamonitriles [PhCH=C(CN)X; X = CN or CO_2Et] as above to give only the 5-benzylidene derivative (**1.124**; R^1 = Ph, R^2 = H, H for Ph), but compounds of this type (**1.124**) can be converted in good yield into pyrrolo[1,2-*c*]imidazoles (**1.123**) by heating them with malononitrile in ethanol. It can be assumed that the formation of **1.123** from **1.122** occurs through **1.124** and thence through a common acyclic intermediate derived from nucleophilic addition of the benzylidene derivative (cf. **1.124**) to malononitrile.

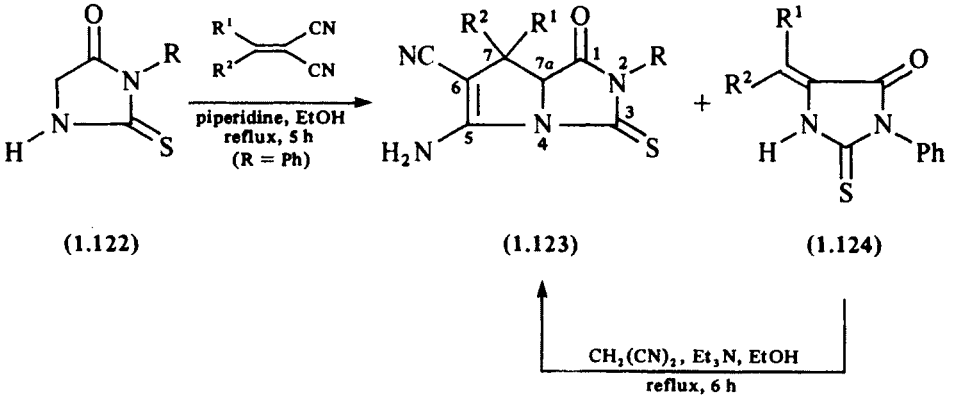


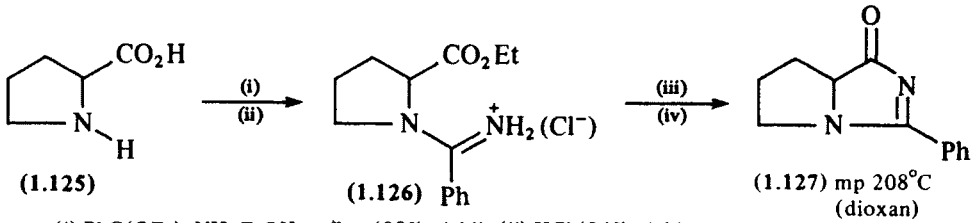
TABLE 1.20. PHYSICAL AND SPECTRAL PROPERTIES OF 1-OXO-3-THIONO-2,3,7,7*a*-TETRAHYDRO-1*H*-PYRROLO[1,2-*c*]IMIDAZOLES (**1.123**)[63]

R^1	R^2	R	Yield (%) From (**1.122**)	Yield (%) From (**1.124**)	mp (°C) (Solvent for Recrystallization)	ir Spectrum (KBr, cm^{-1})	^1H nmr Spectrum (δ, DMSO-d_6, TMS Internal Standard)
H	Ph	Ph	55	78	255–256 (DMF–H_2O)	3360, 3320 (NH_2), 2210 (conjugated CN), 1740 (ring CO), 1630 (C=C)	4.7 (d, 1H, 7*a*-H), 5.0 (d, 1H, 7-H), 7.4–7.5 (m, 10H, Ar-H), 7.6 (s, br, 2H, NH_2)
H	*p*-O_2N-C_6H_4	Ph	50	70	205 (EtOH)	3040–3010 (NH), 2210 (CN), 1760 (ring CO), 1650 (C=C)	4.5 (d, 1H, 7*a*-H), 5.0 (d, 1H, 7-H), 6.2 (s, br, 2H, NH_2), 7.4–7.8 (m, 9H, Ar–H)
Ph	Ph	Ph	70	75	245–247 (DMF–H_2O)	3420, 3280 (NH), 2200 (CN), 1740 (ring CO), 1650 (C=C)	4.6 (d, 1H, 7*a*-H), 6.3 (s, br, 2H, NH_2), 7.2–8.2 (m, 15H, Ar–H)
Fluorenylidene		Ph	77	76	260–261 (EtOH)	3420, 3360, 3330 (NH), 2210 (CN), 1770 (ring CO), 1650 (C=C)	4.6 (d, 1H, 7*a*-H), 6.2 (s, br, 2H, NH_2), 7.2–8.0 (m, 13H, Ar–H)
H	Ph	H	–[a]	60	242–243 (EtOH)	3380, 3000 (chelated NH), 2220 (CN), 1730 (ring CO), 1650 (C=C)	4.16 (s, br, 2H, NH_2), 6.45 (s, br, 1H, 7-H), 7.4–7.8 (m, 5H, Ar–H)

[a] Not available directly from **1.122** (see text).

1.3.4. 5,6,7,7*a*-Tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazoles

The sequence (**1.125** → **1.126** → **1.127**) provides the only example of a derivative (**1.127**) in the 5,6,7,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole category,[64] and no attempt has been made to investigate the scope of this procedure.



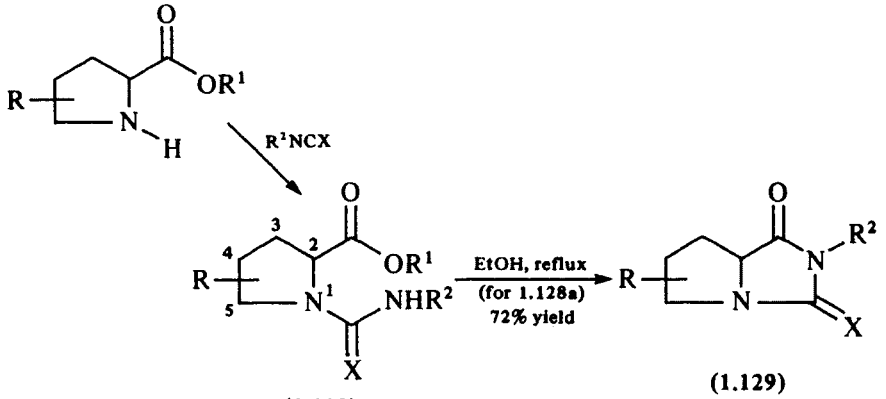
(**1.125**) (**1.126**) Ph (**1.127**) mp 208°C (dioxan)

(i) PhC(OEt)=NH, EtOH, reflux (88% yield); (ii) HCl (84% yield)
(iii) $NaHCO_3$, MeOH; (iv) 2*M* NaOH, 1 h (85% yield)

1.3.5. 2,3,5,6,7,7*a*-Hexahydro-1*H*-pyrrolo[1,2-*c*]imidazoles

1.3.5.1. Synthesis

Compounds in the fully reduced 1*H*-pyrrolo[1,2-*c*]category are usually synthesized from appropriately substituted pyrrolidines and in an isolated example in the patent literature from an imidazoline dione. Thus 1-carbanilide and 2-thiocarbanilide derivatives of pyrrolidines (**1.128**) can be cyclized either by heating them in ethanol (e.g., to **1.129**; R^2 = Ph, X = S)[65] or under acidic conditions (e.g., on transformations of **1.128b**,[66] **1.128c**,[67] **1.128d**,[68] and **1.128e**[69]).

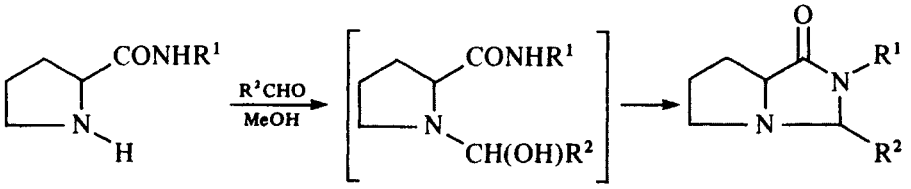


(**1.128**)

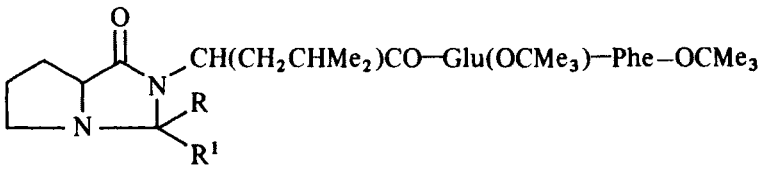
	R	R^1	R^2	X
a	H	Et	Ph	S
b	5-CO_2Et	Et	Ph	S or O
c	H	H	Ar	S or O
d	H	H	3,5-$Cl_2C_6H_3$	O
e	4-OH	H	3,5-$Cl_2C_6H_3$	O

(**1.129**)
R = H, R^2 = Ph, X = S
mp 186°C (EtOH)
λ_{max}^{EtOH} 271 nm (ε, 15130)
237 nm (9510)

In an alternative approach, cyclization can be achieved by generating a 1,2-disubstituted pyrrolidine derivative (**1.131**) *in situ* from the reaction of a 2-carboxamido pyrrolidine (**1.130**), and this route has been used to prepare a variety of 2,3,5,6,7,7*a*-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-ones, including 3-substituted compounds (see **1.132** and Table 1.21).[70] Application of this type of reaction to peptides containing a terminal proline residue gives rise to peptides incorporating the hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one framework (**1.133**).[71]



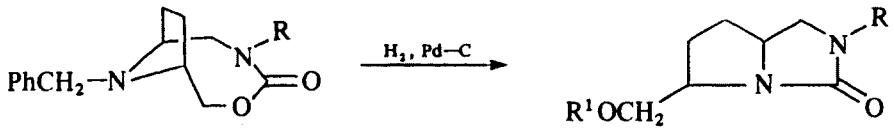
(**1.130**) (**1.131**) (**1.132**)



(**1.133**)

R	R^1	mp (°C)	Yield (%)
H	Me	oil	73
H	H	138–139	90

Closely related to **1.133** are the hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3-ones (**1.135**). The latter are also prepared from substituted pyrrolidines, but in this approach they are generated *in situ* by the hydrogenolytic cleavage of oxadiazabicyclo[5.2.1]decanones of type **1.134**.[72,73] The 5-hydroxymethyl derivatives (**1.135**, R^1 = H) have been transformed routinely into a variety of ether and ester derivatives (see Table 1.22).[72]



(**1.134**) R = *n*-Bu, CH_2Ph (**1.135**) R^1 = H

Synthesis of the fully reduced pyrrolo[1,2-*c*]imidazole derivative (**1.138**) has been achieved in an unexpected manner from the benzyloxycarbonyl (*S*)-proline derivative (**1.136**). Reduction of **1.136** with lithium aluminum hydride (LAH) in ether gave 1-methylpyrrolidines (**1.137a, b**), together with a small quantity of the bicyclic derivative (**1.138**).[74] In contrast, when the reduction is carried out in tetrahydrofuran, the latter (**1.138**) is formed in high yield; the use of lower

TABLE 1.21. SYNTHESIS OF 2,3,5,6,7,7*a*-HEXAHYDRO-1*H*-PYRROLO[1,2-*c*]-IMIDAZOL-1-ONE DERIVATIVES (**1.132**)[70]

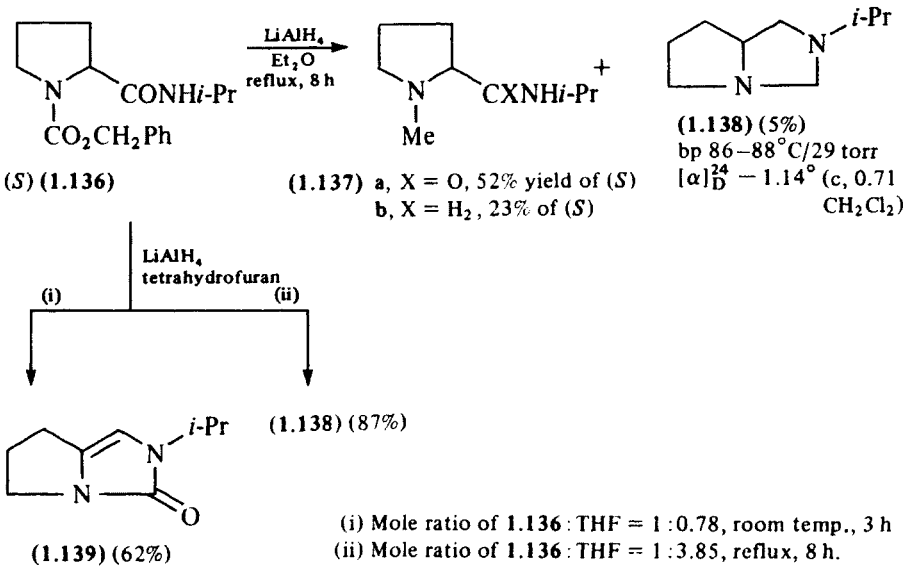
Product (**1.132**)			
R^1	R^2	mp (°C)	mp of Hydrochloride
Ph	H	63–65	203 (dec.)
3-ClC_6H_4	H	107–108	184
4-$MeOC_6H_4$	H	113–115	175–176
Ph	Me	90	151
Ph	$PhCH_2$	135–137	179
Ph	2-Furoyl	173–175	163–165
2-Me-6-pyridyl	H	–[a]	163–165
Pr	H	–[a]	157–159
Bu	H	–[a]	145–147
$PhCH_2$	H	–[a]	169–171
2-ClC_6H_4	H	–[a]	198–199
4-ClC_6H_4	H	95–96	141–143
2-$MeOC_6H_4$	H	–[a]	193–195
3-$O_2NC_6H_4$	H	141–143	196
4-$O_2NC_6H_4$	H	198–200	174–176
4-$H_2NSO_2C_6H_4$	H	300	–
3-$H_2NC_6H_4$	H	–	275
4-AcC_6H_4	H	174–176	300
Ph	Et	–[a]	166–168
Ph	Ph	138–139	190–191
Ph	*i*-Pr	130	152–154
Ph	2-HOC_6H_4	89–91	188–190
Ph	3-$MeOC_6H_4$	117–119	226–228
Ph	3-HOC_6H_4	117–119	–

[a] Compound is an oil with unquoted boiling point.

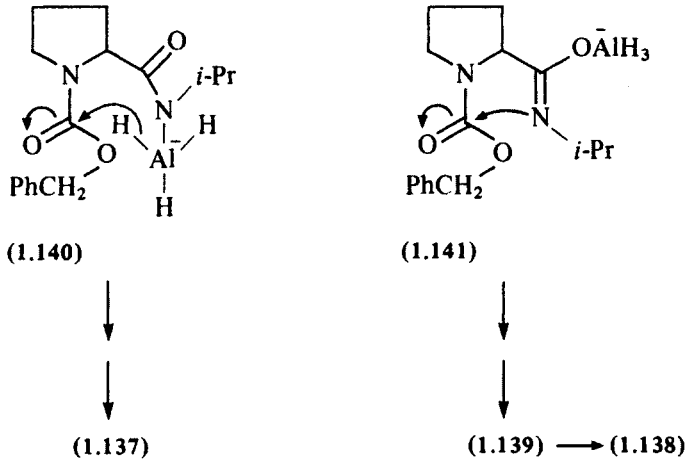
TABLE 1.22. SYNTHESIS[a] OF 2,5-DISUBSTITUTED 2,3,5,6,7,7*a*-HEXAHYDRO-1*H*-PYRROLO[1,2-*c*]IMIDAZOL-3-ONE DERIVATIVES[72,73]

Product (**1.135**)			
R	R^1	mp (°C) or bp (torr)	Yield (%)
n-Bu	H	160 (0.6)	85
n-Bu	COEt	170 (0.6)	68
n-Bu	COC_6H_4Cl-*p*	230 (0.5)	59
n-Bu	$COCH_2C_6H_4OEt$-*p*	260 (0.4)	48
n-Bu	$COC_6H_2(OMe)_3$-3,4,5	40–43	43
CH_2Ph	H	175 (0.4)	83
CH_2Ph	COEt	190–200 (0.5)	83
CH_2Ph	$COCH_2C_6H_4OEt$-*p*	270 (0.5)	51
CH_2Ph	$COC_6H_2(OMe)_3$-3,4,5	79–80	51

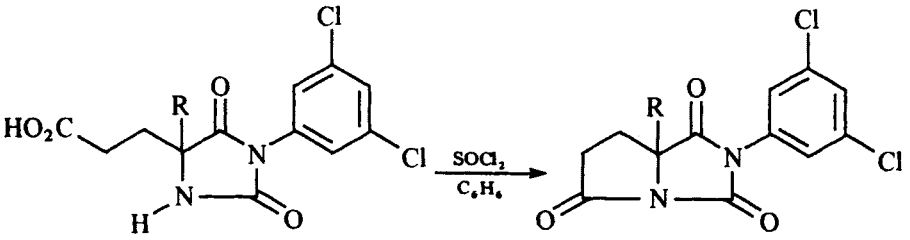
[a] Ester derivatives were prepared by use of appropriate acyl and aroyl chlorides.[73]



reaction temperatures in the last type of reaction gives rise to the formation of 2-isopropyl-2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-*c*]imidazol-2-one (**1.139**) in moderate yield.[74] Reactions of this type are thought[74] to involve intermediate substrate–LAH complexes. Transfer of hydride ion from the *N*-bonded complex (**1.140**) would give rise ultimately to *N*-methylpyrrolidines (**1.137**), whereas intramolecular nucleophilic attack of nitrogen in the *O*-bonded complex (**1.141**) could explain the formation of the tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole derivative. Compound (**1.138**) is characterized by the following spectral data:[74] ^{1}H nmr ($CDCl_3$) δ = 1.03 (3H) and 1.05 (3H, d, J = 6.0 Hz), 1.40–2.05 (4H, m), 2.10–2.80 (4H, m), 3.05 (1H, m) 3.22 (1H, d, J = 7.2 Hz), 3.52 (1H, m); ^{13}C nmr ($CDCl_3$) δ = 22.1 (2C, q), 26.4 (t), 33.0 (t), 53.2 (d), 56.1 (t), 57.8 (t), 63.3 (d), and 76.7 (t).



The use of imidazolines for the synthesis of hexahydro-1*H*-pyrrolo[1,2-*c*]-imidazoles is confined to the acylative ring closure of imidazoline diones (cf. **1.142** → **1.143**).[75] The enantiomers of the 7*a*-unsubstituted derivative (**1.143a**) have been separately characterized, but the 7*a*-methyl derivative (**1.143b**) has been isolated as a racemic mixture.[75]

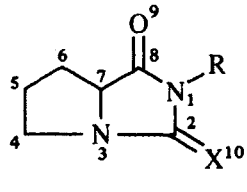


(**1.142**) (**1.143**) **a**, R = H
b, R = Me

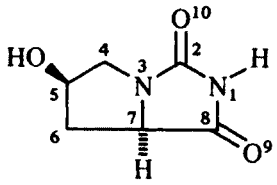
1.3.5.2. Physicochemical and Spectral Studies

The Edman degradation by isocyanates and isothiocyanates (e.g., PhNCX, X = O or S) is a widely used procedure for amino acid sequence analysis of peptides from the terminal amino function.[76] The products are *N*-phenylhydantoins and *N*-phenylthiohydantoins, but for proline the products are bicyclic derivatives (**1.144a**) in the hexahydro-1*H*-pyrrolo[1,2-*c*]imidazole system. Accordingly, there is interest in detailed physical and spectral identification of compounds in this category.

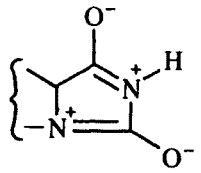
The molecular structure of L-proline hydantoin (**1.144b**) and D-allohydroxy-proline hydantoin (**1.145**) have been determined X-ray crystallographically.[77] From values of interatomic distances in the imidazoline rings (see Table 1.23), it has been concluded[77] that resonance forms as denoted by partial structure (**1.146**) make significant contributions to the total structures of **1.144b** and **1.145**.



(**1.144**) **a**, R = Ph, X = O or S
b, R = H, X = O



(**1.145**)



(**1.146**)

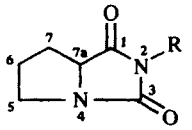
Chemical shift values from ^{1}H nmr spectral measurements of hexahydro-1*H*-pyrrolo[1,2-*c*]imidazoles are illustrated in structures **1.147**[78] and **1.148**,[79] and ^{13}C nmr chemical shifts of proline hydantoins are collected in Table 1.24;[80] ^{1}H nmr spectroscopy has also been used to study detailed conformational equilibria in proline hydantoins[81,82]

TABLE 1.23. INTERATOMIC DISTANCES[a] IN 2,3,5,6,7,7*a*-HEXAHYDRO-1*H*-PYRROLO-[1,2-*c*]IMIDAZOLE DERIVATIVES (**1.144b** and **1.145**)[77]

Interatomic Distance[b]	Structure **1.144b**	Structure **1.145**
N-1–C-2	1.429 (12)	1.383 (3)
N-1–C-8	1.370 (12)	1.358 (3)
C-2–N-3	1.354 (12)	1.363 (3)
C-2–O-10	1.207 (12)	1.223 (3)
N-3–C-4	1.506 (13)	1.472 (3)
N-3–C-7	1.472 (11)	1.470 (3)
C-4–C-5	1.569 (16)	1.519 (4)
C-5–C-6	1.542 (15)	1.511 (5)
C-6–C-7	1.538 (15)	1.540 (4)
C-7–C-8	1.513 (12)	1.503 (4)
C-8–O-9	1.202 (11)	1.220 (3)
C-5–O-11	–	1.423 (3)

[a]The crystallographic numbering system is shown in structures **1.144b** and **1.145**. The ring index numbering system is depicted in structure **1.97**.
[b]In angstrom units.

TABLE 1.24. ^{13}C NMR SPECTRA OF 2,3,5,6,7,7*a*-HEXAHYDRO-1*H*-PYRROLO[1,2-*c*] IMIDAZOLE DERIVATIVES (**1.149**) DERIVED FROM L-PROLINE[80]

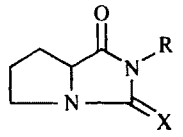


(1.149)

Carbon Atom Number in Structure **1.149**	Chemical Shift[a]	
	R = H	R = Ph
C-1	160.99	173.51
C-3	175.81	183.15
C-5	44.85	–[b]
C-6	26.65	26.33[c]
C-7	26.65	26.57[c]
C-7*a*	63.96	65.64
(Ph)		134.08, 128.98

[a]Chemical shifts are quoted in ppm from tetramethylsilane as internal standard for dimethyl sulfoxide solvent.
[b]Unassigned.
[c]Assigned arbitrarily.

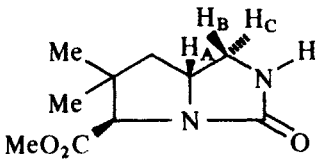
TABLE 1.25. UV AND CD SPECTRA OF HYDANTOINS AND THIOHYDANTOINS DERIVED FROM L-PROLINE[83]



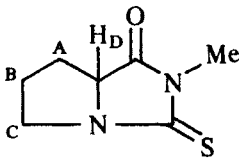
(1.149A)

	R	X
a	H	O
b	Ph	O
c	Ph	S
d	C_3H_7	S

Compound	$[\alpha]_D$ (Solvent)	uv (MeOH) λ_{max} (nm)	Extinction Coefficient	CD (MeOH) λ (nm)	θ
1.149Aa	−143 (H_2O)	210	3,700	213	−49,500
		240	450	238	15,000
1.149Ab	−54.5 (MeOH)	204	16,000	214	−75,000
		216	12,900	241.5	25,300
		240	3,000	275	−3,200
		267	480		
1.149Ac	−5.9 (MeOH)	204	22,000	228.5	−1,800
		227	10,800	248.5	4,350
		238	10,900	274	−2,450
		272	16,000	324	341
		321	100		
1.149Ad	Racemic	202	8,000		
		246	14,000	–	–
		272	17,000		
		321	110		



(1.147)



(1.148)

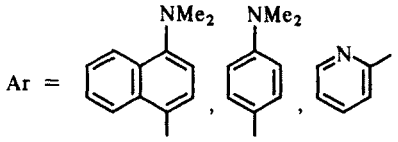
	H_A	H_B	H_C		H_A	H_B	H_C	H_D
δ (ppm)	5.67	3.92	3.58	δ (ppm)	←1.35–2.40(m)→		3.2–3.9	4.40(q)

The uv and circular dichroism spectra of four L-proline-derived hydantoin and -thiohydantoin derivatives have been recorded (Table 1.25).[83] By comparison with related compounds, it has been concluded[83] that there is a hindered rotation about the *N*-phenyl bond in the thiohydantoin derivative (**1.149Ac**) but that this effect is much less pronounced in the 3-phenyl hydantoin (**1.149Ab**).

The measurement of high-resolution mass spectra of proline-containing peptides is aided by their conversion[84] into volatile 3-aryl or 3-(2-pyridyl) derivatives [cf. **1.150** → **1.151** and related compounds (**1.133**) of this type].

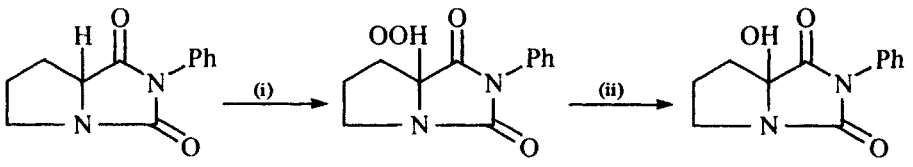
(1.150) (1.151)

R = e.g. $CH(CH_2CHMe_2)CONHCH_2CONH_2$



1.3.5.3. Reactions

Free radical-chain autoxidation of the proline-derived phenyl hydantoin (**1.152**) occurs by attack at the 7*a*-bridgehead hydrogen to give a poor yield of the hydroperoxide (**1.153**); the latter can be transformed in high yield by catalytic hydrogenolysis into the 7*a*-hydroxy compound (**1.154**).[85]

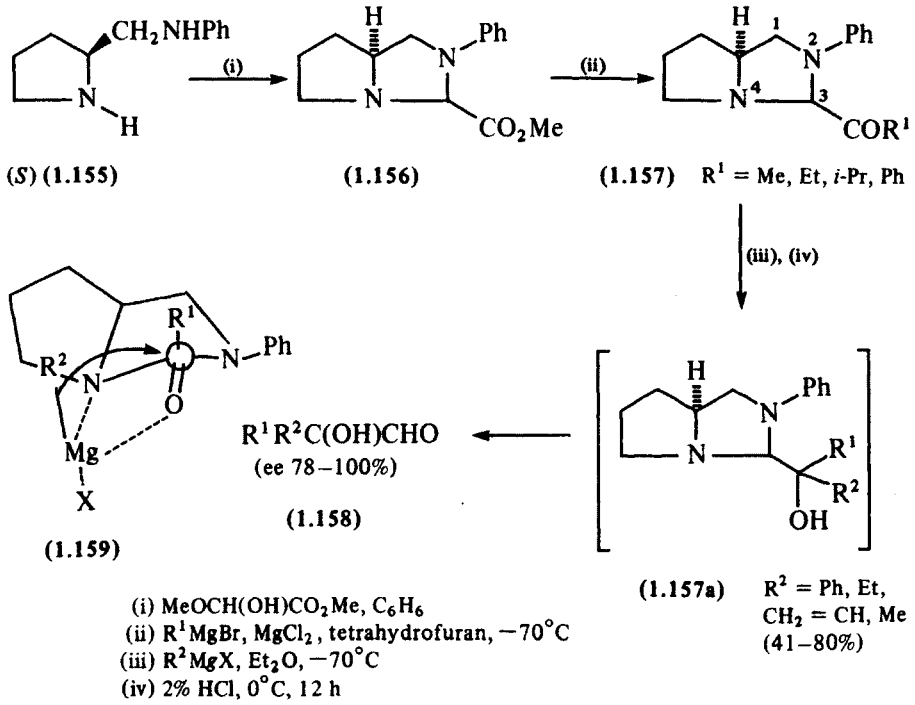


(**1.152**) (**1.153**) (**1.154**)

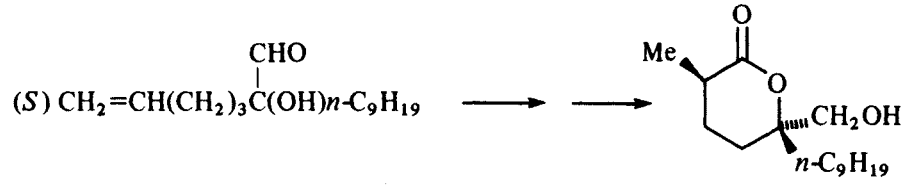
mp 160–170°C (dec) [MeOH–C_6H_6] mp 145–155°C (dec) [Et_2O-petrol]

(i) AcOH, azobisisobutyronitrile, O_2 (5 atm.), 16 h, 80°C (12% yield)
(ii) PdO_2, H_2, dioxan (86% yield).

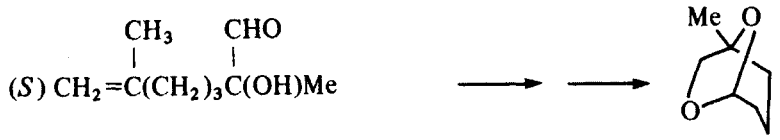
The most valuable of reactions of hexahydro-1*H*-pyrrolo[1,2-*c*]imidazoles concerns their use in the chiral synthesis of aldehydes. Thus (*S*)-2-(anilinomethyl)-pyrrolidine (**1.155**) can be converted stepwise into the ester (**1.156**)[86] and thence by use of Grignard reagents into 3-acyl-2-phenyl hexahydro-1*H*-pyrrolo[1,2-*c*]-imidazole derivatives (**1.157**).[87] Reaction of the latter (**1.157**) with a second Grignard reagent followed by hydrolytic opening of the imidazoline ring provides a chiral synthesis of α-hydroxy aldehydes (**1.158**) with high optical yields. It may



be noted that the chirality of the product aldehydes (**1.158**) is determined by the sequence of introduction of the R^1 and R^2 groups – specifically, when R^1, introduced in the first Grignard reaction, has lower priority than R^2 introduced in the second Grignard process, then (*R*) chirality in the aldehyde is observed. On the other hand, when R^1 has higher priority than R^2, the aldehyde has an (*S*) configuration. From these experimental data it has been concluded[87] that magnesium of the R^2MgX Grignard reagent complexes with the carbonyl oxygen and with *N*-4 during the initial process, leading to **1.157a**. Nucleophilic addition of R^2 to the carbonyl group then occurs from the least hindered side as depicted within **1.159**. Procedures of the type described above (cf. **1.155** → **1.158**) have been used to provide intermediates in the total chiral synthesis of the marine antibiotic Malyngolide (**1.160**)[88] and the insect pheromone (*S*)-Frontalin (**1.161**),[89] and the general route to chiral aldehydes (cf. **1.158**) is covered in the patent literature.[90]

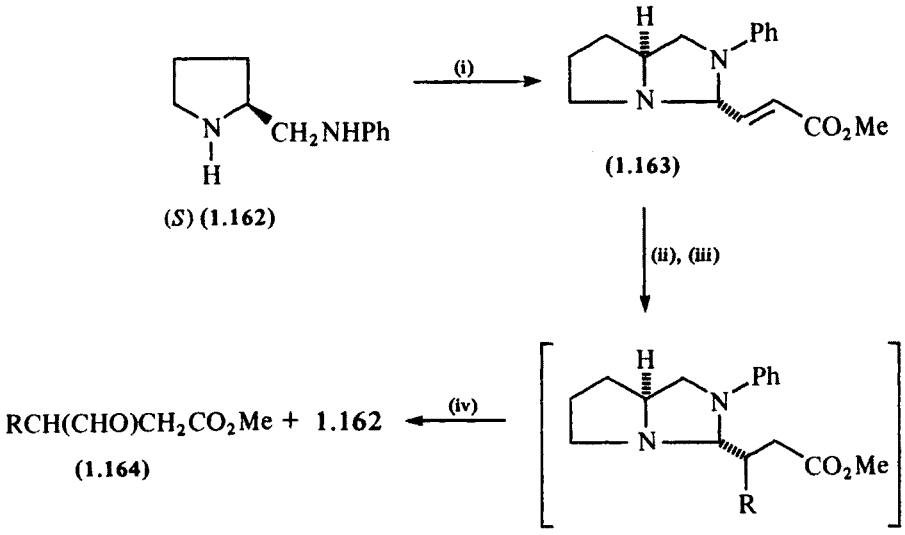


(**1.160**)



(1.161)

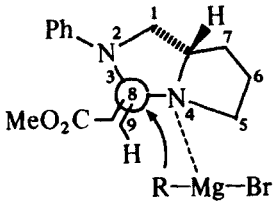
Grignard reagents have also been employed in reactions with the α, β-unsaturated ester derivatives (**1.163**) in an efficient chiral synthesis of 3-alkyl succinaldehydic esters (**1.164**).[91] The sequence **1.162** → **1.164** consists of two stereoselective steps: only one diastereomer (**1.163**) is formed in the initial condensation **1.162** → **1.163**. The second stereoselective process [**1.163** → excess (*R*) isomers of **1.164**] is explained[91] as follows: the most favorable rotational conformation of the C-8–C-3 bond in **1.163** in the transition state is such that the double bond is flanked by the two least bulky groups attached to C-3 (i.e., H and N-4; see structure **1.165**). Preferential coordination of magnesium of the Grignard reagent to N-4 rather than N-2 gives rise to excess of the (*R*) aldehyde (**1.164**).



(*S*) (**1.162**) (**1.163**)

RCH(CHO)CH_2CO_2Me + **1.162** (**1.164**)

(i) *trans*-OHCCH=$CHCO_2Me$, tetrahydrofuran, molecular sieves.
(ii) RMgBr, CuI (catalyst)
(iii) aq. NH_4Cl
(iv) 2% HCl.



(**1.165**)

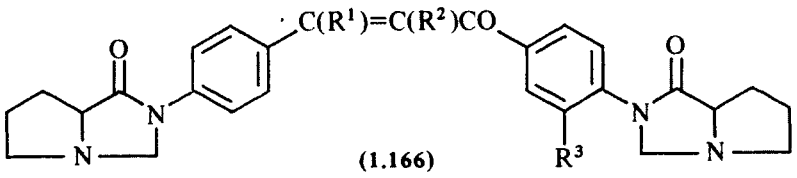
TABLE 1.26. COMPOUNDS OF COMMERCIAL INTEREST IN THE 2,3,5,6,7,7*a*-HEXAHYDRO-1*H*-PYRROLO[1,2-*c*]IMIDAZOLE GROUP

Structure	Functional Groups	Area of Commercial Interest	Reference
1.129	X = O, S; R = H; R^2 = aryl	Agricultural herbicides and fungicides	67
1.129	X = O; R = H; R^2 = 3,5-$Cl_2C_6H_3$	Fungicides	68
1.129	X = O; R = 6-OH; R^2 = 3,5-$Cl_2C_6H_3$	Antibacterial	69
1.132	—[a]	Antiinflammatory, analgesic, antispasmodic	70
1.143	R = H, Me	Antibacterial	75
1.166	$R^1 = R^3 = H$; R^2 = Me; R^1 = Me; $R^2 = R^3 = H$; $R^1 = R^2 = R^3 = H$	Antispasmodic, tranquilizer	92

[a]See Table 1.21.

1.3.5.4. Commercial Applications

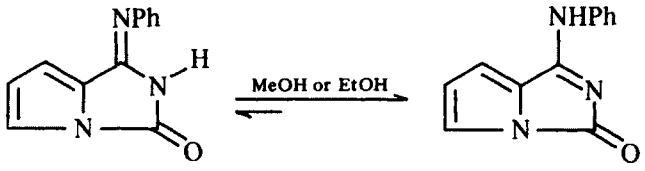
Areas of commercial interest concerning 2,3,5,6,7,7*a*-hexahydro-1*H*-pyrrolo-[1,2-*c*]imidazoles are summarized in Table 1.26.



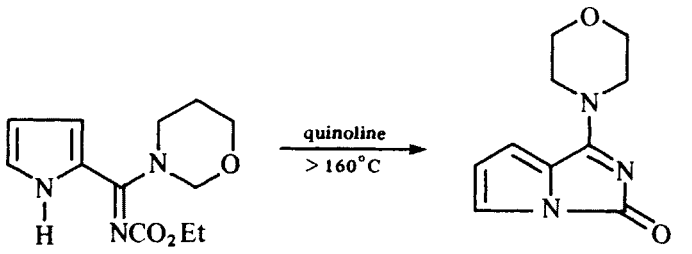
(1.166)

1.3.6. 3*H*-Pyrrolo[1,2-*c*]imidazoles

The preparation of 1-phenylamino-3*H*-pyrrolo[1,2-*c*]imidazol-3-one (**1.118**) has been described earlier[60] (see Section 1.3.1). This compound (**1.118**) is also obtained when the 1-phenylimino derivative (**1.110**) is caused to tautomerize by recrystallizing it from methanol or ethanol. Compound **1.168**, which is analogous to **1.118**, has been prepared by heating the pyrrole derivative (**1.167**) in quinoline.[60]

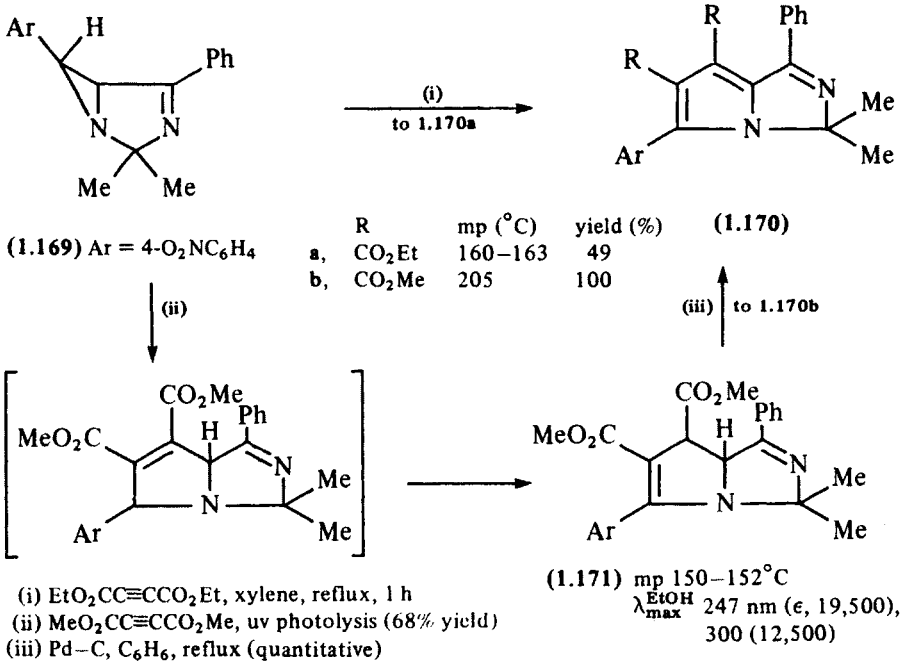


(1.110) (1.118)



(1.167) (1.168) mp 184–185°C

Ring opening of readily available[93] aziridinoimidazoles (cf. **1.169**) and ensuing 1,3-dipolar cycloaddition reactions have provided a rich source of pyrrolo[1,2-*c*]-imidazoles (see also Section 1.3.8). A fully unsaturated derivative (**1.170a**) in the 3*H*-pyrrolo[1,2-*c*]imidazole category is formed by heating the condensed aziridine (**1.169**) with diethyl acetylene dicarboxylate.[94] In contrast, uv photolysis of **1.169** in the presence of dimethyl acetylene dicarboxylate provides the 7,7*a*-dihydro derivative (**1.171**), and a dehydrogenation step is necessary for formation of the fully unsaturated 3*H*-pyrrolo[1,2-*c*]imidazole derivative (**1.170b**).[95]



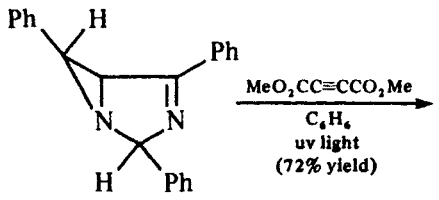
(**1.169**) Ar = 4-$O_2NC_6H_4$

	R	mp (°C)	yield (%)	(**1.170**)
a,	CO_2Et	160–163	49	
b,	CO_2Me	205	100	

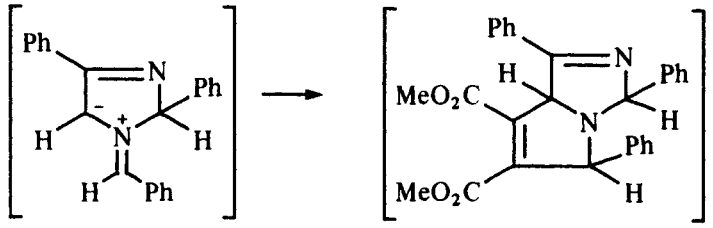
(i) $EtO_2CC{\equiv}CCO_2Et$, xylene, reflux, 1 h
(ii) $MeO_2CC{\equiv}CCO_2Me$, uv photolysis (68% yield)
(iii) Pd–C, C_6H_6, reflux (quantitative)

(**1.171**) mp 150–152°C
λ_{max}^{EtOH} 247 nm (ε, 19,500), 300 (12,500)

Following a more detailed examination of reactions of this type, it has been concluded that the sequence of events is ring cleavage to give an azomethine ylide (**1.172** → **1.173**) and then dipolar cycloaddition followed by a 1,3-suprafacial hydrogen shift to give the product 7,7*a*-dihydro-3*H*-pyrrolo[1,2-*c*]imidazole derivative (**1.174**);[96] dehydrogenation of the latter (**1.174**; cf. **1.171** → **1.170b**) gives rise to a 3-mono-substituted analog (**1.175**) of **1.170**.[96]

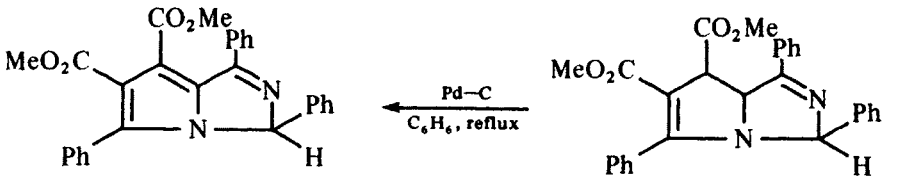


(1.172)



(1.173)

[1,3]H shift



(1.175)

mp 151–152°C
$\lambda_{max}^{95\%\ EtOH}$ 265 nm (ε, 17,350), 290 (14,000), 378 (15,300)

(1.174)

mp 123–124°C
uv $\lambda_{max}^{95\%\ EtOH}$ 240 nm (ε, 19,000)

Compounds in the parent 3*H*-pyrrolo[1,2-*c*]imidazole category have also been isolated, although in a more indirect manner by sulfur extrusion from cyclo adducts derived from 1,3,6-triphenylimidazo[1,2-*c*]thiazole-*S*(IV) (cf. **1.176** → **1.177** → **1.178** + **1.180**[97]). The mechanism of formation of **1.178** is thought[97] to involve an initial hydrogen shift induced by triethylamine followed by sulfur extrusion. Under certain conditions (see Table 1.27) the 3*H*-pyrrolo[1,2-*c*]imidazole derivatives (**1.178**) can be isolated and characterized, but they can also undergo a 10-π cyclization (to **1.179**) with concomitant oxidation to give compounds in the 4,9*c*-diazapentaleno[1,6*a*, 6:*ab*]naphthalene ring system (**1.180**). An advantage of the scheme outlined in the sequence **1.176** → **1.178c, d** is the regioselectivity achieved on cycloaddition of unsymmetrical dipolarophiles to the azomethine ylide 1,3-dipole of **1.176**.

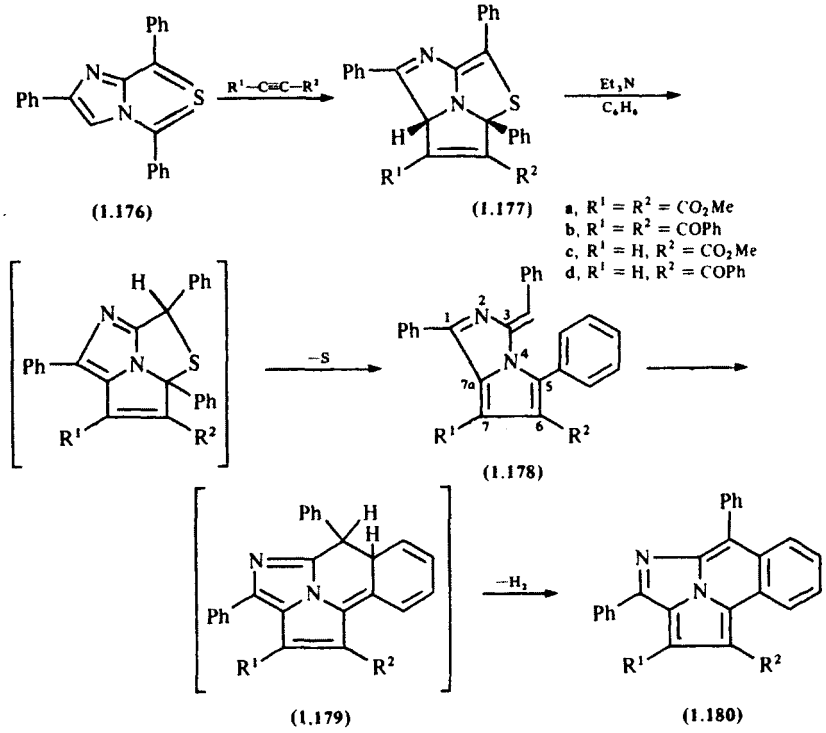


TABLE 1.27. CONVERSION OF CYCLOADDUCTS (1.177) DERIVED FROM 1,3,6-TRIPHENYLIMIDAZO[1,2-*c*]THIAZOLE-*S*(IV) (1.176) INTO 3*H*-PYRROLO[1,2-*c*]IMIDAZOLES (1.178) AND 4,9*c*-DIAZAPENTALENO-[1,6*a*, 6:*ab*]NAPHTHALENES (1.180)

Starting Material	Reaction Conditions	Yield (%) 1.178[a]	1.180
1.177a	*Room temp., 24 h*	25	58[b]
	Reflux, 24 h	0	90[b]
1.177b	Reflux, 24 h	0	86
1.177c	Reflux, 24 h	84	0
	Reflux, 48 h	36	49[c]
	Reflux, 72 h	0	81[c]
1.177d	*Room temp., 24 h*	67	13[d]
	Reflux, 24 h	0	78[d]

[a]Physical and representative spectroscopic data are as follows. Structure **1.178a**, yellow, mp 151.5–153.5°C (dec.); ir (KBr) 1740 and 1700 cm^{-1} (CO); ^1H nmr ($CDCl_3$) 3.64, 3.80 (each 3H, s, CO_2Me), 6.07 (1H, s, =CHPh) and 7.00–8.02 ppm (15H, m, Ar–H); ^{13}C nmr ($CDCl_3$) *51.67, 52.37* (each q, CO_2Me), *110.43* (s, *C-7*), *112.37* (d, =*CH*), *158.75* (*s, C-3*) *and* 164.45 ppm (s, CO_2Me). Structure **1.178c**: yellow, mp 137–139°C (dec.). Structure **1.178d**: yellow, mp 154–155.5°C (dec.).

[b]Also obtained in 92% yield by heating **1.178a** under reflux in benzene without triethylamine.

[c]Also obtained quantitatively from **1.178c**.

[d]Also obtained in 92% yield from **1.178d**.

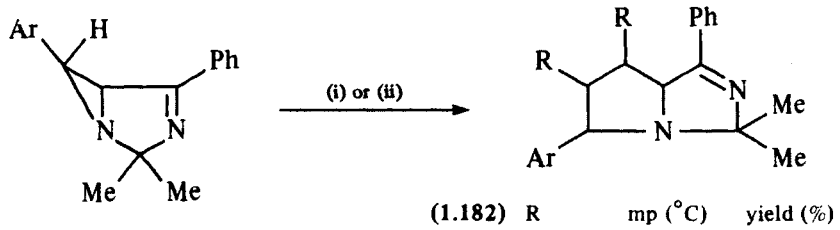
1.3.7. 7,7*a*-Dihydro-3*H*-pyrrolo[1,2-*c*]imidazoles

Compounds of this type (**1.171**, **1.174**) have been obtained from reactions of aziridinoimidazoles with activated acetylenes and are described in Section 1.3.6.

1.3.8. 5,6,7,7*a*-Tetrahydro-3*H*-pyrrolo[1,2-*c*]imidazoles

1.3.8.1. Synthesis

Compounds of this type (**1.182a, b**) have been obtained by heating activated alkenes with the aziridinoimidazole (**1.181**),[94] and the stereochemistry of such reactions has been evaluated.[96] (See section 1.3.6 for a discussion of the reaction



(1.181) Ar = 4-$O_2NC_6H_4$

(1.182)	R	mp (°C)	yield (%)
a	PhCO	200–202	67
b	CO_2Et	165–167	68

(i) cis or trans PhCOCH=CHCOPh (to **1.182a**)
(ii) trans EtO_2CCH=$CHCO_2Et$ (to **1.182b**)

mechanism.) Thus the aziridinoimidazole (**1.183**) is transformed by dimethyl maleate and dimethyl fumarate in separate reactions into a series (**1.184–1.186** and **1.187–1.190**) of tetrahydro-3*H*-pyrrolo[1,2-*c*]imidazoles of known relative stereochemistry (see Table 1.28).[96] From base-promoted (NaOMe, MeOH, 55°C, 4.5 h)

TABLE 1.28. PREPARATION OF 5,6,7,7*a*-TETRAHYDRO-3*H*-PYRROLO[1,2-*c*]-IMIDAZOLES (**1.184–1.190**) FROM AZIRIDINOIMIDAZOLES (**1.183**)[96]

Product	mp (°C)	Yield (%)[a]	Relative Stereochemistry[b]	uv λ_{max} (95% EtOH) (ϵ)
1.184	221–222	9	3*R*, 5*S*, 6*S*, 7*R*, 7*aR*	247 (17,300)
1.185	172–173	9	3*R*, 5*R*, 6*S*, 7*R*, 7*aS*	245 (15,100)
1.186	158–159	51	3*R*, 5*R*, 6*R*, 7*S*, 7*aS*	247 (16,700)
1.187	147–149	27	3*R*, 5*R*, 6*R*, 7*R*, 7*aS*	244 (15,600)
1.188	–[c]	13	3*R*, 5*S*, 6*S*, 7*S*, 7*aR*	–[c]
1.189	196–197	27	3*R*, 5*S*, 6*R*, 7*R*, 7*aR*	247 (16,100)
1.190	137–139	13	3*R*, 5*R*, 6*S*, 7*S*, 7*aS*	244 (15,600)

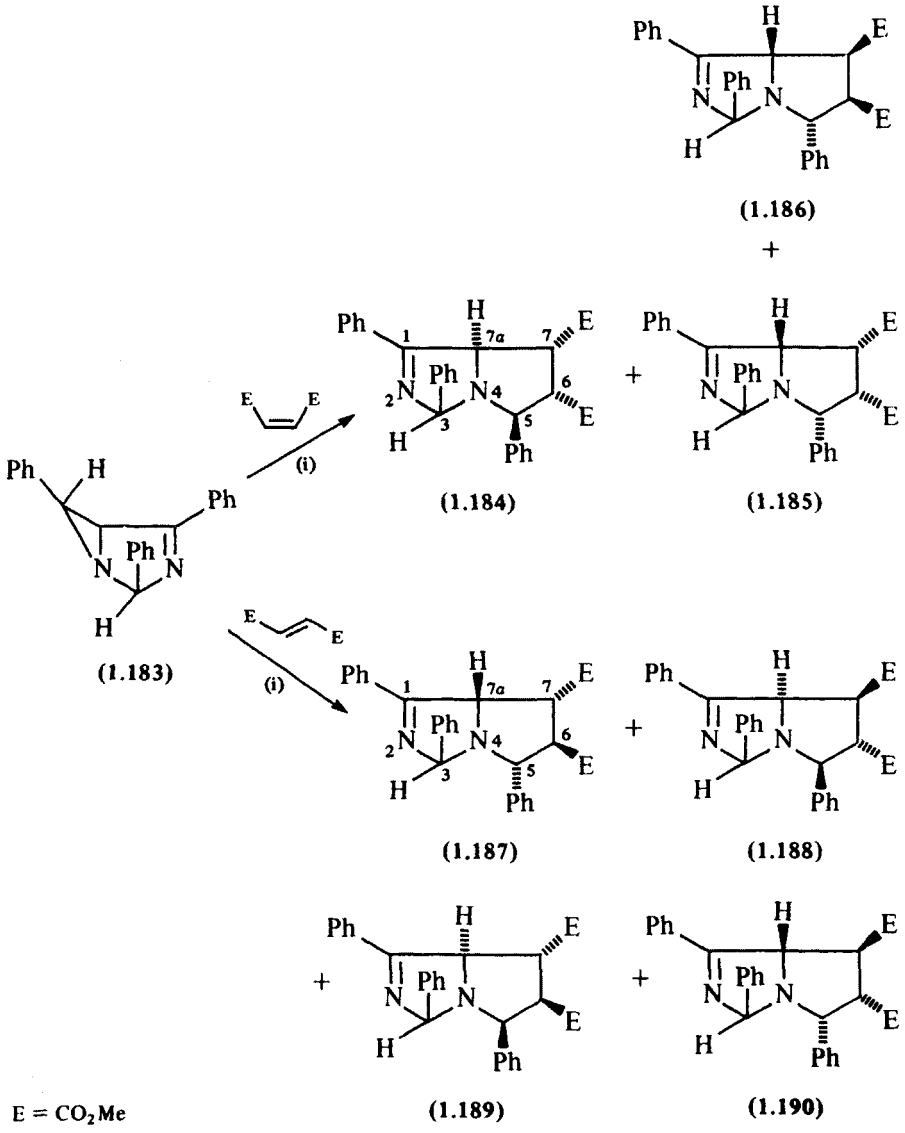
[a] Yields quoted are based on thermal and not photochemical reactions.
[b] Racemic mixtures are formed in all reactions.
[c] Characterized by ^1H nmr spectroscopy.

epimerization experiments it has been possible to attain the following equilibria:

$$(1.188) \rightleftharpoons (1.184) \rightleftharpoons (1.189) \tag{1.1}$$

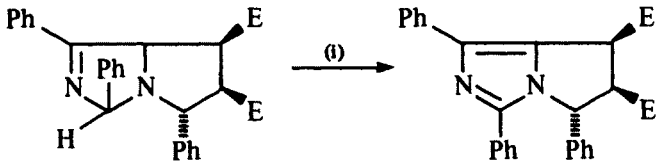
$$(1.186), (1.185), \text{ or } (1.190) \rightleftharpoons (1.187) \tag{1.2}$$

It is thus established that compounds in the first series (1.1) have configurations at C-5 and C-7*a* that are different from those in the second (1.2).



1.3.8.2. Reactions

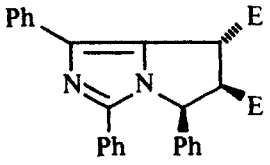
5,6,7,7*a*-Tetrahydro-3*H*-pyrrolo[1,2-*c*]imidazoles undergo palladium-promoted dehydrogenation with concomitant epimerization to give compounds in the 6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole category (e.g., **1.191** → **1.192** + **1.193**).[96] An interesting feature of the products **1.192** and **1.193** is their resistance to further dehydrogenation even under more compelling conditions in processes that would give rise to difficultly accessible compounds in the fully unsaturated 5*H*- or 7*H*-pyrrolo[1,2-*c*]imidazole groups.



(1.191)
E = CO_2Me
(i) Pd–C, C_6H_6, reflux 24 h [95% yield, 4:1 ratio of **(1.192)**:**(1.193)**]

(1.192) mp 193–195°C
uv $\lambda_{max}^{95\%\ EtOH}$
274 nm (ε, 21,700)

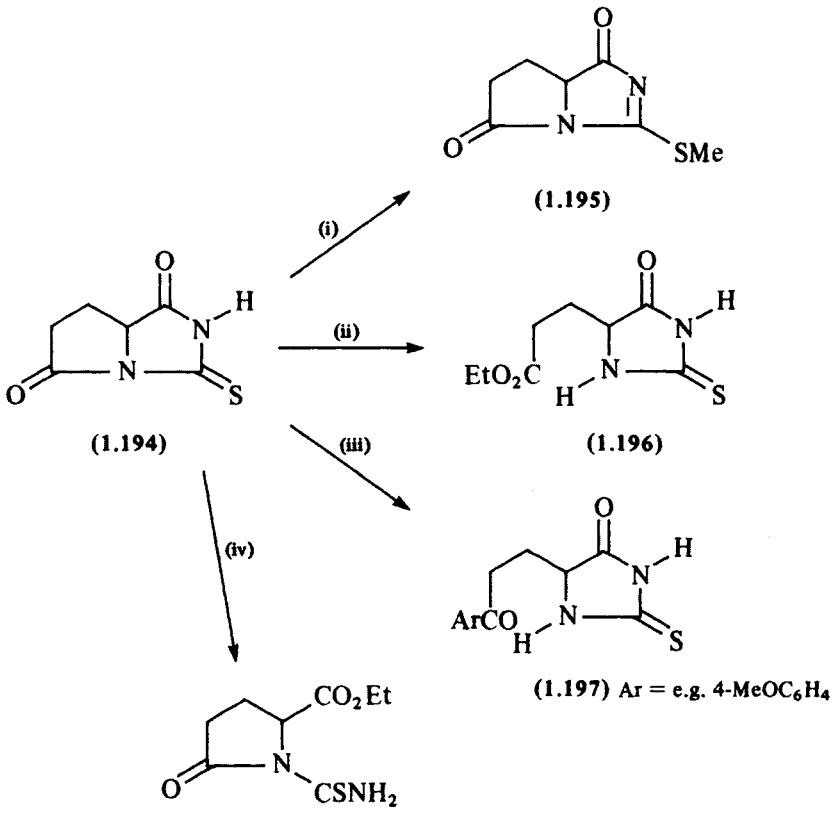
+



(1.193) mp 181–183°C
uv $\lambda_{max}^{95\%\ EtOH}$
274 nm (ε, 21,500)

1.3.9. 2,3,5,6,7,7*a*-Hexahydro-3*H*-pyrrolo[1,2-*c*]imidazoles

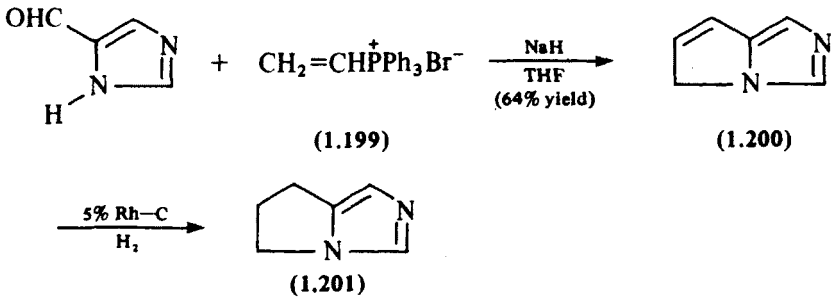
Reactions of one compound of this type (**1.194**) have been studied in detail.[98] The bicyclic ring system remains intact during *S*-alkylation (**1.194** → **1.195**), but treatment with mineral acid or aluminum trichloride and an arene results in fission of the pyrrole ring (**1.194** → **1.196** and **1.197**, respectively). In contrast, treatment of **1.194** with triethylamine and ethanol results in cleavage of the imidazoline ring to give a thiocarbamoylpyrrolidone derivative (**1.198**).



(i) CH_2N_2, tetrahydrofuran, Et_2O
(ii) dry HCl, EtOH
(iii) ArH, $AlCl_3$, $MeNO_2$
(iv) Et_3N, EtOH, heat

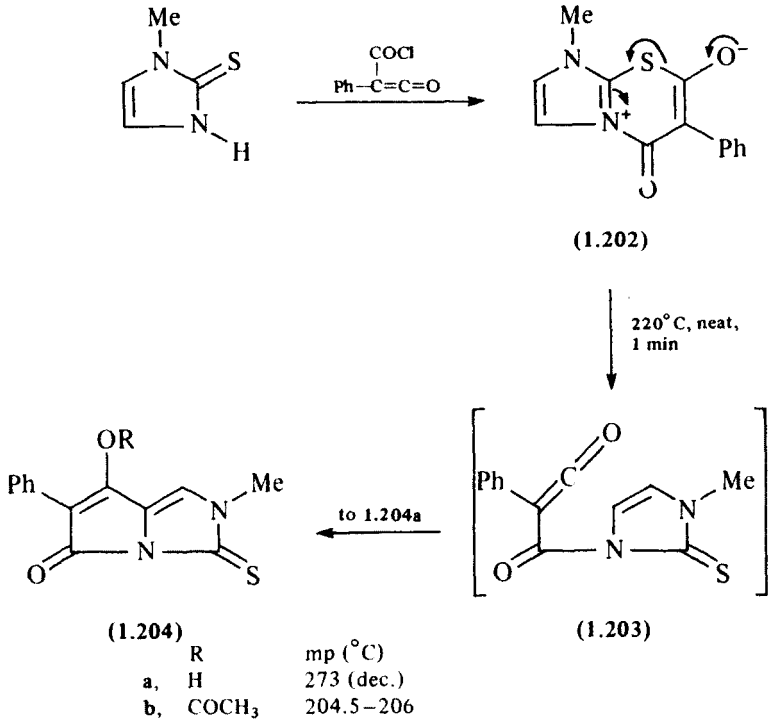
1.3.10. 5*H*-Pyrrolo[1,2-*c*]imidazoles

Reduced compounds in the 5*H*-pyrrolo[1,2-*c*]imidazole group are well documented (see ensuing sections), but there is only one example of a fully unsaturated derivative. Treatment of 4-formylimidazole with the vinyl phosphonium salt (**1.199**) and sodium hydride gives 5*H*-pyrrolo[1,2-*c*]imidazole in reasonable yield.[41] (See also application of this type of reaction in the synthesis of 5*H*-pyrrolo-[1,2-*a*]imidazoles described in Section 1.2.5.) Compound **1.200**, although properly characterized [bp 65°C, 0.25 torr, n_D^{20} 1.5570, uv $\lambda_{max}^{EtOH} = 273$ nm (ϵ, 7607)], rapidly darkens on standing and is transformed into an unidentified mixture. It is converted by catalytic hydrogenation into 6,7-dihydro-5*H*-pyrrolo[1,2-*c*]-imidazole (**1.201**).[41]



1.3.11. 2,3-Dihydro-5*H*-pyrrolo[1,2-*c*]imidazoles

Pyrolysis of the mesomeric betaine (**1.202**) [available in good yield from 1-methylimidazolin-2-thione and (chlorocarbonyl)phenylketene] gives the orange 2,3-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole derivative (**1.204a**) in an isolated reference to compounds in this group;[99] routine acetylation (Ac_2O, reflux) gives the 7-acetoxy derivative (**1.204b**). Formation of the pyrrolo[1,2-*c*]imidazole ring system is considered[99] to involve an initial fragmentation of the thiazine ring of the betaine (**1.202**) to give a ketene intermediate (**1.203**) that cyclizes to give the bicyclic product (**1.204a**).

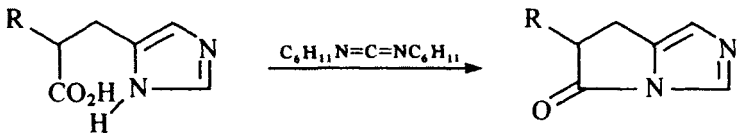


(**1.204**)

	R	mp (°C)
a,	H	273 (dec.)
b,	$COCH_3$	204.5–206

1.3.12. 6,7-Dihydro-5*H*-pyrrolo[1,2-*c*]imidazoles

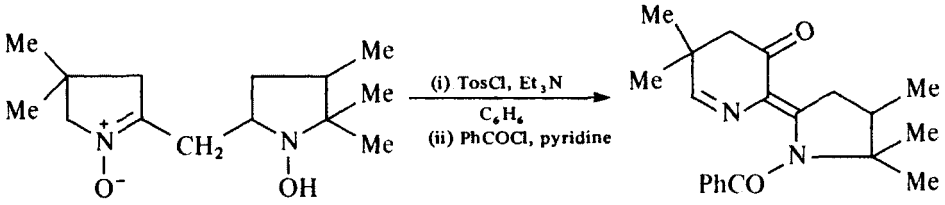
Compounds in this class are uncommon: *N*-(*p*-nitrocarbobenzyloxy)-L-histidine (**1.205**) can be cyclized in good yield to give the 6-substituted-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole derivative (**1.206**) of value in peptide synthesis.[100]



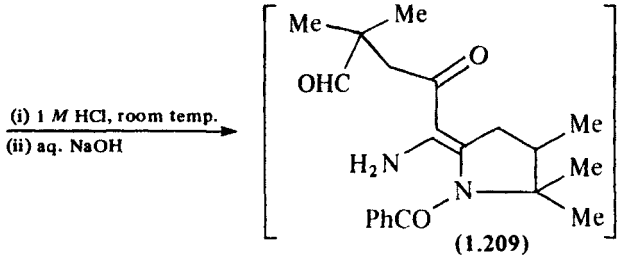
(**1.205**) (**1.206**) mp 186–187°C

R = 4-$O_2NC_6H_4CH_2OCONH$

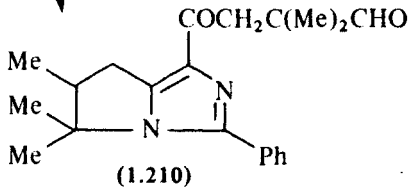
Formation of the 1,3,6-trisubstituted derivative (**1.210**) occurred in the somewhat unexpected sequence **1.207** → **1.208** → **1.210** in studies directed toward corrin syntheses.[101] From experiments using uv spectroscopy, it is apparent that the conversion **1.208** → **1.210**, perhaps[101] by way of **1.209**, is quantitative in dilute solution.



(**1.207**) (**1.208**)



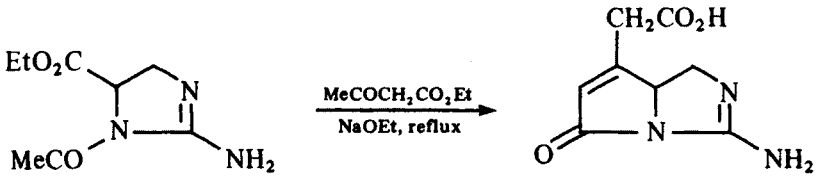
(**1.209**)



(**1.210**)

1.3.13. 1,7*a*-Dihydro-5*H*-pyrrolo[1,2-*c*]imidazoles

In an isolated reference to compounds in this group, the imidazoline derivative (**1.211**) (available in three steps from 2,3-diaminopropionic acid) is treated with ethyl acetoacetate under basic conditions to give a product (**1.212**) of condensative cyclization[102]

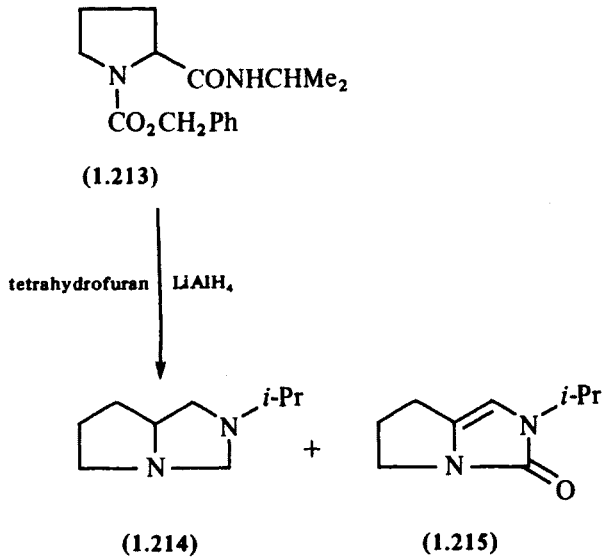


(**1.211**)

(**1.212**)
mp 242°C (EtOH)
picrate, mp 125°C;
N–Ac derivative, mp
224° (dec.)

1.3.14. 2,3,6,7-Tetrahydro-5*H*-pyrrolo[1,2-*c*]imidazole

The formation of pyrrolo[1,2-*c*]imidazole derivatives (**1.214** and **1.215**) by reduction of the pyrrolidine (**1.213**) with lithium aluminum hydride (LAH) in tetrahydrofuran has been discussed in detail in Section 1.3.5.[74] Formation of the 2,3,6,7-tetrahydro-5*H*-pyrrolo[1,2-*c*]imidazole derivative (**1.215**) is exclusive at a mole ratio of reductant: **1.213** of 0.78 at room temperature.



(**1.213**)

(**1.214**) (**1.215**)

REFERENCES

1. B. A. Hess, L. J. Schaad, and C. W. Holyoke, *Tetrahedron*, **31**, 295 (1975).
2. I. Gutman, M. Milun, and N. Trinajstić, *J. Am. Chem. Soc.*, **99**, 1692 (1977).
3. J. H. Müller, M. N. Donin, W. E. Behnke, and K. Hofmann, *J. Am. Chem. Soc.*, **73**, 2487 (1951).
4. T. Takaya, H. Yoshimoto, and E. Imoto, *Bull. Chem. Soc. Japan*, **40**, 2844 (1967).
5. H. C. Wormser, S. Israsena, M. S. Meiling, C. Williams, and D. Perlman, *J. Pharm. Sci.*, **61**, 1168 (1972).
6. H. Schubert, B. Rühberg, and G. Fiedrich, *J. Prakt. Chem.*, **32**, 249 (1966).
7. Yu. G. Putsykin and L. B. Voldarskii, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, **1969**, 86; *Chem. Abstr.*, **72**, 54514a.
8. J. Beger, *J. Prakt. Chem.*, **311**, 549 (1963).
9. T. A. Krasnitskaya, I. V. Smolanka, and A. L. Vais, *Chem. Heterocycl. Compd.*, **1973**, 395; *Khim. Geterotsikl Soedin*, **1973**, 424; *Chem. Abstr.* **78**, 159509e.
10. M. Valentiny and A. Martvon, *Chem. Zvesti*, **36**, 117 (1982).
11. I. V. Smolanka, T. A. Krasnitskaya, and E. G. Mel'nik, *Ukr, Khim. Zh.* **38**, 793 (1972); *Chem. Abstr.*, **77**, 152039x; *Engl. transl.* in *Ukr J. Chem.*, **1972**, 50.
12. C. J. Harris, *J. Chem. Soc., Perkin Trans. I*, **1980**, 2497.
13. H. Gunther and G. Jikeli, *Chem. Rev.*, **77**, 605 (1977).
14. J. P. Ferris and R. W. Trimmer, *J. Org. Chem.*, **41**, 19 (1976).
15. (a) P. F. Wiley, H. K. Jahnke, F. MacKellar, R. B. Kelly, and A. D. Argondelis, *J. Org. Chem.*, **35**, 1420 (1970); (b) D. J. Duchamp, American Crystallographic Association Winter Meeting, Albuquerque, New Mexico (USA), 1972, Abstracts, p. 23; (c) D. D. Weller and K. L. Rinehart, *J. Am. Chem. Soc.*, **100**, 6757 (1978).
16. N. Matsumura, Y. Yagyu, H. Kawai, Y. Otsuji, and E. Imoto, *Nippon Kagaku Kaishi*, **1977**, 362; *Chem. Abstr.*, **87**, 52378v; N. Matsumura, H. Kawai, and E. Imoto, *Bull. Chem. Soc. Japan*, **50**, 2417 (1977).
17. R. G. Pearson, *J. Chem. Educ.*, **45**, 581, 643 (1968).
18. I. P. Trunenkov, B. P. Fabrichnyi, I. F. Shalavina, S. M. Kostrova, Ya. L. Gol'dfarb, and V. V. Filippov, *Vch. Zap. Vladimirskii Gos. Pedagog Inst. Ser. Fiziol Rast*, **31**, 65 (1971); *Chem. Abstr.*, **81**, 34404x.
19. (a) A. A. Druzhinina and P. M. Kochergin, *Chem. Heterocycl. Compd.*, **1967**, 427; *Khim. Geterotsikl. Soedin*, **1967**, 532; *Chem. Abstr.*, **68**, 49510j; (b) P. M. Kochergin, A. A. Druzhinina, and R. M. Palei, *Khim. Geterotsikl. Soedin. Akad. Nauk. Latv. SSR*, 149 (1966).
20. A. A. Druzhinina, P. M. Kochergin, and N. P. Bychkova, *Chem Heterocycl. Compd.* **1969**, 632; *Khim. Geterosikl, Soedin*, **1969**, 865; *Chem. Abstr.*, **72**, 111360y.
21. P. M. Kochergin, A. A. Druzhinina, and R. M. Palei, *Chem. Heterocycl. Compd.*, **1976**, 1274; *Khim. Geterotsikl. Soedin*, **1976**, 1549; *Chem. Abstr.*, **86**, 106474.
22. R. M. Palei and P. M. Kochergin, *Chem. Heterocycl. Compd.*, **1969**, 812; *Khim. Geterosikl, Soedin*, **1969**, 1075, *Chem. Abstr.*, **72**, 132611.
23. G. Tennant, in *Benzimidazoles and Congeneric Tricyclic Compounds* (P. N. Preston, Ed.), Wiley-Interscience, New York, 1980, Chapter 6.
24. V. Boekelheide and N. A. Fedoruk, *J. Am. Chem. Soc.*, **90**, 3830 (1968).
25. L. I. Savranskii, V. A. Kovtunenko, and F. S. Babichev, *Chem. Heterocycl. Compd.*, **1974**, 230; *Khim. Geterotsikl Soedin*, **1974**, 261; *Chem. Abstr.* **80**, 145161q.

26. L. M. Alekseeva, G. G. Dvoryantseva, I. V. Persianova, Yu. N. Sheinker, A. A. Druzhinina, and P. M. Kochergin, *Chem. Heterocycl. Compd.*, **1972**, 449; *Khim. Geterotsikl Soedin*, **1972**, 492; *Chem. Abstr.*, **77**, 61153p.
27. L. M. Alekseeva, G. G. Dvoryantseva, Yu. N. Sheinker, A. A. Druzhinina, R. M. Palei, and P. M. Kochergin, *Chem. Heterocycl. Compd.*, **1976**, 64; *Khim. Geterosikl soedin*, **1976**, 70; *Chem. Abstr.*; **84**, 163946m.
28. A. A. Druzhinina, P. M. Kochergin, and L. M. Alekseeva, *Chem. Heterocycl. Compd.*, **1972**, 370; *Khim. Geterotsikl Soedin*, **1972**, 405; *Chem. Abstr.*, **77**, 88394e.
29. A. A. Druzhinina, P. M. Kochergin, R. M. Palei, and O. N. Minailova, *Chem. Heterocycl. Compd.*, **1977**, 180; *Khim. Geterotsikl. Soedin*, **1977**, 225; *Chem. Abstr.*, **87**, 5863q.
30. A. A. Druzhinina and P. M. Kochergin, *Chem. Heterocycl. Compd.*, **1976**, 1277; *Khim. Geterotsikl. Soedin*, **1976**, 1552; *Chem. Abstr.*, **86**, 89697d.
31. A. A. Druzhinina and P. M. Kochergin, *Chem. Heterocycl. Compd.*, **1976**, 1363; *Khim. Geterotsikl. Soedin*, **1976**, 1658; *Chem. Abstr.*, **86**, 121252t.
32. A. A. Druzhinina and P. M. Kochergin, USSR Patent 417,424 (1974); *Chem. Abstr.*, **80**, 146165f.
33. (a) A. A. Druzhinina and P. M. Kochergin, *Chem. Heterocycl. Compd.*, **1969**, 638; *Khim. Geterotsikl Soedin*, **1969**, 862; *Chem. Abstr.*, **72**, 100600a; (b) P. M. Kochergin, M. D. Mashkovskii, A. A. Druzhinina, and M. E. Kaminka, *Khim.-Farm. Zh.*, **10**, 59 (1976).
34. D. Binder and P. Stanetty, *J. Chem. Res.* (S), **1981**, 102; *J. Chem. Res.* (M), **1981**, 1073.
35. W. J. Lown and B. E. Landsberg, *Can. J. Chem.*, **53**, 3782 (1975).
36. L. Vasvari-Debreczy, A. H. Beckett, and W. Vutthikongsirigool, *Tetrahedron*, **37**, 4337 (1981).
37. H. Wollweber, *Angew. Chem. Internatl. Ed. Engl.* **8**, 69 (1969); H. Wollweber, J. Kurtz, and W. Naegele, *Arch. Pharm.* (Weinheim), **304**, 774 (1971).
38. W. J. Houlihan, U.S. Patent 3,334,099 (1967); *Chem. Abstr.*, **69**, 96769f.
39. C. C. Bell and C. Gochman, U.S. Patent 3,631,061 (1971); *Chem. Abstr.*, **76**, 85818q.
40. W. Rohr, H. Hansen, P. Plath, and B. Wuertzer, German Patent 2,948,535 (1981); *Chem. Abstr.*; **95**, 150697h.
41. I. Antonini, P. Franchetti, M. Grifantini, and S. Martelli, *J. Heterocycl. Chem.*, **13**, 111 (1976).
42. W. Rohr, R. Swoboda, and H. A. Staab, *Chem. Ber.*, **101**, 3491 (1968).
43. J. H. M. Hill, T. R. Fogg, and H. Guttmann, *J. Org. Chem.*, **40**, 2562 (1975).
44. C. B. Kanner and U. K. Pandit, *Tetrahedron*, **37**, 3519 (1981); idem, *Heterocycles*, **9**, 757 (1978).
45. P. E. Bender, U.S. Patent 4,186,205 (1980); *Chem. Abstr.*, **92**, 181195k.
46. J. P. Maffrand, D. Frehel, F. Eloy, D. Aubert, and J. C. Ferrand, *Eur. J. Med. Chem. Chim. Ther.*, **10**, 528 (1975); *Chem. Abstr.*; **85**, 21224w.
47. M. W. Gittos and W. Wilson, *J. Chem. Soc.*, **1962**, 877.
48. A. Shaw, German Patent 2,603, 399 (1976); *Chem. Abstr.*, **85**, 143109h.
49. J. Maillard, T. Vo Van and J. M. Legeai, European Patent Application 15,171 (1980); *Chem. Abstr.*, **94**, 103373u.
50. H. Moehrle and R. Engelsing, *Arch. Pharm.* (Weinheim), **306**, 325 (1973).
51. H. Moehrle, C. Kamper, and R. Feil, *Z. Naturforsch.*, **31B**, 99 (1976).
52. F. Ishikawa, T. Imano, and Y. Abiko, Japanese Patent 78 79,889 (1978); *Chem. Abstr.*, **90**, 23052r.

53. (a) N. M. Bortnick, U.S. Patent 2,984,665 (1961); *Chem. Abstr.*, **55**, 24794e; (b) N. M. Bortnick, U.S. Patent 2,984,666 (1961); *Chem. Abstr.*; **56**, 3483f; (c) N. M. Bortnick, U.S. Patent 2,993,049 (1961); *Chem. Abstr.*, **56**, 476b.
54. D. P. Clough and R. Hatton, *Br. J. Pharmacol.*, **73**, 595 (1981).
55. P. L. De Benneville and W. D. Niederhauser, U.S. Patent 3,267,082 (1966); *Chem. Abstr.*, **65**, 187020g; idem, Belgian Patent 632,820 (1963); *Chem. Abstr.*, **61**, 3271a.
56. P. M. Kochergin, Yu. N. Sheinker, A. A. Druzhinina, R. P. Palei, and L. M. Alekseeva, *Chem. Heterocycl. Compd.*, 771 (1971); *Khim. Geterotsikl. Soedin*, **1971**, 826; *Chem. Abstr.*, **76**, 25170n.
57. E. P. Papadopoulos, *J. Org. Chem.*, **31**, 327 (1966).
58. E. P. Papadopoulos, *J. Org. Chem.*, **31**, 3060 (1966).
59. L. Capuano and M. Welter, *Chem. Ber.*, **101**, 3671 (1968).
60. E. P. Papadopoulos, *J. Org. Chem.*, **38**, 667 (1973).
61. R. S. Budhram, B. C. Uff, R. A. Jones, and R. O. Jones, *Org. Magn. Resonance*, **13**, 89 (1980).
62. H. Behringer and R. Schunk, *Chem. Ber.*, **100**, 564 (1967).
63. H. A. F. Daboun, S. E. Abdou, M. M. Hussein, and M. H. Elnagdi, *Synthesis*, **1982**, 502.
64. W. Ried and W. von der Emden, *Justus Liebigs Ann. Chem.*, **661**, 76 (1963).
65. B. Stanovnik and M. Tisler, *Croat. Chem. Acta*, **35**, 167 (1963).
66. L. Fontanella, German Patent 2,354,086 (1974); *Chem. Abstr.*, **81**, 37545e.
67. (a) O. Wakabayashi, K. Matsutani, H. Ota, T. Naohara, and H. Watanabe, Japanese Patent 77, 83,686 (1977); *Chem. Abstr.*, **88**, 22905t; (b) Mitsubushi Chemical Industries Co. Ltd., British Amended Patent B 1,503,244 (1978); *Chem. Abstr.*, **93**, 46672u.
68. Y. Hisada, C. Takayama, Y. Kato, and H. Fujinami, Japanese Patent 78 07,697 (1978); *Chem. Abstr.*, **89**, 43410p.
69. T. Shigematsu, K. Yoshida, M. Nakazawa, H. Kasugai, and M. Tsuda, Jpn. Kokai. Tokkyo Koho 80, 40,653 (1980); *Chem. Abstr.*, **93**, 239444e.
70. S. Oshito, T. Nakura, T. Okamoto, and K. Okumura, Japanese Patent 71, 16,990 (1971); *Chem. Abstr.*, **75**, 49087w.
71. F. Cardineaux and M. Brenner, in *Report of Proceedings of European Rept. Symp. 11th*, 65–68 (1971); *Chem. Abstr.*, **84**, 31441h; idem, *Helv. Chim. Acta*, **56**, 339 (1973).
72. L. Fontanella, E. Occelli, and A. Perazzi, *Farmaco Ed. Sci.*, **28**, 463 (1973).
73. L. Fontanella and E. Occelli, *Farmaco Ed. Sci.*, **26**, 685 (1971).
74. S. Kiyooka, F. Goto, and K. Suzuki, *Chem. Lett.*, **1981**, 1429.
75. T. Shigematsu, K. Yoshida, M. Nakazawa, H. Kasugai, and M. Tsuda, Jpn. Kokai Tokkyo Koho, 80, 43,057 (1980); *Chem. Abstr.*, **93**, 220740b.
76. D. T. Elmore, *Peptides and Proteins*, Cambridge University Press, 1968, p. 29.
77. E. Arte, B. Tinant, J. P. Declercq, G. Germain, and M. Van Meerssche, *Bull. Soc. Chim. Belg.*, **89**, 379 (1980); *Chem. Abstr.*, **93**, 185641w.
78. S. Wolfe and W. S. Lee, *J. Chem. Soc., Chem. Commun.*, **1968**, 242.
79. T. Suzuki, T. Tomioka, and K. Tuzimura, *Can. J. Biochem.*, **55**, 521 (1977).
80. K. Sobczyk and I. Z. Siemion, *Pol. J. Chem.*, **54**, 1833 (1980); *Chem. Abstr.*, **95**, 43607g; see also I. G. Siemion, K. Sobczyk, and B. Picur, *Pol. J. Chem.*, **52**, 667 (1978); *Chem. Abstr.*, **89**, 110363r.
81. C. A. G. Haasnoot, F. A. A. M. De Deeuw, H. P. M. De Leeuw, and C. Altona, *Biopolymers*. **20**, 1211 (1981); *Chem. Abstr.*, **95**, 187638r.

82. M. J. O. Anteunis, R. Callers, V. Asher, and J. Sleeckx, *Bull. Soc. Chem. Belg.*, **87**, 41 (1978); *Chem. Abstr.*, **90**, 104334m.

83. I. Z. Siemion and M. Szkoda, *Bull. Acad. Pol. Sci. Ser. Sci. Chem.*, **26**, 851 (1978); *Chem. Abstr.*, **91**, 38801d; see also J. H. Poupaert, M. Claesen, J. Degelaen, P. Dumont, and S. Toppet, *Bull. Soc. Chim. Belg.*, **86**, 465 (1977); *Chem. Abstr.*, **87**, 167412u.

84. R. E. Hamilton, G. V. Patil, K. Jayasimhulu, and R. A. Day, *Org. Mass. Spectrom.*, **9**, 211 (1974).

85. J. Haensler, R. John, and V. Schmidt, *Chem. Ber.*, **111**, 361 (1978).

86. T. Mukaiyama, Y. Sakito, and M. Asami, *Chem. Lett.*, **1978**, 1253.

87. T. Mukaiyama, Y. Sakito, and M. Asami, *Chem. Lett.*, **1979**, 705.

88. Y. Sakito, S. Tanaka, M. Asami, and T. Mukaiyama, *Chem. Lett.*, **1980**, 1223.

89. Y. Sakito and T. Mukaiyama, *Chem. Lett.*, **1979**, 1027.

90. T. Mukaiyama, Y. Sakito, and M. Asami, European Patent Application 11,417 (1980); *Chem. Abstr.*, **94**, 47324q.

91. M. Asami and T. Mukaiyama, *Chem. Lett.*, **1979**, 569.

92. S. Oshiro, T. Nagura, Y. Sugihara, K. Okamoto, R. Ishida, and K. Shintomi, Japanese Patent 73 19,595 (1979); *Chem. Abstr.*, **78**, 147966p.

93. H. W. Heine, R. H. Weese, R. A. Cooper, and A. J. Durbetaki, *J. Org. Chem.*, **32**, 2708 (1967).

94. H. W. Heine, A. B. Smith, and J. D. Bower, *J. Org. Chem.*, **33**, 1097 (1968).

95. Thap DoMinh and A. M. Trozzolo, *J. Am. Chem. Soc.*, **92**, 6997 (1970).

96. A. Padwa and E. Glazer, *J. Org. Chem.*, **38**, 284 (1973); idem., *J. Am. Chem. Soc.*, **94**, 7788 (1972).

97. O. Tsuge, S. Kanemasa, and T. Hamamoto, *Chem. Lett.*, **1983**, 763.

98. H. Behringer and R. Schunck, *Chem. Ber.*, **100**, 578 (1967).

99. K. T. Potts, R. Ehlinger, and S. Kanemasa, *J. Org. Chem.*, **45**, 2474 (1980).

100. J. C. Sheehan, *Ann. NY Acad. Sci.*, **88**, 665 (1960).

101. R. F. C. Brown, V. M. Clark, and A. R. Todd, *Tetrahedron*, Suppl. No. 8 (1), 15 (1966).

102. T. Sato, *Bull. Chem. Soc. Japan*, **35**, 1531 (1962).

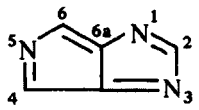
Chemistry of Heterocyclic Compounds, Volume 46
P. N. Preston

CHAPTER 2

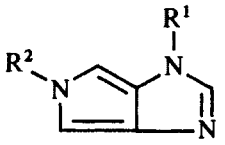
Condensed Imidazoles of Type 5-5 with One Additional Heteroatom

2.1. RING SYSTEM C_3N_2–C_4N: PYRROLO[3,4-*d*]IMIDAZOLE

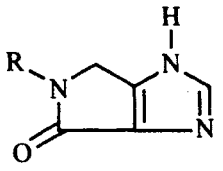
Fusion of a pyrrole ring across the C-4–C-5 bond of an imidazole ring can give rise to either the title pyrrolo[3,4-*d*]imidazole (**2.1**) or the pyrrolo[2,3-*d*]imidazole ring systems (see Section 2.2). Examples of the former in the partially reduced 1,5-dihydro-(**2.2**) and 5,6-dihydro forms (**2.3**) and in the fully reduced octahydro group (**2.4**) are described in this section.



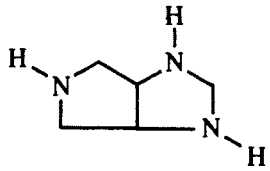
(2.1)



(2.2)
R^1, R^2 = alkyl



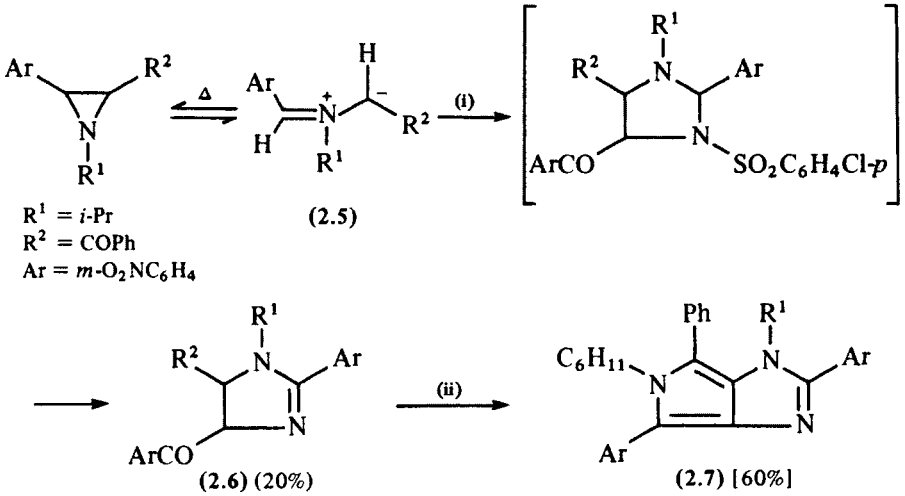
(2.3)



(2.4)

2.1.1. 1,5-Dihydropyrrolo[3,4-*d*]imidazoles

The pyrrole ring of the 1,5-dihydropyrrolo[3,4-*d*]imidazole derivative (**2.7**) has been constructed by use of a Paal–Knorr condensation of cyclohexylamine with the tetrasubstituted imidazoline (**2.6**).[1] The latter is available in modest yield by trapping of an intermediate aroylazomethine ylide (**2.5**) in the manner shown in Scheme 2.1.[1]

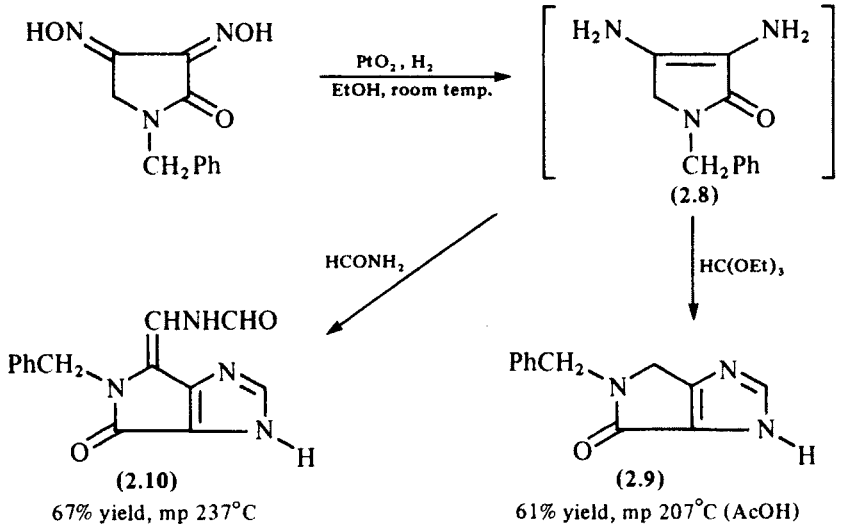


(i) p-$ClC_6H_4SO_2N{=}CHCOAr$; (ii) $C_6H_{11}NH_2$, MeOH, heat

Scheme 2.1

2.1.2. 5,6-Dihydropyrrolo[3,4-*d*]imidazoles

Conventional one-carbon condensations with a 1,2-diamine derivative (**2.8**) have been used for the synthesis of two isolated examples (**2.9, 2.10**) of compounds in the 5,6-dihydropyrrolo[3,4-*d*]imidazol-4(3*H*)-one category (see Scheme 2.2).[2] The initial formamide condensation product evidently undergoes a subsequent electrophilic formylation at the 6-position, and the ultimate product is a 6-



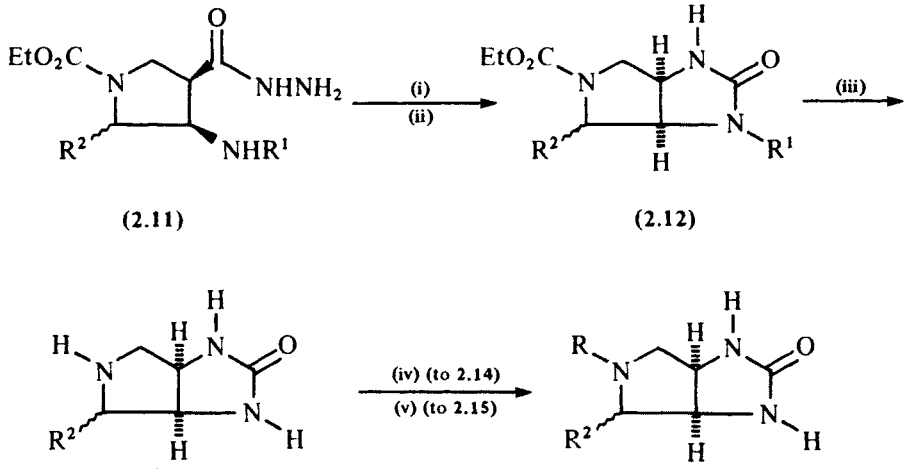
Scheme 2.2

formamidomethylene derivative (**2.10**). Compounds **2.9** and **2.10** are characterized by the following ir bands: **2.9**–3360 (NH), 2920 (CH_2), 1690 (CO), and 1640 cm^{-1}; **2.10**–3440 (NH), 3200 (enolic OH), 3060 (CH), 2935 (CH_2), 2882 (CHO), and 1665 cm^{-1} (CO).

2.1.3. Octahydropyrrolo[3,4-*d*]imidazoles

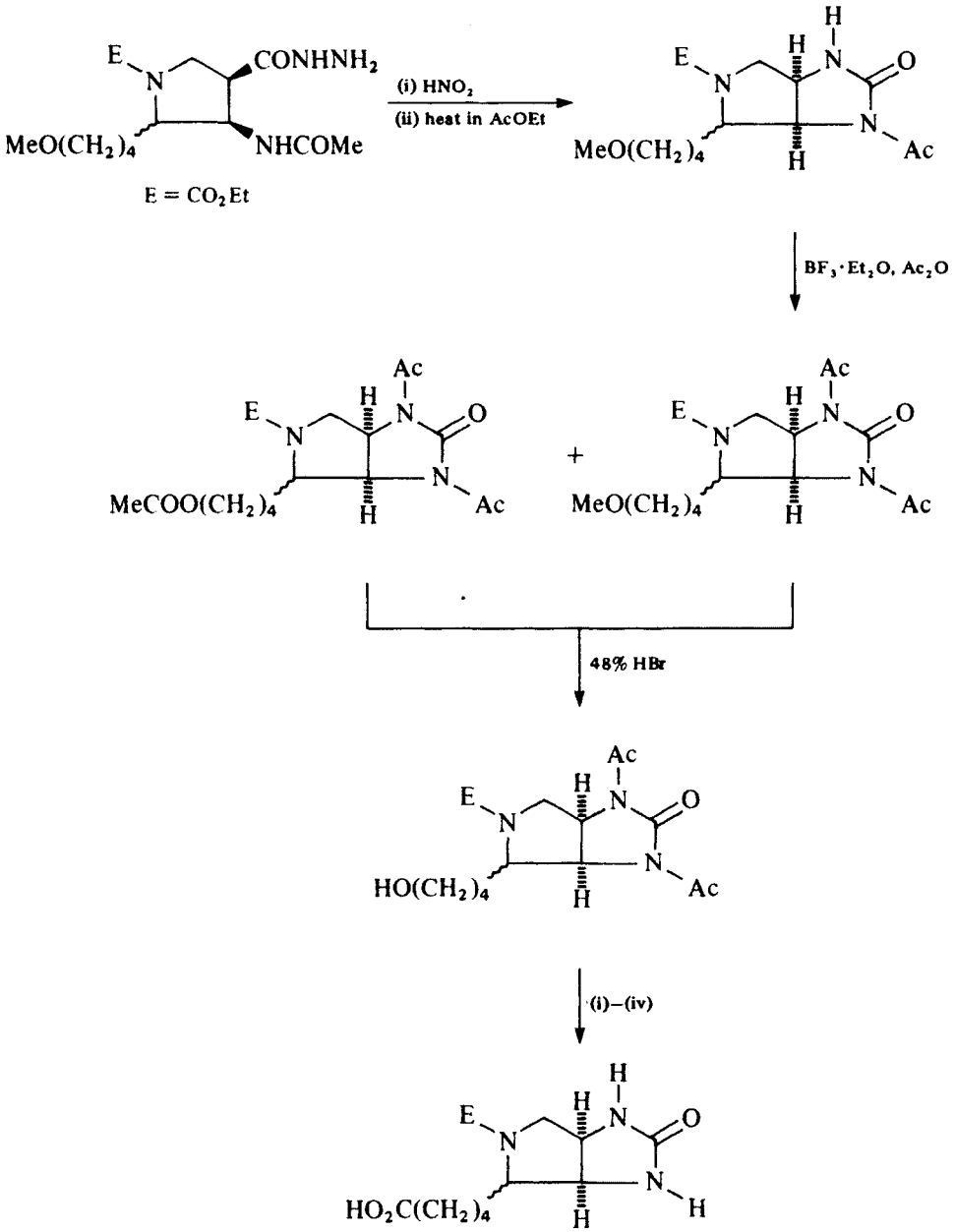
2.1.3.1. Synthesis from Pyrrolidines

Interest in compounds in this group has resulted from their close relationship to analogous thieno[3,4-*d*]imidazoles. (See the extensive chemistry of biotin described in Section 2.15.5 and also cyclopentimidazole isosteres discussed in Section 1.1.2.) The synthetic approach from pyrrolidines involves construction of an imidazolone ring (cf. **2.12**) through a Curtius rearrangement in an intermediate acyl azide (see Scheme 2.3); *cis*-substituted pyrrolidines (cf. **2.11**) are available in a seven-step synthesis from glycine. A variety of compounds has been prepared and characterized by this route (see Table 2.1), and the method has been elaborated to provide biotin analogs with carboxybutyl and carboxyethyl substitutents at the 4-position (see **2.16**[5] and **2.17**[6] in Schemes 2.4 and 2.5, respectively). Synthesis of the unsubstituted octahydropyrrolo[3,4-*d*]imidazol-2-one (**2.13**; $R^2 = H$) has also been accomplished by treating *cis*-3,4-diaminopyrrolidine with phosgene in benzene under alkaline conditions.[3]



(i) HNO_2; (ii) EtOAc, heat; (iii) $Ba(OH)_2$, MeOH, reflux; (iv) $Br(CH_2)_xCN$; (v) HCl

Scheme 2.3



(2.16)

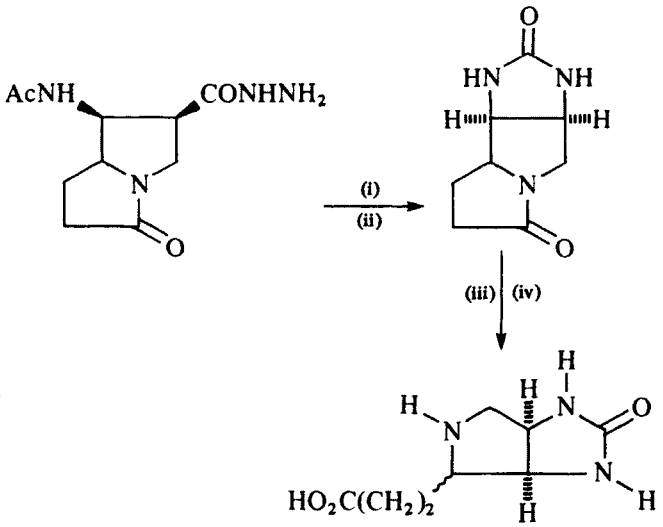
(i) $MeSO_2Cl$, pyridine; (ii) NaCN; (iii) HCl, EtOH; (iv) NaOH

Scheme 2.4

TABLE 2.1. SYNTHESIS OF OCTAHYDRO DERIVATIVES OF PYRROLO[3,4-*d*]-IMIDAZOLE USING THE METHODS OF SCHEME 2.3[3,4]

Structure	Substituent(s)	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reference
2.12	$R^1 = R^2 = H$		221–222	3
2.12	$R^1 = CONH_2$; $R^2 = H$		195–197	3
2.12	$R^1 = H$; $R^2 = Me$	80	145–146 (EtOAc)	4
2.12	$R^1 = H$; $R^2 = (CH_2)_4CO_2H$		192–195	5[a]
2.13	$R^2 = H$	69,[b] 81[c]	213–215; HCl 275–290 (dec.)	3
2.13	$R^2 = Me$	16	209–210	4
2.14	$R^2 = H$; x = 3	93	127–130	4
2.14	$R^2 = H$; x = 4	77	129–130	4
2.14	$R^2 = Me$; x = 3	75	174–175	4
2.14	$R^2 = Me$; x = 4	75	201–202	4
2.15	$R^2 = H$; x = 3	71	247–255 (dec.)	4
2.15	$R^2 = H$; x = 4	79	241–243 (dec.)	4
2.15	$R^2 = Me$; x = 3	64	253–257 (dec.)	4
2.15	$R^2 = Me$; x = 4	68	223–225 (dec.)	4

[a] A more elaborate synthesis than is depicted in Scheme 2.3 is necessary for this compound (see Scheme 2.4).
[b] From **2.12** ($R^1 = R^2 = H$).
[c] From **2.12** ($R^1 = CONH_2$; $R^2 = H$).



(2.17)

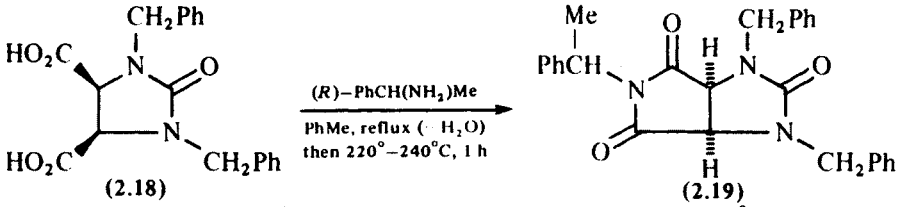
(i) HNO_2; (ii) EtOAc, heat;
(iii) 10% NaOH, 120°C; (iv) HCl, EtOH

mp 178–180°C
(resolidifies and
remelts at 253–255°C)

Scheme 2.5

2.1.3.2. *Synthesis from Imidazolines*

The *cis*-imidazolidine dicarboxylic acid derivative (**2.18**) has been converted into an optically active 2,4,6-trione derivative containing a 5-(*R*)1-phenethyl substituent (**2.19**).[7] Compounds of the latter type are valuable intermediates for the chiral synthesis of biotin[7] (see Section 2.15.5).



(**2.18**)

(**2.19**)

mp 157–159°C

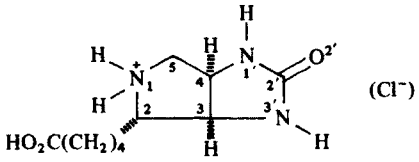
$[\alpha]_D^{20} = +48.0°$ (c, 2, $CHCl_3$)

ir = 1780, 1705, 1680 cm^{-1}

2.1.3.3. *Molecular Structure*

The molecular structure of one derivative (**2.20**) in the fully saturated pyrrolo-[3,4-*d*]imidazole category has been elucidated X-ray crystallographically (see Table 2.2 for bond distances).[8] It is notable that the bond distances and angles relate

TABLE 2.2. BOND DISTANCES (Å) IN THE OCTAHYDROPYRROLO[3,4-*d*]IMIDAZOLE DERIVATIVE (**2.20**) FROM X-RAY CRYSTALLOGRAPHIC ANALYSIS[8]



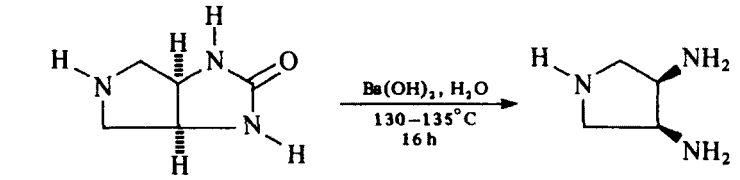
(**2.20**)

Bond in Structure **2.20**	Bond Separation (Å)
C-2′–O-2′	1.243(4)
C-2′–N-1′	1.344(4)
C-2′–N-3′	1.349(4)
C-1′–C-4	1.456(4)
N-3′–C-3	1.452(4)
C-3–C-4	1.555(4)
C-4–C-5	1.516(5)
C-3–C-2	1.525(4)
C-5–N-1	1.505(4)
C-2–N-1	1.503(4)
N-1′–H-1′	0.85
N-3′–H-3′	0.95
N-1–H-1-*a*	1.03
N-1–H-1-*b*	0.93

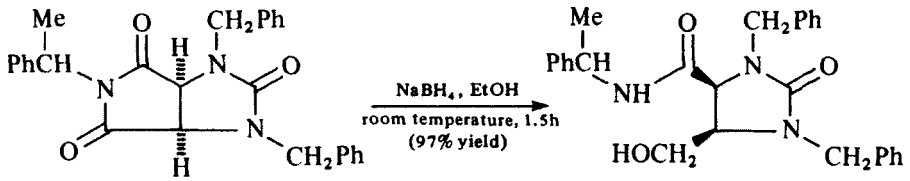
closely to those observed in biotin (see Section 2.15.5). For example, the C=O distance [1.243(4) Å] in the imidazolone ring is significantly longer than those found in barbiturate structures and compares with that found in urea. The C–N distances in this ring [1.344(4) and 1.349(4) Å] are shorter than those (1.370 Å) in barbiturates but comparable to the value (1.326 Å) in urea. It is concluded[8] that canonical forms of **2.20** bearing a formal negative charge on oxygen make an important contribution to the resonance hybrid.

2.1.3.4. Reactions

Ring scission of the octahydropyrrolo[3,4-*d*]imidazole ring system has been achieved in the imidazolone ring of **2.21**[3] and in the pyrrole ring of **2.23**.[7] It may be noted that *cis*-3,4-diaminopyrrolidine (**2.22**) can be recyclized to **2.21** by treating it with phosgene.[3] Purification of **2.24** from its diastereomer provides an optically pure compound of value in the chiral synthesis of biotin[7] (see Section 2.15.5).



(2.21) (2.22)

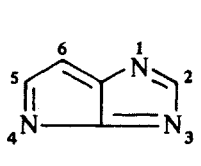


(2.23) (2.24)

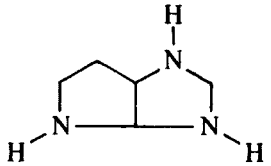
$[\alpha]_D^{20} = +48°$ (c, 2, $CHCl_3$) (+ diastereomer)

2.2. RING SYSTEM C_3N_2–C_4N: PYRROLO[2,3-*d*]IMIDAZOLE

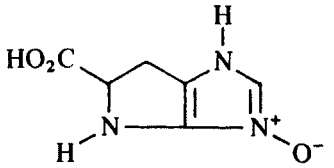
Compounds in the pyrrolo[2,3-*d*]imidazole ring system (**2.25**) are few in number compared with their pyrrolo[3,4-*d*]counterparts (see Section 2.1). They belong entirely to the fully saturated octahydro group (**2.26**), although there is an isolated report describing a poorly characterized compound purported[9] to be either the *N*-oxide (**2.27**) or an isomer thereof (however, see note 4 in ref. 12).



(2.25)

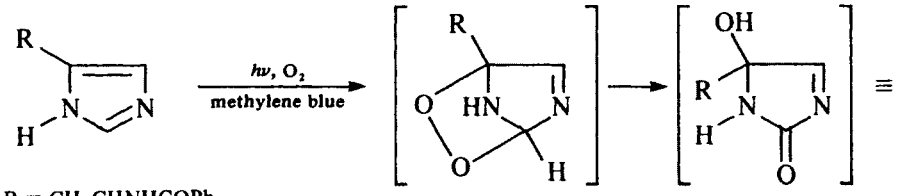


(2.26)



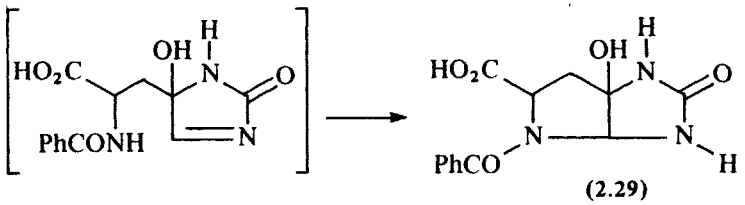
(2.27)

The first example of a derivative of the octahydropyrrolo[2,3-*d*]imidazole category (**2.29**) was formed[10] in very low yield (3%) in a complex mixture during the sensitized photooxidation of *N*-benzoylhistidine (**2.28**). By analogy with related photooxidation processes of imidazoles,[11] the mechanism illustrated in Scheme 2.6 has been proposed for this process.[10]



R = $CH_2CHNHCOPh$
CO_2H

(2.28)

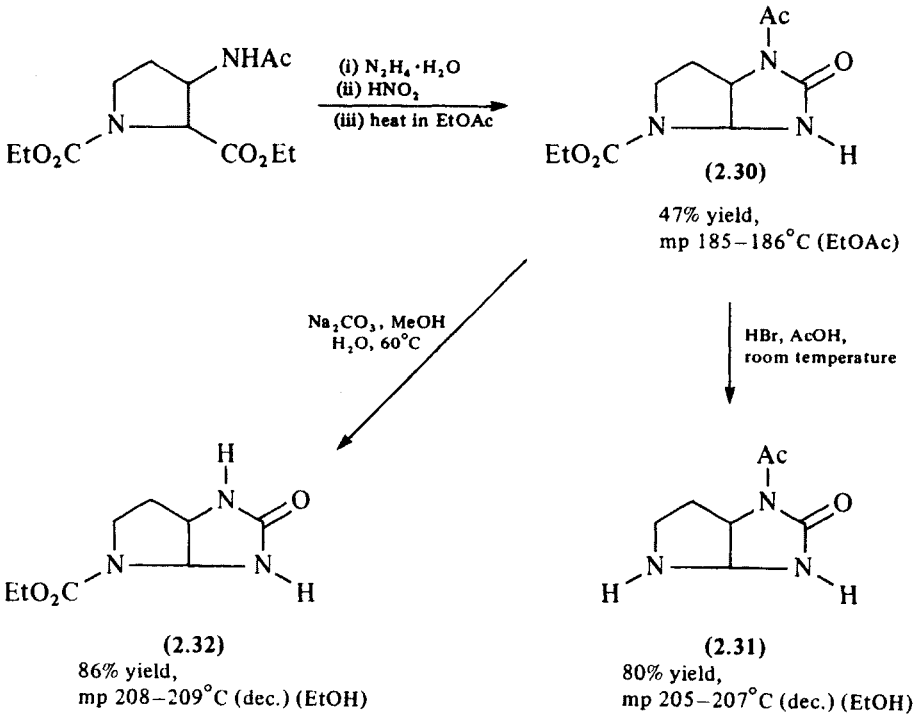


(2.29)

mp 170°C (dec.)
uv $\lambda_{max}^{H_2O}$ 228 nm (ϵ, 5000)
ir 3380 cm^{-1} (OH), 1710 (CO_2H), 1690 (imide CO), 1620 (CON)

Scheme 2.6

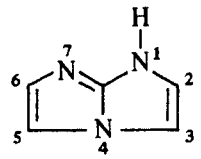
A general synthesis of octahydropyrrolo[2,3-*d*]imidazoles has been developed from pyrrolidines using the methodology developed for analogus pyrrolo[3,4-*d*] imidazoles (cf. Section 2.1.3, and see Scheme 2.7).[12] In this approach the imidazolone ring of the bicyclic products (**2.30**–**2.32**) is constructed through Curtius rearrangement of an intermediate acyl hydrazide. Compounds **2.30**–**2.32** are characterized[12] by the following IR spectral data: **2.30**–3448 (NH), 1795 (NCON), and 1686 cm^{-1} (NCO_2Et); (**2.31**)–3322 (NH), 1739, 1680 cm^{-1} (NCON); **2.32**–3300, 3205 (NH), 1698 (NCON), and 1666 cm^{-1} (NCO_2Et).



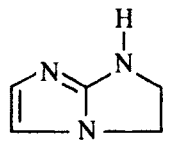
Scheme 2.7

2.3. RING SYSTEM C_3N_2–C_3N_2: 1*H*-IMIDAZO[1,2-*a*]IMIDAZOLE

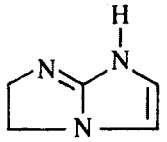
Compounds in the 1*H*-imidazo[1,2-*a*]imidazole group are known in the fully unsaturated ring system (**2.34**) as well as in reduced forms including 2,3-dihydro- (**2.35**), 5,6-dihydro (**2.36**), and 2,3,5,6-tetrahydro (**2.37**) derivatives.



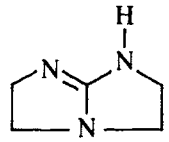
(2.34)



(2.35)



(2.36)

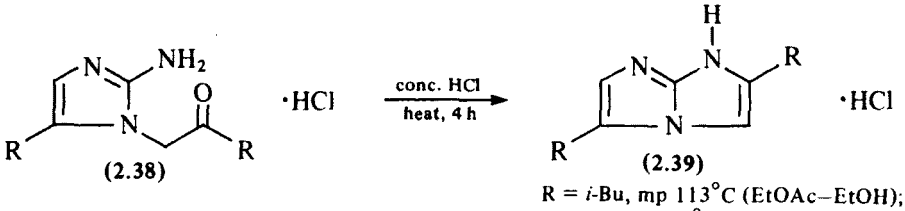


(2.37)

2.3.1. 1*H*-Imidazo[1,2-*a*]imidazoles

2.3.1.1. Synthesis

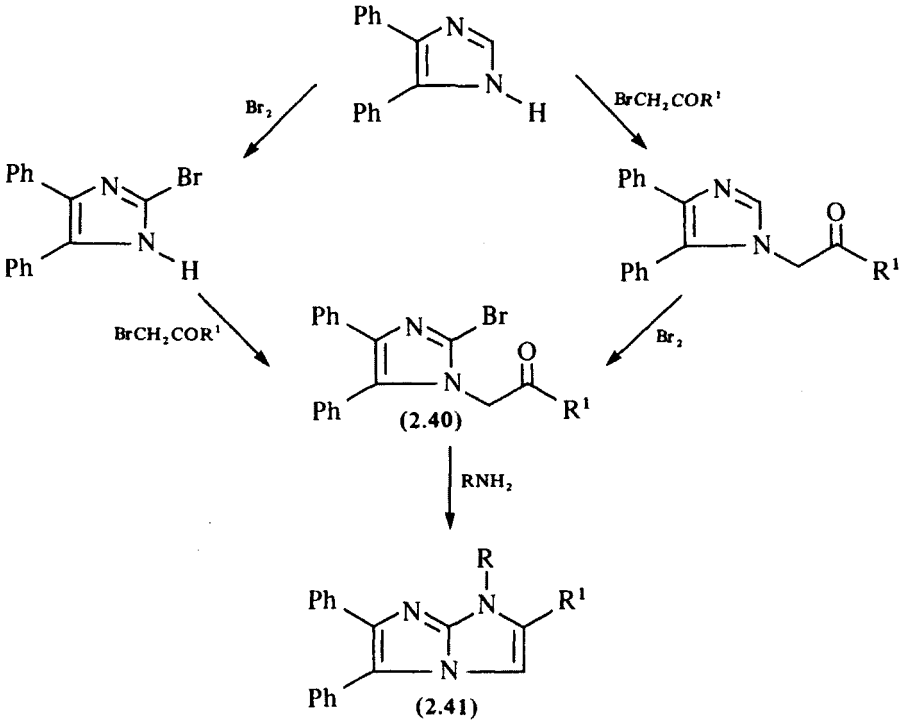
Fully unsaturated 1*H*-imidazo[1,2-*a*]imidazoles are invariably synthesized by ring closure reactions of appropriately functionalized 2-amino- or 2-iminoimidazoles following a procedure devised by Lawson[13] (see **2.38** → **2.39**). It has been subsequently shown[14] that requisite amino derivatives (cf. **2.38**) need not be isolated and



(2.38) **(2.39)**

R = *i*-Bu, mp 113°C (EtOAc–EtOH); picrate, mp 128°C (EtOH)

can be generated ***in situ*** by the reaction of amines with readily available 1-acetonyl- or 1-phenacyl-2-bromoimidazoles (**2.40**) (see Scheme 2.8 and Table 2.3). It may be noted that nucleophilic substitution of bromide by the amine does not occur when the components are heated under reflux in alcohols or even dimethylformamide,



(2.40) **(2.41)**

Scheme 2.8

TABLE 2.3. SYNTHESIS[a] OF 1*H*-IMIDAZO[1,2-*a*]IMIDAZOLES (**2.41**) BY REACTION OF 1-ACETONYL- AND 1-PHENACYL-2-BROMOIMIDAZOLES (**2.40**) WITH AMINES[14]

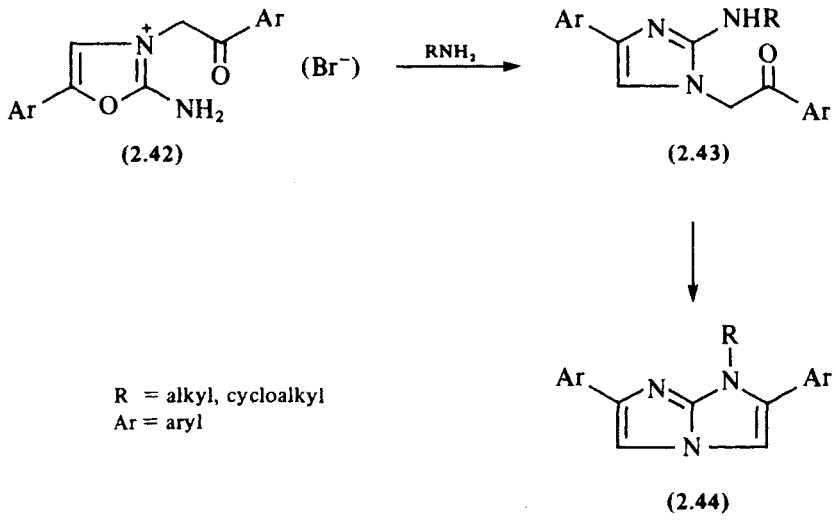
Compound **2.41**			
R^1	R	mp (°C)	Yield (%)
i-C_4H_9	CH_3	126–127	61
C_6H_{11}	CH_3	177–178	56
$C_6H_5CH_2$	CH_3	150–151	83
C_6H_5	CH_3	187–188	57
m-$CH_3C_6H_4$	CH_3	167–168	55
p-$CH_3C_6H_4$	CH_3	203–204	60
p-$CH_3OC_6H_4$	CH_3	183–184	66
p-$C_2H_5OC_6H_4$	CH_3	171–172	56
m-ClC_6H_4	CH_3	183–184	75
H	C_6H_5	239–240	90
CH_3	C_6H_5	157–158	92
$CH{=}CH_2$	C_6H_5	200–202	53
C_2H_5	C_6H_5	90–91	76
C_3H_7	C_6H_5	151–152	81
C_4H_9	C_6H_5	157–158	82
i-C_4H_9	C_6H_5	140–141	92
n-C_6H_{13}	C_6H_5	127–129	68
C_6H_{11}	C_6H_5	212–213	77
$C_6H_5CH_2$	C_6H_5	212–213	56
CH_2CH_2OH	C_6H_5	195–196	53
$CH(CH_3)(CH_2)_3OH$	C_6H_5	95–97	57
$C_2H_4N(C_2H_5)_2$	C_6H_5	40–42	69
C_6H_5	C_6H_5	252–253[b]	95
p-$CH_3C_6H_4$	C_6H_5	225–227	70
m-$CH_3C_6H_4$	C_6H_5	215–216	82
p-HOC_6H_4	C_6H_5	295–297	83
p-$CH_3OC_6H_4$	C_6H_5	172–173	88
p-$C_2H_5OC_6H_4$	C_6H_5	249–250	89
CH_3	*p*-$CH_3C_6H_4$	179–180	92
$CH{=}CH_2$	*p*-$CH_3C_6H_4$	69–70	76
C_2H_5	*p*-$CH_3C_6H_4$	220–221	70
C_3H_7	*p*-$CH_3C_6H_4$	161–162	61
C_4H_9	*p*-$CH_3C_6H_4$	130–131	84
i-C_4H_9	*p*-$CH_3C_6H_4$	169–170	49
n-C_6H_{13}	*p*-$CH_3C_6H_4$	111–112	69
$C_6H_5CH_2$	*p*-$CH_3C_6H_4$	147–149	78
$C_2H_4N(C_2H_5)_2$	*p*-$CH_3C_6H_4$	110–111	76
C_6H_5	*p*-$CH_3C_6H_4$	230–231	47
m-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	189–190	73
p-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	219–220	55
p-HOC_6H_4	*p*-$CH_3C_6H_4$	295–297	68
p-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	224–225	70
p-$C_2H_5OC_6H_4$	*p*-$CH_3C_6H_4$	213–214	64
$CH{=}CH_2$	*p*-$CH_3OC_6H_4$	141–142	66
C_4H_9	*p*-$CH_3OC_6H_4$	143–144	67
i-C_4H_9	*p*-$CH_3OC_6H_4$	181–182	57
n-C_6H_{13}	*p*-$CH_3OC_6H_4$	132–133	67

Table 2.3. (*continued*)

Compound 2.41			
R^1	R	mp (°C)	Yield (%)
$C_6H_5CH_2$	*p*-$CH_3OC_6H_4$	142–143	79
$C_2H_4N(C_2H_5)_2$	*p*-$CH_3OC_6H_4$	134–135	95
C_6H_5	*p*-$CH_3OC_6H_4$	222–223	81
m-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	196–197	66
p-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	250–251	88
p-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	231–232	64
p-$EtOC_6H_4$	*p*-$MeOC_6H_4$	219–220	83
i-C_4H_9	*p*-BrC_6H_4	227–229	72
n-C_6H_{13}	*p*-BrC_6H_4	139–140	59
C_6H_5	*p*-BrC_6H_4	224–225	49
p-$CH_3C_6H_4$	*p*-BrC_6H_4	255–256	60
p-$CH_3OC_6H_4$	*p*-BrC_6H_4	247–249	54
p-$C_2H_5OC_6H_4$	*p*-BrC_6H_4	243–245	56

[a] Reaction conditions: **2.40**, RNH_2, MeOH, or EtOH, 170–180°C, 8–10 h (autoclave).
[b] See also ref. 15.

and rather forcing conditions are required (e.g., heating at 165–190°C in a sealed tube or an autoclave). Synthetic intermediates (**2.43**) related to (**2.38**) and to those in the transformation (**2.40** → **2.41**) have been prepared from 2-aminooxazolium salts in the manner depicted in (**2.42** → **2.43**), and the latter (**2.43**) have been cyclized to give a series (**2.44**) of 1,2,6-trisubstituted 1*H*-imidazo[1,2-*a*]imidazoles.[16]



(**2.42**) (**2.43**) (**2.44**)

TABLE 2.4. SYNTHESIS OF 1*H*-IMIDAZO[1,2-*a*]IMIDAZOLES (**2.47**) BY CYCLIZATION OF 3-ACYLMETHYL- AND 3-AROYLMETHYL-2-IMINO-1-METHYL-IMIDAZOLES (**2.46**)

Compound **2.47**		Reaction		
R^1	R^2	Conditions[a]	mp (°C)	Reference
Ph	H	A	207–208 (dec.)[b]	17
p-BrC_6H_4	H	A	224–225 (dec.)	17
Ph	Me	A	162–163[c]	17
Me	Ph	A	209–210 (dec.)[c]	17
H	Ph	B	122–124	18
H	2-Thienyl	B	126.5–128.5	18
H	Me	C	218–221	18

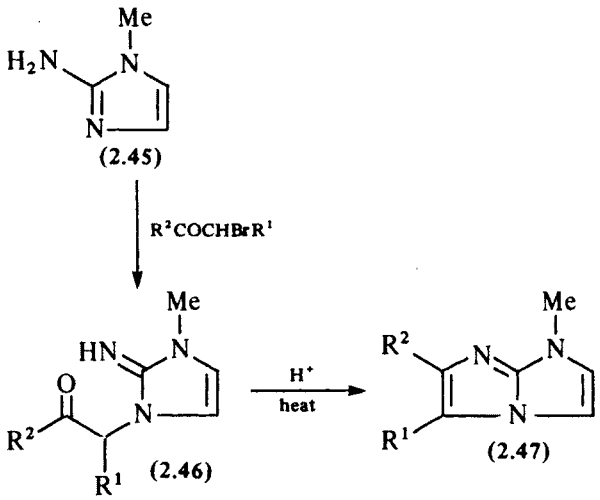
[a] Reaction conditions on (**2.46**): (A) heat in mineral acid; (B) 5% HCl, reflux; (C) polyphosphoric acid, room temperature.
[b] Melting point of HBr salt quoted.
[c] Melting point of picrate quoted.

In an alternative approach to 1*H*-imidazo[1,2-*a*]imidazoles, readily available 3-acylmethyl- or 3-aroylmethyl-2-imino-1-methylimidazoles can be cyclized by heating them in mineral acids (see **2.45** → **2.46** → **2.47** and Table 2.4).[17,18] Cyclizations of this type proceed quite rapidly in warm mineral acid or in acetic or formic acids or by using dehydrating agents such as concentrated sulfuric acid or phosphorus oxychloride in the cold.[19] An even simpler direct procedure leading to a variety of derivatives (cf. **2.47** and Table 2.5) involves heating 2-amino-1-methylimidazole (**2.45**) with the α-bromoketone under reflux in ethanol.[19]

TABLE 2.5. SYNTHESIS[a] OF HYDROBROMIDES OF 1*H*-IMIDAZO[1,2-*a*]IMIDAZOLES (**2.47**) BY REACTION OF 2-AMINO-1-METHYLIMIDAZOLE (**2.45**) WITH α-BROMO KETONES[19]

Hydrobromide of compound **2.47**			
R^1	R^2	mp (°C)	Yield (%)
H	C_6H_5	207–208	70
H	*p*-$CH_3C_6H_4$	239–240	71
H	*p*-$CH_3OC_6H_4$	215–216	84
H	*p*-ClC_6H_4	228–229	69
H	*p*-BrC_6H_4	224–225	80
H	C_4H_3S[b]	233–234	44
C_6H_5	CH_3	284–285	58
CH_3	C_6H_5	255–257	70

[a] Reaction conditions: **2.45** (prepared from the hydrochloride), NaOEt, EtOH, and α-bromoketone; reflux for 3–4 h.
[b] C_4H_3S refers to the 2-thienyl substituent.



2.3.1.2. Reactions

2.3.1.2.1. ELECTROPHILIC AROMATIC SUBSTITUTION

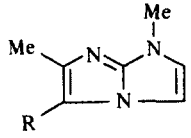
The results of Hückel molecular orbital calculations show, for nitration in acidic media at least, that electrophilic aromatic substitution should occur initially at the 5-position in 1,6-dimethyl-1*H*-imidazo[1,2-*a*]imidazole, and this is borne out in practice;[20] related processes of bromination and formylation also give products of substitution at the 5-position and the above compounds have been used to prepare other 5-substituted 1,6-dimethyl-1*H*-imidazo[1,2-*a*]imidazoles (viz. 5-Br → 5-$C_5H_{10}N$; 5-NO_2 → 5NHAc + 5NAc_2) (see structure **2.48** and Table 2.6). It may be noted that care must be exercised in effecting nitration of the 1,6-dimethyl derivative (**2.48**, R = H) because of its sensitivity to nitric acid; the best yield (66%) of the mono nitro compound (**2.48**, R = NO_2) is obtained by carefully treating cold solutions of **2.48** (R = H) with one molar equivalent of ethyl nitrate. When two equivalents of ethyl nitrate are used, a dinitro compound [mp 190–192°C (from H_2O)] is formed, and whereas the position of one nitro group is almost certainly 5-, the position of the second (at 2- or 3-) is unknown.[20]

Electrophilic substitution in 1- and 1,6-disubstituted 1*H*-imidazo[1,2-*a*]-imidazoles can be achieved in reactions with trichloroacetaldehyde, and the process is claimed as one step in a route to a series of 5-formyl derivatives in this ring system.[21]

2.3.1.2.2. REDUCTION

The stability of the 1*H*-imidazo[1,2-*a*]imidazole ring system to Raney nickel-promoted reductive acetylation (cf. **2.48**; 5-NO_2 → 5-NHAc + 5-NAc_2)[20] and to zinc in acetic acid (see **2.49** → **2.50**)[22] is apparent. There is no information on the attempted synthesis of reduced derivatives in the ring system (cf. **2.35**–**2.37**) by catalytic hydrogenation.

TABLE 2.6. ELECTROPHILIC SUBSTITUTION PRODUCTS (2.48) AND RELATED COMPOUNDS DERIVED FROM 1,6-DIMETHYL-1*H*-IMIDAZO[1,2-*a*]IMIDAZOLE (2.48, R = H)[20]



(2.48)

R in Starting Material (2.48)	R in Product (2.48)	Reaction Conditions	mp (°C) (Solvent for Recrystallization)	^{1}H nmr Spectra[a]		
				1-Me	6-Me	2- and/or 3-H
H	Br	Br_2, $CHCl_3$, 5°C	132–133 ($MeNO_2$)	3.89	2.35	7.74 (s)
H	CHO	DMF, $POCl_3$, 1 h, 25°C	130–135 (petrol)[b]	3.77	2.58	7.55 (d), 6.85 (d) (J = 2 Hz)
H	NO_2[c]	1 equiv. $EtONO_2$, conc. H_2SO_4, − 20°C	181–184 (C_6H_6)	3.73	2.60	7.65 (d), 7.42 (d) (J = 2 Hz)
Br	$C_5H_{10}N$[d]	Piperidine, reflux, 4 h	–[e]	3.40	2.28	6.83 (d), 6.52 (d) (J = 2 Hz)
NO_2	NHAc	Raney Ni, Ac_2O	133–137 (EtOAc)[e]	3.54	2.18	6.69 (d), 6.55 (d) (J = 2 Hz)
NO_2	NAc_2	Raney Ni, Ac_2O	124–127	3.67	2.18	6.73 (s)

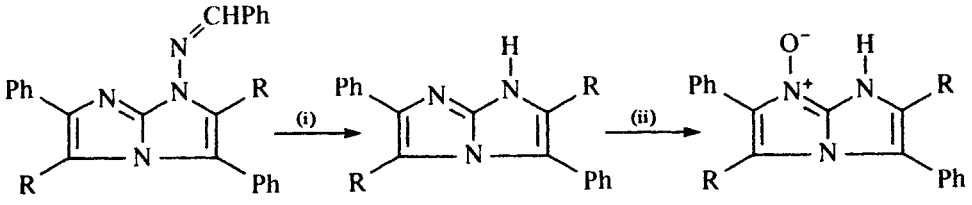
[a] Figures quoted are in ppm. Nuclear magnetic resonance solvents (R in product **2.48** and solvent quoted): Br, DMSO-d_6; CHO, $CDCl_3$; NO_2, DMSO-d_6; $C_5H_{10}N$, $CDCl_3$; NHAc, $CDCl_3$; NAc_2, $CDCl_3$.

[b] Melting point of oxime 280°C (dec.).

[c] See text.

[d] $C_5H_{10}N$ = 1-piperidinyl.

[e] Not obtained analytically pure but characterized spectroscopically.



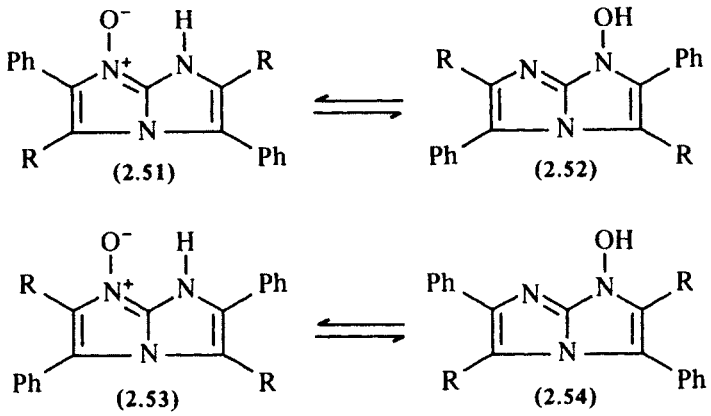
(2.49) (2.50) (2.51)

R	mp (°C)	yield (%)	R	mp (°C)	yield (%)
Me	237–238	50	Me	187.5–188.5	84
Pr	163.5–164.5	48	Pr	146–147	87

(i) Zn, AcOH, 75°C, 0.5 h; (ii) air, C_6H_6, reflux.

2.3.1.2.3. OXIDATION

Purification of tetrasubstituted derivatives (**2.50**) obtained by reduction of 1-benzylideneamino compounds (**2.49**) in the 1*H*-imidazo[1,2-*a*]imidazole group is hampered by air oxidation of the products. The contaminants are *N*-oxides (**2.51**), and the latter can be formed in good yield by heating **2.50** (R = Me,Pr) in air in various solvents (e.g., ethanol, benzene) or by irradiation with uv light.[22] Structural elucidation of the *N*-oxides (**2.51**) is problematical because of the tautomeric nature (1*H* ⇌ 7*H*) of the imidazo[1,2-*a*]imidazole ring system and because of the possibility of *N*-oxide ⇌ *N*-hydroxy tautomerism (see Scheme 2.9). Infrared spectral data (NH str at 3470 cm^{-1} and $\overset{+}{N}$–$\overset{-}{O}$ str at 1135 cm^{-1}) indicate an *N*-oxide structure (**2.51** or **2.53**), and corroborative evidence in this regard has been adduced from X-ray electron spectroscopy.[22] A small low-field shift of the *ortho* protons of one phenyl ring compared to that in **2.50**, and ascribed to an anisotropic influence of the *N*-oxide function, has been used to support the formulation (**2.51**) for these unusual compounds.



Scheme 2.9

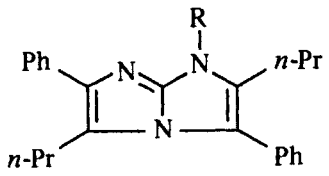
TABLE 2.7. SYNTHESIS OF 1-BENZYLIDENEAMINO-1*H*-IMIDAZO[1,2-*a*]IMIDAZOLES AND RELATED COMPOUNDS[23]

Compound **2.55**, R	Method of Preparation	mp (°C) (Solvent for Recrystallization)	Yield (%)	uv spectrum (λ_{max}, EtOH, log ϵ)
N=CHPh, 2-H for 2-*n*-Pr	–[a]	–[b]	20	245 (4.58), 290 (4.63), 345 (4.56)
N=CHPh	–[a]	–[b]	30	245 (3.88), 285 (3.65), 345 (3.89)
NH_2	**2.55a**, EtOH, HCl, reflux	218.5–219.5 (EtOH)	95	290 (4.13)
H	**2.55b**, $NaNO_2$, AcOH, aq. HCl	143–144 (C_6H_6)	45	260 (4.00), 390 (3.84)

[a]Synthesized from the appropriate 2-amino-1-benzylideneaminoimidazole derivative with an α-bromoketone (see Section 2.3.1.1).
[b]Melting point not quoted.

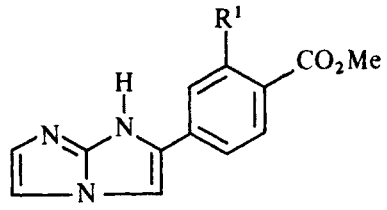
2.3.1.2.4. MISCELLANEOUS REACTIONS

Conversion of the 1-benzylideneamino derivative (**2.55a**) into the 1-unsubstituted compound has been achieved by the stepwise procedure **2.55a** → **2.55b** → **2.55c** (see also Table 2.7).[23]



(**2.55**)

a, R = N=CHPh
b, R = NH_2
c, R = H



(**2.56**)

R^1 = H, Cl

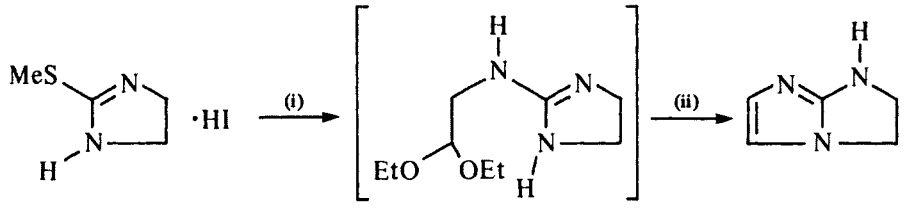
2.3.1.3. Commercial Applications

Analgesic, antipyretic, and antiinflammatory activity is claimed for 2-aryl-1*H*-imidazo[1,2-*a*]imidazole derivatives of type **2.56**.[24]

2.3.2. 2,3-Dihydro-1*H*-imidazo[1,2-*a*]imidazoles

2.3.2.1. Synthesis

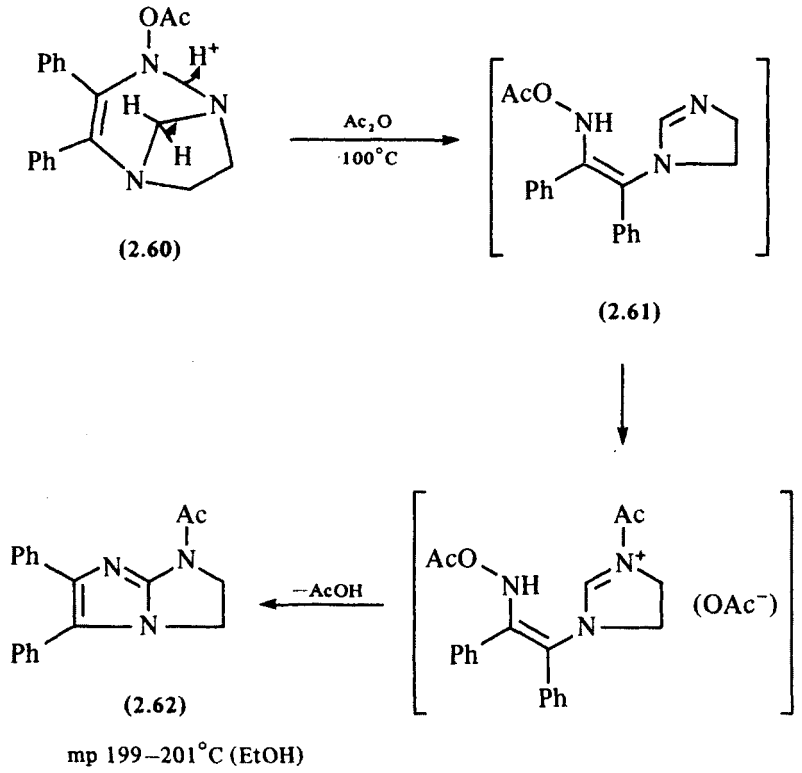
The parent compound of the series, 2,3-dihydro-1*H*-imidazo[1,2-*a*]imidazole (**2.59**), can be synthesized in high yield from 2-methylmercapto-4,5-dihydroimidazole in the manner depicted in **2.57** → **2.58** → **2.59**;[25] the dihydro compound (**2.59**) is characterized by the following spectral data: uv λ_{max} (EtOH) = 215 nm (log ϵ, 3.88); ir $NH_{stretch}$ 3205 cm^{-1}; nmr (δ, DMSO-d_6) 3.86 (s, 4H, H-2 and H-3),



(**2.57**) (**2.58**) (**2.59**)

80% yield,
mp 122–125°C

(i) $H_2NCH_2CH(OEt)_2$, *i*-PrOH, reflux, 13 h;
(ii) concentrated HCl, 100°C, 1 h



(2.60)

(2.61)

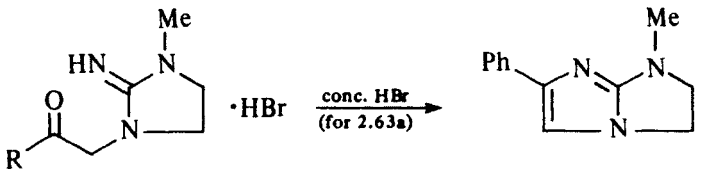
(2.62)

mp 199–201°C (EtOH)

Scheme 2.10

5.40 (s, 1H, NH), and 6.55 (s, 2H, H-5 and H-6). An intermediate imidazoline (**2.61**) is probably also involved in the somewhat esoteric transformation of the 1,2,5-triazabicyclo[3.2.1]oct-3-ene derivative (**2.60**) into 1-acetyl-2,3-dihydro-5,6-diphenyl-1*H*-imidazo[1,2-*a*]imidazole (**2.62**) (see Scheme 2.10).[26]

In an alternative approach from reduced imidazoles, 2-imino-3-methyl-1-phenacylimidazolidine hydrobromide (**2.63a**) can be cyclized under acidic conditions into 2,3-dihydro-1-methyl-6-phenyl-1*H*-imidazo[1,2-*a*]imidazole (**2.64**).[18]



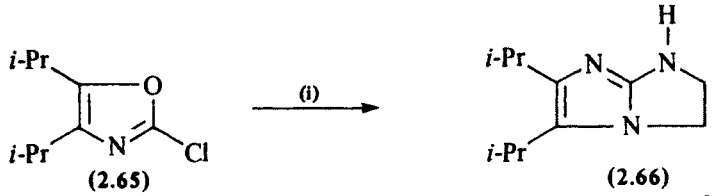
(2.63)

a, R = Ph
b, R = 2-thienyl

(2.64)

mp 233–233.5°C (MeCN);
methiodide, mp 163–164°C

The scope of this process has not been established, but disappointingly the 2-thienyl derivative (**2.63b**) resists cyclization.[18] Intermediate imidazolidines are probably intermediates but are not isolated in the transformation of 2-chloro-4,5-diisopropyloxazoles (**2.65**) into the condensed imidazole (**2.66**).[27]



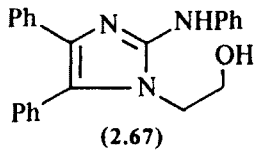
(2.65)

(i) $H_2N(CH_2)_2NH_2$, xylene, reflux, 4 h

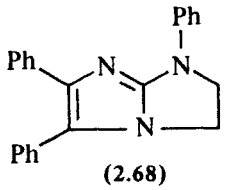
(2.66)

mp 199.5–200.5°C (C_6H_6),
ir 3375 cm^{-1} (NH)
1670 cm^{-1} (C=N)

The use of imidazoles as starting materials for the synthesis of 2,3-dihydro-1*H*-imidazo[1,2-*a*]imidazoles is restricted to the isolated example of thionyl chloride-induced ring closure of the 1-(2-hydroxyethyl)-2-phenylaminoimidazole derivative (cf. **2.67** → **2.68**).[28]



(2.67)



(2.68)

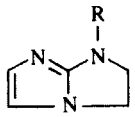
mp 199–200°C (aq. DMF)

2.3.2.2. Reactions

2.3.2.2.1. ACYLATION

A series of N-1 acyl, -aroyl, and -sulfonyl derivatives and also urea and thiourea derivatives of 2,3-dihydro-1*H*-imidazo[1,2-*a*]imidazole have been prepared by conventional procedures (see structure **2.69** and Table 2.8).[25]

TABLE 2.8. ACYLATION AND RELATED REACTIONS OF 2,3-DIHYDRO-1*H*-IMIDAZO-[1,2-*a*]IMIDAZOLES[25]



(2.69)

R in Structure **2.69**	Method[a] of Preparation from **2.69** (R = H)	Yield (%)	mp (°C)	Solvent for Recrystallization
COMe	A	66	123–124	CH_2Cl_2–*n*-hexane
$COC_6H_3Cl_2$-2,6	B	26	175	*n*-Hexane
$COC_6H_2(OMe)_3$-3,4,5	A	60	164–165	EtOAc
5′-Nitro-2-furoyl	C	22	128	$CHCl_3$-*n*-hexane
$SO_2C_6H_4Me$-*p*	D	30	148	CH_2Cl_2–Et_2O
CONH*n*-Bu	E	30	138–140[b]	CH_2Cl_2–Et_2O
CONHPh	E	76	145	CH_2Cl_2–Et_2O
$CONHCH_2Ph$	E	80	182[b]	*i*-PrOH
$CONHC_6H_4Cl$-*p*	E	50	151	MeOH–EtOAc
$CONHC_6H_4NO_2$-*p*	E	64	207[b]	MeOH–Et_2O
$CONHC_6H_3Me_2$-2,6	E	76	210[b]	MeOH-EtOAc
$CONHC_6H_3Cl_2$-2,6	E	–[c]	216[b]	MeOH–EtOAc
$CSNHC_6H_3Me_2$-2,6	F	36	134	Et_2O–*n*-hexane
$CSNHC_6H_3Cl_2$-2,6	F	19	208–210	CH_2Cl_2–Et_2O

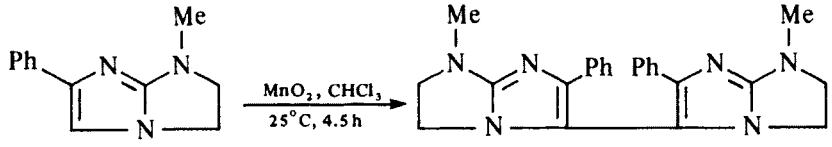
[a]Methods of preparation: (A) acyl or aroyl halide, $CHCl_3$, Et_3N, reflux for 3 h; (B) 2,6-$Cl_2C_6H_3COCl$ (no solvent); (C) cf. A with dioxan solvent replacing $CHCl_3$; (D) *p*-$MeC_6H_4SO_2Cl$, dioxan, pyridine, reflux for 20 h; (E) RNCO, dioxan, reflux for 4 h; (F) aryl isothiocyanate, neat.

[b]Melting point of hydrochloride quoted.

[c]Yield not quoted.

2.3.2.2.2. OXIDATION

The manganese dioxide-promoted oxidation of 2,3-dihydro-1-methyl-6-phenyl-1*H*-imidazo[1,2-*a*]imidazole (**2.70**) gives rise to a fluorescent product of 5,5′-oxidative coupling (**2.71**) rather than the anticipated fully unsaturated 1*H*-imidazo [1,2-*a*] imidazole[18] (see ref. 29 for use of activated manganese dioxide for the conversion of imidazolines into imidazoles).

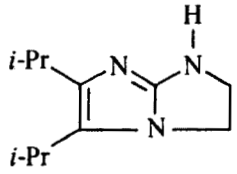


(2.70) (2.71)

mp 217–220°C (Me_2CO)

2.3.2.3. Practical Applications

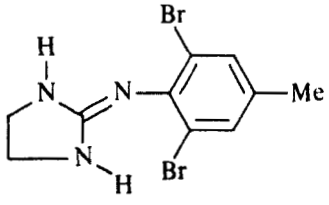
Of the compounds of the type illustrated in Table 2.8 that have been screened for anticonvulsant behavior, the most active is **2.69** (R = $CONHC_6H_3Me_2$-2,6).[25] The 5,6-diisopropyl derivative (**2.72**) has been evaluated for use as a ligand for the complexation and extraction of metals (e.g., Cu) of commercial value.[30]



(2.72)

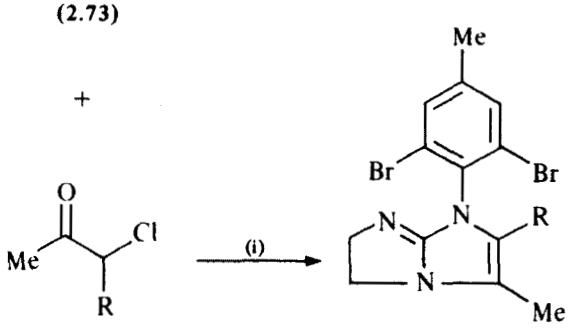
2.3.3. 5,6-Dihydro-1*H*-imidazo[1,2-*a*]imidazoles

The 1-aryl derivatives (**2.75a, b**), formed in poor yield from the iminoimidazoline (**2.73**) and the appropriate α-chloroketone (**2.74**), represent the only examples[31] of 5,6-dihydro-1*H*-imidazo[1,2-*a*]imidazoles during the literature period covered. Compounds of this type cause reduction of heart rate and are claimed as useful agents for treating coronary diseases.[31]



(2.73)

+



(2.74) (2.75)

(i) Reflux in $HO(CH_2)_2OEt$

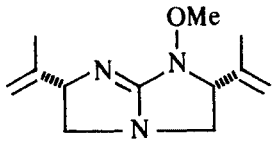
	R	Yield (%)	mp (°C)
a	H	18	144–146
b	Me	7	154–156

2.3.4. 2,3,5,6-Tetrahydro-1*H*-imidazo[1,2-*a*]imidazoles

Because of the tautomeric nature of 1-unsubstituted 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazoles (**2.37**), confusion arises in the literature concerning the nomenclature of such compounds. In this section, compounds are described that contain substituents at C-2 and/or C-3 that could also exist as tautomeric C-5 and/or C-6 derivatives. These are named according to the lower numbering system unless there are physicochemical data indicating that they exist entirely in C-5- and/or C-6-substituted forms.

2.3.4.1. Natural Occurrence

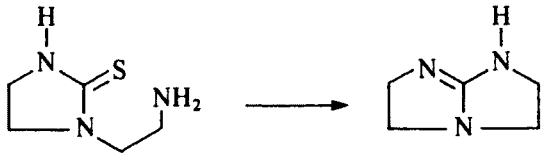
A 1,2,6-trisubstituted derivative (**2.76**) in the 2,3,5,6-tetrahydro-1*H*-imidazo-[1,2-*a*]imidazole series has been isolated from the bark and root bark of *A. floribunda*.[32] Alkylative and hydrogenolytic reactions of this compound (isoalchorneine) are described in Section 2.3.4.4.



(**2.76**)

2.3.4.2. Synthesis

1-(β-Aminoethyl)-imidazolin-2-thione (**2.77**) can be cyclized in modest yield to 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole (**2.78**) by a variety of procedures (e.g., $AgNO_3$, 47% yield; aqueous $ClCH_2CO_2H$, 47%; HgO, 33%),[33,34] but a wider



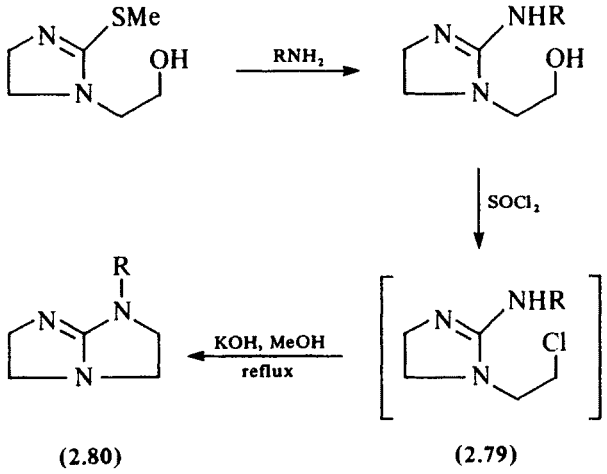
(**2.77**) (**2.78**)
oil (picrate, mp 219–211°C)

variety of derivatives (**2.80**) has been synthesized by the base-promoted cyclization of readily available 1-(2-chloroethyl)-2-substituted(amino) imidazolines (**2.79**); it is not necessary in this sequence to isolate and purify the chloro derivatives (**2.79**) prior to cyclization (see Scheme 2.11 and Table 2.9).[35]

TABLE 2.9. SYNTHESIS OF 1-SUBSTITUTED-2,3,5,6-TETRAHYDRO-1*H*-IMIDAZO-[1,2-*a*]IMIDAZOLES BY CYCLIZATION OF 1-(2-CHLOROETHYL)-2-[(SUBSTITUTED)AMINO]IMIDAZOLINES[35]

Substituent (R) in Structure 2.80	Yield (%)	n_D^{25}	bp (°C) [torr]	mp of Picrate (°C)
n-Octyl	37.0	1.4857	115–117 [0.05]	75–76
n-Dodecyl	45.2	1.4842	143–145 [0.08]	65–66
n-Tetradecyl	44.7	1.4832	172–173 [0.08]	75–76
n-Hexadecyl[a]	67.7	–	188–190 [0.07]	78–79
n-Octadecyl[b]	60.0	–	227–228 [0.2]	86–87
Benzyl[c]	70.0	1.5705	124–126 [0.1]	123–124
β-Phenylethyl	44.0	1.5609	–	145–146
β-Dimethylaminoethyl	50.0	1.5008	–	172–173
β-Diethylaminoethyl		1.4984	100–102 [0.05]	172–173
β-Di-*n*-propylaminoethyl	44.8	1.4938	106–108 [0.05]	169–170
γ-Dimethylaminopropyl	52.5	1.5033	119–121 [0.25]	157–158
γ-Diethylaminopropyl	39.8	1.4942	121–123 [0.2]	139–140

[a] Melting point 33–34°C.
[b] Melting point 36–37°C.
[c] Melting point 40.5°C.



(2.80) (2.79)

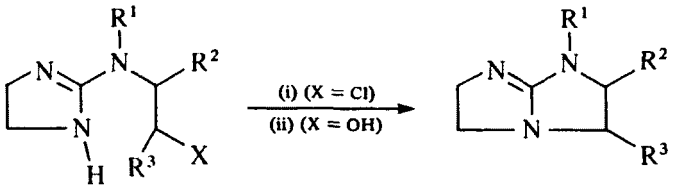
Scheme 2.11

A closely related cyclizative condensation is the base-facilitated conversion of (chloroalkyl)amino derivatives of imidazoline (**2.81**, X = Cl) into 1-substituted compounds in the 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole series (**2.82**),[36] although it may be noted that this type of synthesis can be achieved from precursor hydroxyalkyl (amino)imidazolines (**2.81**, X = OH) by the use of triphenylphosphine–triethylamine,[36] concentrated sulfuric acid,[37] or thionyl chloride[37] (cf. **2.81** → **2.82**, Table 2.10, and the conversion **2.83** → **2.84**).[38]

TABLE 2.10. SYNTHESIS OF 2,3,5,6-TETRAHYDRO-1*H*-IMIDAZO[1,2-*a*]IMIDAZOLES (2.82) BY CYCLIZATION OF CHLOROALKYL(AMINO)- AND HYDROXYALKYL(AMINO)IMIDAZOLINES (2.81)[36,37]

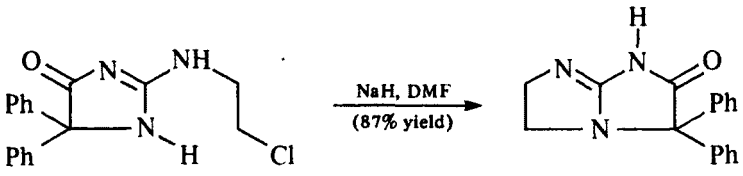
Product 2.82			X in Starting Material	Reaction		
R^1	R^2	R^3	(2.81)	Conditions[a]	mp (°C)	Reference
Ar[b]	H	H	Cl	A	214[d]	36
Ar[c]	H	H	OH	B	260 (dec.)[e]	36
H	H	Ph	OH	C	167–169.5	37
H	Me	Ph	OH	D	179	37
H	H	$C_6H_3Cl_2$-3,4	OH	D	298[f]	37
H	H	C_6H_4F-4	OH	D	260[f]	37
H	H	C_6H_4Cl-4	OH	D	266[f]	37
H	H	C_6H_4Me-3	OH	D	269[f]	37
H	H	C_6H_4Cl-3	OH	D	250[f]	37
H	H	C_6H_4Me-4	OH	D	254[f]	37

[a] Reaction conditions: (A) K_2CO_3; (B) Et_3N, Ph_3P, Et_3N; (C) $SOCl_2$; (D) concentrated H_2SO_4.
[b] Ar = $C_6H_2Cl_2NHEt$-2,4,6.
[c] Ar = $C_6H_2Cl_2NH_2$-2,4,6.
[d] ^1H nmr spectrum (ppm from TMS, d_5-pyridine solvent): 6.70 (s, 2H, Ar–H), 3.92 and 3.06 (2t, 4H, CH_2, J = 6.75 Hz), 3.14 (2t, 4H, CH_2, J = 7.5 Hz), 2.93 (m, 2H, NCH_2), 1.12 (t, 3H, Me, J = 7.25 Hz).
[e] Melting point of dihydrochloride quoted.
[f] Melting point of hydrochloride quoted.



(2.81) (2.82)

(i) K_2CO_3;
(ii) Ph_3P, Et_3N, CCl_4, or conc. H_2SO_4 or $SOCl_2$



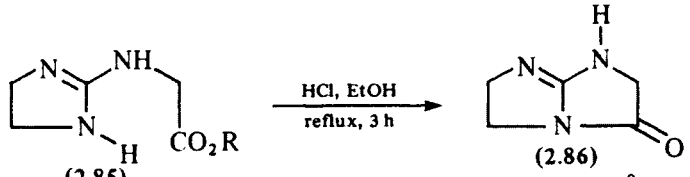
(2.83) (2.84)

mp 280°C ($CHCl_3$–MeOH)

TABLE 2.11. SYNTHESIS[a] OF 2,3,5,6-TETRAHYDRO-1*H*-IMIDAZO[1,2-*a*]IMIDAZOL-2,3-DIONES (**2.90**) FROM (SUBSTITUTED) AMINOIMIDAZOLINES[42]

R in **2.90**	Yield (%)	mp (°C)
$CH_2C_6H_3Cl_2$-2,6	67	166–168
$CH_2C_6H_4Cl$-2	76	169–171
$CH_2C_6H_4Me$-2	56	137–139
$CH_2C_6H_4OMe$-4	25	135–136
$CH_2C_6H_4F$-2	27	111–112
$CH_2C_6H_5$	25	139–140
C_6H_3-2-Cl-6-Me	23	188–190
$C_6H_3Et_2$-2,6	34	152–153
$C_6H_2Br_3$-2,4,6	40	277–279
$C_6H_3Br_2$-2,6	52	209–210

[a] Reaction conditions: see **2.89** → **2.90** in text.

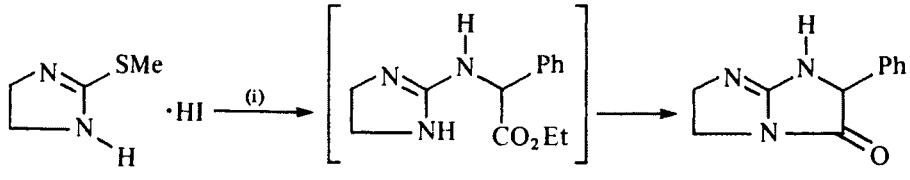


(**2.85**)
R = Me[39] or H[40]

(**2.86**)
mp 169–170°C (ref. 39)
mp 175–176°C (ref. 40)

2-(Substituted)aminoimidazoline derivatives derived from glycine (**2.85**, R = H or Me) can be cyclized in acid media to provide 2,3,5,6-tetrahydro-1*H*-imidazo-[1,2-*a*]imidazol-3-ones (**2.86**);[39,40] in reactions of this type, the glycine derivatives may be isolated prior to cyclization or generated *in situ* [see **2.87** → **2.88**[41] and the examples (**2.89** → **2.90**) quoted in Table 2.11].[42]

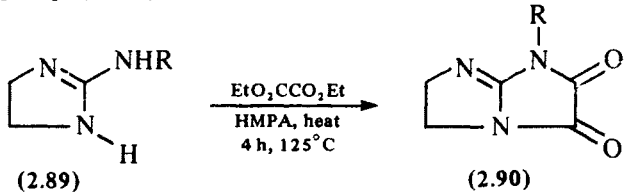
A 1-substituted-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole derivative (**2.92**) has also been obtained[18] by thionyl chloride-induced cyclization of the readily



(**2.87**)

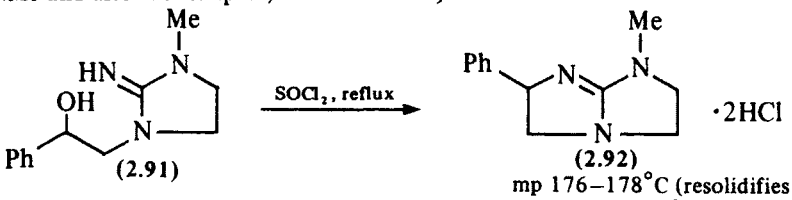
(**2.88**)
mp 230°C (dec.),
25% yield

(i) $PhCH(NH_2)CO_2Et$, KOH, MeOH



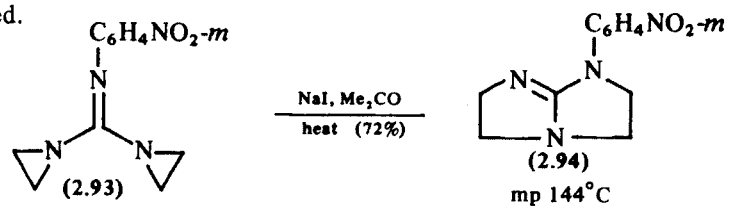
(**2.89**) (**2.90**)

available 2-imino-3-methylimidazolidine (**2.91**). This transformation provides an analog of 6-phenyl-2,3,5,6-tetrahydro[2,1-*b*] thiazole (tetramisole) (cf. **2.92**, S for NMe and also this chapter, Section 2.17.4).



mp 176–178°C (resolidifies and remelts 300°C)

Finally, the unorthodox transformation of an aziridine-derived guanidine (**2.93**) into 1-(3-nitrophenyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole (**2.94**) is described, although the scope of this briefly reported procedure[43] has not been evaluated.



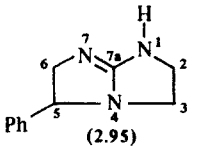
mp 144°C

2.3.4.3. Physicochemical studies

2.3.4.3.1. MOLECULAR STRUCTURE

The X-ray crystal and molecular structure of one derivative (**2.95**) in the 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole category has been determined (see Table 2.12 for bond distances in the bicyclic framework).[44] The angle between the two 5-membered rings is 13°, and the phenyl substituent is nearly perpendicular (99°) to the bicyclic system.

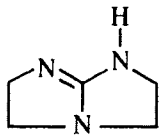
TABLE 2.12. BOND DISTANCES (A) IN 5-PHENYL-2,3,5,6-TETRAHYDRO-1*H*-IMIDAZO[1,2-*a*]IMIDAZOLE (**2.95**) FROM X-RAY ANALYSIS[44]



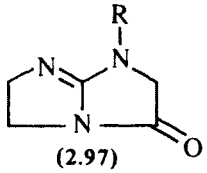
Bond in Structure **2.95**	Bond Separation (A)
N-1–C-2	1.456
C-2–C-3	1.544
C-3–N-4	1.466
N-4–C-7*a*	1.389
N-4–C-5	1.464
C-5–C-6	1.566
C-6–N-7	1.474
N-7–C-7*a*	1.291

2.3.4.3.2. DISSOCIATION CONSTANTS

The basic character of 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazoles is manifest in reactions leading to salt formation (see hydrochlorides listed in Table 2.10). The pK_a value for the parent compound (**2.96**) in the series is 10.60 (in H_2O),[45] whereas the 3-oxo substituent has the anticipated base-weakening effect in compounds **2.97a, b** (values of 6.82[45] and 5.01,[46] respectively).



(2.96)

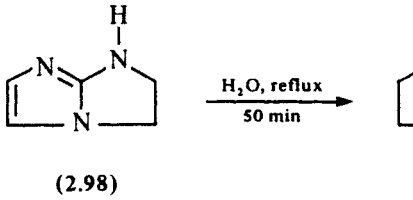


(2.97)
a: R = H
b: R = $CHPh_2$

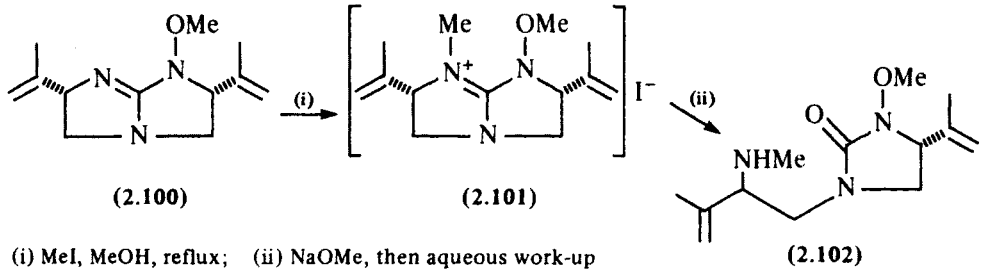
2.3.4.4. Reactions

2.3.4.4.1. RING FISSION

The parent compound of the series, 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]-imidazole (**2.98**) is prone to slow hydrolytic ring fission even at room temperature and can be recovered in only 86% yield (as the picrate) after 16.5 h. This process is considerably accelerated by heating **2.98** under reflux with water to give the imidazolone derivative (**2.99**) in 81% yield.[33] In a related process the bicyclic system of isoalchorneine (**2.100**) is fragmented hydrolytically into an imidazolone derivative (**2.102**) through an intermediate methiodide (**2.101**).[32] As might be anticipated, 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazol-3-one (**2.104**) undergoes acid-catalyzed ring fission at the C-3–N-4 bond to give a glycine derivative (**2.105**), and accordingly care must be given to conditions appropriate to the synthesis of **2.104** (cf. **2.103** → **2.104** → **2.105**).[39]

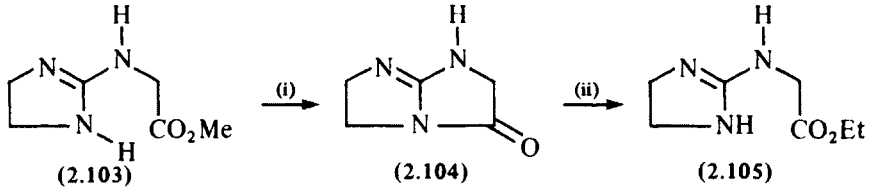


(2.98) (2.99)



(2.100) (2.101) (2.102)

(i) MeI, MeOH, reflux; (ii) NaOMe, then aqueous work-up

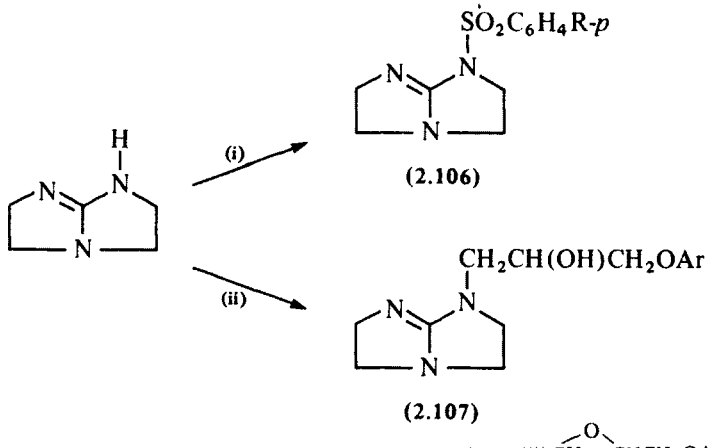


(2.103) (2.104) (2.105)

(i) HCl, EtOH, reflux 3 h; (ii) HCl, EtOH, reflux 17 h

2.3.4.4.2. REACTIONS WITH ELECTROPHILES

A number of 1-substituted 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazoles (**2.106** and **2.107**) formed in reactions of the parent compound with arene sulfonyl halides and with epoxides are collected in Table 2.13.[47] The formation of 1-substituted derivatives (**2.109**) also occurs as a secondary reaction following the base-catalyzed ring closure of 2-methoxycarbonylimino-1-benzhydrylimidazolidines (**2.108**).[48]



(2.106)

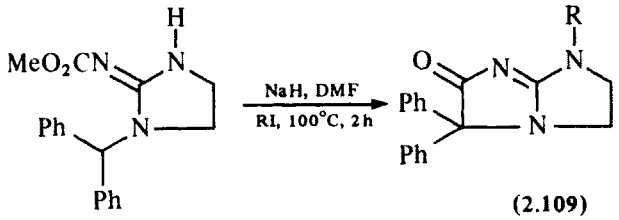
(2.107)

(i) *p*-$RC_6H_4SO_2Cl$, 3.75*M* aqueous NaOH; (ii) $CH_2{-}CHCH_2OAr$ (epoxide)

TABLE 2.13. SYNTHESIS OF 1-SUBSTITUTED-2,3,5,6-TETRAHYDRO-1*H*-IMIDAZO-[1,2-*a*]IMIDAZOLES (**2.106** and **2.107**) FROM ARENE SULFONYL CHLORIDES AND EPOXIDES[47]

Reaction Product	Yield (%)	mp (°C)
2.106, R = Me	99	182–184
2.106, R = NHAc	94	270–271.5
2.106, R = NO_2	98	179–180[a]
2.106, R = NH_2[b]	86	185–186
2.107, Ar = *m*-MeC_6H_4	57	102.5–104[c]
2.107, Ar = 2,4-$Cl_2C_6H_4$	18	155–156.5[d]

[a] Forms a picrate, mp 231–233°C (dec.).
[b] Synthesized from **2.106** (R = NHAc), 5*M* NaOH, aqueous EtOH, reflux.
[c] From Me_2CO–hexane (picrate, mp 143.5–144°C).
[d] From aqueous EtOH (picrate, mp 146–147°C).

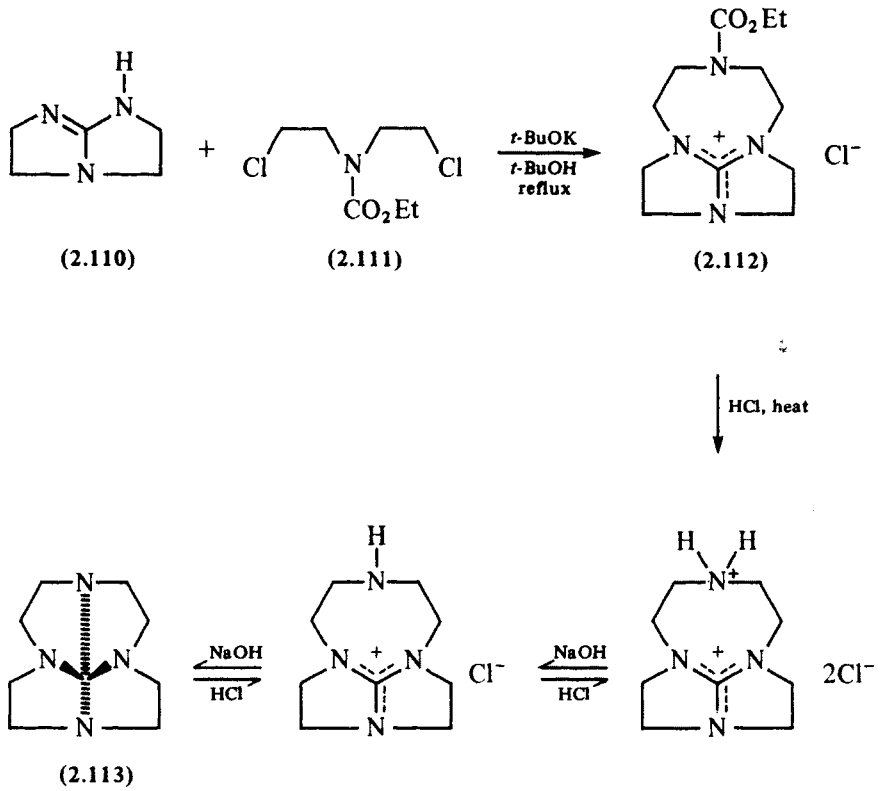


(2.108)

(2.109)

R	Yield (%)	mp (°C)
Me	89	220–221
Et	76	148–149

Treatment of 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole (**2.110**) with the bis electrophile (**2.111**) leads to a tricyclic compound (**2.112**) formed by bridging at N-1 and N-7.[49] Hydrolysis of the ethoxycarbonyl moiety and equilibration in base (see Scheme 2.12) leads to the intriguing, highly symmetrical 1,4,7,10-tetraazatetracyclo[5.5.1.$0^{4,13}$0.10^{13}]tridecane molecule (**2.113**), and these equilibria have been studied in detail by ^{1}H nmr spectroscopy.[49]



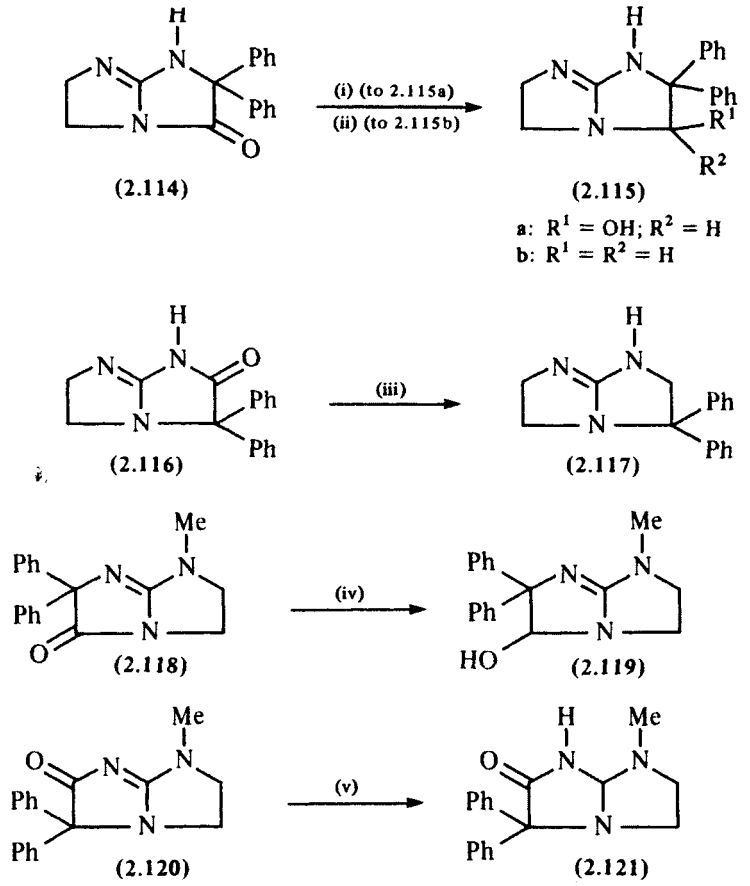
(2.110) (2.111) (2.112)

(2.113)

Scheme 2.12

2.3.4.4.3. REDUCTION

The 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole ring system is stable to lithium aluminum hydride (LAH) in tetrahydrofuran under reflux, and this reductant can be used for converting the nitro compound (**2.94**) into the corresponding arylamine [mp 260°C (dec.)].[43] The reduction of 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazol-2-,3-,5- and 6-ones has been studied in detail by using sodium bis(2-methoxyethoxy)aluminum hydride (REDAL) as a reductant (see Scheme 2.13 and Table 2.14).[38] *It is clear that there are differences in the pattern* of reduction depending on the location of the carbonyl group. For 2-, 3-, and 5-oxo derivatives, the carbonyl function may be partially (e.g., **2.114** → **2.115a**; **2.118** → **2.119**) or completely reduced (e.g., **2.114** → **2.115b**), whereas in the 6-oxo compound (**2.120**) the carbonyl group remains intact and the N-7–C-7*a* bond becomes saturated.



(2.114) (2.115) a: R^1 = OH; R^2 = H b: R^1 = R^2 = H

(2.116) (2.117)

(2.118) (2.119)

(2.120) (2.121)

Reaction conditions: sodium bis(2-methoxyethoxy)aluminum hydride (REDAL), THF, reflux for (i) 3 h, (ii) 9 h, (iii) 1.5 h, (iv) 3 h, (v) 5 h

Scheme 2.13

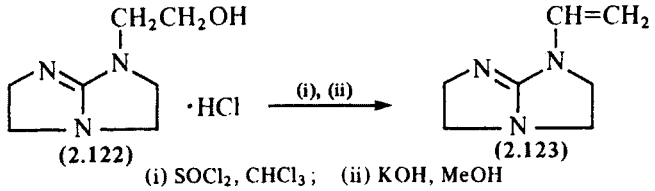
TABLE 2.14. REDUCTION[a] OF 2-, 3-, 5-, and 6-OXO DERIVATIVES OF 2,3,5,6-TETRAHYDRO-1*H*-IMIDAZO[1,2-*a*]IMIDAZOLES WITH SODIUM BIS-(2-METHOXYETHOXY)ALUMINUM HYDRIDE[38]

Starting Material	Product	Yield (%)	mp (°C)	Solvent for Recrystallization
2.114	**2.115a**	93	179–180	EtOAc
2.114	**2.115b**	29	204–206	EtOAc
2.116	**2.117**	62	212–214	EtOAc
2.118	**2.119**	75	215–217	EtOAc
2.120	**2.121**	85	149–151	C_6H_6

[a]For reaction conditions, see Scheme 2.13.

2.3.4.4.4. MISCELLANEOUS REACTIONS

Synthesis of the useful monomer (**2.123**) (see the following section) can be achieved in a conventional manner from 1-(2-hydroxyethyl)-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*] imidazole (**2.122**).[50]



(i) $SOCl_2$, $CHCl_3$; (ii) KOH, MeOH

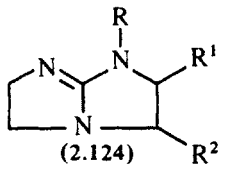
2.3.4.5. Commercial Applications

Areas of commercial interest relating to 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]-imidazoles discussed in Section 2.3.4 are highlighted in Table 2.15.

TABLE 2.15. AREAS OF COMMERCIAL INTEREST RELATING TO 2,3,5,6-TETRAHYDRO-1*H*-IMIDAZO[1,2-*a*]IMIDAZOLES

Compound Structure	Area of Potential Commercial Interest	Reference
2.123	Preparation of copolymers with CH_2=CHCN for improving dyeing properties	50
2.92	Anthelmintic agent	18
2.106, 2.107	Bacteriostatic agent	47
2.80	Surface-active agents	35
2.97b	Hypoglycemic agents	46[a]
2.124 (R = $C_6H_3Cl_2$-2,6; R^1 = H)	Hypotensive agents	52
2.124 (R = R^2 = H; R^1 = aryl)	Hypotensive and diuretic agents	53
2.124 [R = 1-(C_4–C_{24} alkylamino); R^1 = R^2 = H]	Inhibition of tarnishing of Cu alloys	54
2.124 (R = H, benzyl; R^1 = H, Me; R^2 = aryl)	Antidepressant activity	55a

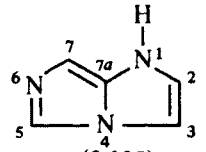
[a]See also ref. 51.



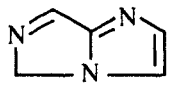
(2.124)

2.4. RING SYSTEM C_3N_2–C_3N_2: 1*H*-IMIDAZO[1,5-*a*]IMIDAZOLE

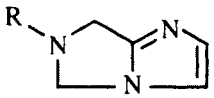
In contrast to the widely studied 1*H*-imidazo[1,2-*a*]imidazole ring system described in the previous section, compounds in the 1*H*-imidazo[1,5-*a*]imidazole system (**2.125**) are rare and actually occur in the 5*H*-tautomeric form (cf. **2.126**) in the guise of substituted 6,7-dihydro compounds (cf. **2.127**).



(2.125)



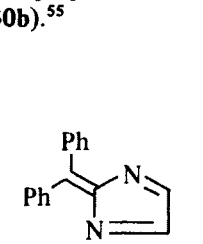
(2.126)



(2.127)

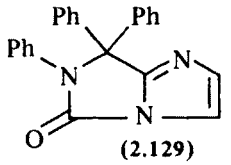
2.4.1. Synthesis

The efficient annulation of phenyl isocyanate to the diphenyl diazafulvene derivative (**2.128**) provides a high-yield synthesis of 5-oxo-6,7,7-triphenyl-6,7-dihydro-5*H*-imidazo[1,5-*a*]imidazole (**2.129**),[55a] and this method can be adapted to the preparation of two other derivatives in the series (see **2.128** → **2.130a** and **2.130b**).[55]



(2.128)

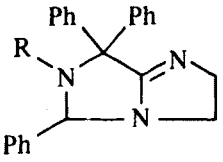
(i)



(2.129)

81% yield; mp 165–166°C

(ii) or (iii)



(2.130)

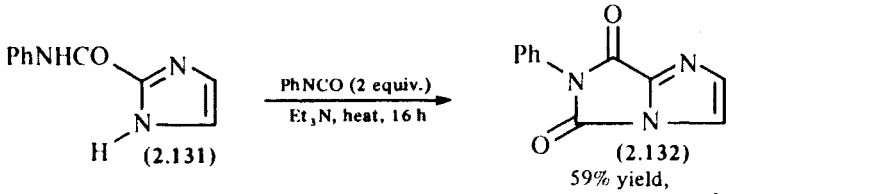
	R	Yield (%)	mp (°C)
a	Ph	25	219–220 (dec.)
b	OH	66	206 (dec.)

(i) PhNCO, tetrahydrofuran, reflux;
(ii) PhN=CHPh, 120°C (to **2.130a**);
(iii) PhCH=NOH, 100°C, 15 min (to **2.130b**)

In a more versatile approach, and by analogy with processes in the chemistry of pyrrole[56] and indole carboxamides,[57] the cyclizative condensation of phenyl isocyanate with the imidazole derivative (**2.131**) can be used to prepare 5,7-dioxo-6-phenyl-6,7-dihydro-5*H*-imidazo[1,5-*a*]imidazole (**2.132**).[58] Compound **2.132** is characterized by the following spectral data: ir = 1825 and 1570 cm^{-1} (CO); nmr (CF_3CO_2D) δ = 7.33 (m, 5H), 7.78 (m, 2H).[58]

2.4.2. Reactions

The imidazoline dione ring of **2.132** is cleaved by brief heating with aqueous sodium hydroxide to give the imidazole *N*-phenyl carboxamide derivative (**2.131**).

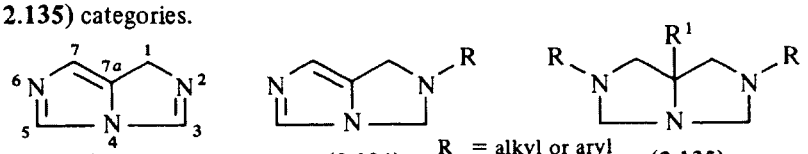


(2.131) (2.132)

59% yield,
mp 179.5–180°C (CCl_4–$CHCl_3$)

2.5. RING SYSTEM $C_3N_2-C_3N_2$: 1*H*-IMIDAZO[1,5-*c*]IMIDAZOLE

There are no citations to compounds in the parent 1*H*-imidazo[1,5-*c*]imidazole ring system (**2.133**) during the literature period covered, and this section is concerned with compounds in the 2,3-dihydro- (cf. **2.134**) and 2,3,5,6,7,7*a*-hexahydro (cf. **2.135**) categories.

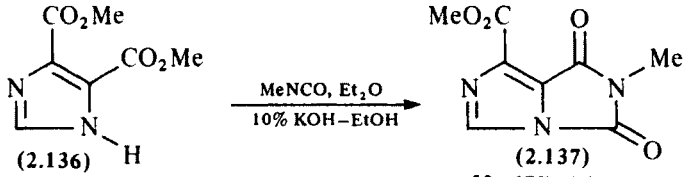


(2.133) (2.134) (2.135)

R = alkyl or aryl
R^1 = H or Me

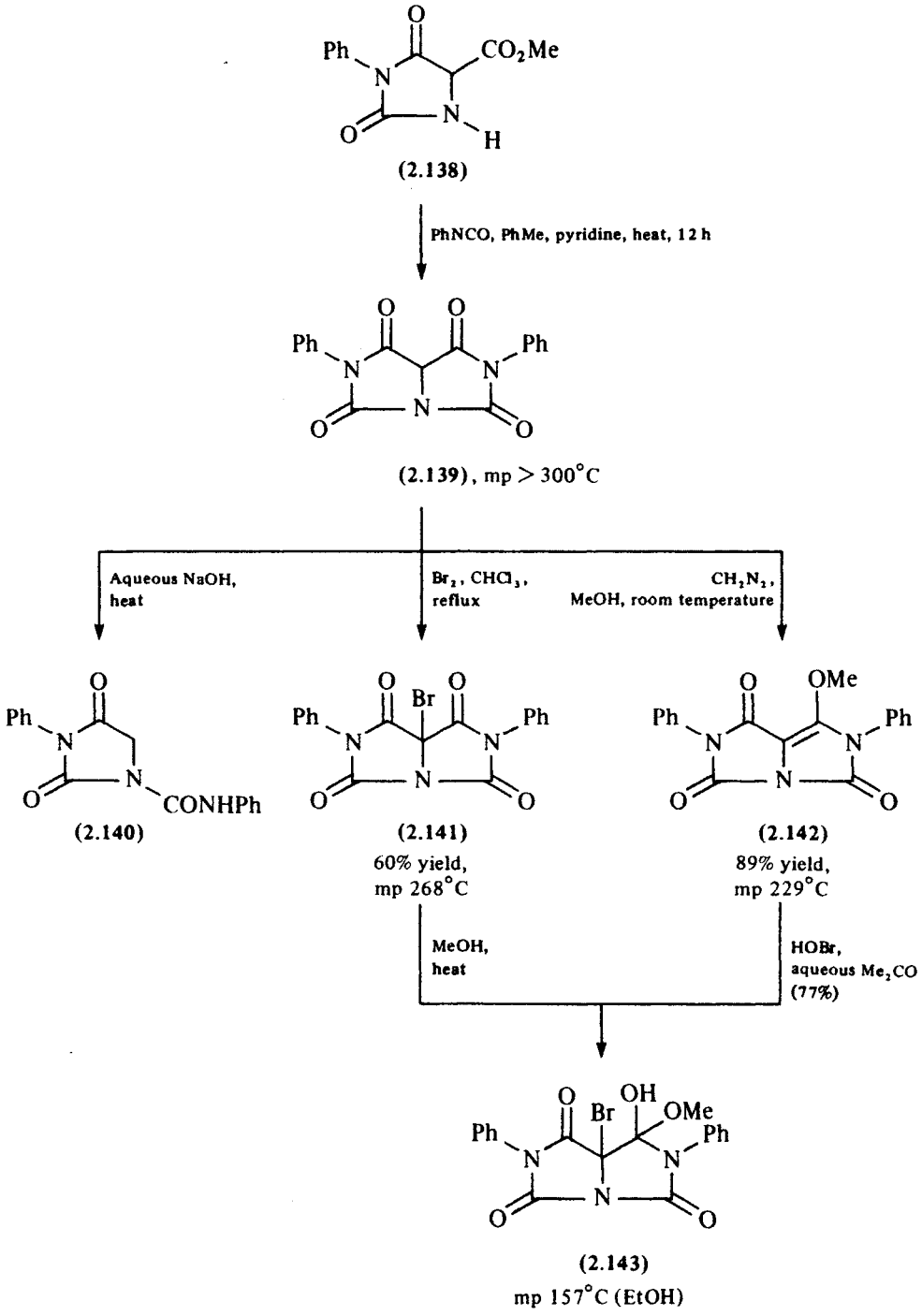
2.5.1. 2,3-Dihydro-1*H*-imidazo[1,5-*c*]imidazoles

The synthesis of 1,3-dioxo-2-methyl-7-methoxycarbonyl-2,3-dihydro-1*H*-imidazo[1,5-*c*]imidazole (**2.137**) from the reaction of methyl isocyanate with the diester (**2.136**) represents the only example of a compound in this group.[59] It may



(2.136) (2.137)

53–67% yield,
mp 159°C (AcOH or C_6H_6-petroleum)


(2.138)
PhNCO, PhMe, pyridine, heat, 12 h
(2.139), mp > 300°C
Aqueous NaOH, heat
Br2, CHCl3, reflux
CH2N2, MeOH, room temperature
(2.140)
(2.141)
60% yield, mp 268°C
(2.142)
89% yield, mp 229°C
MeOH, heat
HOBr, aqueous Me2CO (77%)
(2.143)
mp 157°C (EtOH)

Scheme 2.14

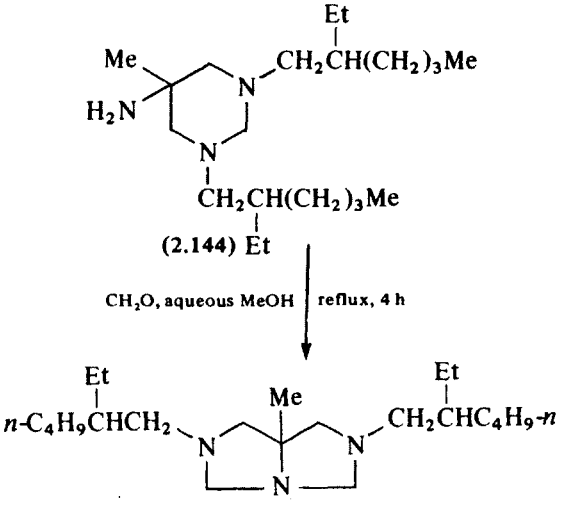
be noted (see **2.131** → **2.132**) that related cyclizations have been used for the synthesis of a 6,7-dihydro derivative in the 5*H*-imidazo[1,5-*a*]imidazole series (see Section 2.4.1).[58]

2.5.2. 2,3,5,6,7,7*a*-Hexahydro-1*H*-imidazo[1,5-*c*]imidazoles

2.5.2.1. Synthesis

Annulation of a second imidazolidine ring to the hydantoin derivative (**2.138**) can be achieved[60] by using phenyl isocyanate in a reaction (see **2.138** → **2.139** in Scheme 2.14) analogous to those described earlier (see **2.136** → **2.137** and **2.131** → **2.132**) for the synthesis of 1*H*-imidazo[1,5-*c*]imidazoles and 5*H*-imidazo[1,5-*a*]-imidazoles, respectively. Compound **2.139** is initially formed as a yellow pyridinium salt. The free base exhibits IR carbonyl bands at 1770 and 1848 cm^{-1} but does not contain bands attributable to enolic OH. The ^1H nmr D_2O-exchangeable resonance (DMSO-d_6 solvent) of the 7*a* hydrogen appears at $\delta = 5.76$.[60]

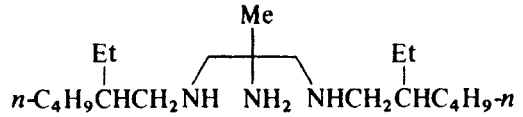
A 2,3,5,6,7,7*a*-hexahydro-1*H*-imidazo[1,5-*c*]imidazole derivative (**2.145**) has also been isolated[61] from the reaction of 5-amino-1,3-bis[2-ethylhexyl]hexahydro-5-methylpyrimidine (Hexetidine) (**2.144**) with formalin in methanol, presumably[62] through an intermediate triamine (**2.146**).



(2.144)

(2.145)

bp 125°C, 0.02 torr,
n_D^{20} 1.4660



(2.146)

2.5.2.2. Reactions

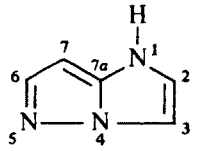
Cleavage of an imidazolidine ring of **2.139** occurs in expected fashion with aqueous sodium hydroxide to give the *N*-phenyl carboxamide derivative (**2.140**).[60] The tetraoxo derivative (**2.139**) has also been converted in conventional processes into products of 7*a*-bromination (see **2.141**) and enolic methylation (see **2.142**), and these compounds can be transformed into a common, isolable, hemiacetal (**2.143**).[60]

2.5.2.3. Commercial Applications

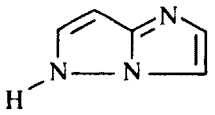
The 2,3,5,6,7,7*a*-hexahydro-1*H*-imidazo[1,5-*c*]imidazole derivative (**2.145**) is claimed as a useful antimicrobial agent, for example, in the inhibition of growth of *Staphylococcus aureus*.[61]

2.6. RING SYSTEM C_3N_2–C_3N_2: IMIDAZO[1,2-*b*]PYRAZOLE

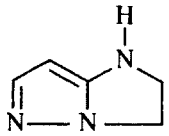
Compounds in the fully aromatic imidazo[1,2-*b*]pyrazole ring system can exist in either 1*H*- (**2.147**) or 5*H*-tautomeric forms (**2.148**), and derivatives of these types are described in this section; 3*H*- and 7*H*-tautomeric forms are also possible but are not described during the literature period covered. 2,3-Dihydro-1*H*-imidazo[1,2-*b*]pyrazoles (cf. **2.149**) are well documented and are described in Section 2.6.2.



(**2.147**)



(**2.148**)

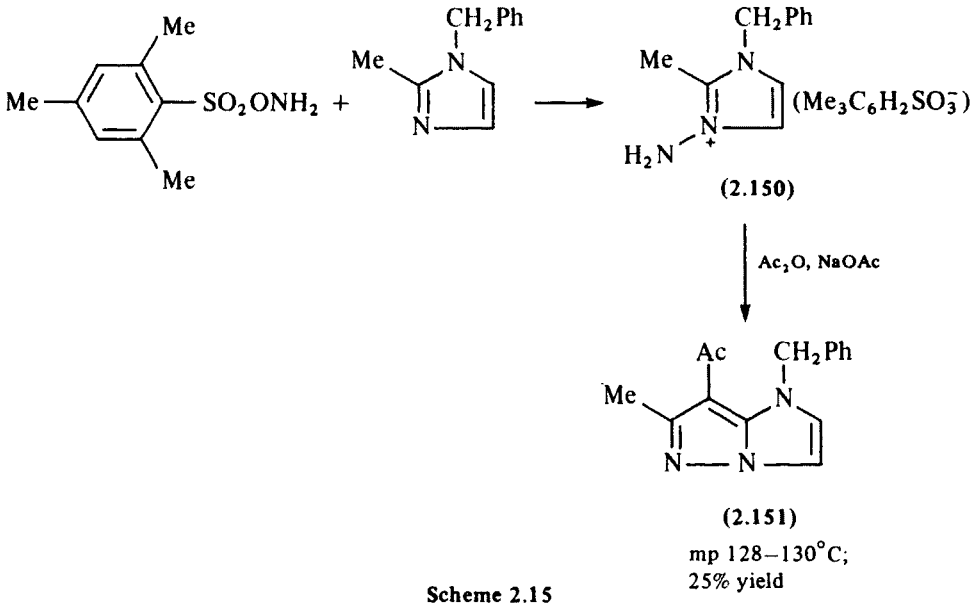


(**2.149**)

2.6.1. 1*H*-Imidazo[1,2-*b*]pyrazoles

2.6.1.1. Synthesis from Imidazoles

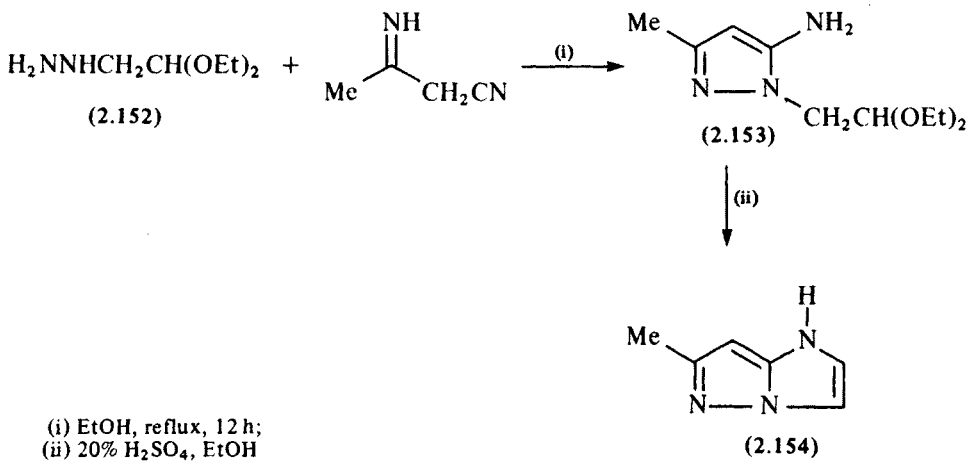
Construction of the trisubstituted 1*H*-imidazo[1,2-*b*]pyrazole derivative (**2.151**) has been achieved[63] in two steps by means of the *N*-amino imidazolium salt (**2.150**) in the manner shown in Scheme 2.15, but this represents the only synthetic approach to this ring system from an imidazole derivative.



Scheme 2.15

2.6.1.2. *Synthesis from Pyrazoles*

Compounds in the imidazo[1,2-*b*]pyrazole group that have been prepared from pyrazoles are collected in Table 2.16. In early work, 6-methyl-1*H*-imidazo[1,2-*b*]-pyrazole (**2.154**) was synthesized by acid-promoted cyclization of the 5-amino-pyrazole derivative (**2.153**);[64,65] the latter is readily available in good yield from condensation of the acetal (**2.152**) with acetonitrile dimer (see Scheme 2.16).[64,65] Evidence relating to the existence of **2.154** in the 1*H*- rather than the 5*H*-tautomeric form is discussed in Section 2.6.1.3.



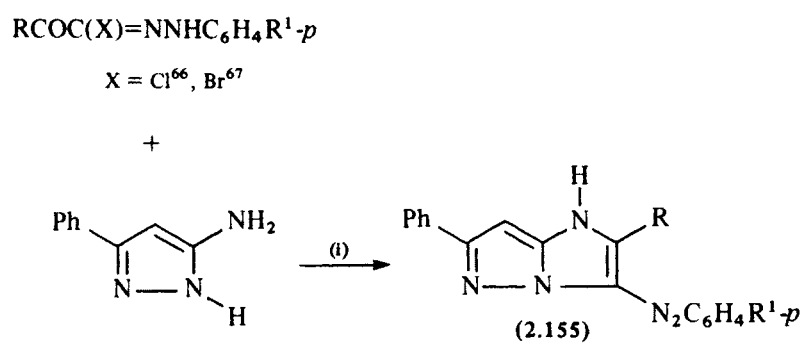
(i) EtOH, reflux, 12 h;
(ii) 20% H_2SO_4, EtOH

Scheme 2.16

TABLE 2.16. SYNTHESIS[a] OF IMIDAZO[1,2-*b*]PYRAZOLES FROM PYRAZOLE DERIVATIVES

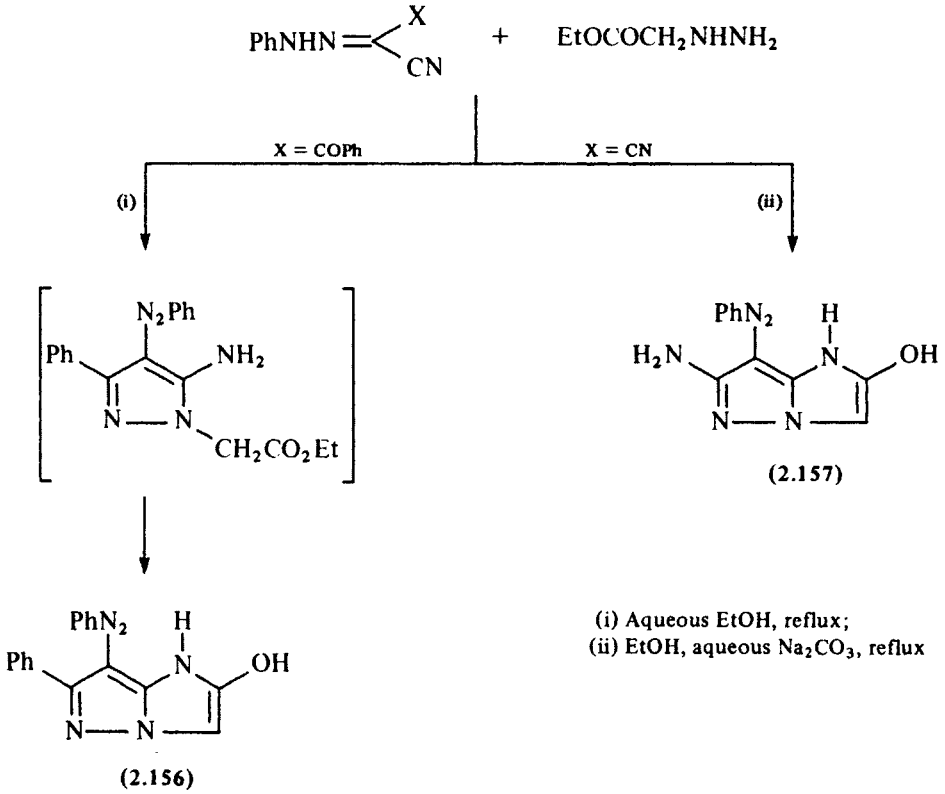
Compound	Yield (%)	mp (°C)	Spectral Parameters	Reference
2.154	40	178–179[b] HCl, mp 130–136°C (dec.)	ir: ν_{max} = 3485, 3350–2900, 1596 cm^{-1} uv:[c] $\lambda_{max}^{H_2O}$ = 219 nm (log ϵ 4.53), 245.5 (3.99) $\lambda_{max}^{95\%\ EtOH}$ = 246.5 (3.87) nmr:[d]	64,65
2.155 (R = Me; R^1 = H)	66	155[g]	–[e]	66
2.155 (R = Ph; R^1 = H)		215	–[f]	67
2.155 (R = Ph; R^1 = MeO)		195	–[f]	67
2.155 (R = Ph; R^1 = Me)		227	–[f]	67
2.155 (R = Ph; R^1 = Br)		232	–[f]	67
2.155 (R = Ph; R^1 = Cl)		228	–[f]	67
2.155 (R = Ph; R^1 = NO_2)		240	–[f]	67
2.156	50	187[g]	ir: ν_{max} = 3470–3400 (chelated NH), 2500, 2900 (OH), 1630 cm^{-1} (N=N); nmr (DMSO-d_6) δ = 3.36 (1H, CH), 6.90–8.05 (br, 10H, Ar–H)	68
2.157	50	285	ir: ν_{max} = 3500, 3100 (NH and OH), 1640, 1620 cm^{-1}	68

[a] See text for reaction conditions.
[b] Purified by vacuum sublimation at 150°C, 0.05 torr.
[c] For hydrochloride salt uv, $\lambda_{max}^{95\%\ EtOH}$ = 247 nm (log ϵ 3.95).
[d] See Section 2.6.1.3.
[e] No spectral data quoted.
[f] Weak ir NH band near 3100 cm^{-1}, uv $\lambda_{max}^{CHCl_3}$ = 400–500 nm in accord with azo tautomeric form.
[g] Recrystallized from ethanol.



(i) EtOH, reflux, 3h (ref. 67)

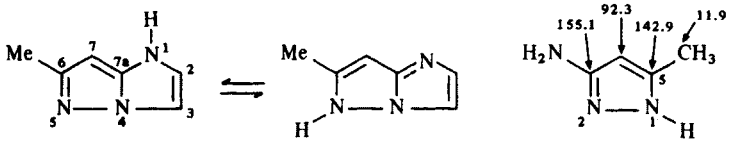
1,3-Disubstituted-5-aminopyrazoles are also generated as intermediates but are not isolated from reactions of 3-phenyl-5-aminopyrazole with hydrazonyl halides leading directly to 2,3,6-trisubstituted derivatives in the 1*H*-imidazo[1,2-*b*]pyrazole system. [See structure **2.155**,[66,67] related reactions leading to 2-hydroxy-1*H*-imidazo[1,2-*b*]pyrazoles (**2.156, 2.157**) described in Scheme 2.17,[68] and Table 2.16.]



(i) Aqueous EtOH, reflux;
(ii) EtOH, aqueous Na_2CO_3, reflux

Scheme 2.17

TABLE 2.17. ^{1}H[71] AND ^{13}C[72] NMR PARAMETERS FOR 6-METHYL-1*H*-IMIDAZO-[1,2-*b*]PYRAZOLE (**2.158**) IN DMSO-d_6



(**2.158**) (**2.159**) (**2.160**)

^{1}H chemical shift (ppm from TMS)	N-1–H, 10.60	H-2, 7.00	H-3, 7.35	CH_3, 2.26	H-7, 5.44	
Coupling constants (Hz)	J_{1-3} = 1.6	J_{1-2} = 2.5	$J_{6-7} = 0$	$J_{3-7} = 0.8$	$J_{2-6} = 0$	$J_{2-3} = 2.3$
^{13}C chemical shift	C-7*a*, 151.1	C-7, 78.0	C-6, C 142.1, CH_3 14.6	C-3, 107.2	C-2, 116.6	

2.6.1.3. Physicochemical Studies

It has been concluded from results of molecular orbital calculations[69] and dipole moment studies[70] that 6-methylimidazo[1,2-*b*]pyrazole exists entirely in the 1*H*- (**2.158**) and not in the 5*H*-tautomeric form (**2.159**), and additional evidence in this regard has been adduced from ^{1}H nmr[71] and ^{13}C nmr spectra[72] (see Table 2.17). For example, under suitable conditions (DMSO-d_6 solutions of concentration 0.5 mol l^{-1}), coupling of N-1–H to H-2 and H-3 can be observed in addition to H-2–H-3 and cross-ring (H-3–H-7) couplings. A characteristic feature observed in the ^{13}C nmr spectrum (see Table 2.17) is the relatively high field position of C-7 (78.0 ppm). It is interesting to compare this value with that of C-4 (92.3 ppm) in 3-amino-5-methylpyrazole (see structure **2.160**);[72] it is also interesting to note that this position (7) is the site of electrophilic attack in 6-methyl-1*H*-imidazo[1,2-*b*]pyrazole (see following section).

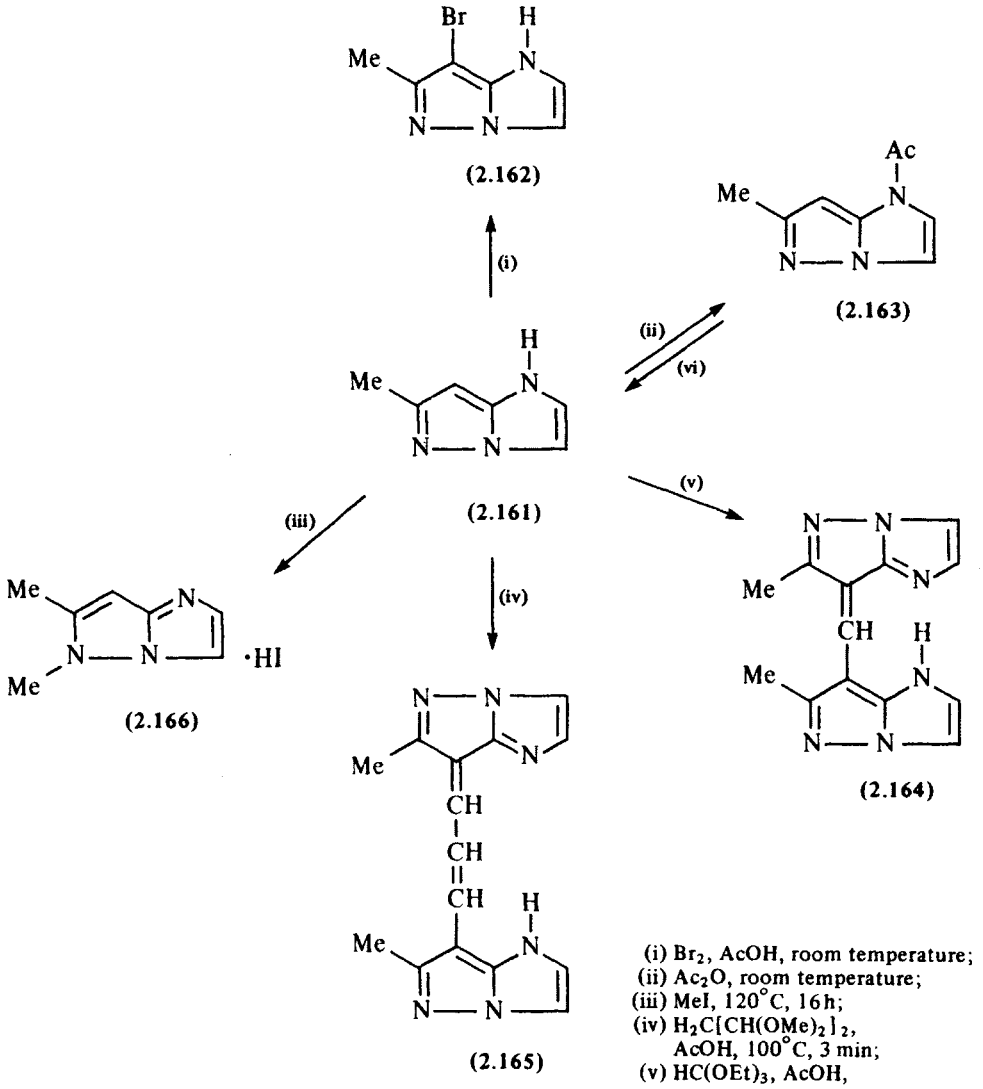
2.6.1.4. Reactions

The physical and spectral parameters of compounds ensuing from reactions in the 1*H*-imidazo[1,2-*b*]pyrazole group are collected in Table 2.18. Electrophilic reactions of bromination[65] and nitrosation[63] occur by substitution at C-7 to give bromo and nitroso derivatives (**2.162, 2.168**) respectively, although the latter process probably occurs by preliminary deacetylation of the 7-acetyl derivative (**2.167**; cf. **2.167** → **2.169**). Reactions with bifunctional electrophiles also occur by substitution at C-7 with formation of poorly characterized products formulated[65] as bis(6-methylimidazo[1,2-*b*]pyrazolyl) derivatives (**2.164** and **2.165**).

TABLE 2.18. PHYSICAL AND SPECTRAL PROPERTIES OF IMIDAZO[1,2-*b*]PYRAZOLES[a]

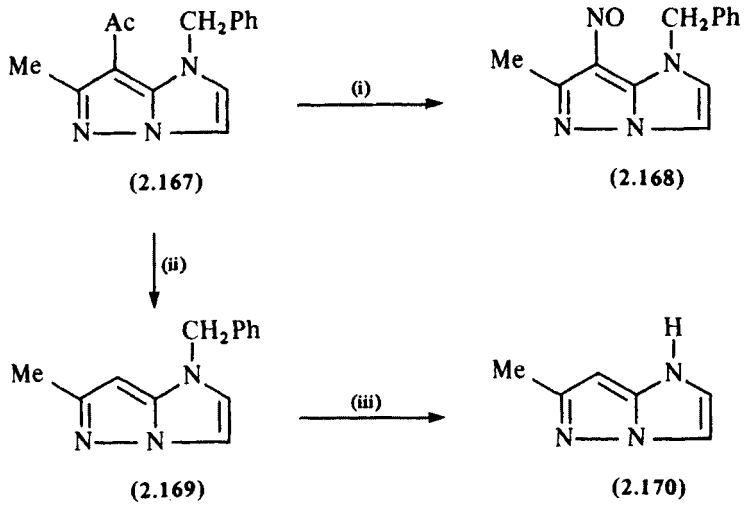
Compound	mp (°C)	Yield (%)	Spectral Parameters	Reference
2.162	–[b]	87	^{1}H nmr ($CDCl_3$) δ = 2.37 (s, 6-Me), 6.83 (d, H-2), 7.27 (d, H-3), J_{2-3} = 1.5 Hz	65
2.163	98	91 (from CCl_4)	Ir ($CHCl_3$); ν_{max} = 1715 cm^{-1}; uv λ_{max}^{EtOH} = 283 nm (log ϵ 4.12)	65
2.164	270–275[c]		^{1}H nmr (CCl_4) δ = 2.38 (s, 6H), 6.93 (m, 2H), 7.13 (m, 2H)	65
2.165	> 360	80	^{1}H nmr (DMSO-d_6) δ = 2.42 (s, 6H), 5.43 (br, 2H), 7.23 (m, 2H), 7.50 (m, 2H)	65
2.166	150–200 (dec.)	84 (from Et_2O–EtOH)	^{1}H nmr (CF_3CO_2H) δ = 2.55 (d, 6-Me), 3.99 (s, N-Me), 6.20 (m, H-7), 7.41 (t, H-2), 7.63 (sept, H-3), 10.2 (N-1–H);[d] uv λ_{max}^{MeOH} = 251 nm (log ϵ 3.98)	65
2.168	132	100		63
2.169	–[e]			63
2.170	177–179	60		63

[a] For reaction conditions, see Schemes 2.18 and 2.19.
[b] Melting point not quoted.
[c] Sample purified by sublimation at 165°C/0.02 torr.
[d] Coupling constants in hertz: J_{1-2} = 2.6, J_{1-3} = 1.5, J_{2-3} = 2.4, J_{3-7} = 0.7, J_{6-7} = 0.8.
[e] Compound in an oil. No other data quoted.



Scheme 2.18

In contrast to acetylation, which occurs at N-1 (see **2.161** → **2.163**), methylation takes place at the most nucleophilic nitrogen to give a rare example (**2.166**) of a compound in the 5*H*-imidazo[1,2-*b*]pyrazole category.[65] Reduction processes of 1*H*-imidazo[1,2-*b*]pyrazoles include the lithium aluminum hydride-induced deacetylation process (**2.163** → **2.161**), presumably by way of a 1-(2-hydroxyethyl) intermediate[65], and the benzylic cleavage effected by sodium in liquid ammonia (see **2.169** → **2.170**).[63]



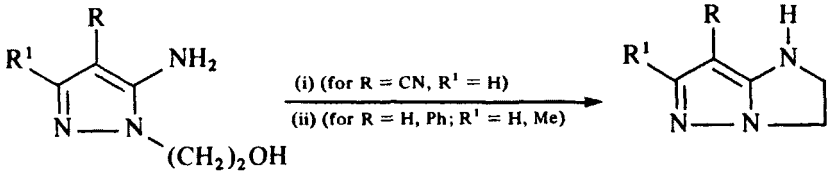
(i) $NaNO_2$, 15% HCl; (ii) heat in HCl; (iii) Na, liquid NH_3

Scheme 2.19

2.6.2. 2,3-Dihydro-1*H*-imidazo[1,2-*b*]pyrazoles

2.6.2.1. Synthesis from Pyrazoles

2,3-Dihydro-1*H*-imidazo[1,2-*b*]pyrazoles (**2.172**) can be obtained albeit in only moderate yield by the acid-promoted cyclization of 1-(2-hydroxyethyl)-5-amino-pyrazoles (**2.171**);[73,74] it may be noted that the bicyclic compound (**2.172a**) is actually formed from a cyanopyrazole (**2.171**, R = CN, R^1 = H) presumably through acid labile nitrile and carboxylic acid derivatives of (**2.172**).[73] Compound (**2.172b**) is characterized by the following ^{1}H nmr spectrum ($CDCl_3$): δ = 2.22 (s, Me), 4.0 (m, CH_2CH_2), and 5.18 (s, H-7).[74]



(**2.171**) (**2.172**)

	R	R^1	Yield (%)	MP (°C)	Ref.
a	H	H	–	68–69	73
b	H	Me	30	92–93	74
c	Ph	H	36	162	74

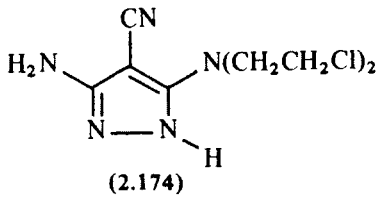
(i) 75% H_2SO_4, 170°C, 3.5 h;
(ii) polyphosphoric acid

The 1,6,7-trisubstituted 1*H*-imidazo[1,2-*b*]pyrazole derivative (**2.175**) is formed when 3-amino-5-[bis(2-chloroethyl)amino]-4-cyanopyrazole (**2.174**) is allowed to stand at room temperature and also when the enamine derivative (**2.173**) is subjected to long reaction times with hydrazine.[75]

$(ClCH_2CH_2)_2NC(CN)=C(CN)_2$

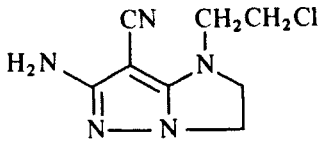
(2.173)

25% N_2H_4, DMF, room temp.



(2.174)

stand at room temp.

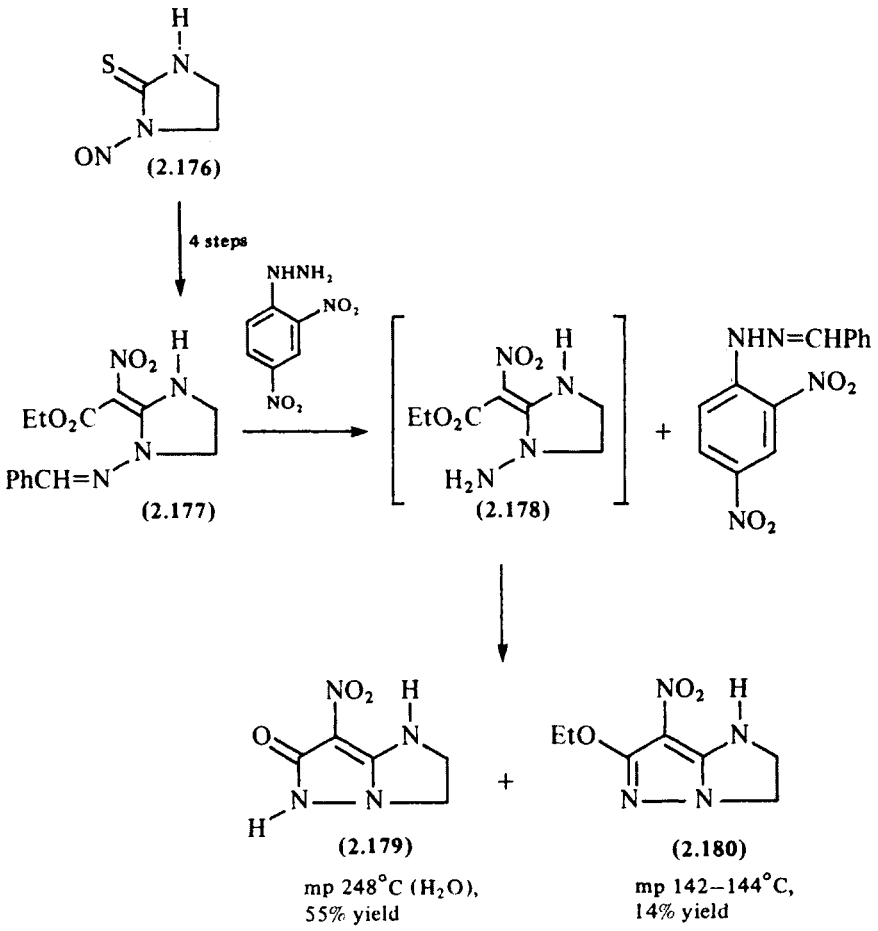


(2.175)

mp 141–142°C (EtOH)

2.6.2.2. Synthesis from Imidazolidines

1-Benzylideneamino-2-(2-ethoxycarbonyl-2-nitromethylidene)imidazolidine (**2.177**) [available in four steps from 1-nitrosoimidazolin-2-thione (**2.176**)] undergoes the hydrazinolysis reaction (cf. **2.177** → **2.178**), but the ensuing 1-aminoimidazolidine derivative (**2.178**) is transformed *in situ* into a mixture of the 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole derivative (**2.180**) and the tetrahydro compound (**2.179**).[76] The two bicyclic derivatives are characterized by the following ^1H nmr spectral data (DMSO-d_6): **2.179**, $\delta = 3.8$ (m, 4H, CH_2CH_2), 9.6 (s, 2H, NH, NH); **2.180**, $\delta = 1.4$ (t, 3H, CH_3), 4.25 (q, 2H, OCH_2), 4.0 (s, 4H, CH_2CH_2), and 8.05 (s, 1H, NH).[76]



2.6.2.3. *Reactions*

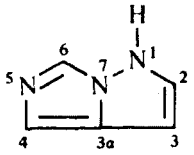
The parent compound of the series, 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazole (**2.172a**), undergoes bromination by bromine in acetic acid to give a 7-bromo derivative (**2.172**, R = Br, R^1 = H, mp 110–111°C);[73] it also forms a 1-acetyl derivative (**2.172**, NAc for NH, R = R^1 = H; mp 110–111°C) on acetylation with acetic anhydride at room temperature.[73]

2.6.2.4. *Commercial Applications*

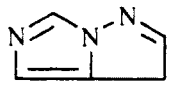
2,3-Dihydro-1*H*-imidazo[1,2-*b*]pyrazole (**2.172a**) possesses sedative and antipyretic properties[73] and also inhibits DNA synthesis in cultures of HeLa cells.[77]

2.7. RING SYSTEM C_3N_2–C_3N_2: 1*H*-IMIDAZO[1,5-*b*]PYRAZOLE

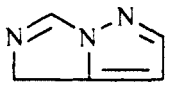
Compounds in the imidazo[1,5-*b*]pyrazole ring system can belong in principle to either 1*H* (**2.181**), 3*H* (**2.182**), or 4*H* categories (**2.183**), but the few derivatives known in this group are in the 1*H* form. Fully unsaturated compounds have not yet been prepared, and compounds in this section belong to the 2,3-dihydro- (**2.184**) and 2,3,3*a*,4,5,6-hexahydro-1*H*-imidazo[1,5-*b*]pyrazole groups (**2.185**).



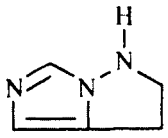
(2.181)



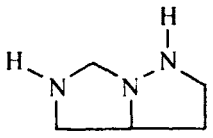
(2.182)



(2.183)



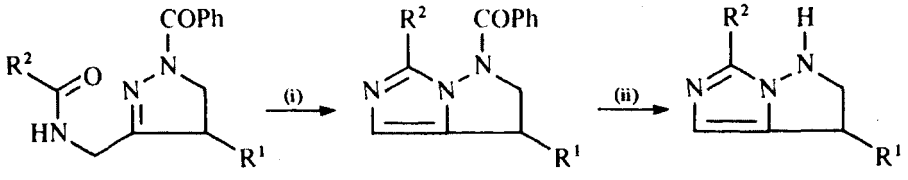
(2.184)



(2.185)

2.7.1. 2,3-Dihydro-1*H*-imidazo[1,5-*b*]pyrazoles

A series (see Table 2.19) of 2,3-dihydro-1*H*-imidazo[1,5-*b*]pyrazoles (**2.187**, **2.188**) has been prepared by means of the phosphorus oxychloride-mediated dehydrative cyclization of amide derivatives of 4,5-dihydropyrazoles (**2.186**), and a similar sequence has been used to synthesize the 2-ethoxycarbonyl derivative (**2.189**);[78] this versatile synthetic approach uses precursor pyrazoles derived from the cycloaddition of diazomethane to acrylnitriles.[78]



(2.186) (2.187) (2.188)

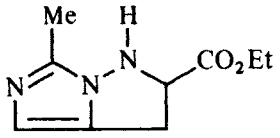
	R^1	R^2
a	H	Me
b	Ph	Me
c	H	Ph

(i) $POCl_3$, room temperature (for **2.186a**, **b**) or reflux (for **2.186c**);
(ii) 12*M* HCl, EtOH, reflux

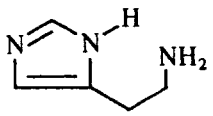
TABLE 2.19. SYNTHESIS[a] OF 2,3-DIHYDRO-1*H*-IMIDAZO[1,5-*b*]PYRAZOLES FROM DIHYDROPYRAZOLES (2.186)[78]

Compound	Yield (%)	mp (°C)	Solvent for Recrystallization	Spectral Parameters[b]
2.187 (R^1 = H, R^2 = Me)	65	122	*i*-PrOH	ir: ν_{max} = 2632, 1695; nmr: 7.9–7.5 (Ar–H), 7.2 (s, =CH), 4.7 (t, J = 7, NCH_2), 3.3 (t, J = 7.0, $=CCH_2$), 2.7 (s, Me)
2.187 (R^1 = Ph, R^2 = Me)	74	199–202	*i*-PrOH	ir: ν_{max} = 2500, 1667; nmr: 7.95, 7.55 (Ar–H), 7.60 (s, =CH), 5.3 (m, NCH_2), 4.65 (m, J = 10.0 and 12.0, PhC*H*), 2.85 (s, Me)
2.187 (R^1 = H, R^2 = Ph)	25	180–181	$CHCl_3$–Et_2O	ir: ν_{max} = 1670; nmr: 7.7, 7.45, and 7.2 (Ar–H), 6.75 (s, =CH), 4.52 (t, J = 7.0, NCH_2), 2.83 (t, J = 7.0, $=CH_2$)
2.188 (R^1 = H, R^2 = Me)	100	122[c]	Et_2O[d]	ir: ν_{max} = 3571, 1626; nmr: 10.26 (br, NH), 7.7 (t, J = 8.0, NH) 6.85 (s, =CH), 4.0 (q, J = 7.0, NCH_2), 3.15 (t, J = 7.0, CH_2CH_2), 2.63 (s, Me)
2.188 (R^1 = Ph, R^2 = Me)	74	115–117	EtOAc	ir: ν_{max} = 3125; nmr: 7.28 (Ar–H), 6.55 (s, =CH), 4.50 (t, J = 7.0, PhC*H*), 4.19 (q, J = 7.0 and 11.0, H_A), 3.68 (q, J = 7.0 and 10.0, H_B), 2.30 (s, Me)
2.189	–[e]	Oil		ir: ν_{max} = 3300, 1705; nmr: (HCl salt in H_2O), 7.45 (s, =CH), 5.40 (CH), 4.55 (q, J = 7.0, OCH_2), 3.80 (m, CH_2), 2.90 (s, Me), 1.5 (t, J = 7.0, OCH_2CH_3)

[a] For reaction conditions, see text.
[b] Nuclear magnetic resonance spectra quoted in ppm (δ) relative to tetramethylsilane ($CDCl_3$ solvent) unless otherwise stated; ir spectra recorded as Nujol mulls (units cm^{-1}).
[c] Melting point of hydrochloride quoted.
[d] Compound also vacuum sublimed after recrystallization.
[e] Yield not quoted.



(2.189)

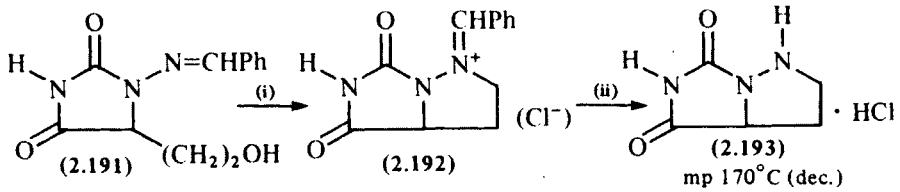


(2.190)

An interesting structural feature of the 2,3-dihydro-1*H*-imidazo[1,5-*b*]pyrazole ring system is its close relationship to histamine (**2.190**); therefore, compounds in the former group are of interest as selective antagonists of the latter. Unfortunately, compound **2.188a** does not possess histamine blocking properties, but **2.188b** possesses moderate amphetamine like CNS activity.[78]

2.7.2. 2,3,3*a*,4,5,6-Hexahydro-1*H*-imidazo[1,5-*b*]pyrazoles

Thionyl chloride-promoted cyclization of the benzylideneamino hydantoin derivative (**2.191**) provides a good yield of the labile iminium salt (**2.192**) in the fully saturated imidazo[1,5-*b*]pyrazole system, and this can be converted by treatment with methanol into the condensed hydantoin derivative (**2.193**).[79] The hydrochloride salt (**2.193**) can be recrystallized from 90% propan-2-ol to provide the free base, mp 205–207°C with the following spectral parameters: uv, no λ_{max} above 220 nm; ^{1}H nmr (DCl–D_2O), $\delta = 2.61$ (m, H-3,3), 3.72 (m, H-2,2), 4.65 (m, H-3*a*).[79]



(2.191) (2.192) (2.193)

mp 170°C (dec.)
(*i*-PrOH, HCl)

(i) $SOCl_2$, reflux, 1 h; (ii) MeOH, room temperature

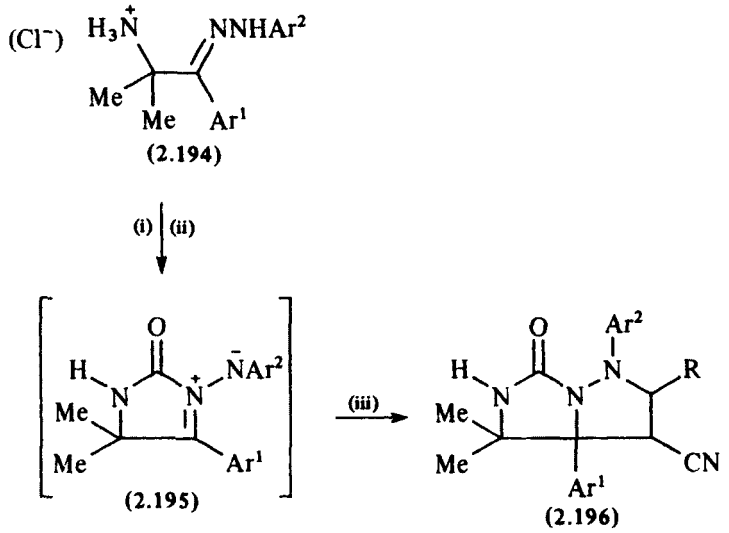
Compounds in the fully saturated 1*H*-imidazo[1,5-*b*]pyrazole group (cf. **2.185**) have also been obtained more recently through 1,3-dipolar cycloaddition processes,[80] although it should be noted that these compounds (**2.196**) are incorrectly named in the original paper and in *Chemical Abstracts* (but not in the compound citation index) as perhydroimidazo[3,4-*b*]pyrazol-3-ones. In this synthetic route, the free bases of α-amino*iso*butyrophenone phenyl hydrazones (cf. **2.194**) are treated with phosgene to generate azomethineimines (**2.195**) that are then converted by cycloaddition processes into hexahydro-4,4-dimethyl-1,3*a*-diaryl-6-oxo-1*H*-imidazo[1,5-*b*]pyrazole-3-carbonitriles (see **2.196** and Table 2.20).[80] From ^{1}H nmr data (see Table 2.20) measured on the 2,3-dicarbonitrile derivatives (**2.196**, R = CN), it has been established that there is no spin–spin coupling between hydrogens at C-2 and C-3. It can be assumed, therefore, that the C-2–H/C-3–H dihedral angle is near 90°, with the nitrile groups in an antiperiplanar (*trans*) arrangement.

TABLE 2.20. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF HEXAHYDRO-4,4-DIMETHYL-1,3*a*-DIARYL-6-OXO-1*H*-IMIDAZO[1,5-*b*]-PYRAZOLE-3-CARBONITRILES[80]

Compound **2.196**					
Ar^1	Ar^2	R	Yield (%)	mp[a] (°C)	Spectral Properties[b]
Ph	Ph	CN	71	88	ir: 2240 (CO), 1710 (CN); uv: 200 (4.4), 237 (4.1), 276 (3.7); nmr: 0.78 (s, CH_3), 1.65 (s, CH_3), 5.07 (s, C*H*CN), 6.02 (s, C*H*CN), 6.8–7.7 (Ar–H), 8.14 (s, NH)
4-MeC_6H_4	Ph	CN	74	80	ir: 2240 (CN), 1720 (CO); uv: 217 (4.2), 231 (4.1), 272 (3.6); nmr: 0.72 (s, Me), 1.37 (s, Me), 2.22 (s, Me), 4.97 (s, C*H*CN), 5.97 (s, C*H*CN), 6.5–7.8 (m, Ar–H), 8.33 (s, NH)
H	H	H	36	95	ir: 3280 (NH), 2240 (CN), 1735 (CO); uv: 198 (4.6), 241 (4.1), 284 (3.3); nmr: 0.72 (s, CH_3), 1.65 (s, CH_3), 2.6–3.0 (m, C*H*CH_2), 3.9–4.5 (m, CHC*H*$_2$), 6.6–7.6 (m, Ar–H), 7.91 (s, NH)
4-MeC_6H_4	H	H	71	110 (dec.)	ir: 3280 (NH), 2240 (CN), 1735 (CO); uv: 198 (4.6), 217 (4.1), 241 (4.1), 270 (3.6); nmr: 0.71 (s, Me), 1.63 (s, Me), 2.18 (s, Me), 2.6–3.1 (m, C*H*CH_2), 3.9–4.4 (m, CHC*H*$_2$), 6.5–7.4 (m, Ar–H), 7.85 (s, NH)

[a] Compounds recrystallized from benzene–diethylether.

[b] Infrared spectra quoted in cm^{-1} (KBr); uv quoted in nm (log ϵ); ^1H nmr quoted in δ values from tetramethylsilane standard (DMSO-d_6 solution).



(2.194)

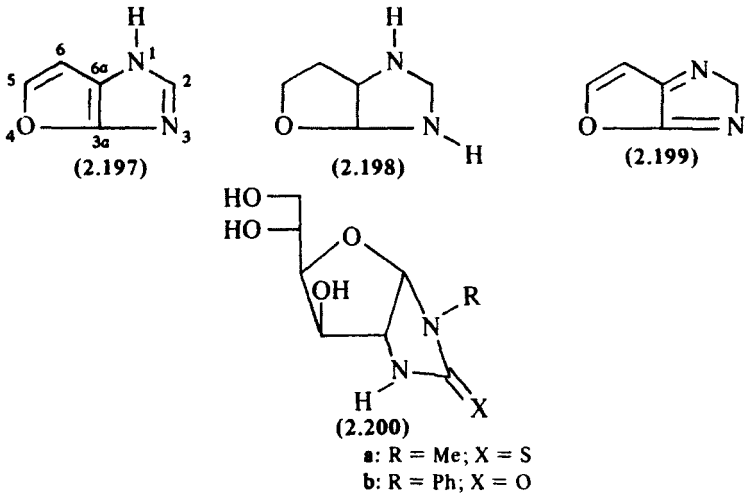
(2.195)

(2.196)

(i) Et_3N, tetrahydrofuran, reflux; (ii) $COCl_2$, tetrahydrofuran, −20 to −30°C; (iii) RCH=CHCN (*trans* for R = CN), tetrahydrofuran

2.8. RING SYSTEM C_3N_2–C_4O: 1*H*-FURO[2,3-*d*]IMIDAZOLES

There are no citations to fully unsaturated furo[2,3-*d*]imidazoles (cf. **2.197**) during the literature period covered, but fully saturated (hexahydro) derivatives (cf. **2.198**) are well documented. Compounds in the latter category have emerged from synthetic studies in carbohydrate chemistry, and care must be exercised in the correct use of IUPAC nomenclature. For example, the furanose derivative (**2.200a**) is usually named as 1-methyl-4,5(*cis* 1,2-D-glucofurano)imidazolidin-2-thione[81] but appears in *Chemical Abstracts* as 5-(1,2-dihydroxyethyl)hexahydro-6-hydroxy-



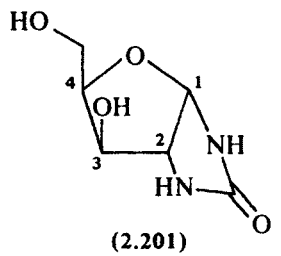
(2.197)

(2.198)

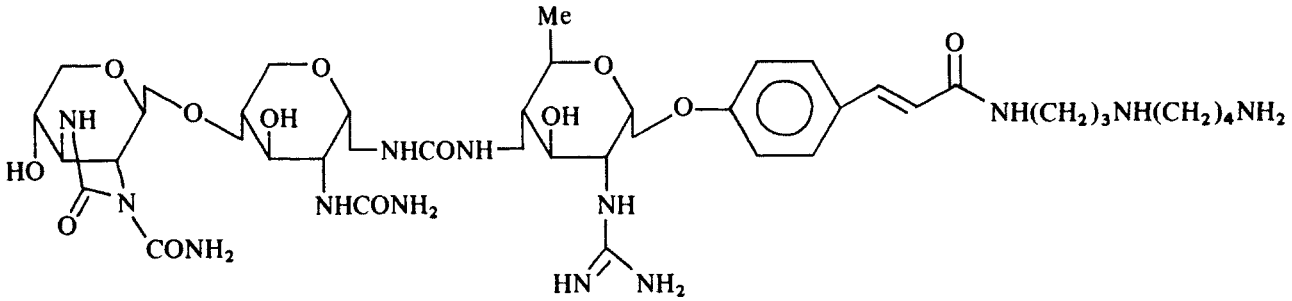
(2.199)

(2.200)

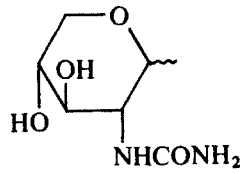
a: R = Me; X = S
b: R = Ph; X = O



(2.201)



(2.202)



(2.203)

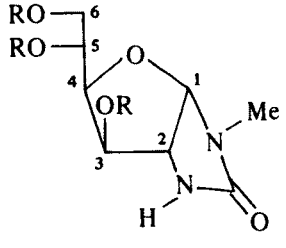
3-methyl-1*H*-furo[2,3-*d*]imidazole 2-(3*H*)thione; in a later nomenclature procedure, the condensed imidazolidinone (**2.200b**)[82] is cited in *Chemical Abstracts* as 5-(1,2-dihydroxyethyl)hexahydro-6-hydroxy-3-phenyl-2*H*-furo[2,3-*d*]imidazol-2-one, using 2*H*-furo[2,3-*d*]imidazole (**2.199**) as the parent ring system. The more common carbohydrate nomenclature is used widely in this section.

2.8.1. Hexahydro-1*H*-furo[2,3-*d*]imidazoles

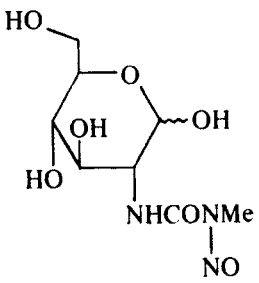
2.8.1.1. Occurrence in Degradation of Natural Products

1,2-Dideoxy-1,2-ureylene-D-xylofuranose (**2.201**) has been isolated as one component in the acid-catalyzed (AcOH, 37°C) degradation product of a broad-spectrum antibiotic in the glycocinnamoylspermidine class (**2.202**).[83] It is likely that this compound (**2.201**) originates from the corresponding 2-deoxy-2-ureido-D-xylopyranoside (**2.203**) (cf. ref. 91 and the following section on synthesis of hexahydro-1*H*-furo[2,3-*d*]imidazoles). Compound **2.201** is a solid [no mp quoted; $[\alpha]_D$ −67.2° (H_2O)] exhibiting the following spectral data: ir = 3390, 3335, 3205, 1690, and 1670 cm^{-1}; ^1H nmr (D_2O), δ = 3.82 (1H, q, CH_2OH, J = 11.5 and 7.0 Hz), 3.93 (1H, q, CH_2OH, J = 11.5 and 4.4 Hz), 4.14 (1H, m, H_4, J = 7.0, 4.4 and 2.5 Hz), 4.24 (1H, d, H_3, J = 2.5 Hz), 4.30 (1H, d, H_2, J = 6.3 Hz), and 5.88 (1H, d, H_1, J_{12} = 6.3 Hz).[83]

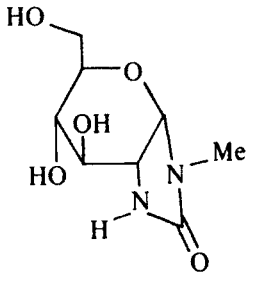
A condensed imidazolidinone (**2.204a**) has also been obtained from the sulfamic acid-mediated degradation of the broad-spectrum antibacterial agent streptozocin (**2.205**),[84] although this had been earlier[85] incorrectly assigned as a pyranose derivative (**2.206**). Compound **2.204a** [mp 177–178°C, $[\alpha]_D$ −21° (c, 0.768, H_2O)] forms a triacetoxy derivative (**2.204b**, mp 100–102°C) and is characterized by the following spectroscopic data:[84] ^1H nmr (D_2O), δ = 2.66 (s, 3H, CH_3N), 3.47 (m, 1H, J = 8.8, 2.2, 6.0 Hz, H-5), 3.67 (dd, 1H, J = 6.0, 12.2 Hz, H-6$_\beta$), 3.79 (dd, 1H, J = 2.5, 8.8 Hz, H-4), 3.83 (dd, 1H, J = 2.2, 12.2 Hz, H-6$_\alpha$), 4.18 (d, 1H, J = 6.0 Hz, H-2), 4.26 (d, 1H, J = 2.5 Hz, H-3), 5.69 (d, 1H, J = 6.0 Hz, anomeric H); ^{13}C nmr (D_2O)–163.5 (CO), 92.8 (anomeric), 79.7, 76.1 (C-4 and C-5), 69.9 (C-3), 64.9 (C-2), 62.4 (C-6), 28.4 (CH_3N).



(**2.204**)
a: R = H
b: R = Ac



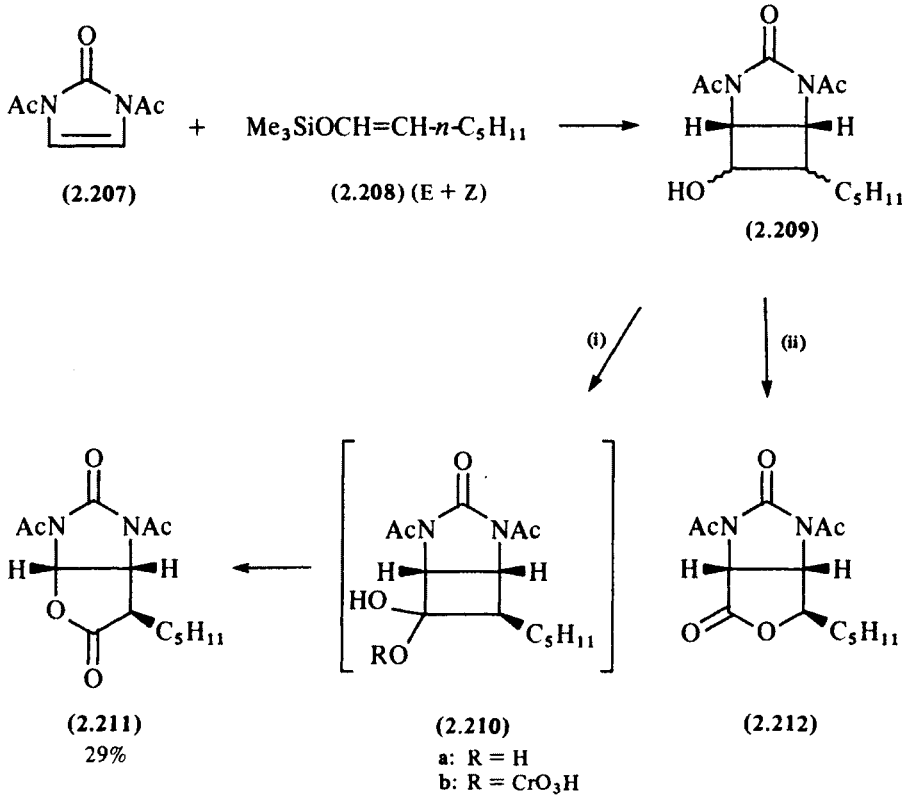
(**2.205**)



(**2.206**)

2.8.1.2. *Synthesis from Condensed Cyclobutanols*

Photochemically induced [2 + 2] cycloaddition of 1,3-diacetylimidazolin-2-one (**2.207**) with the silyl enol ether (**2.208**) gives rise to a diastereoisomeric mixture of condensed cyclobutanols (**2.209**) in good yield.[86] During an attempt to synthesize the condensed cyclobutanone oxidation product of **2.209** it was observed that the use of chromic acid as oxidant gave a low yield of the lactone (**2.211**); it is assumed[86] that this reaction occurs through the hydrate (**2.110a**) with the oxidative rearrangement proceeding by means of a chromate ester (**2.110b**). It may be noted that oxidation of the butanol derivative (**2.209**) with ruthenium oxide causes an alteration in regiochemistry of the process with formation of a mixture of **2.211** and an isomeric lactone (**2.212**) in the 1*H*-furo-[3,4-*d*]imidazole system.[86] Compound **2.111** is an oil with the following spectral characteristics:[86] ^{1}H nmr ($CDCl_3$), δ = 6.35 (1H, H-3*a*, *d*, *J* = 6.5 Hz), 4.45 (1H, H-6*a*, dd, *J* = 6.5 and 1.0 Hz), 2.9 (1H, H-6, dt, *J* = 6.0 and 1.0 Hz), 2.58 (3H, s, COMe), 2.55 (3H, s, COMe), 2.2–0.7 (11H, m); ^{13}C nmr ($CDCl_3$) δ = 175.2, 170.8, 169.6, 150.3, 80.3, 57.1, 45.8, 31.4, 30.6, 25.9, 24.5, 24.1, 22.4, and 14.0 ppm.



(i) Chromic acid, acetone, room temperature; (ii) RuO_4, CCl_4, H_2O, room temperature

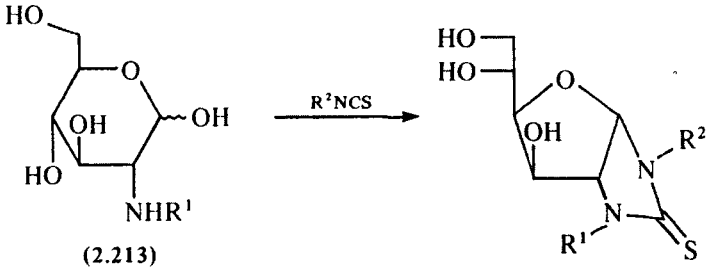
TABLE 2.21. PHYSICAL CHARACTERISTICS OF HEXAHYDRO-1*H*-FURO[2,3-*d*]IMIDAZOLES DERIVED FROM CARBOHYDRATES

Compound	Yield (%)	mp (°C)	$[\alpha]_D$	Reference
2.214 ($R^1 = CH_2C_6H_3Cl_2$-3,4; $R^2 = C_6H_3Cl_2$-3,4)	60	207–209	+ 79.4° (c, 1.01, DMF, 23°C)	91[a]
2.214 ($R^1 = H$; $R^2 = C_6H_4Cl$-4)	71	250	+ 76° (c, 1.41, pyridine, 24°C)	92
2.214 ($R^1 = H$; $R^2 = C_6H_4Br$-4)	73	250–252	+63° (c, 2.005, pyridine, 17°C)	92
2.214 ($R^1 = H$; $R^2 = C_6H_3Cl_2$-3,4)	60	185	+ 88° (c, 1.09, pyridine, 30°C)	92
2.216	24	180	–	93[b]
2.218 (R = Ph)	48	196–198	−36.4° (c, 1.09, pyridine, 27°C)	94[c]
2.218 ($R = C_6H_4Me$-4)	36	145–146	−46.9° (c, 0.63, pyridine, 20°C)	94[d]
2.218 ($R = C_6H_4Br$-4)	75	185–187	−59.3° (c, 0.72, pyridine, 27°C)	94[e]

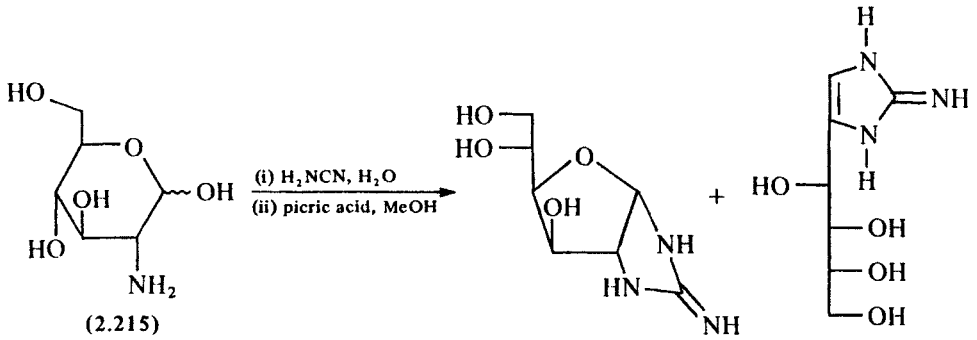
[a] Forms a triacetate (92%), mp 135–136°C, $[\alpha]_D^{25}$ + 101.9° (c, 1.03, DMF).
[b] Infrared spectral data: $\nu_{max} = 1670\ cm^{-1}$ (CN), 1560 (NO_2). Forms a hydrochloride, no mp quoted; $[\alpha]_D^{23} = -25.4°$ (c, 1.0, H_2O).
[c] Ultraviolet spectral data $\lambda_{max}^{EtOH} = 245$ nm; pentaacetate, mp 204–206°C.
[d] Ultraviolet spectral data $\lambda_{max}^{H_2O} = 238$ nm; pentaacetate, mp 201–203°C.
[e] Ultraviolet spectral data $\lambda_{max}^{EtOH} = 242$ nm; pentaacetate, mp 179–181°C.

2.8.1.3. Synthesis from Carbohydrates

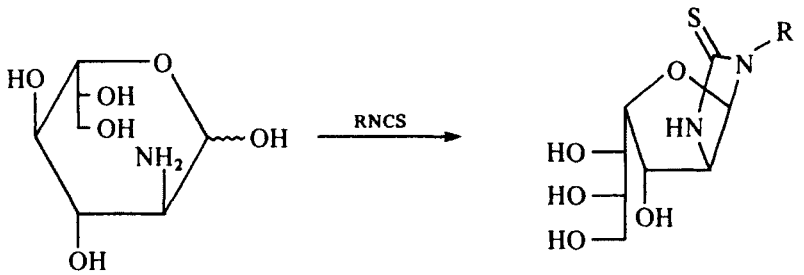
In early publications[87–90] a pyranoid (6-5) structure had been proposed for the condensed imidazole products resulting from the reaction of 2-amino-2-deoxy-D-glucose with aryl isocyanates and -thiocyanates, but it was later recognized from nmr spectral evidence that the structures are 4,5-(*cis*-1,2-D-glucofurano)imidazolidines[91] (cf. **2.213** → **2.214**,[91,92] the related transformations **2.215** → **2.216**[93] and **2.217** → **2.218**,[94] and data in Table 2.21). Additional evidence for the condensed furanose type of structure exemplified by **2.214** arises from oxidative degradation studies using sodium periodate[91] (see Section 2.8.1.5).



(2.213) (2.214)



(2.215) (2.216) (as picrate)



(2.217) (2.218)

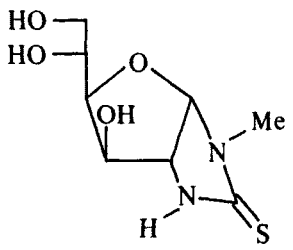
2.8.1.4. Physicochemical Studies

A number of 4,5(*cis*-1,2-D-glucofurano)imidazolidine structures have been evaluated by X-ray crystallographic analysis,[95–99] including 1-methyl-4,5-(*cis*-1,2-glucofurano)imidazolidin-2-thione (**2.219**)[81] and 1-phenyl-4,5(*cis* 1,2-D-glucofurano)imidazolidin-2-one (**2.220**).[82] The C–S bond length in **2.219** (1.689 Å) is intermediate between the sum of the covalent radii (1.81 Å) and the double-bond value (1.35 Å), which indicates that some importance should be placed on resonance forms with the partial canonical structure ($N^+ = CS^-$–N-). In contrast, the C=O bond of **2.220** (1.237 Å) indicates considerable double-bond character in the cyclic urea system. An interesting feature in the bond lengths in structure **2.220**[82] (see Table 2.22) is the asymmetry of the endocyclic O-1–C-2 (1.426 Å) and O-1–C-5 bonds (1.465 Å), a phenomenon that may be ascribed[82] to an anomeric effect. The glucofurano ring adopts a conformation intermediate between an envelope and a twist form, and the phenyl ring forms a dihedral angle of 15.1°

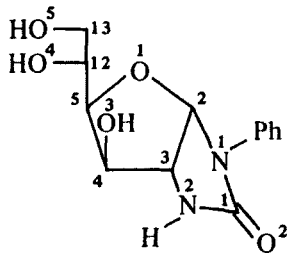
TABLE 2.22. BOND DISTANCES (Å) AND ANGLES (°) DERIVED FROM X-RAY CRYSTALLOGRAPHIC ANALYSIS OF 1-PHENYL-4,5-(*cis*-1,2-D-GLUCOFURANO)IMIDAZOLIDIN-2-ONE (**2.220**)[82a,b]

C-1–N-1	1.383(8)	C-5–C-12	1.525(10)
C-1–N-2	1.345(7)	C-12–O-4	1.419(6)
C-1–O-2	1.237(9)	C-12–C-13	1.514(9)
N-1–C-2	1.447(9)	C-13–O-5	1.452(10)
N-2–C-3	1.452(9)	N-1–C-6	1.428(7)
C-2–C-3	1.543(8)	C-6–C-7	1.405(10)
O-1–C-5	1.465(6)	C-7–C-8	1.400(9)
C-2–O-1	1.462(7)	C-8–C-9	1.370(11)
C-3–C-4	1.566(9)	C-9–C-10	1.389(11)
C-4–C-5	1.511(9)	C-10–C-11	1.394(8)
C-4–O-3	1.414(8)	C-11–C-6	1.384(10)
N-1–C-1–N-2	108.0(5)	O-1–C-5–C-12	108.3(5)
N-1–C-1–O-2	125.8(6)	C-4–C-5–C-12	115.8(5)
N-2–C-1–O-2	126.2(6)	C-5–C-12–O-4	107.7(5)
C-1–N-1–C-2	111.3(5)	O-4–C-12–C-13	111.9(5)
N-1–C-2–C-3	104.7(5)	C-5–C-12–C-13	112.0(5)
C-2–C-3–N-2	101.8(5)	C-12–C-13–O-5	108.2(5)
C-3–N-2–C-1	114.2(5)	C-1–N-1–C-6	126.0(5)
N-1–C-2–O-1	113.7(5)	C-2–N-1–C-6	122.5(5)
O-1–C-2–C-3	106.7(5)	N-1–C-6–C-7	118.0(6)
C-2–C-3–C-4	105.3(5)	C-6–C-7–C-8	119.3(7)
C-3–C-4–C-5	102.3(5)	C-7–C-8–C-9	121.3(7)
C-4–C-5–O-1	105.9(5)	C-8–C-9–C-10	119.2(7)
N-2–C-3–C-4	111.7(5)	C-9–C-10–C-11	120.7(7)
O-3–C-4–C-3	110.4(5)	C-10–C-11–C-6	120.1(6)
O-3–C-4–C-5	111.9(5)	C-11–C-6–N-1	122.7(6)

[a] The final *R* values for 1246 independent reflections was 0.068.
[b] See structure **2.220** for the crystallographic numbering system.



(2.219)

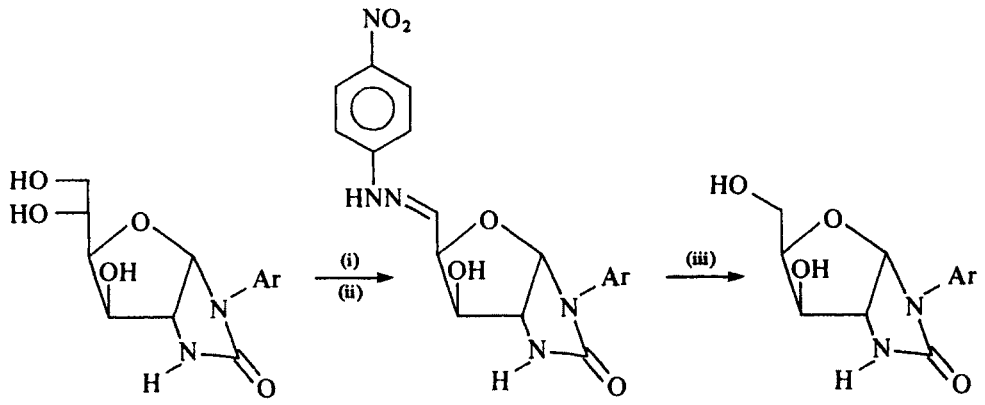


(2.220)

with the imidazolidine ring; the bicyclic system is *cis*-fused with a dihedral angle of 70.2°.

2.8.1.5. Reactions

The sodium periodate-promoted oxidative cleavage of compound **2.221** was used in early work as evidence for the condensed furanose structure in such molecules (see **2.221** → **2.222** → **2.223**).[91] The periodate cleavage procedure has also been used[91] on condensed imidazolines (cf. **2.225**) derived from Raney nickel-induced desulfurization of 1-aryl-4,5-(*cis*-1,2-D-glucofurano)imidazolidin-2-thiones[91,100] (see Table 2.23 for a summary of the physical properties of compounds described in Schemes 2.20 and 2.21).



(2.221)
Ar = $C_6H_3Cl_2$-3,4

(2.222)

(2.223)

(i) $NaIO_4$, aqueous MeOH;
(ii) *p*-$O_2NC_6H_4NHNH_2$;
(iii) $NaBH_4$, THF

Scheme 2.20

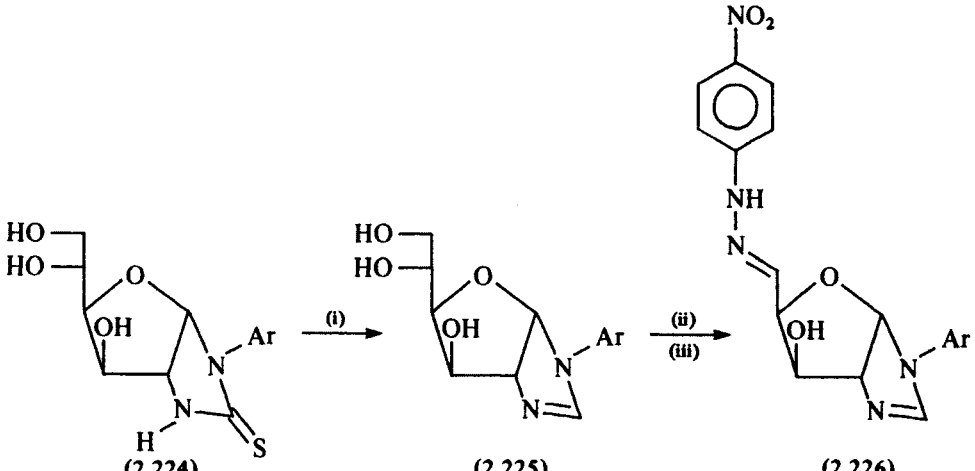
TABLE 2.23. PHYSICAL PROPERTIES OF CONDENSED FURANOSE DERIVATIVES DERIVED FROM 1-ARYL-4,5(*cis*-1,2-GLUCOFURANO)-IMIDAZOLIN-2-ONES AND -THIONES

Compound	Yield (%)	mp (°C)	$[\alpha]_D$	Reference
2.222 (Ar = $C_6H_3Cl_2$-3,4)	79	255 (dec.)	+ 364.3° (c, 0.62, DMF, 25°C)	91
2.223 (Ar = $C_6H_3Cl_2$-3,4)	81	175–176	+ 115.8° (c, 1.06, DMF, 25°C)	91
2.225 (Ar = $C_6H_3Cl_2$-3,4)	64	204–206	+ 251.8° (c, 1.00, pyridine, 23°C)	91
	55	202–204	+ 302° (c, 1.00, pyridine, 25°C)	100
2.225 (Ar = Ph)	70	141–143	–	100
2.225 (Ar = C_6H_5Cl-2)	60	146–150	+ 124° (c, 1.00, pyridine, 25°C)	100
2.226 (Ar = $C_6H_3Cl_2$-3,4)	80	230–231 (dec.)	+ 648.5° (c, 0.89, DMF, 25°C)	91

TABLE 2.24. PHYSICAL PROPERTIES OF 1-ARYL-4,5(*cis*-1,2-D-GLUCOFURANO)-IMIDAZOLIDIN-2-THIONES BEARING A 6″-DIALKYLAMINO FUNCTION[101]

Compound 2.230				
R^1	R^2	Ar	mp (°C)	$[\alpha]_D^{23}$[a]
Et	Et	$C_6H_3Cl_2$-3,4	136–138	+54.2° (c, 1.006)
Et	Et	C_6H_4OMe-4	147–149	+58° (c, 1.09)
Me	Me	$C_6H_3Me_2$-3,4	210–211	+62.2° (c, 1.00)
Et	Et	$C_6H_3Me_2$-3,4	143–145	+59.5° (c, 1.01)
Me	Me	C_6H_3-3-Cl-4-Me	205–207	+55.5° (c, 1.04)

[a] Measured in dimethylformamide.

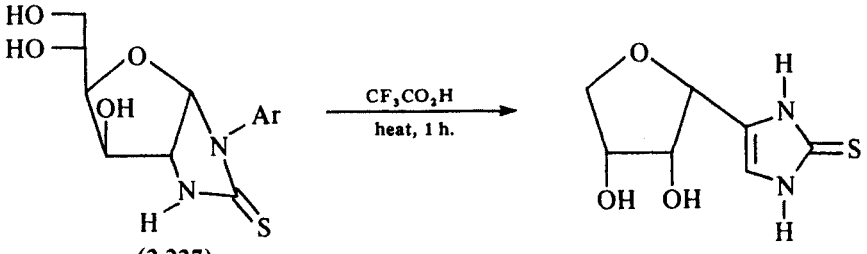


(2.224) (2.225) (2.226)

(i) Raney nickel, EtOH, reflux, 45 min;[91]
(ii) $NaIO_4$, aqueous MeOH; (iii) p-$O_2NC_6H_4NHNH_2$

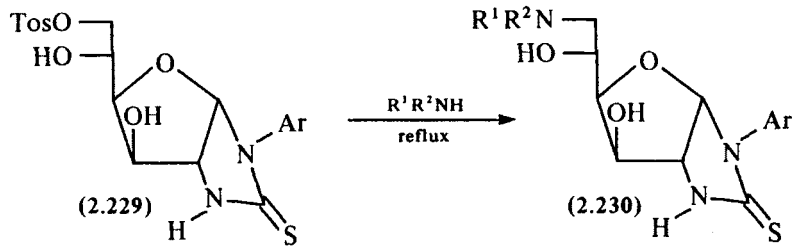
Scheme 2.21

Other reactions of 1-aryl-4,5-(*cis*-1,2-D-glucofurano)imidazolidin-2-ones and -thiones include their acid-promoted transformation into erythrofuranosyl imidazoline thiones (see 2.227 → 2.228)[92] and the conversion of appropriate tosylates (cf. 2.229) into 6″-deoxy-6″-dialkylamino derivatives (2.230) of (D-glucofurano) imidazolidines (see Table 2.24).[101]



(2.227)
Ar = aryl

(2.228)



2.8.1.6. *Practical Applications*

The 6″-dialkylamino derivatives (**2.230**) described in the previous section are patented[101] for use as antiphlogistic, analgetic, and antipyretic agents, and the related compound (**2.230**, HO for R^1R^2N; Ar = C_6H_4Cl-2) is reported to be useful as a radiosensitizer at the cellular level.[102]

2.9. RING SYSTEM C_3N_2–C_4O: 1*H* and 4*H*-FURO[3,4-*d*]-IMIDAZOLES

There are no citations to fully unsaturated 1*H*- and 4*H*-furo[3,4-*d*]imidazoles (cf. **2.231A,B**) during the literature period covered, but 4,6-dihydro 1*H*-compounds (cf. **2.232**) are described as well as tetrahydro derivatives of 4*H*-furo[3,4-*d*]-imidazoles; there are also many compounds in the fully saturated ring system (cf. **2.233**) of interest because of their isosteric relationship to analogous fully saturated 1*H*-thieno[3,4-*d*]imidazoles (cf. biotin and related compounds described in Section 2.15.5). It should be noted that compounds in the last group (cf. **2.233**) are cited in *Chemical Abstracts* under the 1*H*-furo[3,4-*d*]imidazole heading but are often described in the primary chemical literature according to carbohydrate nomenclature (e.g. **2.234** is correctly named as 1-phenyl-5′-*O*-methanesulfonyl-1′-*O*-methyl-β-D-ribofurano[3′,2′:4,5]imidazolidinone[103]).

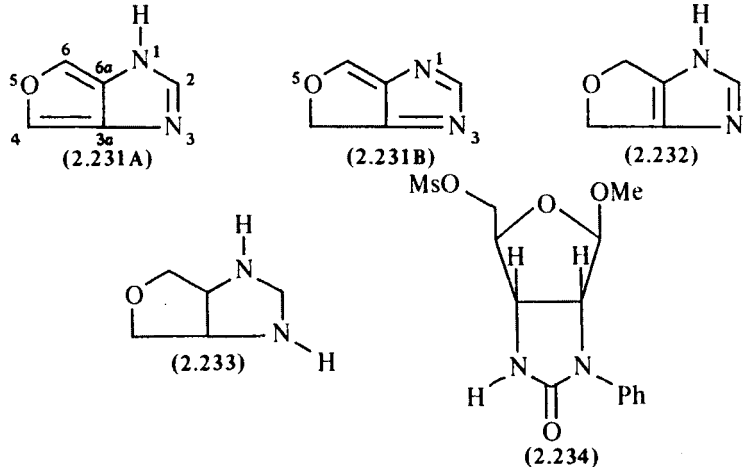


TABLE 2.25. SYNTHESIS OF 4,6-DIHYDRO-1*H*-FURO[3,4-*d*]IMIDAZOLE DERIVATIVES[104,105]

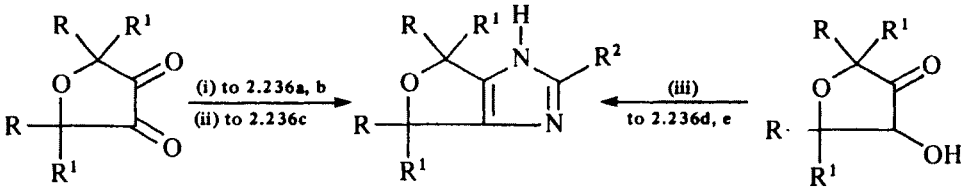
Starting material	Product	Reaction Conditions[a]	Yield (%)	mp (°C)	Solvent for Recrystallization	Reference
2.235a	**2.236a**	A	70	288–289	Pyridine	104
2.235b	**2.236b**	A	80	193–194	Dichloromethane	104
2.235a	**2.236c**	B	82	253–254	Acetone	104
2.237a	**2.236d**[b]	C	64	292–293	Cyclohexane	105
2.237b	**2.236e**[b]	C	51	300–300.5	Aqueous ethanol	105

[a]Reaction conditions: (A) $CH_3CO_2NH_4$, AcOH, hexamethylenetetramine, reflux, 1 h; (B) PhCHO, $CH_3CO_2NH_4$, AcOH, reflux, 1 h; (C) thiourea, AcOH, reflux, 5 h.
[b]Formulated in the text for convenience in the 2-mercapto tautomeric form.

2.9.1. 4,6-Dihydro-1*H*-furo[3,4-*d*]imidazoles

2.9.1.1. Synthesis

The synthesis of 2-unsubstituted (**2.236a,b**) and 2-phenyl-4,4,6,6-tetraalkyl-4,6-dihydro-1*H*-furo[3,4-*d*]imidazoles (**2.236c**) can be achieved in good yield by the cyclocondensation of tetraalkyltetrahydrofuran-3,4- diones (**2.235**) with ammonia and aldehydes (see Table 2.25).[104] Analogous compounds in the 4,6-dihydro-1*H*-furo[3,4-*d*]imidazolin-2-thione series (see **2.236d,e** and Table 2.25) can be obtained in condensative cyclizations of 4-hydroxy tetraalkyltetrahydrofuran-3-one derivatives (**2.237**) with thiourea;[105] it may be noted that imidazolin-2-one derivatives related to (**2.236d,e**) cannot be synthesized in comparable reactions with urea since processes of this type terminate at the carbamide stage (see, e.g., **2.238** → **2.239**).[105]



(**2.235**)

	R	R^1
a	Me	Me
b	Me	Et

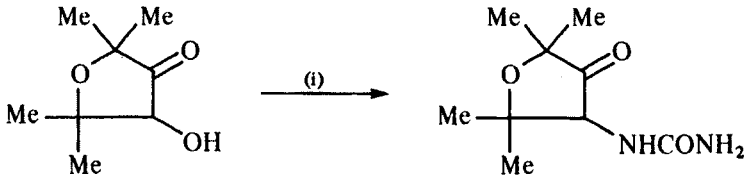
(**2.236**)

	R	R^1	R^2
a	Me	Me	H
b	Me	Et	H
c	Me	Me	Ph
d	Me	Me	SH
e	$-(CH_2)_5-$		SH

(**2.237**)

	R	R^1
a	Me	Me
b	$-(CH_2)_5-$	

(i) Hexamethylenetetraamine, $AcONH_4$, AcOH, reflux;
(ii) PhCHO, $AcONH_4$, AcOH, reflux; (iii) H_2NCSNH_2



(2.238) (2.239)

(i) H_2NCONH_2, AcOH, reflux, 5 h

2.9.1.2. *Physicochemical Studies*

The basicity constants and acidity constants of four compounds in the tetraalkyl-4,6-dihydro-1*H*-furo[3,4-*d*]imidazole series have been determined[106] and compared with values for aniline, phenol, imidazole, and benzimidazole (see Table 2.26). From these data it can be seen that the former are stronger bases than aniline and weaker acids than phenol; they are weaker in basicity than imidazole and show about the same order of basicity as benzimidazole.

2.9.1.3. *Reactions*

The basic character of the imidazole ring of 4,4,6,6-tetraalkyl-4,6-dihydro-1*H*-furo[3,4-*d*]imidazoles is manifest in their conversion[106] into hydrochloride salts and methiodides (see **2.240** → **2.241a, b**); the hydrochloride (**2.241a**) is a stable crystalline compound and is not decomposed when heated under reflux in ethanol for many hours. Acylation of the 4,6-dihydro compound (**2.240**) with acetic anhydride with a short reflux time (20 min) gives rise to a 1-acyl derivative (**2.242**), but the use of a longer reaction time (2 h) causes cleavage of the imidazole ring of **2.240** with formation of a 3,4-diacetylamino-2,5-dihydrofuran derivative (**2.243a**); a similar fragmentation of **2.240** is effected under conditions of Schotten–Baumann benzoylation (see **2.240** → **2.243b**). Mannich reactions of **2.240** proceed in anticipated fashion with the formation of 1-(dialkylamino)methyl derivatives

TABLE 2.26. BASICITY CONSTANTS[a] AND ACIDITY CONSTANTS[a] OF 4,4,6,6-TETRAALKYL-4,6-DIHYDRO-1*H*-FURO[3,4-*d*]IMIDAZOLES AND OTHER COMPOUNDS[106]

Compound	pK_b	pK_a
2.236a	9.08	13.02
2.236b	11.76	–
2.236 [R,R¹ = $(CH_2)_4$; R² = H]	9.32	12.88
2.236 [R,R¹ = $(CH_2)_5$; R² = H]	8.07	12.94
$PhNH_2$	10.14	–
PhOH	–	11.33
Imidazole	7.05	–
Benzimidazole	8.6	12.7

[a] From potentiometric titration.

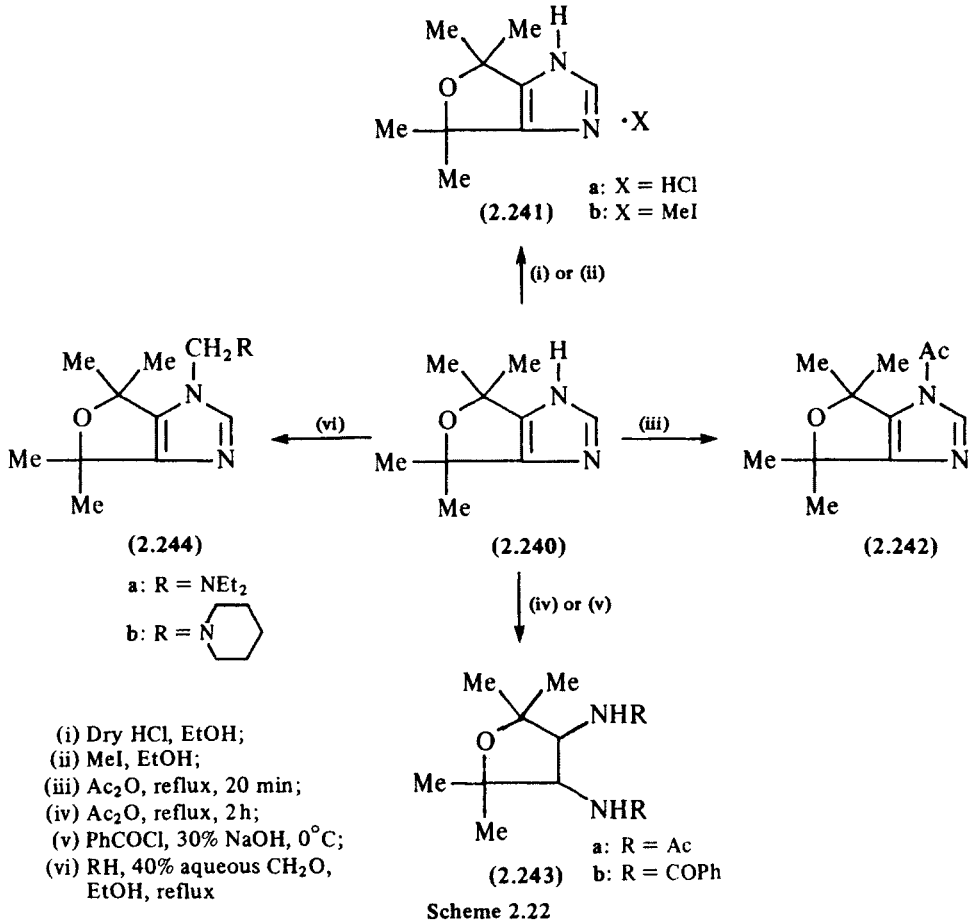
TABLE 2.27. COMPOUNDS DERIVED[a] FROM REACTIONS OF 4,4,6,6-TETRAMETHYL-4,6-DIHYDRO-1*H*-FURO[3,4-*d*]IMIDAZOLE[106]

Compound	Yield (%)	mp (°C)	Solvent for Recrystallization
2.241a	76	203–203.5	EtOH
2.241b	100	191	Me_2CO
2.242	80	111–112.5	Petroleum ether
2.244a	40	170	Petroleum ether
2.244b	38	219	Me_2CO

[a]For reaction conditions, see Scheme 2.22.

(see **2.244a,b** and Table 2.27 for a summary of 4,4,6,6-tetraalkyl-4,6-dihydro-1*H*-furo[3,4-*d*]imidazoles described in this section.)

Finally it may be noted that severe oxidative conditions (acidic potassium dichromate) causes a fragmentation of the furan ring of **2.240** with concomitant formation of imidazole-4,5-dicarboxylic acid.[106]



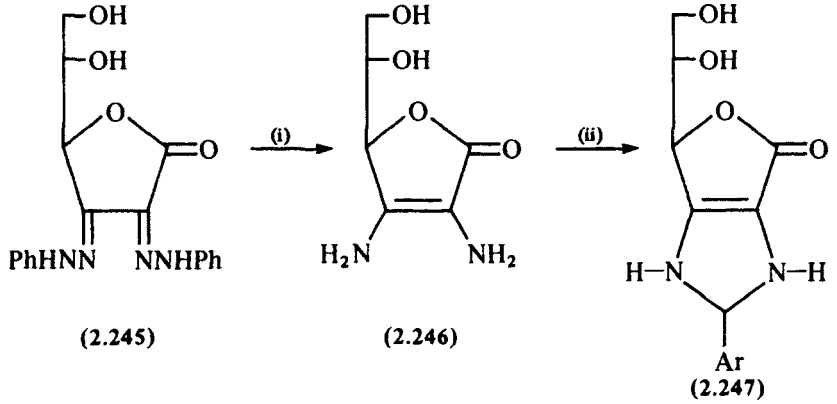
Scheme 2.22

TABLE 2.28. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF 2-ARYL-6-(1,2-DIHYDROXYETHYL)-TETRAHYDRO-4*H*-FURO[3,4-*d*]-IMIDAZOL-4-ONES (**2.247**)[107]

			uv Spectrum		ir Spectrum, ν (cm^{-1})		
Ar in Compound **2.247**	mp (°C)	Yield (%)	$\lambda_{max(nm)}$	log ϵ	CO	NO	OH
Phenyl	220–221	85	212, 238, 278, 337	3.83, 4.02, 4.16, 4.26	1700	3160	3400
o-Methoxyphenyl	220–221	91	218, 238, 278, 348	4.00, 4.00, 4.18, 4.28	1760	3220	3400
2,4-Dimethoxyphenyl	192–193	80	217, 247, 278, 352	2.97, 4.11, 4.26, 4.31	1700	3200	3400
p-Nitrophenyl	253–254	90	233, 272, 343	4.16, 4.32, 4.30	1740	3200	3400
p-Dimethylaminophenyl	237–239	85	212, 243, 280, 358	4.09, 4.00, 4.07, 4.43	1720	3210	3420
o-Chlorophenyl	228–229	79	216, 247, 278, 246	3.89, 3.89, 4.03, 4.15	1720	3200	3420
p-Chlorophenyl	231–232	80	216, 243, 278, 343	3.79, 4.01, 4.01, 4.11	1700	3180	3420
2,6-Dichlorophenyl	218–219	78	217, 267, 320	4.08, 4.19, 4.12	1730	3200	3440

2.9.2. Tetrahydro- and Hexahydro-4*H*-furo[3,4-*d*]imidazoles

A series of 2-aryl-6-(1,2-dihydroxyethyl)-tetrahydro-4*H*-furo[3,4-*d*]imidazol-4-ones (**2.247**) has been synthesized in high yield from dehydro-L-ascorbic acid bis(phenylhydrazone) (**2.245**) by the two-step procedure shown in Scheme 2.23 (see also Table 2.28).[107] The ir and uv spectral parameters of these derivatives (**2.247**) are unexceptional, but a useful, characteristic feature in their mass spectra is the apperance of strong peaks at *m/z* values corresponding to a loss of 60 amu from the molecular ion; it is surmised[107] that the latter arise by participation of the $HOCH_2CH(OH)$ side chain in a McLafferty type of rearrangement.

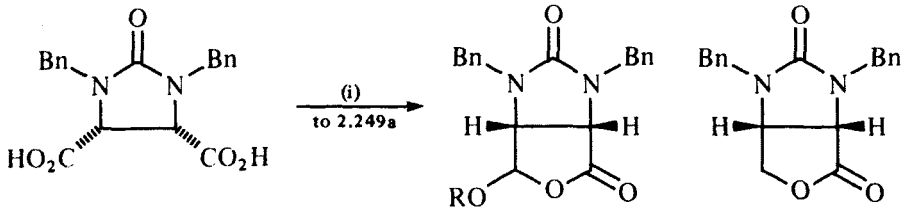


(**2.245**) (**2.246**) (**2.247**)

(i) 10% Pt–C, EtOH; (ii) ArCHO, aqueous EtOH, AcOH (cat.); reflux, 1 h

Scheme 2.23

In an alternative approach to the synthesis of reduced derivatives in the 4*H*-furo[3,4-*d*]imidazole group, *cis*-1,3-dibenzyl-2-oxo-imidazolidin-4,5-dicarboxylic acid (**2.248**) can be reductively cyclized to give the 2,4-dione derivative (**2.249a**), and this, in turn, can be hydrolyzed (1 *M* NaOH, aqueous dioxan) to give a 6-hydroxy-2,4-dione (**2.249b**).[108] The latter has been used for the synthesis[108] of optically active (3a*S*, 6a*R*)-1,3-dibenzyl-tetrahydro-4*H*-furo[3,4-*d*]imidazol-2,4-(1*H*)dione (**2.250**), a valuable intermediate[109–113] for the chiral synthesis of biotin



(**2.248**)

Bn = $PhCH_2$

(i) Zn, Ac_2O, AcOH, reflux

(**2.249**)

	R	mp (°C)
a	Ac	124–125
b	H	110–113

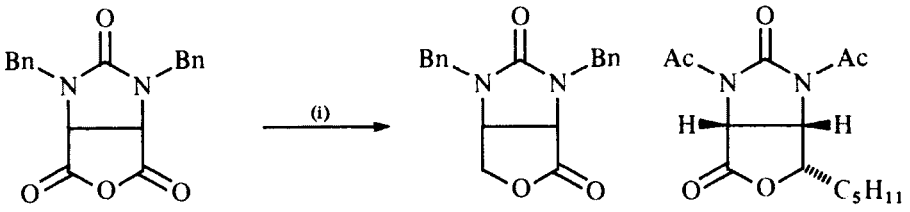
(**2.250**)

mp 117–118°C
$[\alpha]_D^{24}$ + 56.2°
(c, 1.00, C_6H_6)

TABLE 2.29. PHYSICAL PROPERTIES OF HEXAHYDRO-1*H*-FURO[3,4-*d*]IMIDAZOL-2-ONES

Starting Material	Product	Reaction Conditions	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reference
2.256 ($n = 4$)	**2.257** ($n = 4$)	–[a]	44	153–154 (dioxan)	116
2.257 ($n = 4$)	**2.258a**	–[a]	48	206–208 (H_2O)	116
2.256 ($n = 2$)	**2.257** ($n = 2$)	–[a]	37	137–139 (dioxan–methanol)	117
2.257 ($n = 2$)	**2.258b**	–[a]	31	202–204 (H_2O)	117
2.259a	**2.259b**	$SOCl_2$, room temperature	76	122–124 (EtOAc)	117
2.259b	**2.259c**	1. KCN, aqueous EtOH, reflux 2. NaOH, reflux, then H^+, H_2O	–	219–220 (H_2O)	117
2.259b	**2.259d**	1. $Na^+\bar{C}H(CO_2Et)_2$, EtOH, reflux 2. 10% aqueous $Ba(OH)_2$, reflux 3. 2*M* H_2SO_4	–	180–183 (H_2O)	117
2.259d	**2.259e**	Heat, 180–190°C	–	203–204 (aq. EtOH)	117
–[b]	**2.259f**	–[b]	–	207–208 (H_2O)	117
–[b]	**2.259g**	–[b]	–	184–185 (H_2O)	117
2.259h	**2.259i**	$SOCl_2$	–	124–126	118
2.259i	**2.259j**	$PhCH_2SNa$	–	76–79	118
2.259j	**2.259k**	Reductive cleavage	–	–	118
2.259k	**2.2591**[c]	Barium permanganate	81	–	118

[a] See Scheme 2.24.
[b] Compounds **2.259f** and **g** are prepared by procedures similar to those used for the synthesis of **2.258**.
[c] A compound [**2.2591**, $(CH_2)_5$ for $(CH_2)_4$ analogous to **2.2591**] has also been synthesized.[118]



(2.251) (2.252) (2.253)

Bn = $PhCH_2$

55% yield,
mp 107.4–108.2°C (MeOH)

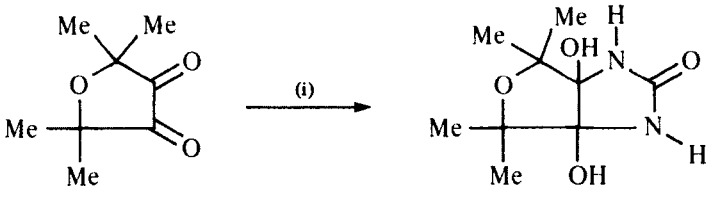
(i) $NaBH_4$, DMF, 1 h, room temperature

(see Section 2.15.5). The dione (**2.250**), albeit of undescribed stereochemistry (cf. **2.252**), has also been synthesized by the reductive process (**2.251** → **2.252**),[114] and a closely related compound (**2.253**) has been described in Section 2.8.1.

2.9.3. Hexahydro-1*H*-furo[3,4-*d*]imidazol-2-one Derivatives

2.9.3.1. Synthesis and Reactions

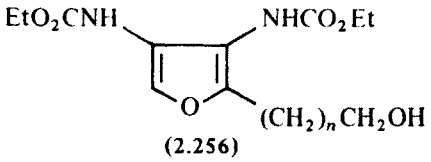
With few exceptions (e.g., **2.254** → **2.255**),[115] synthetic studies of hexahydro-1*H*-furo[3,4-*d*]imidazol-2-ones have been concerned with the preparation of oxygen analogs of biotin (oxybiotins) (see Section 2.15.5). In early work, the imidazolidinone ring was constructed from appropriately substituted *cis*-3,4-ethoxycarbonylamino derivatives of tetrahydrofuran (cf. **2.256** → **2.257** → **2.258**),[116,117] and the biotin-like 4-carboxyalkyl side chains–although of undefined stereochemistry–were generated in simple oxidative procedures. Related 4-(ω-hydroxyalkyl) derivatives (**2.259a, h**) have been used to provide intermediates (**2.259b,d,i–k**) for the synthesis of *nor*-oxybiotin (**2.259c**),[117] oxybiotins with extended carboxyalkyl side chains (**2.259f, g**),[117] and a sulfonic acid analog (**2.2591**).[118] [See Table 2.29 for a summary of the physical properties of oxybiotin analogs described above and the transformation (**2.260** → **2.261**) for the synthesis of iminium salts related to oxybiotins).[119]]



(2.254) (2.255)

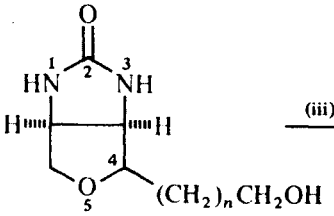
(i) H_2NCONH_2, H_2O, HCl (cat.), reflux, 0.5 h.

88% yield,
mp 202–203°C (dec.) (EtOH)



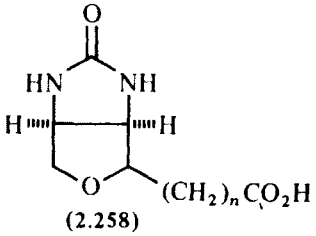
(2.256)

(i) (ii)



(2.257)

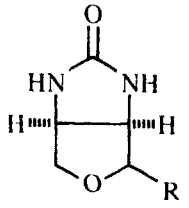
(iii)



(2.258)

a: n = 4
b: n = 2

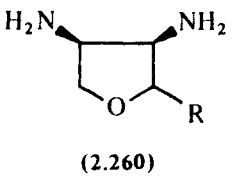
(i) H_2, Pd–$BaSO_4$, AcOH;
(ii) 10% aqueous $Ba(OH)_2$, 90°C, 2 h;
(iii) $KMnO_4$, aqueous NaOH, room temperature



(2.259)

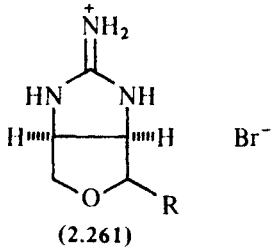
	R		R
a	$(CH_2)_3OH$	g	$(CH_2)_6CO_2H$
b	$(CH_2)_3Cl$	h	$(CH_2)_4OH$
c	$(CH_2)_3CO_2H$	i	$(CH_2)_4Cl$
d	$(CH_2)_3CH(CO_2H)_2$	j	$(CH_2)_4SCH_2Ph$
e	$(CH_2)_4CO_2H$	k	$(CH_2)_4SH$
f	$(CH_2)_5CO_2H$	l	$(CH_2)_4SO_3H$ (Ba salt)

Scheme 2.24



(2.260)

(i)

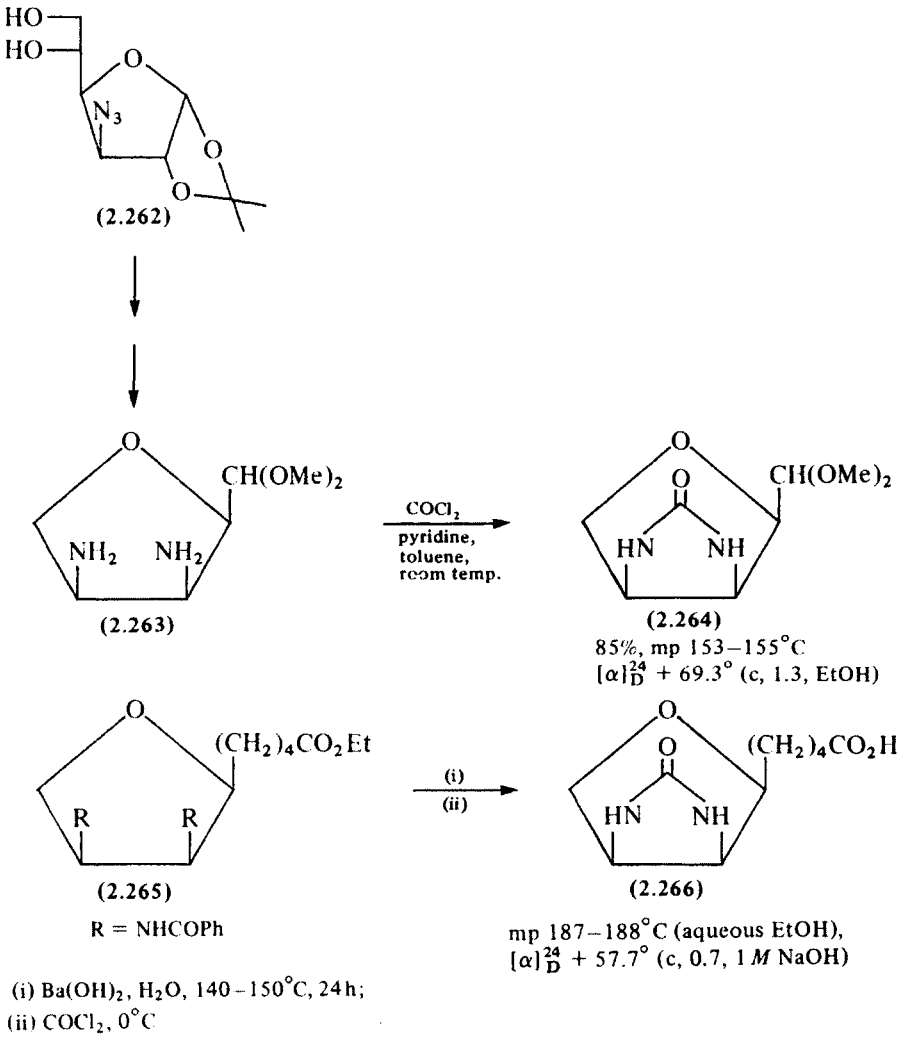


(2.261)

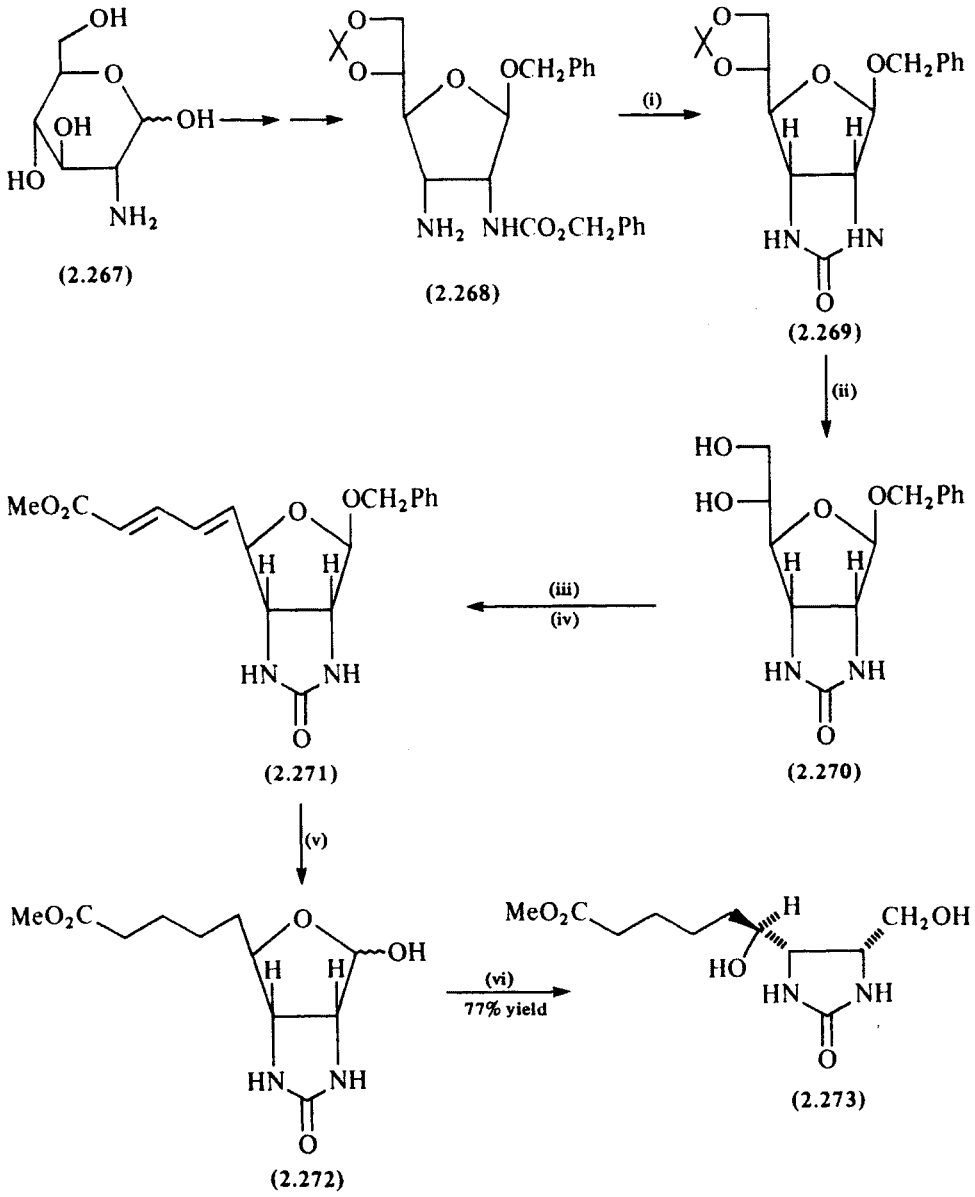
(i) BrCN, room temperature (to **2.261a**) or heat for 1 h (to **2.261b**)

	R	mp (°C)
a	Me	186–188 (EtOH)
b	$(CH_2)_4CO_2H$	174–175 (Me_2CO–EtOAc)

A total chiral synthesis of *d*-oxybiotin has been developed from 3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**2.262**),[120] including multistep transformation[121,122] into the diamine (**2.263**) and cyclization with phosgene (cf. **2.263** → **2.264**);[122] the key intermediate (**2.263**) can be converted in four steps into a precursor (**2.265**) of *d*-oxybiotin (**2.266**). The latter is reported[122] to show biotin-like activity for some microorganisms.



A carbohydrate derivative (D-glucosamine, **2.267**) has also been used to construct a series of hexahydro-1*H*-furo[3,4-*d*]imidazol-2-ones (see **2.269**–**2.272** and Table 2.30),[123] and one such intermediate (**2.272**) has been reductively cleaved to give a useful compound (**2.273**) for the chiral synthesis of *d*-biotin (see Scheme



(i) NaH, DMF, room temperature;
(ii) 70% aqueous AcOH, 4 h, 40°C;
(iii) $NaIO_4$, aqueous Me_2CO, 0°C;
(iv) $MeO_2CCH{=}CH\bar{C}H\overset{+}{P}Ph_3$, CH_2Cl_2, $CHCl_3$;
(v) 10% Pd–C, EtOH;
(vi) $NaBH_4$, MeOH, 0°C

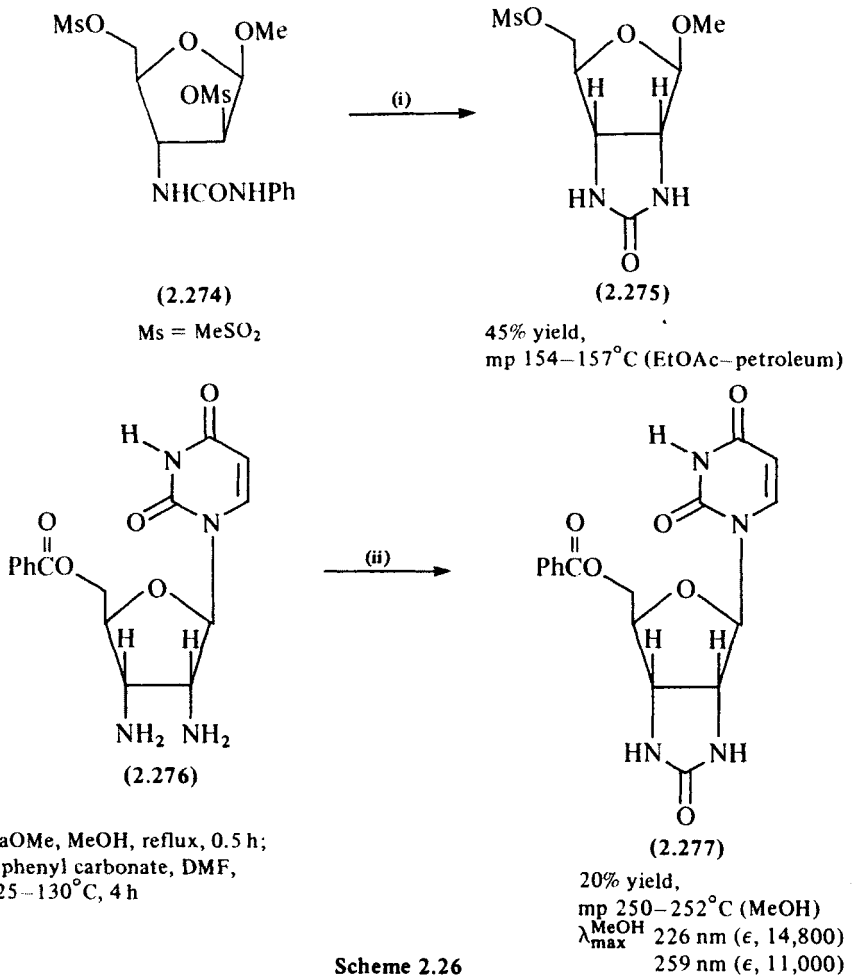
Scheme 2.25

TABLE 2.30. PHYSICAL PROPERTIES OF HEXAHYDRO-1*H*-FURO[3,4-*d*]IMIDAZOL-3-ONES (**2.269**–**2.272**) SYNTHESISED[a] FROM D-GLUCOSAMINE[123]

Compound	Yield (%)	mp (°C) (Solvent for Recrystallization)	$[\alpha]_D^{20}$
2.269	76	113–115	− 74.0° (c, 1.0, $CHCl_3$)
2.270	97	128.5 (MeOH–*i*-Pr_2O)	− 76.2° (c, 0.5, H_2O)
2.271	67	54	+ 108° (c, 1.0, $CHCl_3$)
2.272	76	(Oil)	+ 19.5° (c, 1.0, $CHCl_3$)[b]

[a] See Scheme 2.25 for reaction conditions.
[b] The $[\alpha]_D^{20}$ value is + 14.7° after 5 min and constant at + 19.5° after 5 h.

2.25 and Section 2.15.5). Additional syntheses (**2.274** → **2.275**,[103] **2.276** → **2.277**)[124] of hexahydro-1*H*-furo[3,4-*d*]imidazol-2-ones, including the preparation of a uracil-derived nucleoside (**2.277**), are illustrated in Scheme 2.26.



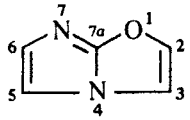
Scheme 2.26

2.9.3.2. Practical Applications

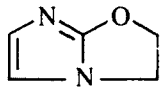
Sulfur-containing hexahydro-1*H*-furo[3,4-*d*]imidazol-3-ones (**2.259j–k**) are reported to possess antibiotic properties.[118c]

2.10. RING SYSTEM C_3N_2–C_3NO: IMIDAZO[2,1-*b*]OXAZOLE

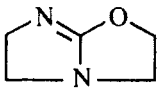
Compounds in the fully unsaturated imidazo[2,1-*b*]oxazole group (**2.278**) are rare despite their relative ease of preparation, and most derivatives in this section belong to the 2,3-dihydro (**2.279**) and 2,3,5,6-tetrahydro (**2.280**) categories; there is also an isolated publication describing 2,3,5,6,7,7*a*-hexahydroimidazo[2,1-*b*]-oxazoles (**2.281**).



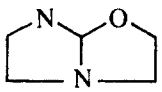
(2.278)



(2.279)



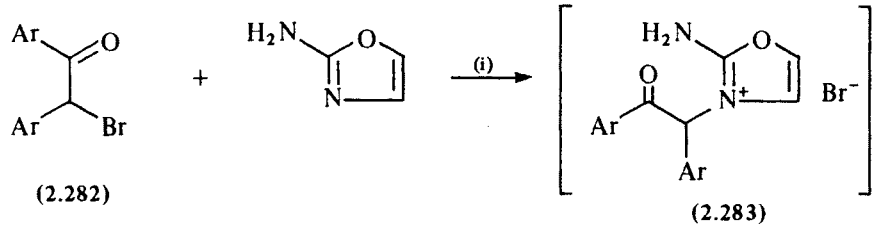
(2.280)



(2.281)

2.10.1. Imidazo[2,1-*b*]oxazoles

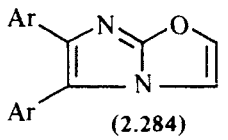
The 5,6-diarylimidazo[2,1-*b*]oxazole (**2.284**) has been prepared by treating α-bromodesoxyanisoin (**2.282**) with 2-aminooxazole at room temperature;[125] it is likely that 2-aminooxazolium compounds (cf. **2.283**) are intermediates in this process since an isolable salt of this type has been transformed into the appropriate imidazo[2,1-*b*]oxazole (cf. **2.284**) by the action of ethanolic potassium hydroxide.[126] Compound **2.284** and related condensed dianisylimidazoles have been synthesized for use in the treatment of allergic inflammation.[125]



(2.282)

Ar = *p*-$MeOC_6H_4$

(2.283)



(2.284)

mp 227°C (dec.) (MeCN)

(i) MeCN, room temperature

TABLE 2.31. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF 2,3-DIHYDROIMIDAZO[2,1-*b*]OXAZOLES (**2.287**) DERIVED FROM 2,4-DINITROIMIDAZOLE (SEE SCHEME 2.27)

R^1 in Epoxide Starting Material	Reaction Conditions	Product	Yield (%)	mp (°C) (Solvent for Recrystallization)	IR NO_2 Spectral Bands (KBr) (cm^{-1})	^1H nmr Spectra (δ, Solvent)	Reference
H	EtOH, 70°C	**2.287a**[a]	18	107–108 (Et_2O)	1500, 1330	7.65 (s, H-6), 5.22 (t, H-2, 2), 4.57 (t, H-3,3) ($CDCl_3$)	127
Me	EtOH, room temp.	**2.287b**[b]	23	68–69 (Et_2O–hexane)	1540, 1340	7.53 (s, H-6), 5.88 (m, H-2), 4.36 (m, H-3,3), 1.69 (d, Me) ($CDCl_3$)	128
CH_2Cl	EtOH, 60°C	**2.287c**[c]	25	98–99 ($CHCl_3$–hexane)	1515, 1335	7.57 (s, H-6), 5.64 (m, H-2), 4.56 (m, H-3,3), 3.89 (d, CH_2Cl) ($CDCl_3$)	128
		2.287d[c]	37	170–171 (EtOH)	1505, 1310	8.03 (s, H-5), 5.65 (m, H-2), 4.28 (m, H-3,3), 4.07 (d, CH_2 Cl (DMSO-d_6)	
CH_2OMe	EtOH, 60°C	**2.287e**[d]	26	71–72 (Et_2O–hexane)	1510, 1335	7.57 (s, H-6), 5.54 (m, H-2), 4.52 (m, H-3,3), 3.78 (d, CH_2O), 3.42 (s, Me) ($CDCl_3$)	128
		2.287f[d]	35	159–160 (EtOH)	1500, 1320	8.04 (s, H-5), 5.47 (m, H-2), 4.20 (m, H-3,3), 3.70 (d, CH_2O), 3.28 (s, Me) ($CDCl_3$)	
CH_2OH	Neat, room temp.	**2.287g**	31	167–168 (EtOAc)	1516, 1310[e]	8.35, (s, H-5), 5.44 (m, H-2), 4.31 (m, H-3,3), 3.77 (dd, CH_2O) (DMSO-d_6)	128

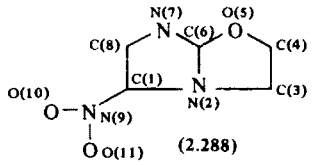
[a] Compound **2.286a** [50% yield] is also formed.
[b] Compound **2.286b** (53%) is also formed.
[c] Compound **2.286c** (15%) is also formed.
[d] Compound **2.286d** (14%) is also formed.
[e] The $OH_{stretch}$ band appears at 3336 cm^{-1}.

2.10.2. 2,3-Dihydroimidazo[2,1-*b*]oxazoles

2,3-Dihydro-5-nitroimidazo[2,1-*b*]oxazole (**2.287a**) is formed as a minor product with 1-(2-hydroxethyl)-2,4-dinitroimidazole (**2.286a**) when 2,4-dinitroimidazole is treated with ethylene oxide.[127] This bicyclic compound (**2.287a**) is thermally unstable in various solvents, and crystallization may be effected from cold ether. The procedure **2.285** → **2.287**, which presumably involves the intramolecular nucleophilic displacement of a nitro group, has been extended to provide a series of 2,5- and 2,6- disubstituted compounds albeit in poor yields (see **2.287b–g** and Table 2.31).[128] The 2,3-dihydro-5- and 6-nitroimidazo[2,1-*b*]oxazole derivatives formulated in Scheme 2.27 are characterized by the higher solubility of the former in organic solvents and the significant downfield shift experienced by protons at C-3 in the 5-nitro compounds compared to that for the 6-nitro isomers (see Table 2.31).

The molecular structure of 2,3-dihydro-5-nitroimidazo[2,1-*b*]oxazole (**2.287a**) has been determined X-ray crystallographically (see Table 2.32 for bond distances).[129] Values of interatomic distances are unexceptional, indicating the delocalized arrangement in the imidazole ring and the possibility for exocyclic delocalization within the nitro group (dihedral angle 2.4°, C-1–N-9 = 1.400 Å).

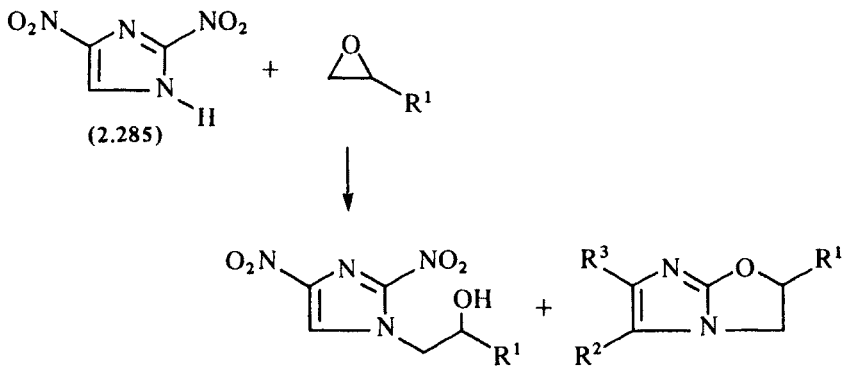
TABLE 2.32. BOND DISTANCES IN 2,3-DIHYDRO 5-NITROIMIDAZO[2,1-*b*]OXAZOLE (**2.288**) FROM X-RAY CRYSTALLOGRAPHIC ANALYSIS[129]



(2.288)

Bond in Structure **2.288**	Interatomic Distance (Å)[a]
C-1–N-2	1.383(3)
C-1–C-8	1.360(3)
C-1–N-9	1.400(3)
N-2–C-3	1.458(3)
N-2–C-6	1.328(3)
C-3–C-4	1.536(3)
C-3–H-3	1.02(2)
C-3–H′-3	1.08(3)
C-4–O-5	1.468(3)
C-4–H-4	1.02(3)
C-4–H′-4	1.02(3)
O-5–C-6	1.330(3)
C-6–N-7	1.312(4)
N-7–C-8	1.368(3)
C-8–H-8	0.94(3)
N-9–O-10	1.226(3)
N-9–O-11	1.237(3)

[a]Estimated standard deviations are in parentheses.



(2.285)

(2.286)

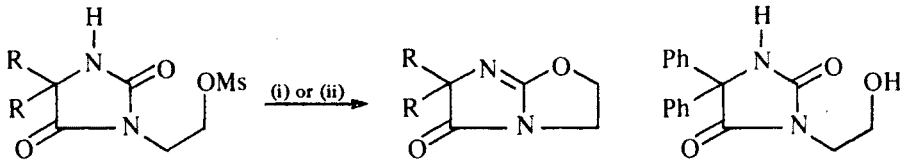
	R^1
a	H
b	Me
c	CH_2Cl
d	CH_2OMe
e	CH_2OH

(2.287)

	R^1	R^2	R^3
a	H	NO_2	H
b	Me	NO_2	H
c	CH_2Cl	NO_2	H
d	CH_2Cl	H	NO_2
e	CH_2OMe	NO_2	H
f	CH_2OMe	H	NO_2
g	CH_2OH	H	NO_2

Scheme 2.27

2,3-Dihydro-6,6-disubstituted-imidazo[2,1-*b*]oxazoles (**2.290a, c**) have been prepared by base-promoted intramolecular cyclization of appropriately substituted hydantoin methane sulfonates (**2.289**) (see Table 2.33).[130,131] It is not possible to prepare the 6-unsubstituted bicyclic derivative (**2.290**, R = H) by this method, and the dialkyl derivatives (**2.290b,c**) are more labile than the diphenyl analog (**2.290a**). The dialkyl derivatives polymerize over a period of several months on storing at 4°C, whereas the diphenyl analog is stable at this temperature; the latter (**2.290a**) is, however, decomposed by a trace of acid (CF_3CO_2H in CD_3COCD_3) to give the hydantoin derivative (**2.291**) (nmr analysis).[130]



(2.289)

Ms = SO_2Me

(2.290)

	R
a	Ph
b	Et
c	Me

(2.291)

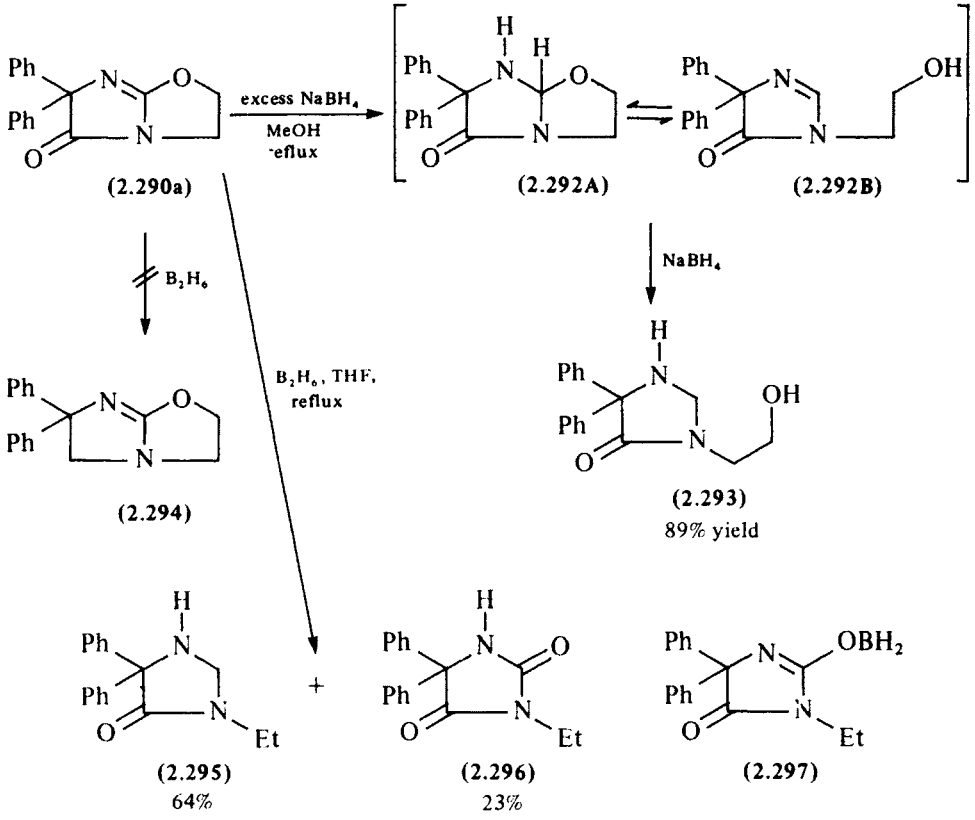
(i) NaH, C_6H_6, reflux (leading to **2.290a**);
(ii) NaH, monoglyme, room temperature (leading to **2.290b, c**)

Scheme 2.28

TABLE 2.33. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF 2,3-DIHYDRO-6,6-DISUBSTITUTED IMIDAZO[2,1-*b*]OXAZOLE-5(6*H*)-ONE DERIVATIVES (**2.290**)[a]

R in Structure **2.290**	Yield (%)	mp (°C) (Solvent for Recrystallization)	ir Spectral Bands (cm^{-1})	^1H nmr Spectral Data[b]	Reference
Ph	91	188–190 (PhMe)	1750, 1690, 1270, 1030, 975 850, 770, 760, 730, 710, 705	3.80 (t, 2p), 4.88 (t, 2p)	130
Et	49	77–79 (Et_2O)	1720, 1680, 1250, 1190, 1110, 1060, 1010, 940, 860, 790, 750	0.80 (t, Me), 1.70 (q, CH_2), 3.70 (t, H-3,3), 4.82 (t, H-2,2)	131
Me	76	116.5–118 (EtOAc)	1730, 1680, 1325, 1260, 1022, 1008, 990, 945, 915, 842, 750	1.40 (s, Me), 3.79 (t, H-3,3), 4.90 (t, H-2,2)	131

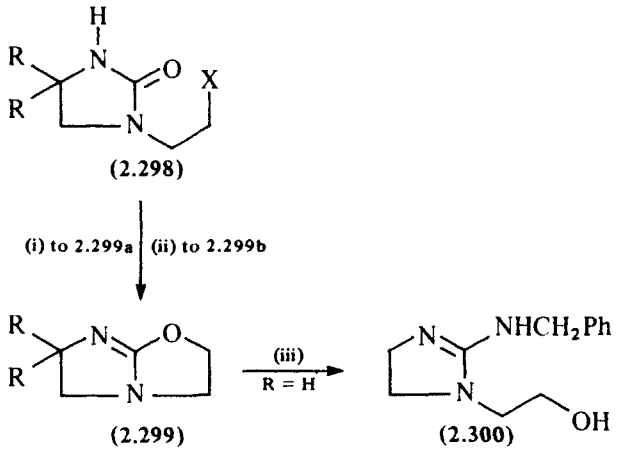
[a]See Scheme 2.28 for reaction conditions.
[b]Parts per million from tetramethylsilane.



Ring opening of the diphenyl derivative (**2.290a**) can also be effected by excess sodium borohydride in a process presumably occurring by a primary step of reduction of the 7,7*a*-double bond (see **2.290a** → **2.292** → **2.293**).[132] An attempt to achieve selective reduction of the C-5 carbonyl group by diborane (cf. **2.290a** → **2.294**) gave, surprisingly, an imidazolidinone derivative (**2.295**) and a hydantoin (**2.296**), and it must be assumed that reduction in this case is initiated by reductive opening of the oxazolidine ring at the O-1–C-2 bond (i.e., generation of **2.297** as the presumed[132] precursor of **2.295** and **2.296**).

2.10.3. 2,3,5,6-Tetrahydroimidazo[2,1-*b*]oxazoles

The parent compound of this group, 2,3,5,6-tetrahydroimidazo[2,1-*b*]oxazole (**2.299a**) has been synthesized by base-promoted intramolecular cyclization of 1-(2-chloroethyl)imidazolidin-2-one (**2.298**, X = Cl),[133] and a related process has been used to prepare the 6,6-disubstituted analog (**2.299b**).[130] Little is known of the reactivity of these compounds, except that the oxazolidine ring of **2.299a** is cleaved by benzylamine at room temperature to give 1-(2-hydroxyethyl)-2-benzylamino-2-imidazoline (**2.300**).[133]

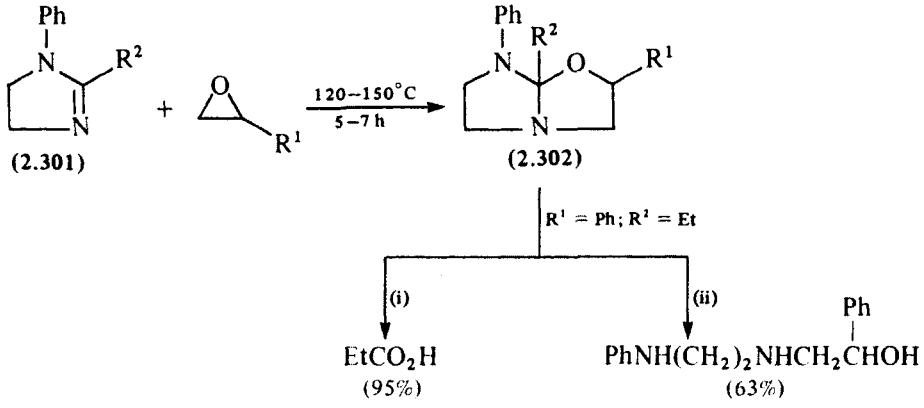


	R	mp (°C) or bp (°C/torr)	Yield (%)
a	H[133]	78–80/0.07	–
b	Ph[130]	197–198	85

(i) KOH, MeOH, reflux (X = Cl);
(ii) NaH, PhMe, reflux (X = OSO_2Me);
(iii) $PhCH_2NH_2$, EtOH, room temperature

2.10.4. 2,3,5,6,7,7*a*-Hexahydroimidazo[2,1-*b*]oxazoles

Compounds in this category have been prepared by the thermal reaction of 1-phenyl-2-imidazoline derivatives (**2.301**) with epoxides (see **2.302** and Table 2.34).[134] Perhydro compounds of this type (**2.302**) are cleaved hydrolytically under acidic or basic conditions to give the 7*a*-alkyl-derived carboxylic acid or a substituted ethylene diamine, respectively (see Scheme 2.29).[134]



(i) 20% H_2SO_4, reflux, 2h;
(ii) 20% NaOH, reflux;

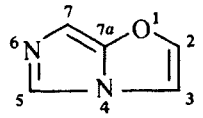
Scheme 2.29

TABLE 2.34. PHYSICAL PROPERTIES OF HEXAHYDROIMIDAZO[2,1-*b*]OXAZOLES (**2.302**) PREPARED FROM 1-PHENYL-2-IMIDAZOLINES[134]

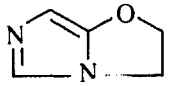
Compound **2.302**				
R^1	R^2	Yield (%)	bp (°C)/torr	n_D^{20}
H	C_2H_5	18	107–108/0.2	1.5615
CH_3	C_2H_5	79	114–115/0.4	1.5519
C_6H_5	C_2H_5	92	171–172/0.2	1.5920
CH_2–O-C_6H_5	C_2H_5	86	174–176/0.05	1.5800
CH_2–O-allyl	C_2H_5	85	135–136/0.5	1.5428
CH_2–O-lauryl	C_2H_5	66	212–213/0.1	1.5071
CH_2–O-allyl	n-C_3H_7	71	126–127/0.05	1.5395

2.11. RING SYSTEM C_3N_2–C_3NO: IMIDAZO[5,1-*b*]OXAZOLE

The chemistry of derivatives in the imidazo[5,1-*b*]oxazole ring system is little explored. There are no citations to the fully unsaturated ring system (**2.303**) during the literature period covered, and only an isolated example of a 2,3-dihydroimidazo-[5,1-*b*]oxazole derivative (cf. **2.304**) has been described.

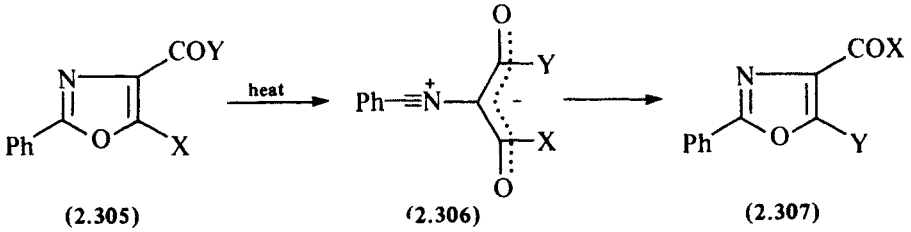


(2.303)

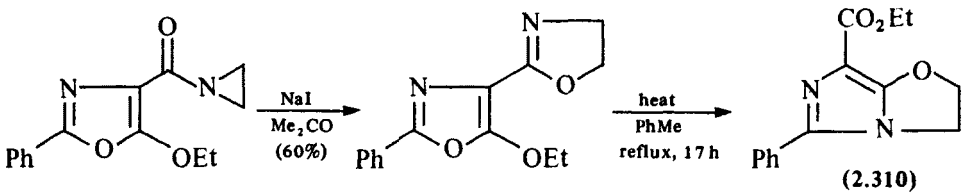


(2.304)

The scope and limitations of the Cornforth rearrangement[135] of 4-acyl-substituted oxazoles have been established[136] (cf. **2.305** → **2.307** via the nitrile ylide intermediate **2.306**), and this type of rearrangement has been adapted to the synthesis of 7-carboethoxy-2,3-dihydro-5-phenylimidazo[5,1-*b*]oxazole (see **2.308** → **2.309** → **2.310**).[136] Compound **2.310** is characterized by the following physical and spectral properties: mp 166–167°C (C_6H_6); ir (KBr) 3160, 2900–2975, 1695 (CO) and 1590 cm^{-1} (CN); ^1H nmr (δ, $CDCl_3$) 7.7 (m, 2p, Ar–H), 7.3 (m, 3p, Ar–H), 5.2 (br t, 2p, H-3,3), 4.3 (m, 4p, H-2,2 and OCH_2CH_3), 1.35 (t, 3p, OCH_2CH_3).



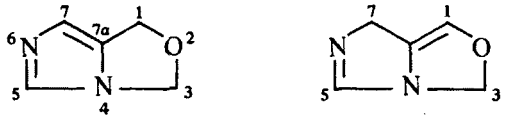
(2.305) (2.306) (2.307)



(2.308) (2.309) (2.310) 97% yield

2.12. RING SYSTEM C_3N_2–C_3NO: IMIDAZO[1,5-*c*]OXAZOLE

Compounds belonging to the imidazo[1,5-*c*]oxazole ring system are rare: two derivatives of 1*H*,3*H*-imidazo[1,5-*c*]oxazole (cf. **2.311**) have been described, and there is an isolated example of a tetrahydro derivative in the 3*H*,7*H* ring system (cf. **2.312**).



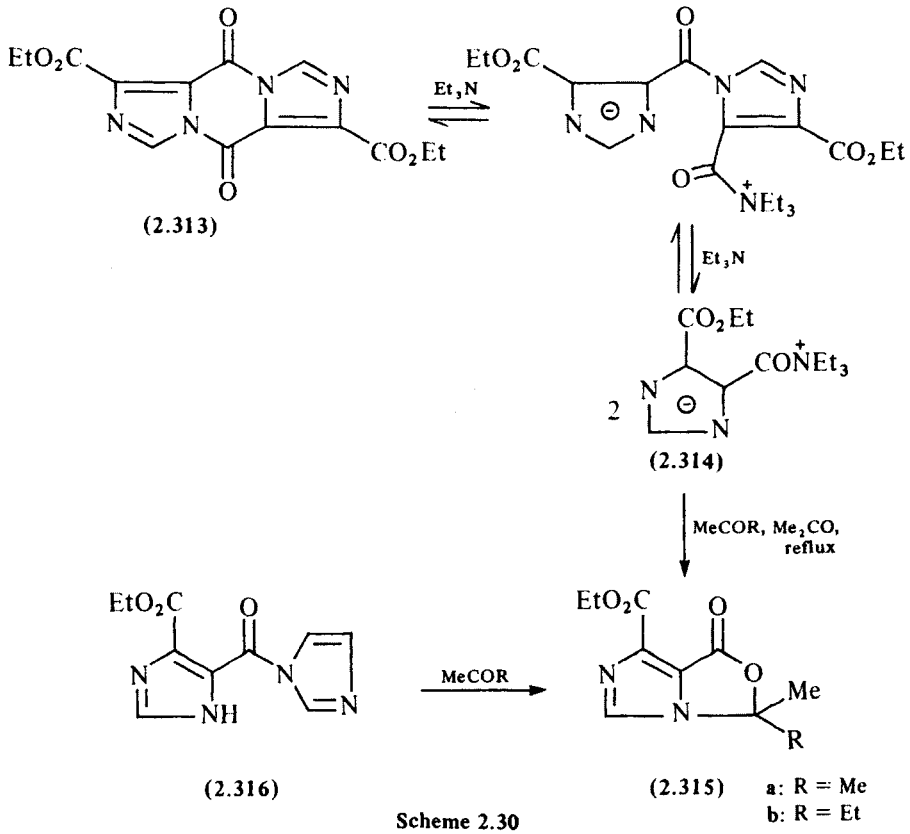
(2.311) (2.312)

3,3-Dialkyl-1-oxo-1*H*,3*H*-imidazo[1,5-*c*]oxazole-7-carboxylic acid ethyl esters (**2.315a,b**) have been prepared in good yields from the diimidazo[1,5-*a*:1′,5′-*d*]-pyrazine-5,10-dione (**2.313**) in the manner shown in Scheme 2.30 (see Table 2.35).[137] Annulation leading to the bicyclic compounds (**2.315a,b**) is assumed[137] to occur through zwitterionic intermediates (cf. **2.314**), and the syntheses can also be achieved by treating the imidazolide (**2.316**) (prepared from **2.313** and imidazole in dichloromethane) with the dialkyl ketone (see **2.316** → **2.315a,b**).

TABLE 2.35. PHYSICAL AND SPECTRAL PROPERTIES OF 1*H*,3*H*-IMIDAZO[1,5-*c*]-OXAZOLE DERIVATIVES (**2.315**)[137]

Compound[a]	Yield (%)	mp (°C)	^{1}H nmr Spectrum[b] (δ ppm)	ir Spectrum[c] (cm^{-1})
2.315a	67	193–195	1.03 (t, 3p, $CO_2CH_2CH_3$), 1.7 (s, 6p, 3,3-Me), 4.18 (q, 2p, $CO_2CH_2CH_3$), 8.95 (s, 1p, H-5)	1720, 1780, 3120
2.315b	78	127–128	0.79 (t), 1.23 (t), 2.18 (q), 4.36 (q), 8.91 (s)	1720, 1760, 3120

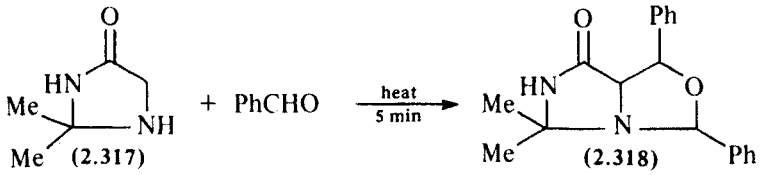
[a] Reaction conditions: **2.313**, Et_3N, MeCOR, reflux, 3 h.
[b] Measured in trifluoroacetic acid with tetramethylsilane as an external standard.
[c] Recorded as KBr disks.



(2.313) (2.314) (2.316) (2.315) a: R = Me b: R = Et

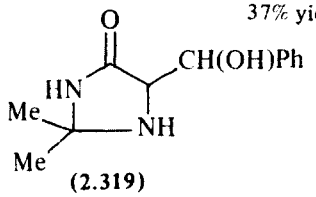
Scheme 2.30

1,5,6,7*a*-Tetrahydro-5,5-dimethyl-1,3-diphenyl-3*H*,7*H*-imidazo[1,5-*c*]oxazol-7-one (**2.318**) can be obtained in modest yield by heating the imidazolidinone (**2.317**) with benzaldehyde.[138] Compound **2.318** is stable in hot water but decomposes slowly when heated in aqueous sodium hydroxide; it is rapidly transformed into the imidazolidinone derivative (**2.319**) and benzaldehyde when heated with concentrated hydrochloric acid.



(2.317) (2.318)

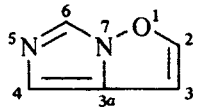
mp 187°C (EtOAc), 37% yield



(2.319)

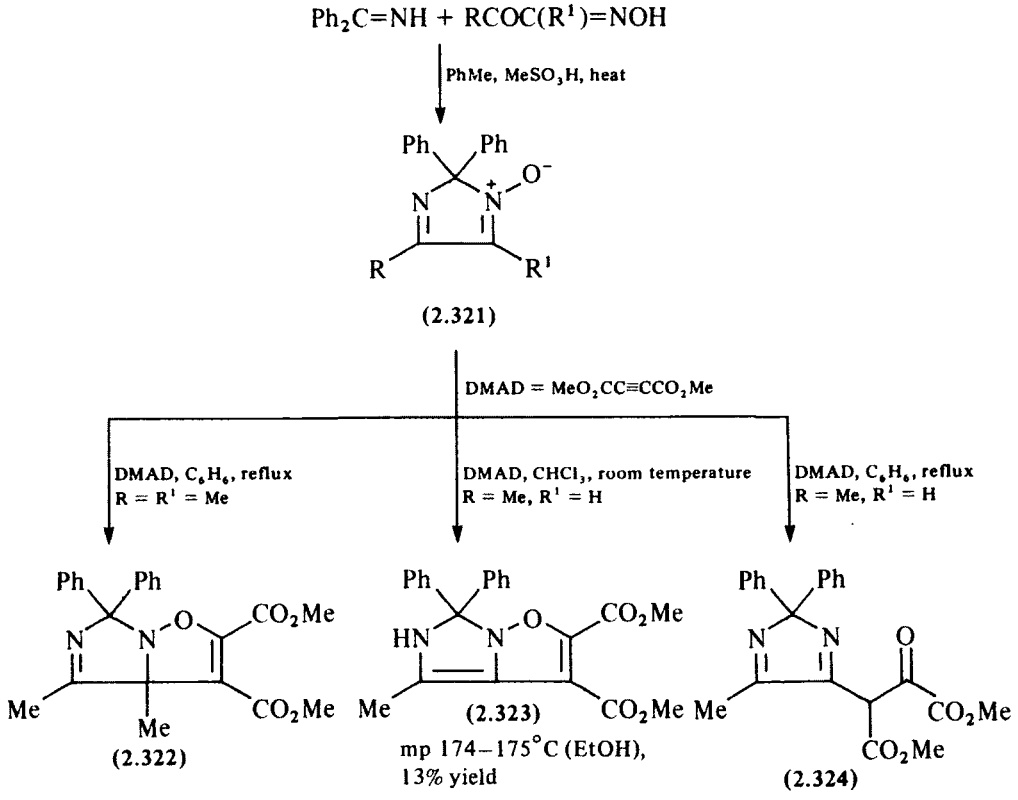
2.13. RING SYSTEM C_3N_2–C_3NO: IMIDAZO[1,5-*b*]ISOXAZOLE

Compounds in the fully unsaturated imidazo[1,5-*b*]isoxazole ring system (**2.320**) are not cited during the literature period covered, and the few examples of derivatives in this group belong to the dihydro and hexahydro categories.



(2.320)

Dimethyl 3*a*,6*a*-dihydro-3*a*,4-dimethyl-6,6-diphenylimidazo[1,5-*b*]isoxazole-2,3-dicarboxylate (**2.322**) has been synthesized by 1,3-dipolar cycloaddition of dimethylacetylene dicarboxylate (DMAD) and the 2*H*-imidazole-1-oxide derivative (**2.321**, R = R^1 = Me).[139] Compound **2.322** is an oil that was not obtained analytically pure but was characterized spectroscopically [ir (Nujol mull) = 1761 cm^{-1} (CO), 1734 (CO); ^1H nmr ($CDCl_3$) δ = 1.48 (3H, s, 3*a*-Me), 2.27 (3H, s, 4-Me), 3.55 (3H, s, CO_2Me), 3.66 (3H, s, CO_2Me), 7.18–7.79 (10H, Ar–H)]. In contrast, the trisubstituted 2*H*-imidazole-*N*-oxide (**2.321**, R = Me, R^1 = H) gives rise to a crystalline adduct (**2.323**) with DMAD at room temperature, although it may be noted that the product exists in the tautomeric 5,6-dihydro form.



Very little is known about the chemistry of the bicyclic adducts (**2.322** and **2.323**); it appears that the isoxazole ring of **2.323** is prone to thermolysis since efforts to prepare it in benzene under reflux resulted in formation of the 2*H*-imidazole derivative (**2.324**).[139]

Hexahydro-6-oxo derivatives in the imidazo[1,5-*b*]isoxazole ring system (**2.326**) have been prepared by 1.3-dipolar cycloaddition reactions of analogous 2-oxo-3-imidazoline-3-oxides (see **2.325** → **2.326** and Table 2.36), although these products (**2.326**) are incorrectly named in the primary literature[140,141] as hexahydroimidazo-[3,4-*b*]isoxazoles. An interesting feature in the chemistry of *N*-oxide (**2.325**; $R^1 = R^3 = Me$; $R^2 = Ph$) is the existence of a tautomeric equilibrium [cf. **2.325** ⇌ **2.327** (nmr analysis)]. The exocyclic methylene group of **2.327** behaves as a dipolarophile in the self-cycloaddition leading to the spiro compound (**2.328**).[141]

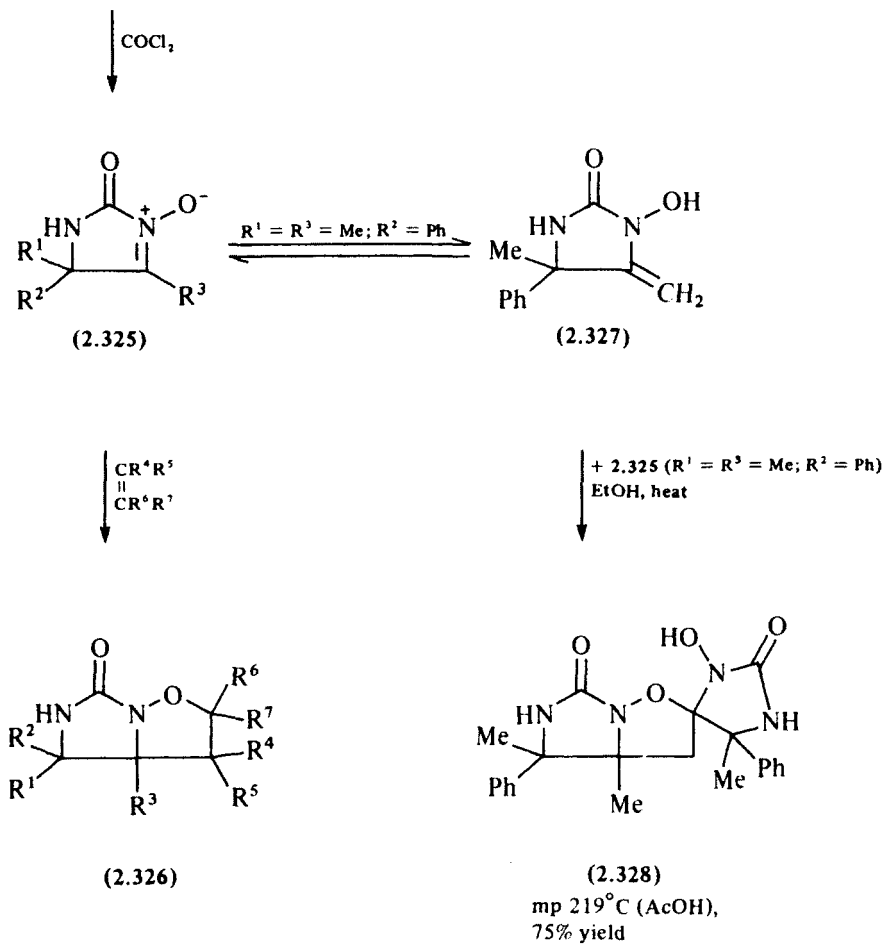
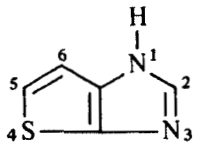


TABLE 2.36. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF HEXAHYDRO-6-OXO-IMIDAZO[1,5-*b*]ISOXAZOLE DERIVATIVES (2.326) DERIVED FROM 2-OXO-3-IMIDAZOLINE-3-OXIDES (2.325)

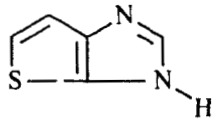
Compound 2.326							Yield (%)	mp (°C) (Solvent for Recrystallization)	ir Spectrum (KBr, cm^{-1})	nmr Spectrum [Solvent, δ (ppm)]	Reference
R^1	R^2	R^3	R^4	R^5	R^6	R^7					
Et	Et	Me	CN	H	H	H	28	193 (EtOH)	1723, 1143, 1122, 928	Pyridine-d_5: 1.00 (t, 6H), 1.60 (s, 3H), 1.75 (q, 4H), 4.40 (m, 3H)	140
Et	Et	Me	CO_2Et	H	H	H	48	152 (Et_2O)	1716, 1342, 1319, 1212, 1053, 938		140
Me	Me	Me	CN	H	H	H	14	226 (EtOH)	2970, 1750, 1390, 1325, 1174, 1140, 930	DMSO-d_6: 1.28, 1.33, 1.36 (3s, 9H), 4.15 (m, 3H), 7.80 (s, 1H)	140
Me	Me	Ph	H	H	H	CN	32	220 ($CHCl_3$–Et_2O)	2250, 1760, 1460, 1390, 1035, 700	DMSO-d_6: 0.77 (s, Me), 1.41 (s, Me), 3.0 (CH_2CH, AB part of ABX), 5.33 (CH_2CH, X part of ABX), 7.45 (m, 5H), 8.0 (br, NH)	141
Me	Et	Ph	CN	CN	CN	CN	50	236 (EtOH)	2220, 1770, 1610, 1440, 1300	DMSO-d_6: 0.6–1.2 (m, 5H), 1.60 (s, Me), 7.4–7.9 (m, 5H)	141
Me	Ph	Me	H	H	H	CN	50	105 (Et_2O–C_6H_6)	2250, 1740, 1630, 1500, 1450, 1390, 1330, 770	DMSO-d_6: 1.56 (s, Me), 1.52 (s, Me), 0.8–2.2 (m, 2H, AB part of CH_2CH), 5.06–4.20 (m, 1H, X part of CH_2CH), 7.35 (m, 5H), 8.46 (br, NH)	141
$-(CH_2)_5-$		Ph	CN	H	H	CN	65	245 (EtOH)	2240, 1755, 1630, 1450, 1280, 770	DMSO-d_6: (1.0–2.0) (br, 10H), 6.63 (d, 1H, J = 17 Hz), 7.39 (d, 1H, J = 17 Hz), 7.44 (m, 5H), 9.06 (s, 1H)	141

2.14. RING SYSTEM C_3N_2–C_4S: THIENO[2,3-*d*]IMIDAZOLE

Knowledge of the chemistry of the potentially tautomeric thieno[2,3-*d*]-imidazole ring system (**2.329** ⇌ **2.330**) is very limited despite its close relationship to the extensively explored thieno[3,4-*d*]imidazole group (see Section 2.15). In general, compounds of the former type are constructed from thiophene derivatives, but there is an isolated example of a thieno[2,3-*d*]imidazole synthesis from an imidazole substrate.



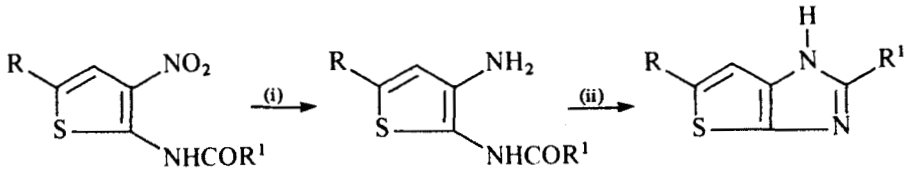
(2.329)



(2.330)

2.14.1. Synthesis from Thiophene Derivatives

The imidazole ring of the 2- and 2,5-disubstituted 1*H*-thieno[2,3-*d*]imidazoles (**2.333a,b**) has been constructed[142] in conventional fashion[143] from 2-amido-3-aminothiophenes (cf. **2.332**) in the manner outlined in **2.331** → **2.333**. 2-(4′-Thiazolyl) derivatives of the latter type are of interest because of their structural analogy with commercially used anthelmintic agents in the benzimidazole series.[144] The annulation step (cf. **2.332** → **2.333**) can also be effected by heating the thiophene derivative with copper above 300°C, and this approach has been used to prepare 3-ethyl-2-methyl-3*H*-thieno[2,3-*d*]imidazole (see **2.334** in Scheme 2.31);[145] the quaternary salt (**2.335**) has been used to prepare a symmetrical carbocyanine dye (λ_{max} = 528 nm) and a 3-ethylrhodanine dimethine merocyanine (λ_{max} = 541 nm).[145]



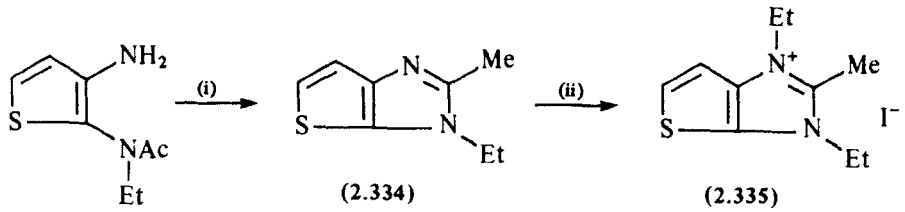
(2.331)
R^1 = 4-thiazolyl

(2.332)

(2.333)

	R	mp (°C)
a	H	288–292
b	Ph	241–242

(i) H_2, 10% Pd–C, EtOH, HCl;
(ii) $POCl_3$, DMF, reflux



(i) Cu, >300°C; (ii) EtI

Scheme 2.31

Despite the relative simplicity of the syntheses of derivatives **2.333** and **2.334**, this approach is unsatisfactory because of the poor yields in the reduction step (cf. **2.331** → **2.332**). A valuable alternative route, exemplified by the synthesis of 2,3-dimethyl-3*H*-thieno[2,3-*d*]imidazole (**2.339**, R = H; $R^1 = R^2 = Me$), involves generation of the appropriately substituted 3-aminothiophene derivative (**2.338**) through a Curtius rearrangement (cf. **2.336** → **2.337**).[146] An alternative shorter

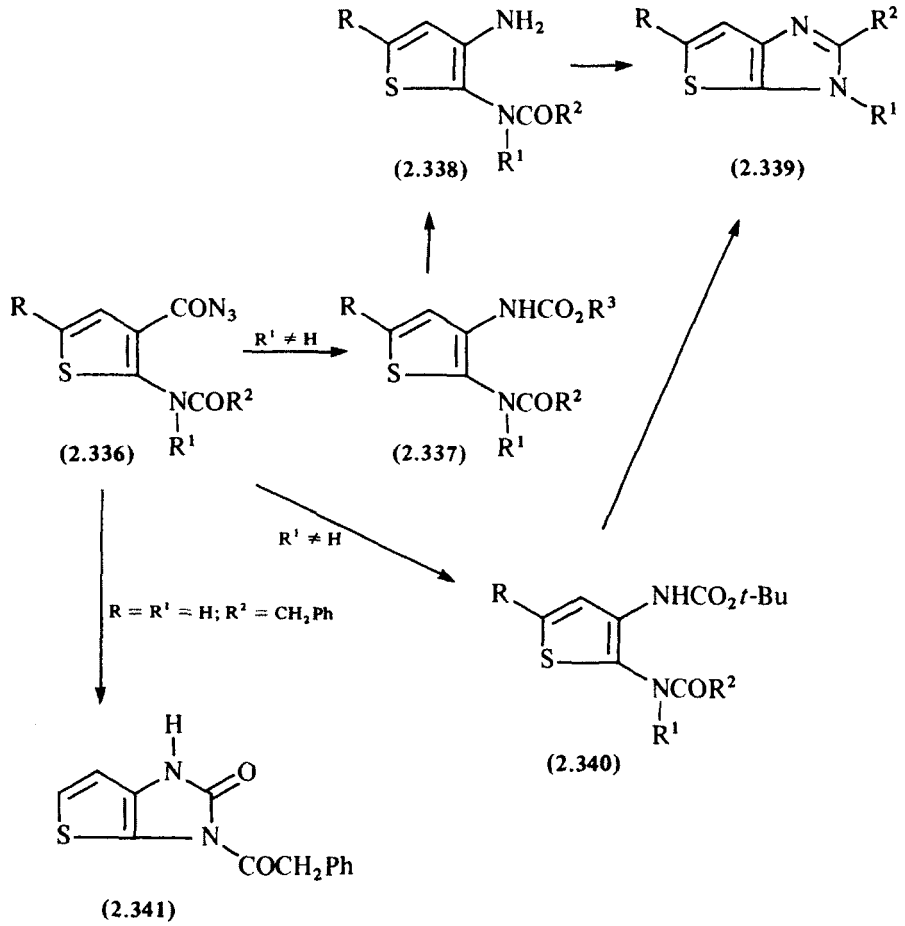


TABLE 2.37. PHYSICAL AND SPECTRAL PROPERTIES OF THIENO[2,3-*d*]IMIDAZOLES

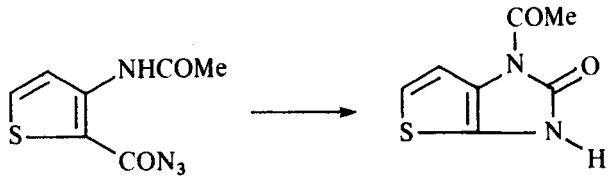
Compound	Method of Preparation	Yield (%)	mp (°C) (Solvent for Recrystallization)	^{1}H nmr Spectrum [Solvent, δ (ppm)]	Reference
2.339 (R = H; $R^1 = R^2$ = Me)	**2.340** (R = H; $R^1 = R^2$ = Me), PPA,[a] warm for 30 min	95	80–81 (Et_2O)	$CDCl_3$: 2.45 (s, 2-Me), 3.60 (s, 3-Me), 6.8–7.1 (AB, J = 6 Hz, H-5,6)	146
2.339 (R = H; $R^1 = CH_2CONEt_2$; $R^2 = CH_2C_6H_4OEt$-*p*)	**2.340** (R = H; $R^1 = CH_2CONEt_2$; $R^2 = COCH_2C_6H_4OEt$-*p*), PPA,[a] heat	10	118–119 (Et_2O–C_6H_6)	$CDCl_3$: 1.0–1.5 (m, 9H, CH_3), 3.05–3.50 (m, 4H, NCH_2CH_3), 3.95 (q, 2H, OCH_2CH_3), 4.15 (s, 2H, CH_2Ar), 4.53 (s, 2H, CH_2CO), 6.70–7.20 (m, 6H, Ar–H)	147
2.339 (R = Et; $R^1 = CH_2CONEt_2$; $R^2 = CH_2C_6H_4OEt$-*p*	**2.340** (R = Et; $R^1 = CH_2CONEt_2$; $R^2 = COCH_2C_6H_4OEt$-*p*, PPA,[a] heat	19	95–96	$CDCl_3$: 0.9–1.5 (m, 12H, CH_3), 2.63–3.50 (m, 6H, NCH_2CH_3), 3.95 (q, 2H, OCH_2CH_3), 4.13 (s, 2H, CH_2Ar), 4.50 (s, 2H, CH_2CO), 6.78 (s, 1H, H-5 or H-6), 6.68–7.18 (m, 4H, Ar–H)	147
2.341	**2.336** (R = R^1 = H; $R^2 = CH_2Ph$), PhMe, reflux, 2h	74	163–165 (C_6H_6)	Me_2CO-d_6; 4.4 (s, 2H, $COCH_2Ph$), 6.8–7.40 (m, 7H, C_6H_5 + H-5, 6), 10.5 (s, br, NH)	146
2.343	**2.342**, PhMe, reflux, 2 h	65	202–205		146
2.348	**2.347**, 2*M* NaOH, 5 min, room temperature	64	192–195	3.45 (s, 3H, OMe), 6.75 (s, 2H, H-5 and H-6), 11.1 (s, br, 1H, NH)[b]	146
2.351	**2.350**, $LiAlH_4$	52	Oil[c]	$CDCl_3$: 0.90 (t, 6H, NCH_2CH_3), 1.37 (t, 3H, OCH_2CH_3), 2.42 (q, 4H, NCH_2CH_3), 2.52 (t, 2H, $CH_2CH_2NEt_2$), 3.90 (t, 2H, $CH_2CH_2NEt_2$), 3.95 (q, 2H, OCH_2CH_3) 4.16 (s, 2H, CH_2Ar), 6.70–7.20 (m, 6H, Ar–H)	147
2.352	**2.350**, $LiAlH_4$	–	203–205 (MeOH)	$CDCl_3$: 1.28 (t, 3H, CH_2CH_3), 3.95 (q, 2H, OCH_2CH_3), 4.0 (s, 2H, CH_2Ar), 6.70–7.22 (m, 6H, Ar–H), 12.4 (s, br, 1H, NH)	147

[a] PPA = polyphosphoric acid

[b] Nuclear magnetic resonance solvent not quoted.

[c] Forms a hydrochloride, mp 129–131°C and a dipicrate, mp 183–184°C.

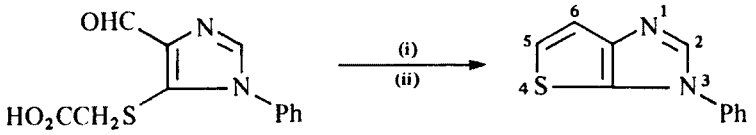
procedure to the thieno[2,3-*d*]imidazole derivative is to effect the Curtius rearrangement in *t*-butanol and to convert the ensuing *t*-butoxycarbonyl-protected 3-aminothiophene derivative (cf. **2.340**) directly into the bicyclic compounds (cf. **2.339** and Table 2.37);[146,147] a restriction on the synthesis described above (cf. **2.336** → **2.339**) holds for acyl azides possessing a secondary amino function (cf. **2.336**, $R^1 = H$) in which intramolecular ring closure of the isocyanate provides access to 3-acylated 1,3-dihydrothieno[2,3-*d*]imidazol-2-ones (e.g., **2.341**). Curtius rearrangement of appropriately substituted 2-thienyl acyl azides proceeds in similar fashion to give, for example, 1-acetyl-1,3-dihydrothieno[2,3-*d*]imidazol-2-one (**2.343**).[146]



(**2.342**) (**2.343**)

2.14.2. Synthesis from Imidazoles

The use of imidazole substrates for the synthesis of thieno[2,3-*d*]imidazoles is restricted to the base-promoted cyclization of 1-phenyl-4-formyl-5-imidazolylthioglycolic acid (**2.344**); decarboxylation of the initially formed thieno[2,3-*d*]-imidazole-5-carboxylic acid derivative is achieved by heating above the melting point to provide 3-phenyl-3*H*-thieno[2,3-*d*]imidazole (**2.345**) in high yield.[148]



(**2.344**) (**2.345**)

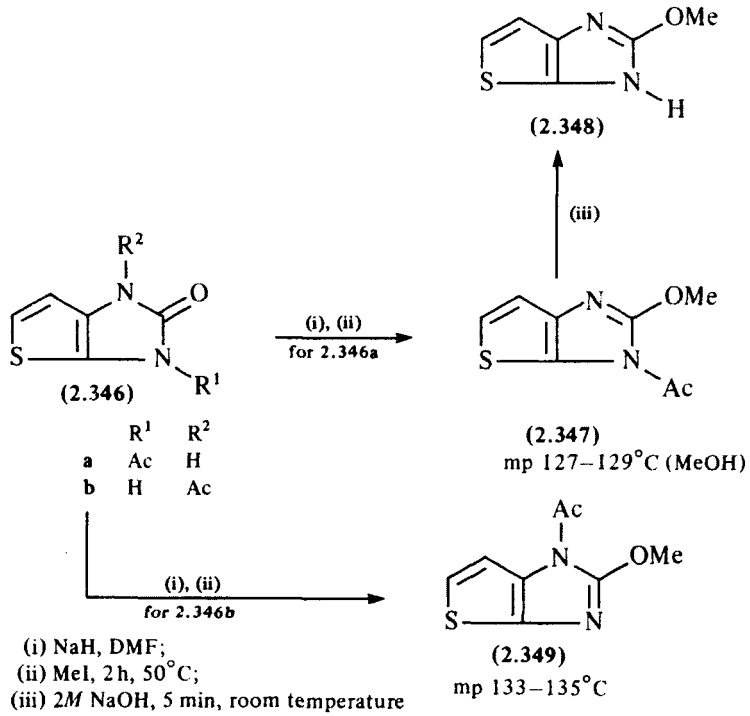
(i) NaOMe, MeOH; (ii) heat behond mp

80% yield
mp 102–103°C (hexane),
uv λ_{max}^{EtOH} 234 nm (log ϵ, 4.37)
256 (sh) (3.97)

2.14.3. Reactions

2.14.3.1. Reactions with Electrophiles

3-Phenylthieno[2,3-*d*]imidazole (**2.345**) is formylated at the 5-position under the conditions of the Vilsmeier procedure ($HCONMe_2$, $POCl_3$, 60°C) to give a product [mp 149°C (aq. EtOH), 70% yield] with λ_{max}^{EtOH} = 237 nm (log ϵ, 4.24) and 322 (4.20).[148]



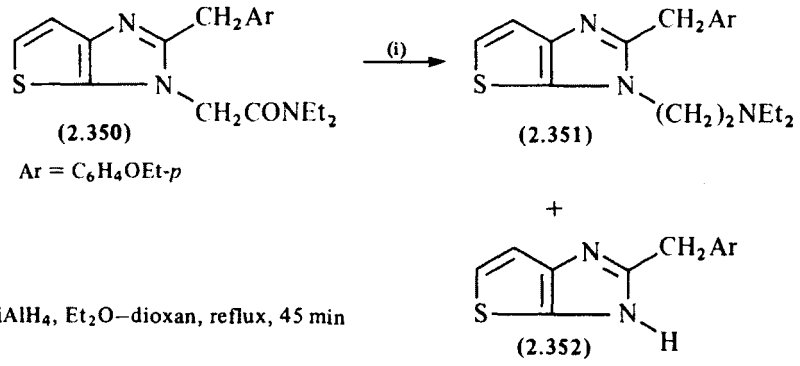
	R^1	R^2
a	Ac	H
b	H	Ac

(i) NaH, DMF;
(ii) MeI, 2 h, 50°C;
(iii) 2*M* NaOH, 5 min, room temperature

Methylation of the condensed imidazolones (**2.346a,b**) occurs exclusively at oxygen to give 2-methyl derivatives (**2.347** and **2.349**), and the former can be deacylated by alkaline hydrolysis (see **2.347** → **2.348** and data in Table 2.37).[146]

2.14.3.2. Reduction

Lithium aluminum hydride-promoted reduction of the amide derivative (**2.350**) proceeds in anticipated fashion to give the β-diethylaminoethyl compound (**2.351**), but dealkylation also occurs with concomitant formation of 2-(4-ethoxybenzyl)-3*H*-thieno[2,3-*d*] imidazole (**2.352**) as a by-product (see data in Table 2.37).[147]

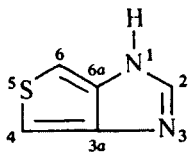


Ar = C_6H_4OEt-*p*

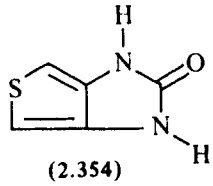
(i) $LiAlH_4$, Et_2O–dioxan, reflux, 45 min

2.15. RING SYSTEM C_3N_2–C_4S: 1*H*-THIENO[3,4-*d*]IMIDAZOLE

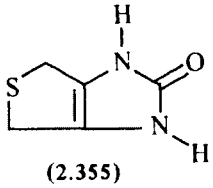
Compounds in the fully unsaturated 1*H*-thieno[3,4-*d*]imidazole ring system (**2.353**) are uncommon, as are partially reduced derivatives, as exemplified by 2,3-dihydro-2-oxo- (**2.354**) and 2,3,4,6-tetrahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazoles (**2.355**), respectively. In contrast, hexahydro-2-oxo compounds (**2.356**) are extensively studied; the most important member of this category is biotin [vitamin H – formally [3a*S*-(3aα,4β,6aα)]hexahydro-2-oxo-1*H*-thieno[3,4-*d*]-imidazole 4-pentanoic acid (**2.357**)]. This section is organized in the usual manner in terms of increasing saturation of the ring system, but separate subsections are included to cover the synthesis and spectral properties of biotin and the chemistry of biotin analogs.



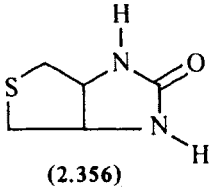
(2.353)



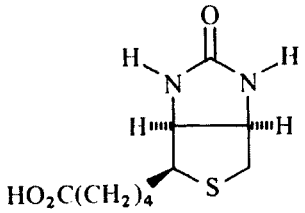
(2.354)



(2.355)



(2.356)



(2.357)

2.15.1. 1*H*-Thieno[3,4-*d*]imidazoles

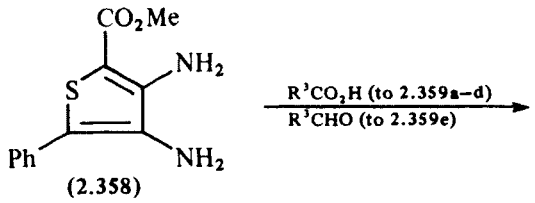
The imidazole ring of a series of 1*H*-thieno[3,4-*d*]imidazoles (**2.359a–e**) has been constructed in conventional fashion from methyl-3,4-diamino-5-phenylthiophene-2-carboxylate and carboxylic acids or benzaldehyde. (See Table 2.38 for a summary of these and related derivatives.)[149] Reactions of **2.358** with phenylacetic acid in xylene and mandelic acid in benzene proceed normally to give the bicyclic products **2.359a** and **b** respectively, but reactions of the latter in anisole and *o*-xylene give rise to products of electrophilic substitution (cf. **2.359b** → [**2.359f**] → **2.359c,d**).

The 1*H*-thieno[3,4-*d*]imidazole ring system is stable to a variety of reagents employed for substituent oxidation, reduction, and hydrolysis. For example, the benzyl and benzhydryl groups of **2.359a** and **2.359c** can be oxidized by manganese dioxide and selenium dioxide to give 2-benzoyl- (**2.360b**) and 2-(α-hydroxy-*p*-methoxyphenyl-benzyl) (**2.360c**) derivatives, respectively. The 2-(α-hydroxybenzyl) derivative (**2.359b**) is formed in good yield when the 2-benzoyl compound (**2.360b**) is reduced at room temperature by sodium borohydride in propan-2-ol,

TABLE 2.38. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF 1*H*-THIENO[2,3-*d*]IMIDAZOLES (**2.359**)[149]

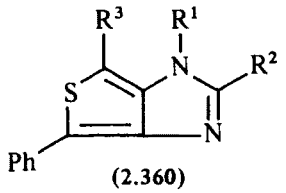
Starting Material	Reaction Conditions	Product	Yield (%)	Mp (°C) (Solvent for Recrystallization)	Spectroscopic properties[a]
2.358	$PhCH_2CO_2H$, xylene, *p*-$MeC_6H_4SO_3H$, reflux, 2 h	**2.359a**	64	161–163 (C_6H_6–petroleum ether)	uv λ_{max}^{MeOH} = 357 nm (ϵ, 26,520); 320 (11,150); 305 (10,140); 238 (19,260); ir ν_{max} = 1695 cm^{-1} (CO)
2.358	PhCH(OH)CO_2H, C_6H_6, *p*-$MeC_6H_4SO_3H$, reflux, 10 h	**2.359b**	25	174–176 (petroleum ether)	uv λ_{max}^{MeOH} = 357 nm (ϵ, 24,500); 306 (9,830); 319 (10,580); 239 (18,760); ir ν_{max} = 3380 (NH, OH), 1670 cm^{-1} (CO)
2.358	PhCH(OH)CO_2H, PhOMe, *p*-$MeC_6H_4SO_3H$, reflux, 3 h	**2.359c**	16	88–90 (hexane)	uv λ_{max}^{MeOH} = 357 nm (ϵ, 24,730); 309 (11,690): 323 (13,430); 232 (26,320); ir ν_{max} = 3250 cm^{-1} (NH), 1680 (CO)
2.358	PhCH(OH)CO_2H, *o*-xylene, *p*-$MeC_6H_4SO_3H$, reflux, 3 h	**2.359d**	72	110–112 (Me_2CO–petroleum ether)	uv λ_{max}^{MeOH} = 357 nm (ϵ, 22,400); 322 (11,000); 239 (19,660); ir ν_{max} = 3250 cm^{-1} (NH), 1670 (CO)
2.358	PhCHO, xylene, *p*-$MeC_6H_4SO_3H$, reflux, 3 h	**2.359e**[b]	50	184–186 (Me_2CO–petroleum ether)	uv λ_{max}^{MeOH} = 371 nm (ϵ, 21,300); 339 (18,000); 328 (17,950); 249 (21,400); ir ν_{max} = 1660 cm^{-1} (CO)
2.359a	MnO_2, dioxan, reflux, 1 h	**2.360b**	62	218–219 (MeOH)	uv λ_{max}^{MeOH} = 400 nm (ϵ, 11,790); 311 (30,150); ir ν_{max} = 3200 cm^{-1} (NH), 1680 (CO)
2.359c	SeO_2, dioxan, reflux, 1 h	**2.360c**	77	199–201 (C_6H_6–petroleum ether)	uv λ_{max}^{MeOH} = 357 nm (ϵ, 25,900); 321 (12,000); 307 (10,800); 232 (28,700); ir ν_{max} = 3340 cm^{-1} (NH, OH), 1660 (CO)
2.360b	$LiAlH_4$, $AlCl_3$, Et_2O, reflux, 2 h	**2.360d**	40	103–105 (C_6H_6–petroleum ether	nmr ($CDCl_3$) 2.32 (s, 3H, Me), 5.86 [s, 1H, CH(OH)], 7.2 (br, 10 H, Ar–H)
2.359b	NaOH, aqueous EtOH, reflux, 1 h	**2.360e**	64	190–192 (Me_2CO–hexane)	ir ν_{max} = 1660 cm^{-1} (CO)

[a] Infrared spectra are recorded as KBr disks.
[b] Compound **2.360a** [mp 148–150°C (Me_2CO–petroleum ether) is also isolated in 14% yield].



(2.358) (2.359)

	R^3
a	$PhCH_2$
b	PhCH(OH)
c	$PhCH(C_6H_4OMe\text{-}4)$
d	$PhCH[C_6H_3(OMe)_2\text{-}3,4]$
e	Ph
f	$PhC\overset{+}{H}$



(2.360)

	R^1	R^2	R^3
a	CH_2Ph	Ph	CO_2Me
b	H	COPh	CO_2Me
c	H	$C(OH)(Ph)(C_6H_4OMe\text{-}4)$	CO_2Me
d	H	CH(OH)Ph	Me
e	H	CH(OH)Ph	CO_2H

but concomitant reduction of the methoxycarbonyl substituent occurs under more forcing conditions ($LiAlH_4$, $AlCl_3$, reflux) (see **2.360b** → **2.360d**); routine hydrolysis of the latter substituent can be effected by aqueous ethanolic sodium hydroxide (see **2.359b** → **2.360e**).[149]

It may be noted that the α-hydroxybenzyl derivatives (viz., **2.359b**, **2.360c–e**) of 1*H*-thieno[3,4-*d*]imidazole are analogous to antiviral 2-(α-hydroxybenzyl)-benzimidazoles[150,151] and the benzyl derivative (**2.359a**) may be of medicinal interest because of its structural relationship to the vasodilator, 2-benzylbenzimidazole.[152]

2.15.2. 2,3-Dihydro-1*H*-thieno[3,4-*d*]imidazoles

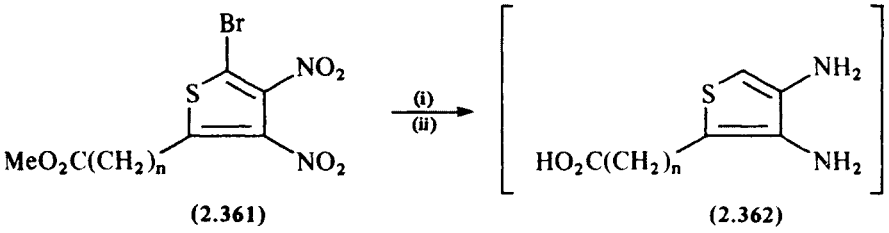
Studies of derivatives in this class (cf. **2.354**) have been directed toward the synthesis of analogs of biotin (**2.357**) ("aromatic biotins") not only because of their potential biochemical interest, but also because they are valuable intermediated in biotin synthesis.

2.15.2.1. Synthesis from Thiophenes

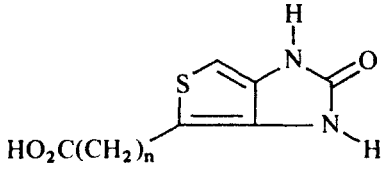
The synthesis of "aromatic norbiotin" (**2.363a**) and "aromatic biotin" (**2.363b**) from the thiophene nucleus involves the generation *in situ* and then phosgene-promoted cyclization of appropriately substituted diamines (**2.362**). The latter are prepared by reduction of methyl 4-(5-bromo-3,4-dinitro-2-thienyl)-butyrate

and -valerate (cf. **2.361**),[153] but it may be noted that synthesis of the esters (**2.361**) requires seven steps from 4-(2-thienyl)butyric and -valeric acids. Compound **2.363b** is characterized by a uv spectral band at $\lambda_{max}^{EtOH} = 260$ nm.[153]

The synthesis described above (**2.362** → **2.363**) has been adapted to the cyclization of methyl-3,4-diaminothiophene-2-carboxylate to methyl-2,3-dihydro-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-carboxylate [89% yield, mp 245–250°C (dec.)].[154]



(**2.361**) (**2.362**)



(**2.363**)

(i) Sn, conc. HCl, 25–30°C;
(ii) aqueous KOH, $COCl_2$

	n	Yield (%)	MP(°C) (dec)
a	3	45	244–245 (H_2O)
b	4	70	253–254 (H_2O)

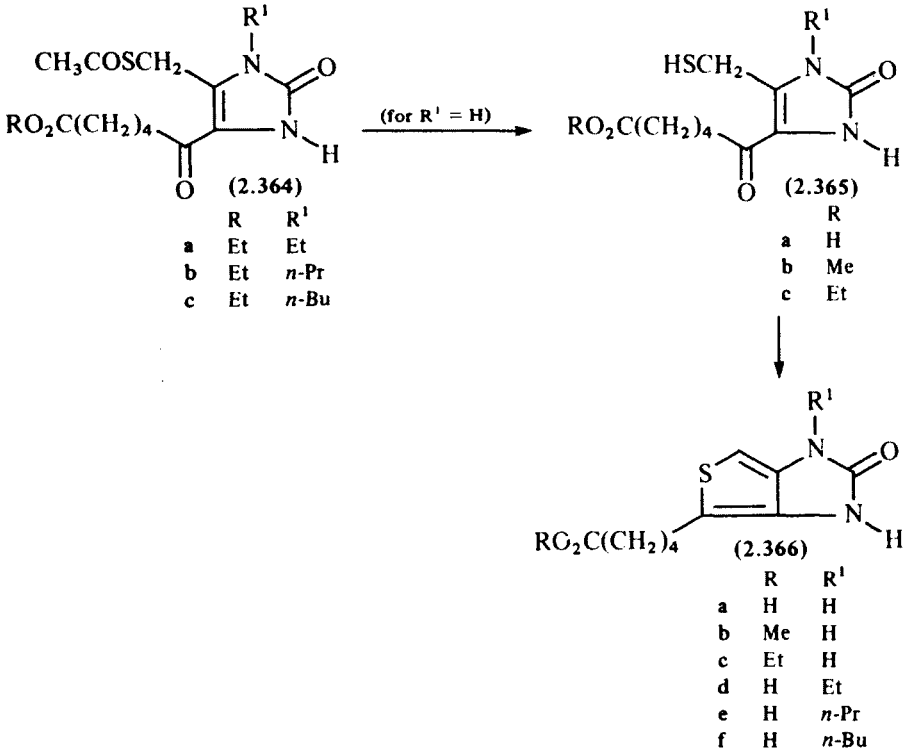
2.15.2.2. Synthesis from Imidazolinones

The synthesis of "aromatic biotin" and its analogs (cf. **2.366**) have been achieved in good yield by cyclization of suitably substituted 5-mercaptomethyl imidazolinones (**2.365**) either with water under reflux or under acidic conditions (e.g., BF_3 or CH_3CO_2H) (see Table 2.39).[155] The requisite 5-mercaptomethyl substitutent of **2.365** is introduced by the sequence 5-Me → 5-CH_2Br → 5-CH_2SCOCH_3 (cf. **2.364**), and bicyclic products (viz., **2.366d–f**) can also be obtained from **2.364** by base treatment and cyclization of mercapto derivatives (cf. **2.365**) *in situ*.[156]

TABLE 2.39. PHYSICAL AND SPECTRAL PROPERTIES OF 2,3-DIHYDRO-2-OXO-1*H*-THIENO[3,4-*d*]IMIDAZOLES (AROMATIC BIOTIN AND ANALOGS)

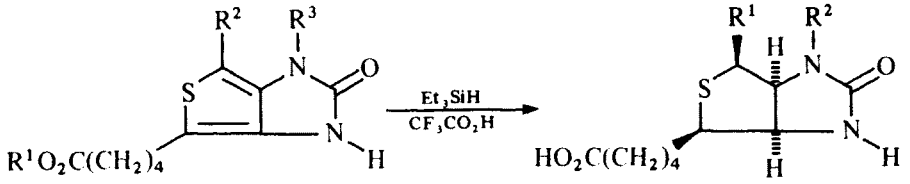
Starting Material	Product	Reaction Conditions	Yield (%)	mp (°C) (Solvent for Recrystallization)	Spectroscopic Properties[b,c]	Reference
2.365a	**2.366a**	H_2O, reflux or BF_3–Et_2O, 20°C, 3.5 h[a]	73	239–241 (H_2O)	–	155
2.365b	**2.366b**	AcOH, 120–130°C, 8h	46	147–148 (C_6H_6)	uv 260 (15,800); ir ν_{max} = 3400–2750 (NH, CH), 1738 (CO_2Me), 1703 (NCON)	155
2.365c	**2.366c**	H_2O, reflux	44	92–94 (C_6H_6)	uv 260 (15,850); ir 3400–2750 (NH, CH), 1730 (CO_2Et), 1730 (NCON)	155
2.364a	**2.366d**	A[d]	62	160–161 (H_2O)	uv 260 (11,740); ir 1720–1660	156
2.364b	**2.366e**	A[d]	88	152–153 (H_2O–EtOH)	uv 263 (17,800); ir 1720–1660	156
2.364c	**2.366f**	A[d]	90	130–140 (H_2O–EtOH)	uv 263 (15,300); ir 1710, 1670	156

[a] Gives a product (**2.366a**), mp 240–242°C in 57% yield.
[b] Ultraviolet spectra are quoted as λ_{max}^{EtOH} values in nanometers with molar extinction coefficients in parentheses.
[c] Infrared spectra recorded (cm^{-1}) as KBr disks.
[d] Reaction conditions: (i) aqueous KOH, 20°C; (ii) 10% HCl, 20°C.



2.15.2.3. Reduction

The 2,3-dihydro-1*H*-thieno[3,4-*d*]imidazole derivative (**2.367a**) ("aromatic biotin") undergoes a sequential protonation and hydride transfer in triethylsilane and trifluoroacetic acid to provide a short, simple synthesis of (±)biotin[157,158] (see Table 2.40). The reaction is highly stereoselective with protonation and hydride transfer occurring presumably from the least sterically hindered side of the thiophene ring (see Scheme 2.32). Although the yield of (±)biotin produced by this method is poor, the process is aided by the presence of electron-donating



(2.367)

	R^1	R^2	R^3
a	H	H	H
b	Me	H	Me
c	H	Me	H

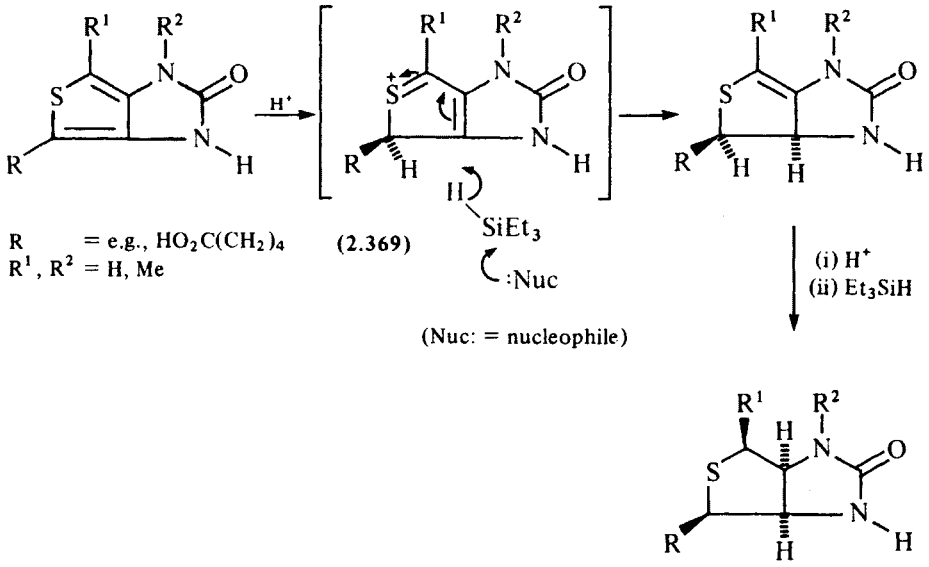
(2.368)

	R^1	R^2
a	H	H
b	H	Me
c	Me	H

TABLE 2.40. SYNTHESIS OF (±)BIOTIN AND ITS DERIVATIVES BY CHEMICAL REDUCTION OF 2,3-DIHYDRO-2-OXO-1*H*-THIENO[3,4-*d*]-IMIDAZOLES

Starting material	Product	Reaction conditions[a]	Yield (%)	mp (°C) (Solvent for Recrystallization)	nmr Spectral Parameters[b]	Reference
2.367a	**2.368a**	A	10	216–218 (H_2O)	1.30 (m, 6H, $CH_2CH_2CH_2$), 2.16 (m, 2H, CH_2CO), 2.63 (s, 2H, CH_2S, 3.06 (1H, m), 4.35 (m, 2H)	157
2.367b	**2.368b**	B	82	205–206	1.24 (m, 6H, $CH_2CH_2CH_2$), 2.06 (d, 2H, CH_2CO), 2.52 (s, 3H, CH_3N), 2.64 (s, 2H, CH_2S), 2.90 (m, 1H, CHS), 4.00 and 4.18 (m, 2H, NCHCHN)	158
2.367c	**2.368c**	C	72	264–265	0.96 (t, 3H, CH_3CH), 1.30 (m, 6H, $CH_2CH_2CH_2$), 2.06 (d, 2H, CH_2CO), 3.02 (m, 2H, CHSCH)	158

[a] Reaction conditions: (A) Et_3SiH, CF_3CO_2H, 50°C, 120 h; (B) (i) Et_3SiH, CF_3CO_2H, 50°C, 30 h; (ii) conc. HCl, EtOH; (C) Et_3SiH, CF_3CO_2H, 50°C, 30 h.
[b] δ values (CF_3CO_2H solvent).



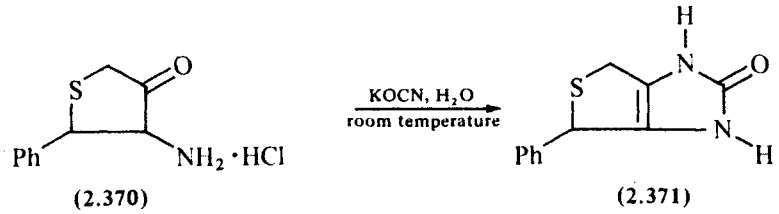
Scheme 2.32

groups on either the thiophene ring (e.g., **2.367c**) or the imidazolinone ring (e.g., **2.367b**), and this effect may reflect the ease of formation of protonated species such as **2.369** (see Scheme 2.32). In contrast, unsatisfactory results were obtained[158] in attempts to reduce 1,3-dimethyl analogs of **2.367** where approach of triethylsilane may be hindered.

2.15.3. 2,3,4,6-Tetrahydo-1*H*-thieno[3,4-*d*]imidazoles

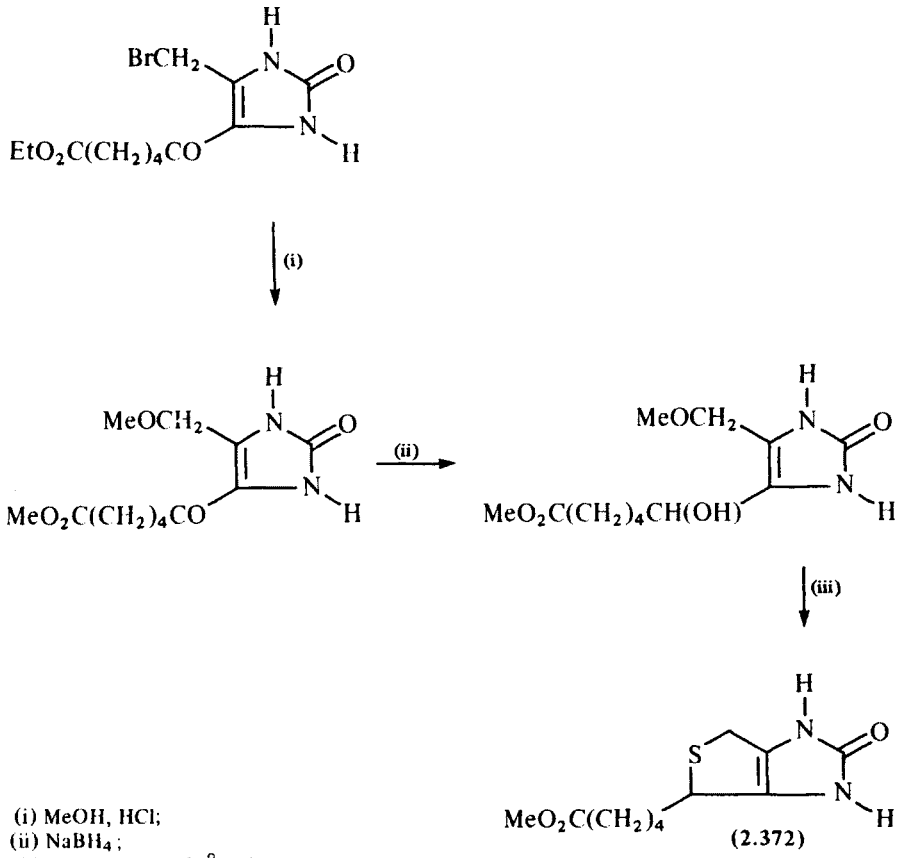
2.15.3.1. Synthesis from Thiophene Derivatives

2,3,4,6-Tetrahydro-2-oxo-4-phenyl-1*H*-thieno[3,4-*d*]imidazole (**2.371**) can be prepared by the potassium cyanate-mediated cyclization of the tetrahydrothiophene derivative (**2.370**).[159] The latter can be obtained in good overall yield in three steps from the azlactone of α-benzamido crotonic acid.[159]



(**2.370**) (**2.371**)

mp 130°C (Me_2CO)



(i) MeOH, HCl;
(ii) $NaBH_4$;
(iii) $TiCl_4$, H_2S, $-70°C$, 2 h

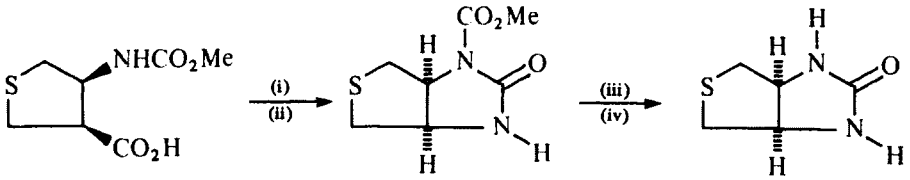
Scheme 2.33

2.15.3.2. Synthesis from Imidazolinones

A patented procedure for the synthesis of methyl-2,3,4,6-tetrahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-pentanoate (**2.372**) is illustrated in Scheme 2.33.[160]

2.15.4. 2,3,3*a*,4,6,6*a*-Hexahydro-1*H*-thieno[3,4-*d*]imidazoles

The chemistry of hexahydro derivatives in the 1*H*-thieno[3,4-*d*]imidazole system is extensive, particularly in regard to biotin synthesis (see Section 2.15.5) and to biotin analogs (Section 2.15.6). The compounds described in this section are closely related to biotin but lack the 4-carboxybutyl substituent; they are usually constructed from tetrahydrothiophenes, but there is an isolated example illustrating the use of an imidazolidinone derivative.



(2.373) (2.374) (2.375)

42% yield, mp 179–180°C (C_6H_6)

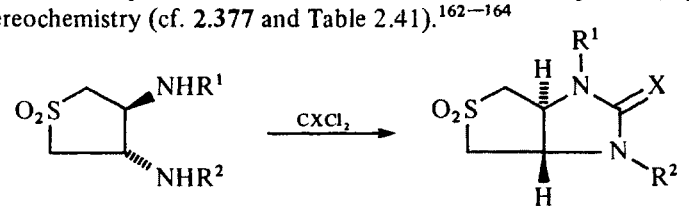
80% yield, mp 229–231°C

(i) $ClCO_2Et$, aqueous Me_2CO; (ii) NaN_3; (iii) 10% $Ba(OH)_2$, EtOH, 100°C; (iv) 6*M* HCl

2.15.4.1. *Synthesis from Thiophene Derivatives*

Curtius rearrangement of the acyl azide derived from **2.373** and ensuing cyclization gives rise to a 1-methoxycarbonyl derivative (**2.374**), and this can be transformed routinely into the parent member (**2.375**) of the hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazole ring system.[161] Although this type of synthesis appears to be straightforward, it may be noted that the preparation of the starting material (**2.373**) requires a six-step procedure from readily available 2,5-dihydrothiophene-3,4-dicarboxylic acid.[161]

In contrast, *trans*-tetrahydro-3,4-bis(amino)thiophene-1,1-dioxides (cf. **2.376**) are readily available by a route from inexpensive 2,5-dihydrothiophene-1,1-dioxide, and the former are transformed by phosgene and thiophosgene in good yield into hexahydro-1*H*-thieno[3,4-*d*]imidazolin-2-ones and -thiones, respectively, possessing a *trans* stereochemistry (cf. **2.377** and Table 2.41).[162–164]



(2.376) (2.377)

	R^1	R^2	X
a	Me	Me	O
b	H	H	O
c	CH_2Ph	H	O
d	CH_2Ph	CH_2Ph	S
e	Me	Me	S

The existence of *trans* fusion in bicyclo[3,3,0] ring systems is unusual and the stereochemistry of (**2.377a**) has been confirmed by X-ray crystallographic analysis.[162] In contrast to the normal envelope conformation associated with biotin derivatives (cf. structure **2.431** in Section 2.15.5), both rings of (**2.377a**) are highly twisted with a number of intramolecular bond angles differing markedly from anticipated values (see Fig. 2.1).

TABLE 2.41. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF *trans*-2,3,3*a*,4,6,6*a*-HEXAHYDRO-1*H*-THIENO[3,4-*d*]IMIDAZOLE-*S*,*S*-DIOXIDE DERIVATIVES (2.377)

Starting Material	Product	Reaction Conditions	Yield (%)	mp (°C) (Solvent for Recrystallization)	Spectroscopic Properties	Reference
2.376a	**2.377a**	$COCl_2$, 10% aqueous Na_2CO_3, PhMe, room temperature	44	198–199 (H_2O)	nmr[a] (4 *M* NaOD in D_2O) δ = 2.8 (6H, s), 3.25 ($2H_1$ s)	162
2.376b	**2.377b**	$COCl_2$, ca. 20% aqueous Na_2CO_3, C_6H_6, room temperature[162] or 0–5°C[163]	24[162] 68[163]	298 (H_2O)	nmr[b] (CF_3CO_2H), 3.6–4.4 (4H, m), 5.0 (2H, m)	162, 163
2.376c	**2.377c**	$COCl_2$, 10% aqueous Na_2CO_3, xylene, 0–5°C, 1–1.5 h	90	258–260 (Me_2CO)	ir ν_{max}^{KBr} = 3210, 1700, 1315, 1115, 740, 700 cm^{-1}; nmr (DMSO-d_6) δ = 2.90–3.70 (6H, m) 4.32 (2H, s, CH_2N), 7.25 (1H, br, NH), 7.34 (5H, s, Ar–H)	163
2.376d	**2.377d**	$CSCl_2$, dioxan, pyridine, room temperature	47	218 (50% aq. dioxan)	ir ν_{max}^{KBr} = 3030, 2920, 2860, 1335, 1305, 1215, 1110, 990, 730, 470 cm^{-1}	164
2.376e	**2.377e**	$CSCl_2$, dioxan, pyridine, room temperature	85	316 (50% aq. dioxan)	ir ν_{max}^{KBr} = 3015, 2935, 2880, 1450, 1430, 1335, 1310, 1220, 1115, 1085, 750, 465 cm^{-1}	164

[a] Protons alpha to the sulfoxide group are exchanged.
[b] Taken from ref. 162.

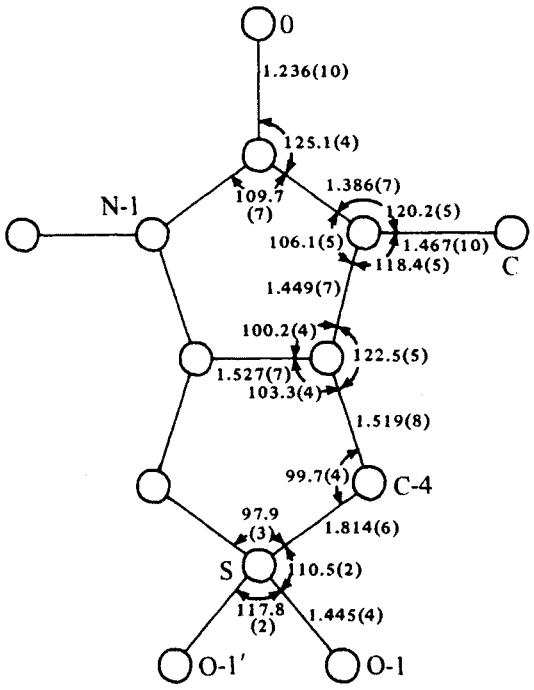
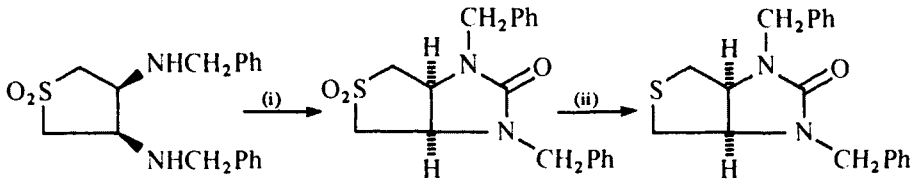


Figure 2.1 Intramolecular bond lengths and angles of **2.377a** with standard deviations in parentheses. The term O-1′ refers to the twofold axis atom related to O-1. The C-4–S–O-1′ angle is 109.2 ± 0.3°.

2,5-Dihydrothiophene-1,1-dioxide can also be used to synthesize the *cis*-3,4-dibenzylaminothiophene derivative (**2.378**), and this can be converted with phosgene into a *cis*-fused hexahydro-1*H*-thieno[3,4-*d*]imidazole (**2.379**).[165] The stereochemistry of compound **2.379** has been determined by LAH-promoted reduction to **2.380** and comparison of the latter with an authentic sample.[165]



(**2.378**) (**2.379**) mp 184°C (**2.380**) mp 110–111°C

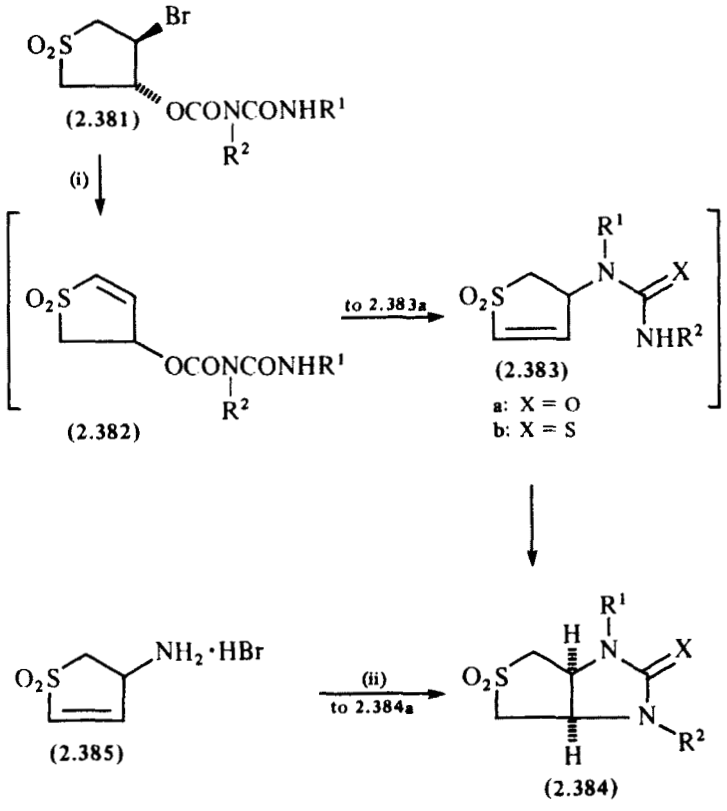
(i) $COCl_2$, Et_3N, CH_2Cl_2 room temperature (quantitative);
(ii) $LiAlH_4$, Et_2O, room temperature

TABLE 2.42. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF *cis*-2,3,3*a*,4,6,6*a*-HEXAHYDRO-1*H*-THIENO[3,4-*d*]IMIDAZOLE-*S*,*S*-DIOXIDE DERIVATIVES[164,166]

Starting Material	Product	Reaction conditions	Yield (%)	mp (°C) (Solvent for Recrystrallization)	Spectroscopic Properties	Reference
2.381	**2.384a**[a]	Aqueous Na_2CO_3, reflux, 2 h	45	318–320[b] (H_2O)	ir ν_{max} (Nujol) = 3200, 3100, 1710, 1325, 1150 cm^{-1}; nmr δ (CF_3CO_2H) = 3.1 (br, 4H), 4.5 (br, 2H)	166
2.383 (R^1 = R^2 = Ph)	**2.384b**	0.5 *M* NaOEt, EtOH		176–177 (MeOH)	ir ν_{max} (Nujol) = 1695, 1600, 1500, 1295, 1160 cm^{-1}; nmr δ (CF_3CO_2H), 3.1 (br, s, 4H), 5.1 (s, 2H), 7.1 (br, 10H, s)	166
2.383a (R^1 = Ph, R^2 = Me)	**2.384c**	0.5 *M* NaOEt, EtOH		191–192 (aq. EtOH)	ir ν_{max} = 1695, 1600, 1510, 1315, 1120 cm^{-1}; nmr δ (CF_3CO_2H) = 3.0–3.6 (3H, s), 4.4–4.8 (1H, m), 4.8–5.2 (1H, m), 7.0 (5H, m)	166
2.383b (R^1 = R^2 = Ph)	**2.384d**	C_6H_6, pyridine, reflux, 1–2 h	98	236–237 (aq. Me_2CO)	ir ν_{max} (KBr) = 3010, 2860, 1490, 1435, 1395, 1290, 1265, 1165, 1120, 1070, 890, 660 cm^{-1}	164
2.383b (R^1 = Ph, R^2 = $PhCH_2$)[c]	**2.384e**	C_6H_6, pyridine reflux, 1–2 h	91	229–230 (aq. Me_2CO)	ir ν_{max} (KBr) = 3010, 2930, 2860, 1490, 1450, 1400, 1300, 1265, 1240, 1160, 1115, 705, 660 cm^{-1}	164

[a] Forms a 1,3-diacetyl derivative, mp 236–238°C and a mono acetyl derivative, mp 260–262°C (H_2O)
[b] Melting point determined by use of a sealed and evacuated tube.
[c] This compound is prepared *in situ* from 3-anilino-2,3-dihydrothiophene-1,1-dioxide and the appropriate isothiocyanate derivative.

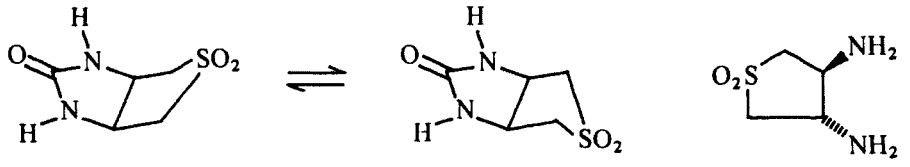
The readily available 2,5-dihydrothiophene-1,1-dioxide can also be used to prepare *trans*-4-bromo-tetrahydro-3-thienyl allophanate *S,S*-dioxide (**2.381**, $R^1 = R^2 = H$), and this can be transformed in aqueous alkali by means of an allylic allophanate and an allylic urea into a *cis*-fused hexahydro-1*H*-thieno[3,4-*d*]-imidazole-*S,S*-dioxide (see **2.381** → **2.382** → **2.383a** → **2.384a**).[166] The synthesis of 1,3-disubstituted derivatives in the series (**2.384b–e**) can also be achieved by preparing ureas and thioureas (cf. **2.383a,b**) from the appropriate 3-amino-2,3-dihydrothiophene-1,1-dioxide and an isocyanate or isothiocyanate derivative and cyclizing the former in base[164,166] (see Table 2.42). An alternative, simple method of generation of the 2,3-dihydro-3-ureidothiophene-1,1-dioxide (**2.383a**, $R^1 = R^2 = H$) involves reaction of the amino derivative (**2.385**) with aqueous potassium cyanate; the presence of 2 molar equivalents of the latter reagent ensures *in situ* conversion of the ureido derivative into the unsubstituted bicyclic compound (**2.384a**) in 47% yield.[167]



(i) Na_2CO_3, H_2O, reflux, 2h;
(ii) KONC (2 mol. equiv.), H_2O, reflux, 3h (47% yield)

	R^1	R^2	X
a	H	H	O
b	Ph	Ph	O
c	Ph	Me	O
d	Ph	Ph	S
e	Ph	$PhCH_2$	S

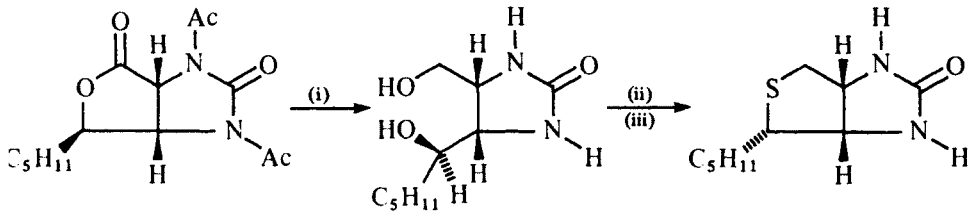
The unsubstituted *cis*- and *trans*-hexahydro-1*H*-thieno[3,4-*d*]imidazole-*S*,*S*-dioxide derivatives (**2.384a** and **2.377b**) are characterized by quite different spectral and chemical properties. For example, the *cis* compound shows ν_{max} = 1710 cm^{-1} for its carbonyl ir absorption, whereas the *trans* compound shows ν_{max} = 1705 and 1690 cm^{-1}. The ^1H nmr spectrum of the *trans*-fused compound possesses a complex pattern for the ring protons with multiplets centered at δ = 3.95 and 4.95, whereas the *cis* isomer shows broad resonances centered on δ = 3.1 and 4.5. The absence of recognizable spin–spin splitting in the latter spectrum can be attributed[166] to a conformational mobility of the perhydrothiophene ring as illustrated in **2.386** ⇌ **2.387**. The chemical difference between the *cis* and *trans* isomers is demonstrated by their behavior toward 6*M* hydrochloric acid. The relatively unstrained *cis* compound forms a hydrochloride salt, whereas the *trans* isomer (**2.377b**) is quantitatively hydrolyzed to the *trans* diamine derivative (**2.388**).[166]



(2.386) (2.387) (2.388)

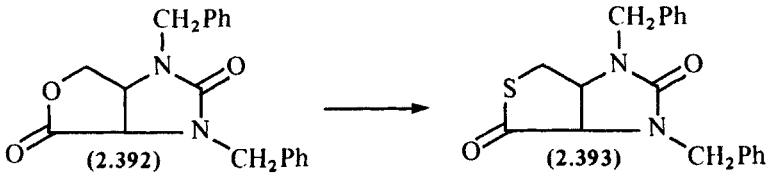
2.15.4.2. *Synthesis from Imidazolidinones*

Construction of the perhydro-1*H*-thieno[3,4-*d*]imidazole ring system from imidazolidinone precursors is less widely adopted, and there is a single example involving cyclization of an isolated intermediate of this type (see **2.389** → **2.390** → **2.391** and Section 2.8.1 for a description of the synthesis of the furo[3,4-*d*]-imidazolin-2,6-dione starting material).[86] It may be noted that compound **2.391** possesses the relative stereochemistry of biotin (**2.357**) but bears a modified 4-substituent.



(2.389) (2.390) (2.391)

(i) $NaBH_4$, LiBr, diglyme, room temperature (78% yield);
(ii) CH_3SO_2Cl, pyridine, −10°C
(iii) Na_2S, dimethylformamide, 95°C (32% yield)

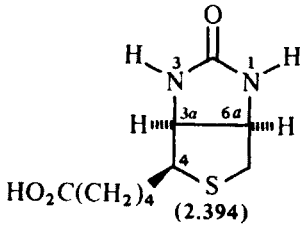


There is also a number of patented procedures for the direct transformation of perhydro-furo[3,4-*d*]imidazol-2,4-diones into perhydro-thieno[3,4-*d*]imidazol-2,4-diones. [See, e.g., **2.392** → **2.393** using the following reagents: $RNHCS_2M$(R = alkyl, cycloalkyl, etc.; M = alkali metal),[109–111], P_2S_5,[113] and $MeCSNH_2$, S, base.[168]]

2.15.5. Synthetic, Spectroscopic, and Theoretical Studies of Biotin

2.15.5.1. General Comments

Chemical and biochemical aspects of biotin (vitamin H) have been covered in a number of review articles.[169–176] This compound (**2.394**) contains three chiral centers, but of the eight possible stereoisomers, only the (+) enantiomer illustrated in structure **2.394** is biologically active. Structure **2.394** is described formally as [3*aS*-(3*aα*,4*β*,6*aα*)]hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic acid.



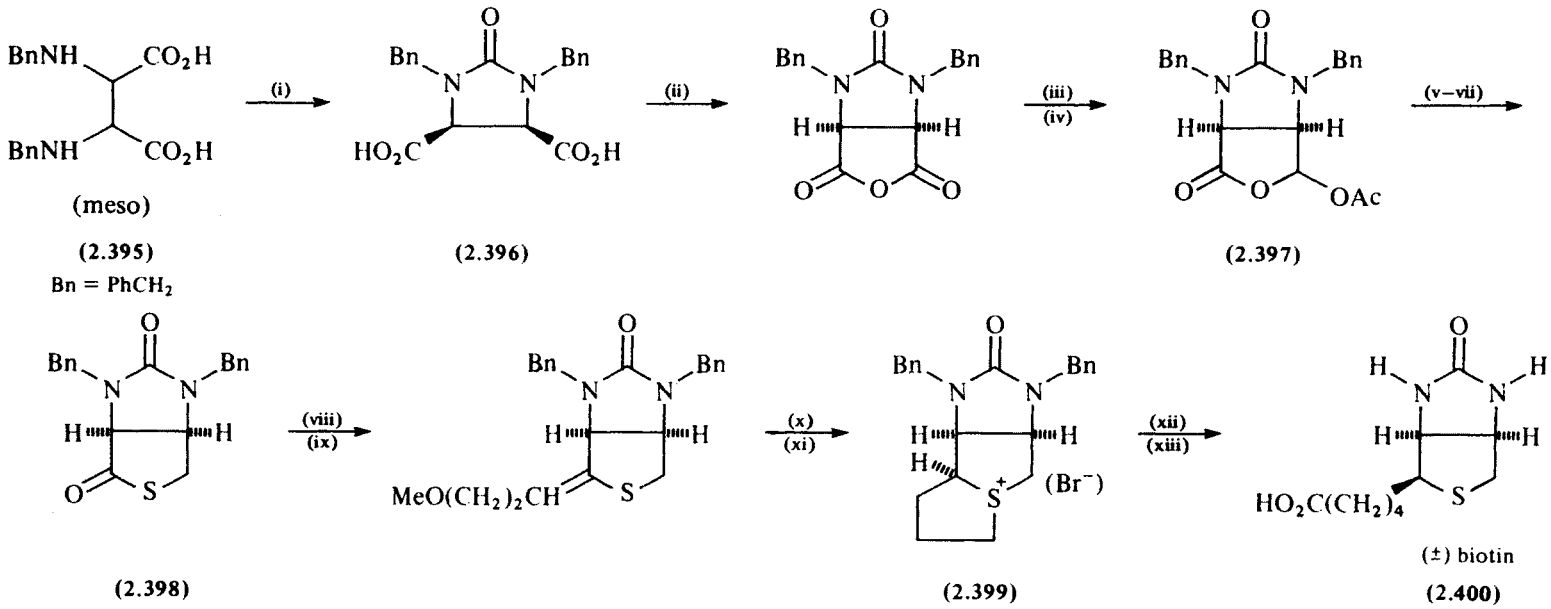
(2.394)

Biotin can be isolated from dried egg yolk, in which it is present as approximately 80 mg/250 kg and from which it may be extracted as 1.1 mg/250 kg. It is considered to play an important role in numerous naturally occurring carboxylation process, probably by the following mechanism:[177]

$$\text{Enzyme–biotin} + HCO_3^- + \text{ATP} \rightleftharpoons \text{enzyme–biotin–}CO_2^- + P_i$$

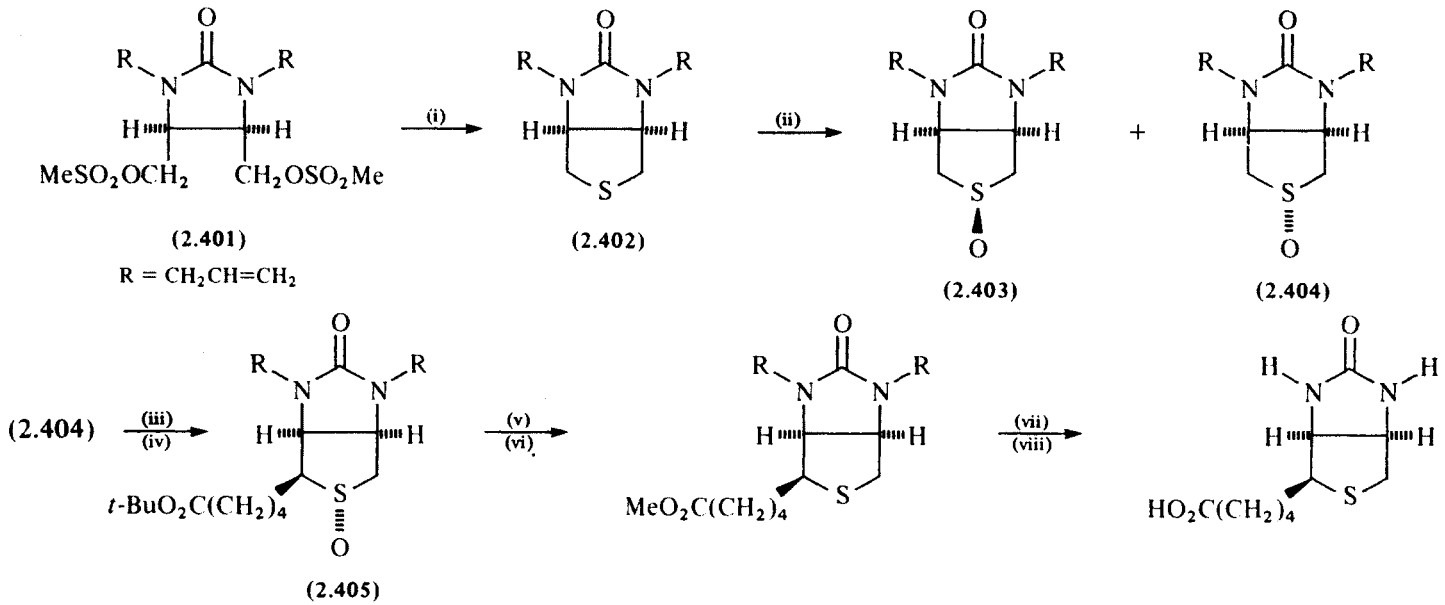
$$\text{Enzyme–biotin–}CO_2^- + \text{acceptor} \rightleftharpoons \text{acceptor–}CO_2^- + \text{enzyme–biotin}$$

In these processes, the enzymatic components may be carboxylases, transcarboxylases, and decarboxylases, and the site of carboxylation of enzyme-bound biotin is probable at N-1.[178] From early studies, it appeared that the useful biological activity of biotin was confined to the prevention of dermatitis in experimental animals,[179] but more recently new applications have been found in the areas of nutrition and growth promotion.[180–182] Accordingly, there is a continuing interest in the synthesis, and particularly in the chiral synthesis of (+)biotin and in the preparation of compounds structurally related to it.



(i) $COCl_2$; (ii) Ac_2O; (iii) Zn, AcOH; (iv) Ac_2O; (v) H_2S, HCl; (vi) KHS; (vii) Zn, AcOH; (viii) $BrMg(CH_2)_3OMe$; (ix) AcOH, heat; (x) H_2, Pd; (xi) HBr; (xii) $NaCH(CO_2Et)_2$; (xiii) HBr

Scheme 2.34



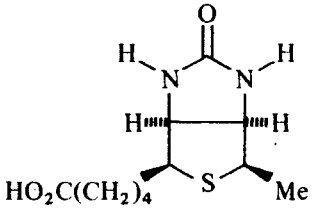
(i) Na_2S, EtOH, reflux, 3h; (ii) $NaIO_4$, H_2O, 5°C; (iii) MeLi, diglyme; (iv) $I(CH_2)_4CO_2t$-Bu; (v) aq. $TiCl_3$; (vi) MeOH, H_2SO_4; (vii) $(Ph_3P)_3RhCl$, 1,4-diazabicyclo[2.2.2]octane, C_6H_6, H_2O; (viii) HCl, MeOH

Scheme 2.35

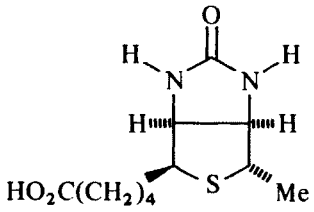
2.15.5.2. Synthesis from Imidazolidinone Derivatives

An early total synthesis of (±)biotin (**2.400**) by Goldberg and Sternbach[183] is based on the readily available 1,3-dibenzyl-2-imidazolidinone-*cis*-4,5-dicarboxylic acid (cf. *meso*-dibromosuccinic acid → **2.395** → **2.396** and Scheme 2.34). A key intermediate in this sequence is the trimethylene thiophanium bromide (**2.399**), and resolution can be effected at this stage in a conventional manner by using silver *d*-camphor sulfonate.[183] Subsequent improvements in the overall synthesis include a resolution method for intermediates derived from **2.397**,[184] a procedure (CH_3CS_2K in $HCONMe_2$) for the conversion of **2.397** (H for OAc) into **2.398**,[184] and a superior reagent ($MeSO_3H$ for HBr) for the decarboxylation step (Scheme 2.34, xiii) in the transformation of **2.399** into **2.400**.[185]

A *cis*-4,5-disubstituted imidazolidinone (**2.401**) has also been used to construct the hexahydro-1*H*-thieno[3,4-*d*] imidazole skeleton with subsequent introduction of the valeric acid side chain through stereoselective alkylation of the sulfoxide (**2.404**)—formed fortuitously in 9:1 ratio with **2.403** (see Scheme 2.35).[186] A single stereoisomer (**2.405**) is formed in the alkylation of **2.404**, and in this context the process is analogous to the methylation behavior of six-membered ring sulfoxides in which axial and equatorial sulfoxides give products of axial and equatorial methylation, respectively;[187] methylation is thus *trans* to the S–O bond. The synthesis illustrated in Scheme 2.35 has considerable potential for the preparation of biotin analogs with defined stereochemistry and has been used, for example, to prepare 6-methyl-substituted derivatives epimeric at C-6 (**2.406** and **2.407**).[186]

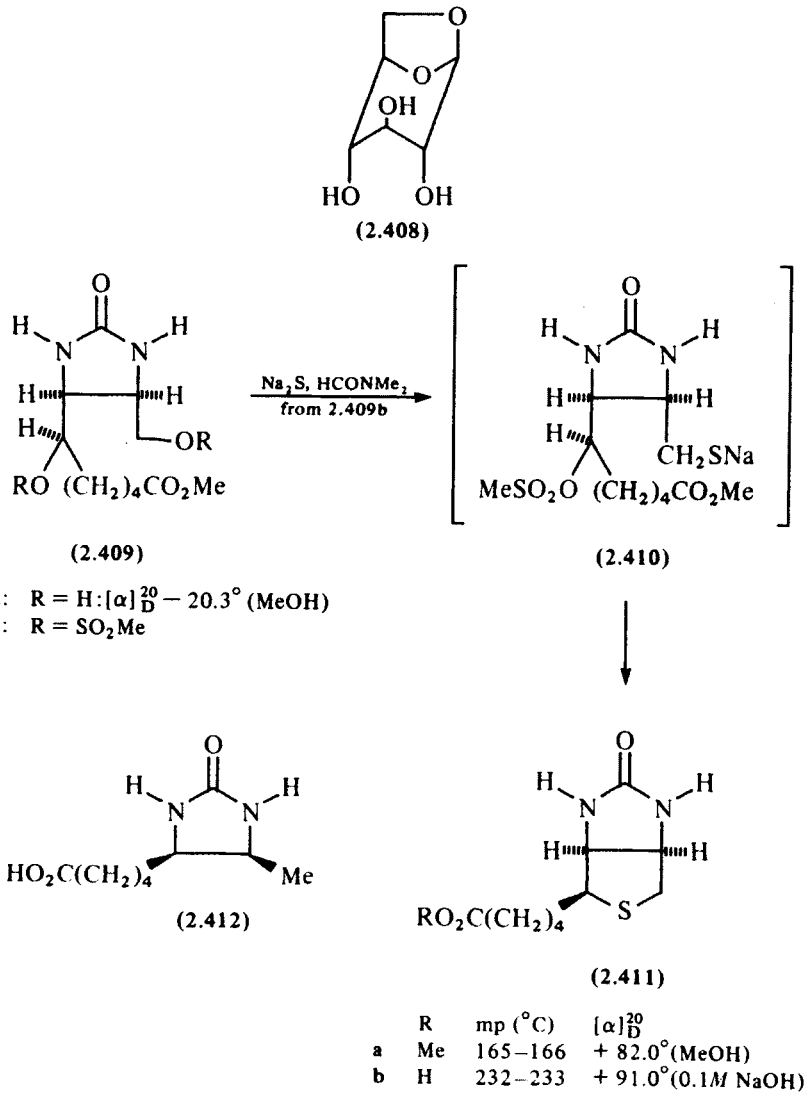


(2.406)
mp 260°C (H_2O)



(2.407)
mp 240°C (MeOH)

A key optically active imidazolidinone synthetic intermediate (**2.409a**) has been derived from 1,6-anhydro-β-D-glucose (**2.408**) as part of a successful chiral synthesis of (+)biotin[188] (see Scheme 2.36). Transformation of this intermediate (**2.409a**) to a labile mesylate (**2.409b**) is followed by cyclization with sodium sulfide to give (+)biotin methyl ester (**2.411a**) in 30% overall yield from **2.409a**. A notable feature of this synthesis is its close relationship to the biosynthesis of biotin in which the precursor (+)desthiobiotin (**2.412**) is cyclized in a stereospecific oxidative sulfurization process.[189] A serious disadvantage of the synthesis described in Scheme 2.36 is that approximately 20 steps are required[188] to convert D-glucose into the intermediate (**2.409**). Subsequently, a shorter synthesis of



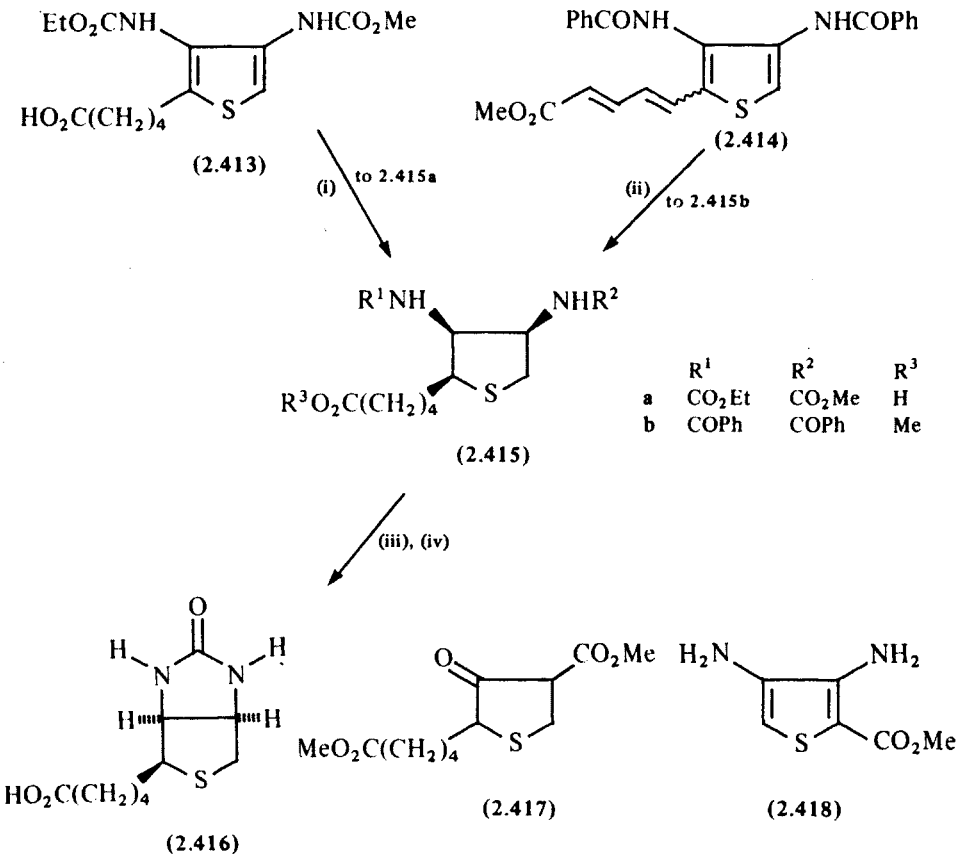
	R	mp (°C)	$[\alpha]_D^{20}$
a	Me	165–166	+ 82.0°(MeOH)
b	H	232–233	+ 91.0°(0.1*M* NaOH)

Scheme 2.36

(**2.409a**) has been devised from D-glucosamine (see **2.273** in Scheme 2.25[123]), and racemic (**2.409a**) derived from chromene has been used in an analogous route to (±)biotin.[190]

2.15.5.3. Synthesis from Thiophene Derivatives

The synthesis of (±)biotin (**2.416**) from thiophene derivatives involves the preparation of suitably functionalized compounds (**2.415**) relating to 3,4-diamino-

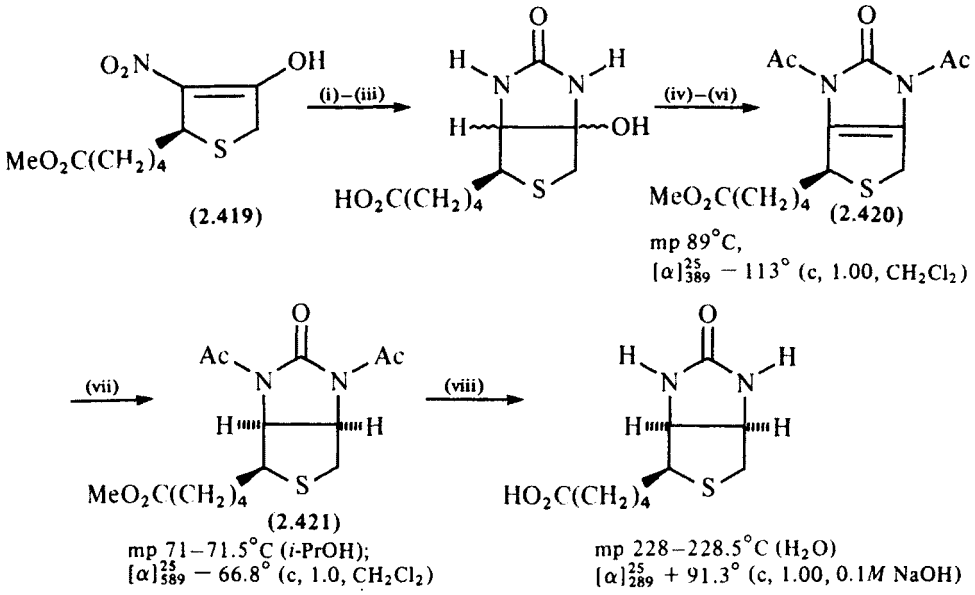


(i) H_2, 10% Pd–C, AcOH, 124 bar, 50°C, 16 h;
(ii) H_2, 5% Pd–C, AcOH, 90 bar, 100°C;
(iii) aqueous $Ba(OH)_2$;
(iv) $COCl_2$

Scheme 2.37

thiophenes (e.g., **2.413**[191] and **2.414**,[192] derived in eight- and four-step sequences from **2.417** and **2.418**, respectively) followed by a straightforward cyclization process (see Scheme 2.37). The overall yield in the synthesis from **2.417** is relatively good (37%), but the severe conditions required in the catalytic hydrogenation step (**2.413** → **2.415a**) are problematical;[191] accordingly, an alternative synthetic route to an amide related to **2.415a** has been devised by use of a 2,5-dihydrothiophene precursor.[193]

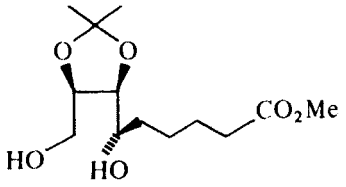
A 2,5-dihydrothiophene derivative (**2.419**) has also been used in a synthesis of (+)biotin in which resolution is effected at an early stage (through the α-methylbenzylamine salt of **2.419**; see Scheme 2.38).[194] A key, somewhat surprising feature in this approach (contrast **2.413** → **2.415a**) is the efficient, almost stereospecific catalytic hydrogenation of the dehydrobiotin derivative (see **2.420** → **2.421**).[194]



(i) H_2, 10% Pd–C, AcOH, HCl; (ii) KOCN; (iii) KOH; (iv) AcOH, 55°C ($-H_2O$); (v) H^+, MeOH; (vi) Ac_2O; (vii) H_2, 10% Pd–C, 550 psi; (viii) alkaline aqueous MeOH

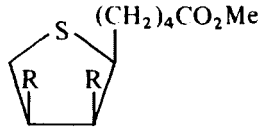
Scheme 2.38

The total chiral synthesis of (+)biotin has been achieved from D-mannose by a multistep procedure through the optically active perhydrothiophene intermediate (**2.423**), and routine cyclization of the diamine derived therefrom.[195] A key intermediate in the synthesis is methyl 2,3,4,5-tetradeoxy-7,8-*O*-isopropylidene-L-lyxo-nonanate (**2.422**), and this can also be prepared from D-arabinose.[196]



(**2.422**)

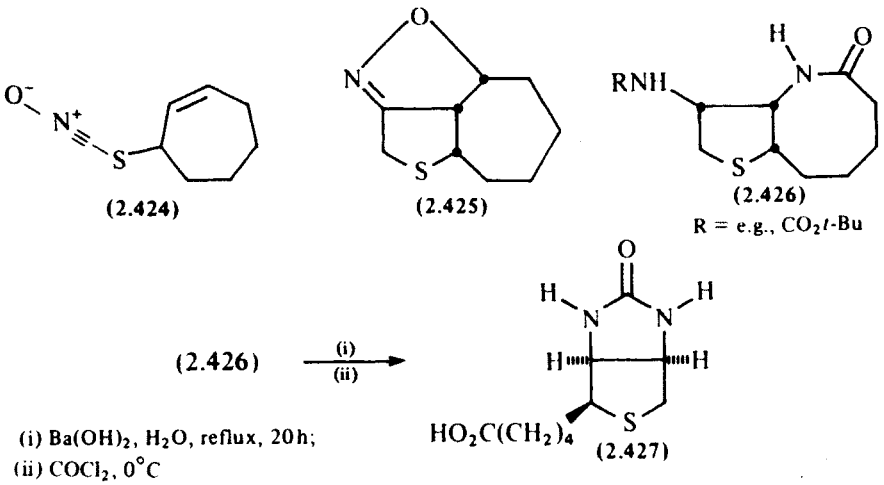
$[\alpha]_D^{20}$ − 91.2° (c, 1.8, $CHCl_3$)

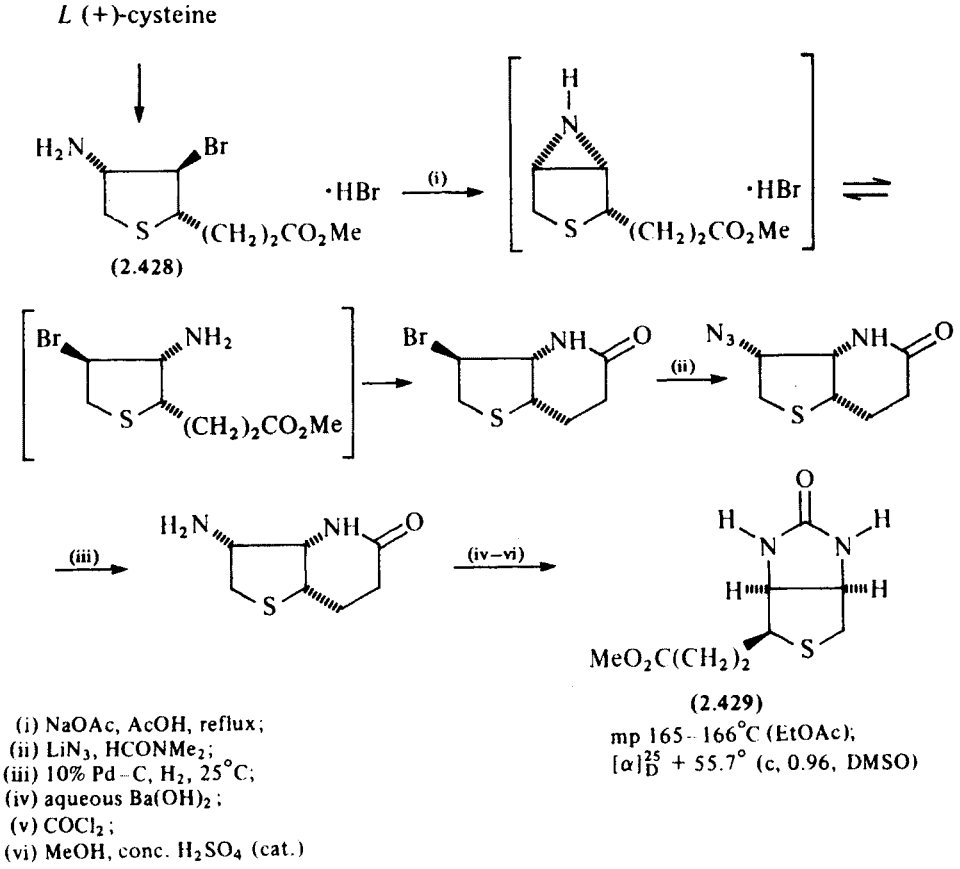


(**2.423**)

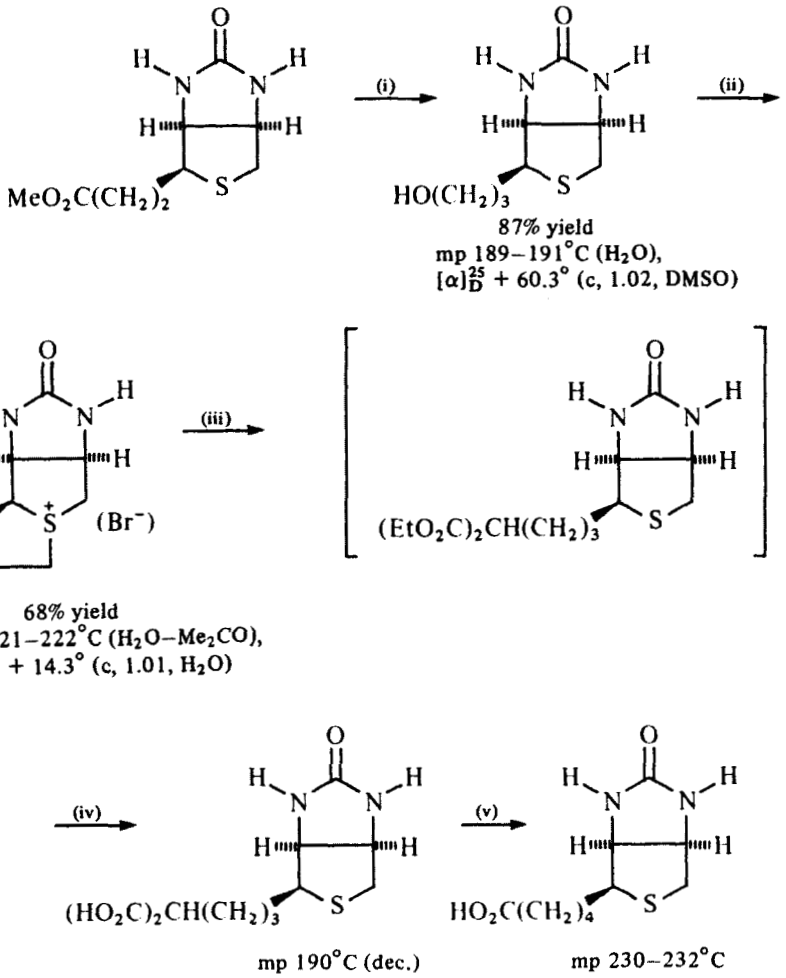
$[\alpha]_D^{20}$ − 123.9° (c, 1.7, EtOH)

The remaining routes to biotin described in this section concern the subtle synthesis of condensed thiophene derivatives with the appropriate relative stereochemistry relating to (±)biotin. 3-Bromocycloheptene is the starting material in a synthesis[197] leading in an initial five steps to the intermediacy of a nitrile oxide (**2.424**). Intramolecular cycloaddition of the latter and subsequent transformations of the ensuing condensed isoxazolidine (**2.425**) provide a valuable intermediate (**2.426**) possessing the correct relative stereochemistry for a straightforward transformation to (±)biotin (see **2.426** → **2.427**). An alternative route to intermediates related to **2.425** and employing a nitrone intermediate akin to **2.424** is incorporated in a subsequent patent.[198]


(2.424)
(2.425)
(2.426)
R = e.g., CO_2t-Bu
(2.426)
(i)
(ii)
(i) $Ba(OH)_2$, H_2O, reflux, 20h;
(ii) $COCl_2$, 0°C
$HO_2C(CH_2)_4$
(2.427)


L (+)-cysteine
(2.428)
·HBr
(i)
·HBr
(ii)
(iii)
(iv–vi)
$MeO_2C(CH_2)_2$
(2.429)
mp 165–166°C (EtOAc);
$[\alpha]_D^{25}$ + 55.7° (c, 0.96, DMSO)
(i) NaOAc, AcOH, reflux;
(ii) LiN_3, $HCONMe_2$;
(iii) 10% Pd–C, H_2, 25°C;
(iv) aqueous $Ba(OH)_2$;
(v) $COCl_2$;
(vi) MeOH, conc. H_2SO_4 (cat.)

Scheme 2.39



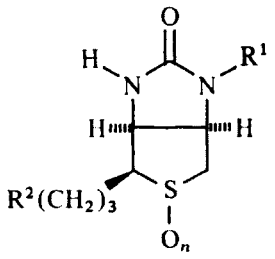
(i) $LiBH_4$, THF, reflux; (ii) AcOH, HBr, 100°C; (iii) Na, $CH_2(CO_2Et)_2$, 120°C; (iv) $Ba(OH)_2$, aqueous MeOH; (v) H_2O heat

Scheme 2.40

A successful total chiral synthesis of (+)biotin from L(+)-cysteine is illustrated in Schemes 2.39 and 2.40.[199] Generation of the key optically active synthetic intermediate (**2.428**) requires eight steps from L(+)-cysteine, and this is then transformed stereospecifically into the methyl ester of *d*-bisnorbiotin (**2.429**). Chain elongation to introduce the valeric acid side chain is then achieved[199] by minor modifications of the original Goldberg–Sternbach procedure (see Scheme 2.40, and cf. Scheme 2.34). [For subsequent alternative patented chiral syntheses of (+)biotin from L(+)-cysteine, see refs. 200 and 201.]

2.15.5.4. *Crystal and Molecular Structure*

The molecular and crystal structures of (+)biotin (**2.430e**) and four related compounds (**2.430a**,[202] **b**,[178] **c**,[202] and **d**[202]) have been elucidated by X-ray crystallographic analysis. The interatomic bond distances in (+)biotin (**2.431**) collected in Table 2.43 are the average of two independent structure determinations.[204] Of particular interest is the length of the imidazolidinone carbonyl group (C-2′–O-2′) (1.249 Å), which is significantly longer than the average (1.21 Å) found for the ureido carbonyl group of 12 barbiturates[205] and approaches the very long value (1.27 Å) found in urea.[206] The lengths of the C-2′–N-1′ and C-2′–N-3′ bonds (average 1.34 Å) are correspondingly shorter than these found in barbiturates (1.37 Å) are relate more closely to the 1.33 Å value found in urea. The cause of such ureido polarization in (+)biotin may be a strong intramolecular hydrogen bond from O-10α–H to O-2′ as indicated by a bond separation of 2.54 Å. As an extrapolation of this model, it has been suggested[204] that the carboxylation of enzyme-bound biotin may be preceded by ureido bond polarization induced by intermolecular hydrogen bonding with bicarbonate.



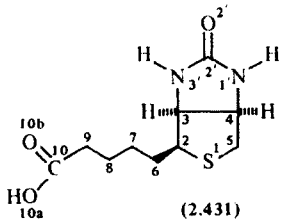
(2.430)

	R^1	R^2	n
a	$CONHC_6H_4Br$-*p*	$CH_2CONHC_6H_4Br$-*p*	0
b	CO_2Me	CH_2CO_2Me	0
c	H	indol-3-yl	0
d	H	indol-3-yl	1
e	H	CH_2CO_2H	0

2.15.5.5. *Ultraviolet Spectra*

The uv spectra[207] of biotin (**2.431**) and thiobiotin (**2.431**, S for O-2′) can be interpreted in terms of existing data on simple thioesters, ureides, and thioureides. The spectra of biotin [$\lambda_{max}^{MeOH} = 235$ nm (ϵ, 70, sh); $\lambda_{max}^{H_2O} < 195$ (6500)] correspond to the sum of urea and thioether contributions, and the spectrum of thiobiotin [$\lambda_{max}^{H_2O} = 212$ nm (ϵ, 10,000), 235 (15,900)] is dominated by the intense thioureide absorption.[207]

TABLE 2.43. INTERATOMIC BOND DISTANCES[a] AND ANGLES[a] IN (+)BIOTIN (2.431) FROM X-RAY CRYSTALLOGRAPHIC ANALYSIS[204]



(2.431)

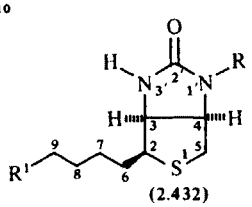
S-1–C-2	1.823 Å	C-2–H-2	0.93 Å
S-1–C-5	1.807 Å	C-3–H-3	0.90 Å
C-2–C-3	1.531 Å	C-4–H-4	0.99 Å
C-2–C-6	1.510 Å	C-5–H-5*a*	0.88 Å
C-3–C-4	1.548 Å	C-5–H-5*b*	1.06 Å
C-3–N-3′	1.446 Å	N-1′–H-1′	0.94 Å
C-4–C-5	1.536 Å	N-3′–H-3′	1.00 Å
C-4–N-1′	1.459 Å	C-6–H-6*a*	1.09 Å
N-1′–C-2′	1.332 Å	C-6–H-6*b*	1.02 Å
C-2′–O-2′	1.249 Å	C-7–H-7*a*	1.06 Å
C-2′–N-3′	1.351 Å	C-7–H-7*b*	0.95 Å
C-6–C-7	1.548 Å	C-8–H-8*a*	1.03 Å
C-7–C-8	1.533 Å	C-8–H-8*b*	1.15 Å
C-8–C-9	1.538 Å	C-9–H-9*a*	1.02 Å
C-9–C-10	1.499 Å	C-9–H-9*b*	1.21 Å
C-10–O-10*a*	1.299 Å	O-10*a*–H-10*a*	0.96 Å
C-10–O-10*b*	1.207 Å		
S-1–C-2–C-3	104.6°	C-5–C-4–N-1′	113.0°
S-1–C-2–C-6	116.6°	C-4–N-1′–C-2′	112.5°
C-2–S-1–C-5	89.4°	N-1′–C-2′–O-2′	126.9°
S-1–C-5–C-4	106.2°	N-1′–C-2′–N-3′	109.5°
C-2–C-3–C-4	109.7°	O-2′–C-2′–N-3′	123.7°
C-2–C-3–N-3′	113.5°	C-6–C-7–C-8	113.9°
C-3–C-2–C-6	111.9°	C-7–C-8–C-9	110.2°
C-2–C-6–C-7	117.2°	C-8–C-9–C-10	110.9°
C-3–C-4–C-5	108.6°	C-9–C-10–O-10*a*	113.6°
C-3–C-4–N-1′	102.6°	C-9–C-10–O-10*b*	123.9°
C-4–C-3–N-3′	103.0°	O-10*a*–C-10–O-10*b*	122.5°
C-3–N-3′–C-2′	112.3°		

[a]Figures quoted are the average of two independent determinations.

2.15.5.6. *Nuclear Magnetic Resonance Spectra*

The high-resolution ^1H nmr spectra of (+)biotin and its methyl ester have been recorded in a variety of solvents,[208] and line-broadening effects have been used to elucidate the nature of interaction of biotin and its derivatives with metal ions;[209] more recent ^1H and ^{13}C nmr spectral data are collected in Tables 2.44 and 2.45, respectively.[210] A notable change observed in ^1H nmr spectra is the downfield

TABLE 2.44. ^{1}H NMR CHEMICAL SHIFT VALUES[a] FOR (+)BIOTIN AND ITS DERIVATIVES[210]



(2.432)

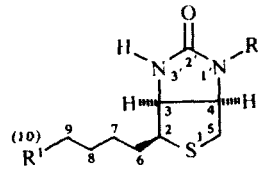
R,R^1 in 2.432 Solvent	H, CO_2H DMSO-d_6	H, CH_2OH, CD_3OD	H, CO_2CH_3, DMSO-d_6	CO_2CH_3,CO_2CH_3 $CDCl_3$
C-2-H	2.94–3.32, m	3.00–3.20, m	2.92–3.30, m	3.06–3.28, m
C-3–H	3.97–4.50, m	4.10–4.64, m		4.10–4.30, m
C-4–H				4.70–4.92, m
C-5–H_2	2.64–2.90, m	2.72–2.90, m	2.60–2.86, m	2.92–3.08, m
C-6–H_2 C-7–H_2 C-8–H_2	1.17–1.97, m	1.20–2.00, m	1.18–1.94, m	1.20–1.95, m
C-9–H_2	1.97–2.40, m		2.10–2.44, m	2.12–2.42, m
C-10	–[b]	3.34–3.75, m[c]	–[d]	–[e]
R=CO_2CH_3				3.82, s
N-H (s)	6.23–5.57, br, s	f	5.20–7.24, br, s	7.00–7.24, br, s

[a]The initial number of each entry in the table is the chemical shift value (δ) observed in ppm relative to TMS, which is followed by the multiplicity observed for the signal.
[b]The carboxylic acid proton was not detected in the spectrum.
[c]The chemical shift value for the hydroxyl proton could not be assigned.
[d]Hydrogen-1 nmr data for CO_2CH_3 signal: δ = 3.59, s.
[e]Hydrogen-1 nmr data for CO_2CH_3 signal: δ = 3.62, s.
[f]The chemical shift value for this proton could not be assigned.

shift of the two imidazolidinone methine protons (C-3–H and C-4–H) caused by introduction of a methoxycarbonyl substitutent at N-1′. Comparison of the ^{13}C nmr data in Table 2.45 indicates three effects caused by introduction of the methoxycarbonyl group at N-1′: upfield shifts in the adjacent sp_2 carbon (C-2′, $\Delta \sim 8.4$ ppm) and the sp^3 carbons beta to the methoxycarbonyl substituent (C-3, $\Delta \sim 4.8$ ppm and C-5, $\Delta \sim 2.3$ ppm) and a downfield shift in the sp_3 carbon alpha to this substituent (C-4, $\Delta \sim 2.3$ ppm). The multiplicities illustrated in Table 2.45 are in accord with those expected on the basis of first-order $^{13}C-^1H$ coupling. The magnitudes of coupling constants are dependent on the nature of the atom adjacent to the carbon atom, with the value increasing in the order $C < S < O \sim N$.

Interpretation of the ^{15}N nmr spectrum of (+)biotin has been achieved from natural-abundance ^{15}N spectra coupled with data from a sample enriched with ^{15}N at N-1.[211] Comparison of values of nitrogen chemical shift values (283.5 and 292.6 ppm for N-1 and N-3, respectively, in 0.1 *M* $NaHCO_3$ solution) with those of model urea derivatives[212] suggests that in this medium (+)biotin possesses urea-type nitrogen environments rather than an imino-type tautomeric system.

TABLE 2.45. ^{13}C NMR CHEMICAL SHIFTS[a] AND $^{13}C-^{1}H$ COUPLING CONSTANTS[a] FOR (+)BIOTIN AND ITS DERIVATIVES[210]



(2.433)

R, R^1 in **2.433** Solvent	H, CO_2H Pyridine-d_5	H, CH_2OH Pyridine-d_5	H, CO_2CH_3 Pyridine-d_5	H, $CH_2OC(O)CH_3$ Pyridine-d_5	CO_2CH_3, CO_2CH_3 $CDCl_3$
C-2′	164.4, s	164.7, s	164.5, s	164.6, s	156.0, s
C-2	56.3, d, 144	56.5, d, 138	56.2, d, 136	56.4, d, 142	55.3, d, 139
C-3	62.4, d, 144	62.5, d, 141	62.5, d, 147	62.5, d, 140	57.8, d, 147
C-4	60.6, d, 148	60.6, d, 149	60.6, d, 152	60.6, d, 148	62.9, d, 153
C-5	41.1, t, 141	41.0, t, 141	41.0, t, 141	41.0, t, 141	38.7, t, 143
C-6	25.7, t, 124	26.6, t, 122	25.2, t, 124	26.2, t, 125	24.6, t, 126
C-7	29.1,[b] t, 128	29.4, t, 132	28.9, t, 127	29.1, t, 131	28.1, t, 126
C-8	29.1,[b] t, 128	29.5, t, 132	29.0, t, 127	29.2, t, 131	28.3, t, 126
C-9	35.0, t, 126	33.4, t, 126	33.9, t, 124	28.7, t, 129	33.6, t, 129
C-10	176.4, s	61.9, t, 139	173.7, s[c]	64.4, t, 145[a]	174.0, s;[e]
$R = CO_2CH_3$					152.4, s;
$R = CO_2CH_3$					53.5, q, 153

[a] The initial number in each entry in the table is the chemical shift value (δ) observed in ppm relative to TMS, which is succeeded by the multiplicity of the signal in the corresponding $^{13}C-H$-coupled spectrum, followed by the $^{13}C-H$ coupling constant in Hz (± 4 Hz).

[b] This signal is approximately double the intensity of the neighboring peaks.

[c] ^{13}C nmr data for CO_2CH_3 signal: 51.3 δ, q, 146.

[d] ^{13}C nmr data for the $CH_2OC(O)CH_3$ signal: 170.7 δ, s; ^{13}C nmr data for $CH_2OC(O)CH_3$ signal: 20.8, q, 129.

[e] ^{13}C nmr data for CO_2CH_3 signal: 51.5 δ, q, 150.

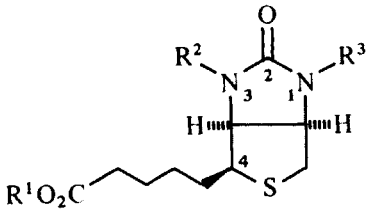
2.15.5.7. Molecular Orbital Studies

Theoretical aspects of the structural chemistry of biotin and several *N*-carboxy and *O*-carboxy biotin molecules have been studied by using all valence–electron self-consistent field (SCF) molecular orbital calculations (CNDO/2).[213] The following conclusions have emerged from this study: the ureido carbonyl oxygen of biotin has considerably more negative charge than the nitrogens; the keto form of biotin is dominant; and in the carboxylation step of biotin, the net atomic charge on the carbonyl oxygen in greater than that on the ureido nitrogens.

2.15.6. Synthesis and Reactions of Biotin Analogs

2.15.6.1. Compounds Modified in the Imidazolidinone Ring

Analytical procedures involving the silylation of biotin by $CR_3CON(SiMe_3)_2$ (R = H[214] and F[215]) have been developed. It may be noted that use of the latter silyating reagent gives a tris silyl derivative (**2.434a**) and not a mono silyl compound (**2.434b**) as had earlier been suggested.[216] The N^3-hexafluoroisobutyryl derivative (**2.434c**) has been prepared as an oil from the acylation of **2.434d** with bistrifluoromethylketene in dimethoxyethane,[217] and the isotopically labeled methoxycarbonyl derivative (**2.434e**) has been derived from the product of enzymatic carbonylation of biotin using $KH^{14}CO_3$.[218] The possible involvement of the biotin N-1 site in enzymatic CO_2 transfer is thus implicated.

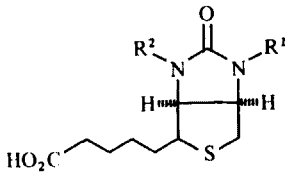


(2.434)

a $R^1 = R^2 = R^3 = SiMe_3$
b $R^2 = R^3 = H$; $R^1 = SiMe_3$
c $R^1 = Me$; $R^2 = COCH(CF_3)_2$; $R^3 = CO_2Me$
d $R^1 = Me$; $R^2 = H$; $R^3 = CO_2Me$
e $R^1 = Me$; $R^2 = H$; $R^3 = {}^{14}CO_2Me$

(+)Biotin has been converted routinely into products of dialkylation, bismethylolation, and nitrosation (see Table 2.46),[219] but a more subtle synthesis has been devised for the 3-methyl congener of biotin (see **2.439** in Scheme 2.41).[221] Debenzylation of the norbiotin analog (**2.436**) by sodium in liquid ammonia occurs selectively at the more hindered site to give the monobenzyl derivative (**2.437**),

TABLE 2.46. SYNTHESIS OF BIOTIN ANALOGS WITH MODIFICATIONS IN THE IMIDAZOLIDINONE RING[219a]



(2.435)

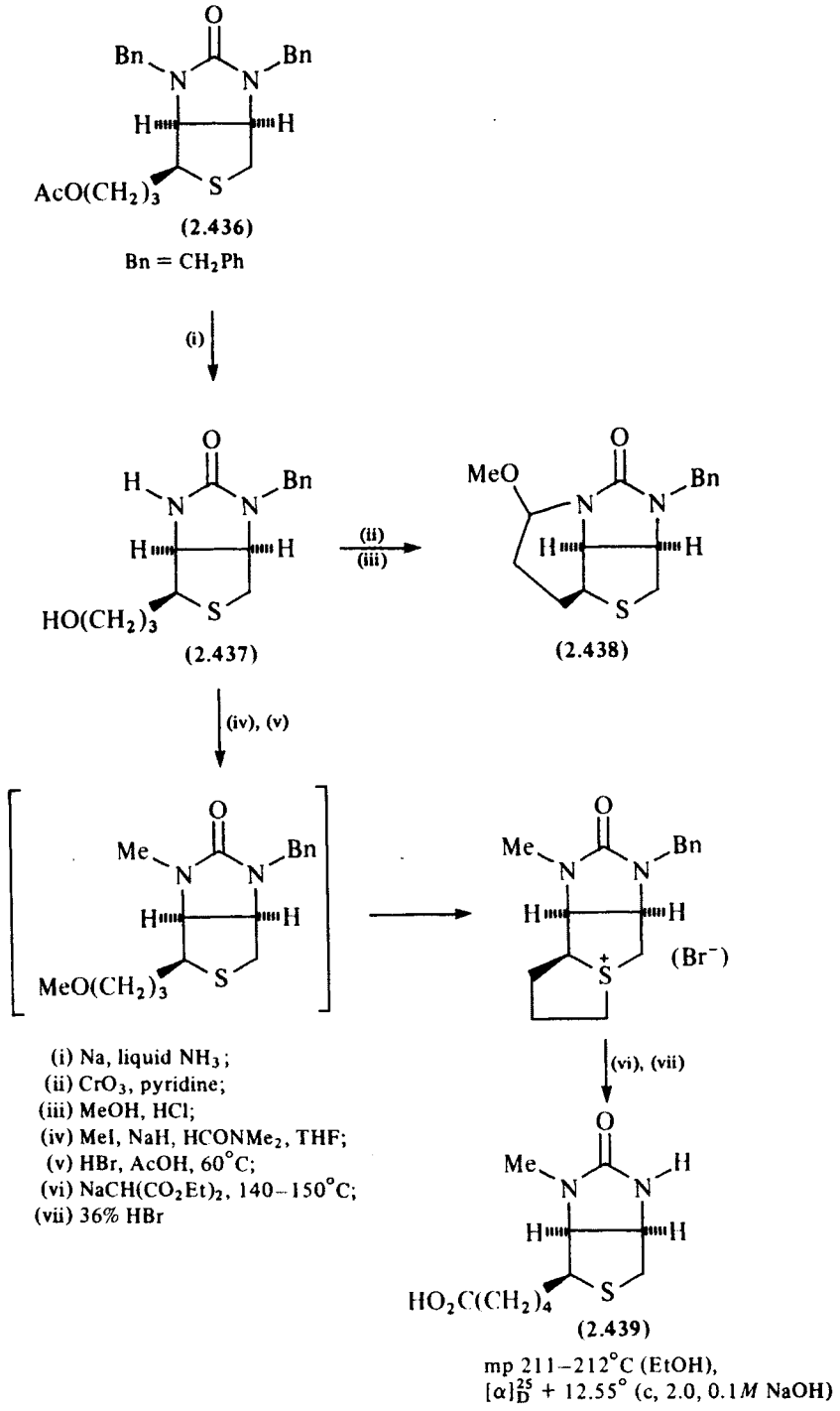
	R^1	R^2
a,	H	H
b,	Me	Me
c,	CH_2OH	CH_2OH
d,	NO	H
e,	N=CHPh	H

Starting Material	Product	Reaction Conditions	Yield (%)	mp (°C)	$[\alpha]_D$
2.435a	**2.435b**[b]	Aqueous HCHO, aqueous HCO_2H, 100°C, 40 h	34	172–174	+ 46° (c, 1.0, 0.1 *M* NaOH)
2.435a	**2.435c**	(i) HCHO, NaOMe, 1 h, 50°C; (ii) aqueous HCl	45	140.5–141.5[c]	+ 95° (c, 1.0, saturated aq. $NaHCO_3$)
2.435a	**2.435d**	$NaNO_2$, HCl, 0°C, 2.5 h	67	131.5 (dec.)	
2.435d	**2.435e**	(i) Zn, 2*M* H_2SO_4; (ii) PhCHO, EtOH	52	188.5–191.5	

[a] A compound described in ref. 219 as *N*-phenylbiotin was subsequently reported[220] to be *N*-benzylbiotin by comparison with an authentic sample.
[b] Converted by diazomethane into a methyl ester, mp 86.5–87.5°C.
[c] Melting point determined with rapid heating; the value recorded with slow heating of the sample is 171–179°C.

and chemical evidence in this regard has been adduced from the subsequent conversion of **2.437** into the tricyclic compound (**2.438**). Methylation of **2.437** is then followed by introduction of the valeric acid side chain by the Goldberg–Sternbach procedure (see **2.437** → **2.439** and the original method outlined in Scheme 2.34).

The synthesis of (±)biotin analogs in which the imidazolidinone carbonyl is replaced by the thiocarbonyl group ("thiobiotins") has been achieved by cyclization of an appropriately substituted diaminothiophene derivative (see **2.440** → **2.441a,b** and Table 2.47, and cf. analogous routes to (±)biotin illustrated in Scheme 2.37). Simple transformations, including alkylation, in the thiobiotin series are also collected in Table 2.47; it may be noted that methylation reactions with trimethyloxonium tetrafluoroborate (**2.441a** → **2.442a** and **2.441c** → **2.442b**) give rise to *S*-methyl derivatives with no evidence of formation of isomeric *N*-methyl compounds.

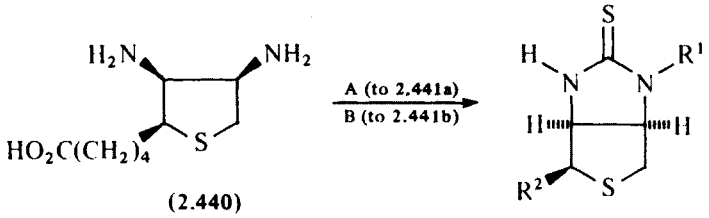

(2.436)
Bn = CH_2Ph
(i)
(2.437)
(ii)
(iii)
(2.438)
(iv), (v)
(vi), (vii)
(2.439)
(i) Na, liquid NH_3;
(ii) CrO_3, pyridine;
(iii) MeOH, HCl;
(iv) MeI, NaH, $HCONMe_2$, THF;
(v) HBr, AcOH, 60°C;
(vi) $NaCH(CO_2Et)_2$, 140–150°C;
(vii) 36% HBr
mp 211–212°C (EtOH),
$[\alpha]_D^{25}$ + 12.55° (c, 2.0, 0.1 M NaOH)

Scheme 2.41

TABLE 2.47. SYNTHESIS OF THIOBIOTIN (**2.441a**) AND ITS DERIVATIVES

Starting Material	Product	Reaction Conditions	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reference
2.440	**2.441a**	(i) CS_2, aqueous EtOH; (ii) heat	94	232–235 (H_2O)	210
2.441b	**2.441a**	(i) 2*M* NaOH; (ii) HCl	22	234–235 (dec.) (aq. EtOH)	219
2.440	**2.441b**	(i) $CSCl_2$, NaOMe, MeOH; (ii) 2*M* HCl, reflux	65	214–215 (dec.) (95% EtOH)	219
2.441a	**2.441b**	*p*-$MeC_6H_4SO_3H$, MeOH, reflux	77	215–217 (MeOH)	210
2.441a	**2.442a**	$Me_3\overset{+}{O}\overset{-}{B}F_4$, $MeNO_2$, room temperature	97	151–154 (CH_2Cl_2–MeCN–Et_2O)	210
2.441b	**2.441c**	$ClCO_2Me$, CH_2Cl_2, reflux	36	168–169	210
2.441c	**2.442b**	$Me_3\overset{+}{O}\overset{-}{B}F_4$, $MeNO_2$, room temperature	98	–[a]	210
2.441a	**2.441d**	$LiAlH_4$, pyridine, Et_2O, reflux	86	210–211 (MeOH–Et_2O)	210
2.441d	**2.441e**	Ac_2O, pyridine	98	169–170 (MeOH–Et_2O)	210
2.441e	**2.441f**	$ClCO_2Me$, CH_2Cl_2, pyridine, reflux	43	132–135	210

[a] Melting point of this hygroscopic solid not quoted.

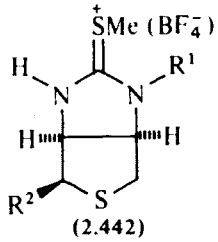


(2.440)

(A) (i) CS_2, aqueous EtOH;
(ii) heat;
(B) (i) $CSCl_2$, NaOMe, MeOH;
(ii) 2*M* HCl, reflux

(2.441)

	R^1	R^2
a	H	$(CH_2)_4CO_2H$
b	H	$(CH_2)_4CO_2Me$
c	CO_2Me	$(CH_2)_4CO_2Me$
d	H	$(CH_2)_5OH$
e	H	$(CH_2)_5OAc$
f	CO_2Me	$(CH_2)_5OAc$



(2.442)

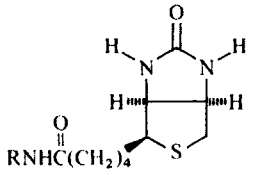
	R^1	R^2
a	H	$(CH_2)_4CO_2H$
b	CO_2Me	$(CH_2)_4CO_2Me$

2.15.6.2. Compounds Modified in the Valeric Acid Side Chain

Biotin is an essential part of the active site of a number of enzymes[222] and also binds strongly by a noncovalent interaction with the egg white protein, avidin. In other proteins it is attached to the ϵ-amino group of lysine residues, and controlled hydrolysis produces biocytin (ϵ-biotinyl-L-lysine). Accordingly, there is much interest in the synthesis of model peptides containing biotin in their sequence. Of the examples of such derivatives (**2.443a–j**) collected in Table 2.48, the spin-labeled derivatives **2.443g–j** are particularly valuable. Despite the increased steric bulk of the modified valeric acid side chain, there is evidence[228a] to suggest that these compounds occupy the same binding sites in avidin as does biotin itself; application of the electron-spin resonance (esr) method is thus available for investigation of the nature of such interactions.[228b,c]

The synthesis of biocytin (**2.444**) is illustrated in Scheme 2.42.[227] The compound is obtained by this method in 73% yield with mp 243–246°C and $[\alpha]_D^{25}$ + 55° (c, 1.0, 0.1 *M* NaOH) and has been used to prepare biocytin-containing peptides such as biocytinyl-L-threonine.[227]

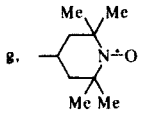
TABLE 2.48. SYNTHESIS AND PHYSICAL PROPERTIES OF BIOTINYL PEPTIDES

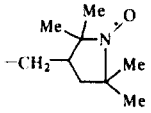


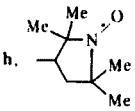
(2.443)

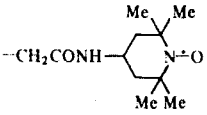
R

a, tryptamyl
b, tryamyl
c, propamyl
d, histamyl
e, $(CH_2)_nNHCO$-biotinyl (n = 6–12)
f, $CH_2CO(NHCH_2CO)_5NH(CH_2)_2NHCH_2CH(OH)CH_2O$-1-naphthyl

g. 

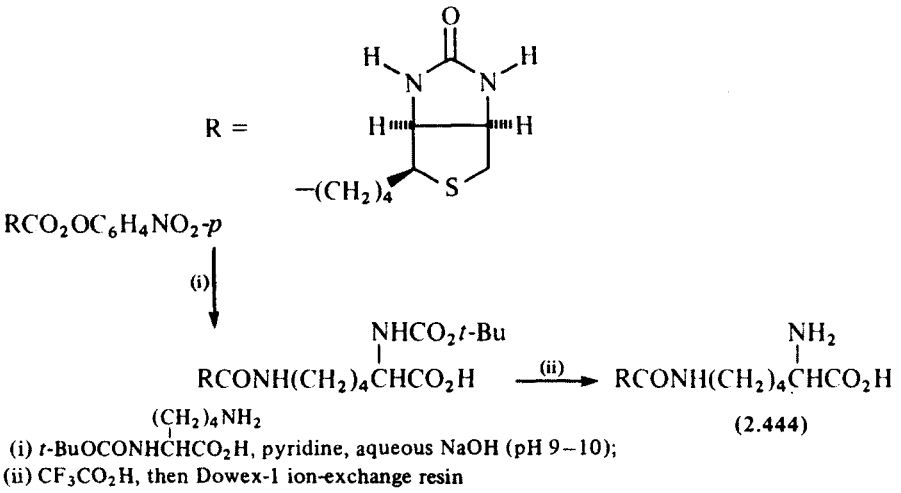
i. 

h. 

j. 

Compound	Method of Synthesis[a]	mp (°C)	Reference
2.443a	A	135–140	223
2.443b	A	190–195	223
2.443c	A	195–200	223
2.443d	A	200–205	223
2.443e	B	–[b]	224
2.443f	C	227–235 (dec.)	225
2.443g	D	197.5–198.5	228
2.443h	D	139–140	228
2.443i	D	181–183	228
2.443j	D	132–135	228

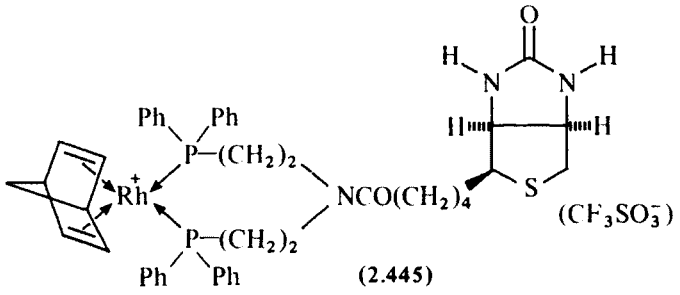
[a]Synthesis method: (A) prepared from the *p*-nitrophenyl ester of biotin[226,227], RNH_2, dimethylsulfoxide, room temperature; (B) prepared from the mixed anhydride derived from biotin and methyl chloroformate, $H_2N(CH_2)_nNH_2$, Et_3N, dimethylformamide, room temperature; (C) prepared from biotinyl hexaglycine, 1,1′-carbonyldiimidazole, 1-$C_{10}H_7OCH_2CH(OH)CH_2NH(CH_2)_2NH_2$, dimethylsulfoxide, 25°C, 40 h; (D) prepared from biotin, appropriate amino derivative, EtOH, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, room temperature.
[b]The bis biotinyl amines (**2.443e**) do not crystallize well but were obtained analytically pure; they do not melt below their decomposition points.



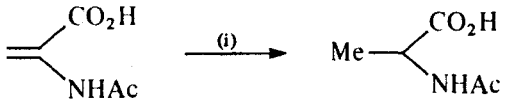
Scheme 2.42

Biotin has also been incorporated into a peptide containing 25 amino acid units ([25 biocytin]$ACTH_{1-25}$-amide),[229] and the *N*-hydroxysuccinimido esters of biotin[230] and iminobiotin[231] have been used to acylate phospholipids and insulins, respectively.

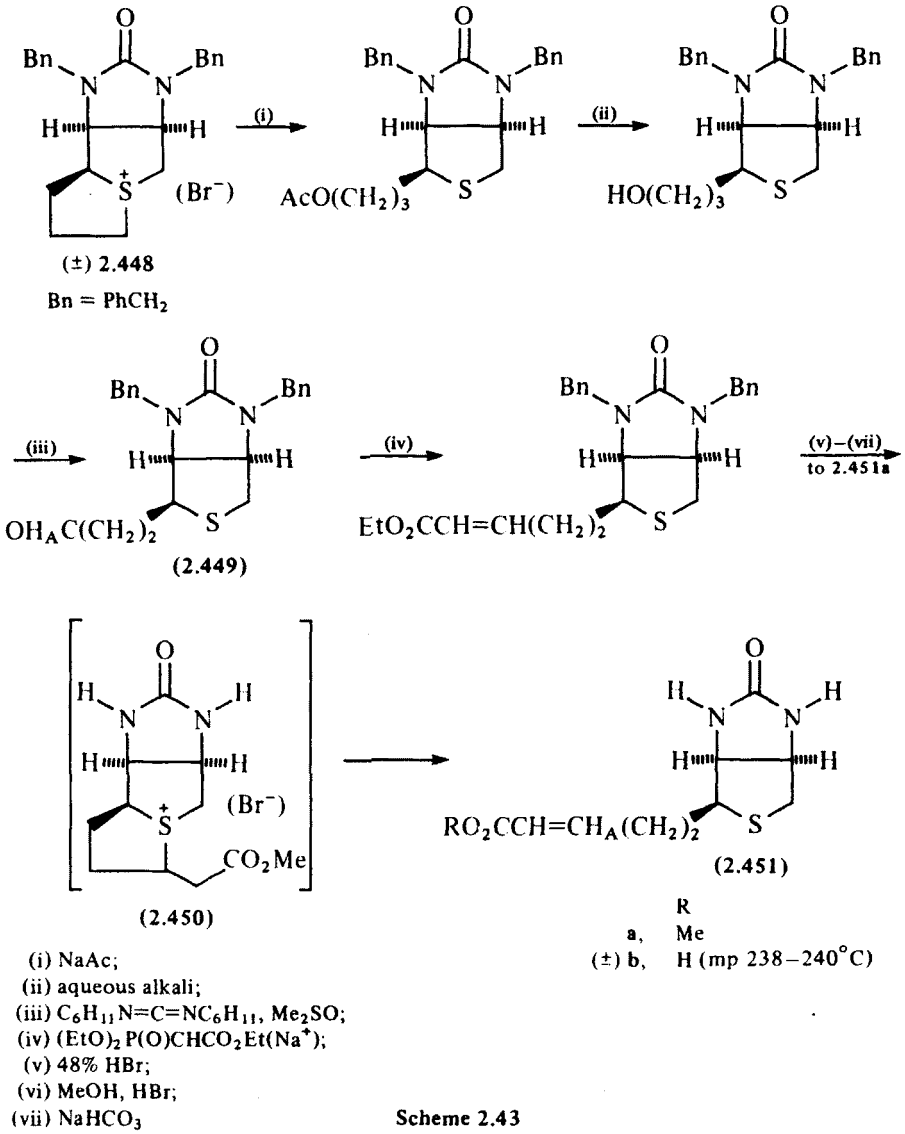
The dissymmetric environment of avidin has been used in a subtle manner to prepare new supported catalysts for homogeneous hydrogenation of prochiral alkenes. The cationic rhodium species (**2.445**) is a moderately active hydrogenation catalyst for the transformation **2.446** → **2.447** but affords poor enantioselectivity (ee < 2%). In contrast to this behavior, when the catalyst is bound to avidin, the enantiomeric excess is approximately 40% (*S*), with a turnover of over 500.[232] Since prebinding of excess biotin to the avidin causes elimination of the enantioselectivity, it can be assumed that the active catalyst is one in which the complex **2.445** is associated with the protein at the normal sites of biotin binding.



(2.445)



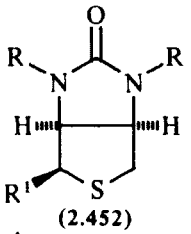
(2.446) (i) 2.445, H_2 (2.447)



Scheme 2.43

2.15.6.3. Miscellaneous Compounds

d-α-Dehydrobiotin (**2.451b**) has been characterized as a natural antimetabolite of biotin and exhibits antibiotic activity against a variety of microorganisms and several strains of mycobacteria.[233] Preparation of the racemic material [(±)**2.451b**] is based on the use of thiophanium intermediates, in accordance with the procedure devised by Goldberg and Sternbach in early synthetic studies of biotin (see **2.448** and **2.450** in Scheme 2.43, and cf. Scheme 2.34).[234] Repetition of the sequence



(2.452)

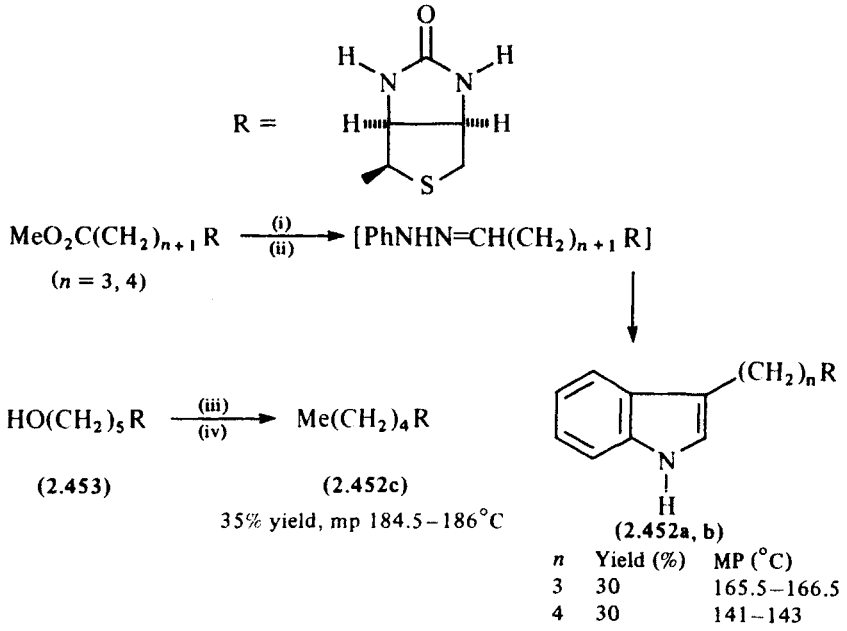
	R	R^1
a	H	$(CH_2)_3$-indol-3-yl
b	H	$(CH_2)_4$-indol-3-yl
c	H	$(CH_2)_4Me$
d	H	$(CH_2)_3CH(Me)CO_2H$
e	H	n-C_7H_{13}
f	e.g., alkyl	$(CH_2)_nOR^2$ (R^2 = e.g., alkyl, n = 3, 4)
g	CH_2Ph	$(CH_2)_nOR^2$ (R^2 = e.g., alkyl, n = 3, 4)
h	e.g., alkyl	ZCO_2H (Z = alkylene, alkenylene)

illustrated in Scheme 2.43, using the *l*-thiophanium-*d*-camphorsulfonate analog of **2.448** provided an optically active *d*-α-dehydrobiotin product, mp 256–257.5°C, $[\alpha]_D^{25}$ + 105.7° (c, 1.2, 0.1*M* NaOH).[234] The synthesis outlined in Scheme 2.43 has also been used to incorporate tritium into the olefinic part of the side chain (see H_A in **2.449** and **2.451**), and the labeled *d*-α-dehydrobiotin has been used as a probe to elucidate the mechanism of its antibiotic action.[235]

Other examples of biotin derivatives modified in the 4-position are illustrated by structures **2.452a–c**,[236] **d**,[237] **e**,[238] **f**,[239] **g**,[240] and **h**.[241] Compounds in the group **2.452e–h** are synthetic materials described in the patent literature, and **2.452d** has been isolated as one of two antimetabolites from culture filtrates of *Streptomyces lydicus*. The indolyl derivatives (**2.452a,b**) have been prepared[236] (see Scheme 2.44) with the intention of providing model compounds that might mimic a contributory tryptophan–biotin interaction in the biotin–avidin complex. 4-Pentyl-hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazole (pentyl biotin) (**2.452c**) has been synthesized[236] from (+)biotinol (**2.453**) by lithium aluminum hydride-promoted reduction of its tosylate (see Scheme 2.44).

2.15.6.4. Isotopically Labeled Derivatives

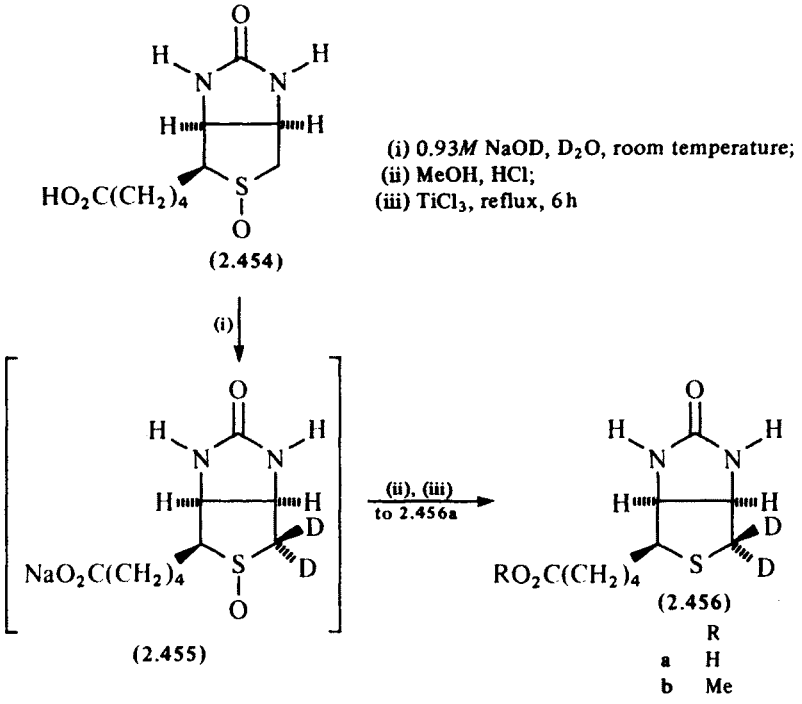
Tritiated and ^{14}C-labeled biotins ($^{14}C{=}O$, $^{14}CO_2H$) are commercially available and are valuable for the assay[242] and study of the bacterial degradation[243] of biotin, respectively. Carbon-14-carbonyl-labeled biotin-*l*-sulfoxide has been synthesized by oxidizing labeled (+)biotin with an equimolar quantity of hydrogen peroxide.[244] Synthesis of the methyl ester of biotin labeled with deuterium at the 6-position (**2.456b**) has been achieved[245] by harnessing the property of biotin sulfoxides to undergo selective hydrogen–deuterium exchange at that position in basic media (see **2.454** → **2.455** → **2.456a**). Ensuing esterification by diazomethane gives the methyl ester (**2.456b**) mp 128–130°C with no ^1H nmr resonances that would correspond to the hydrogens at C-6 and C-6′ (δ = 2.66 and 2.90).



n	Yield (%)	MP (°C)
3	30	165.5–166.5
4	30	141–143

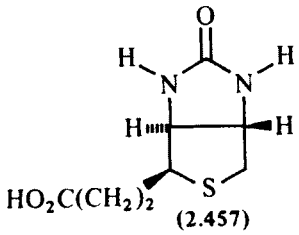
(i) Diisobutyl aluminum hydride, hexane; (ii) $PhNHNH_2$, $BF_3 \cdot Et_2O$, AcOH; (iii) *p*-$MeC_6H_4SO_2Cl$, pyridine; (iv) $LiAlH_4$, THF, Et_2O

Scheme 2.44

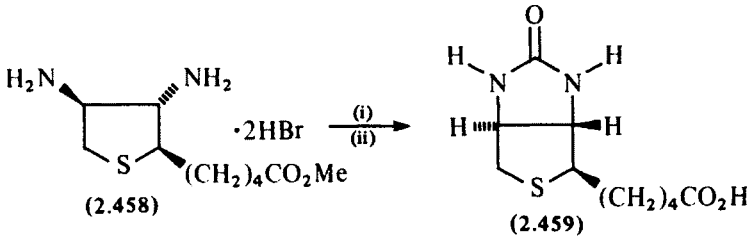


2.15.6.5. Compounds in the allo Series

d-Allobisnorbiotin (**2.457**), containing a *trans*-fused ring system and a shortened side chain, has been isolated as a bacterial degradation product of (+)biotin,[246] and (±)epiallobiotin (**2.459**) has been obtained in moderate yield by reaction of the *trans*-diamine derivative (**2.458**) with phosgene.[247]



(**2.457**)



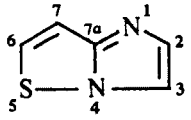
(**2.458**) (**2.459**)

(i) aqueous NaOH (ii) $COCl_2$, 0–3°C, 16h

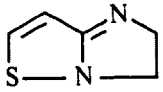
22% yield, mp 195°C (dec.) (MeOH)

2.16. RING SYSTEM C_3N_2–C_3NS: IMIDAZO[1,2-*b*]ISOTHIAZOLE

Compounds of the 2,3-dihydro type (**2.461**) are known in the imidazo[1,2-*b*]-isothiazole ring system, but there are no citations to compounds in the fully unsaturated system (**2.460**) during the literature period covered.



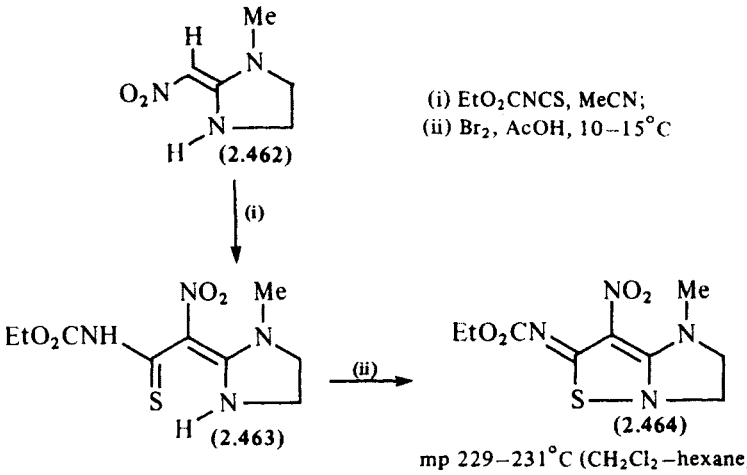
(**2.460**)



(**2.461**)

2.16.1. Synthesis of 2,3-Dihydroimidazo[1,2-*b*]isothiazoles

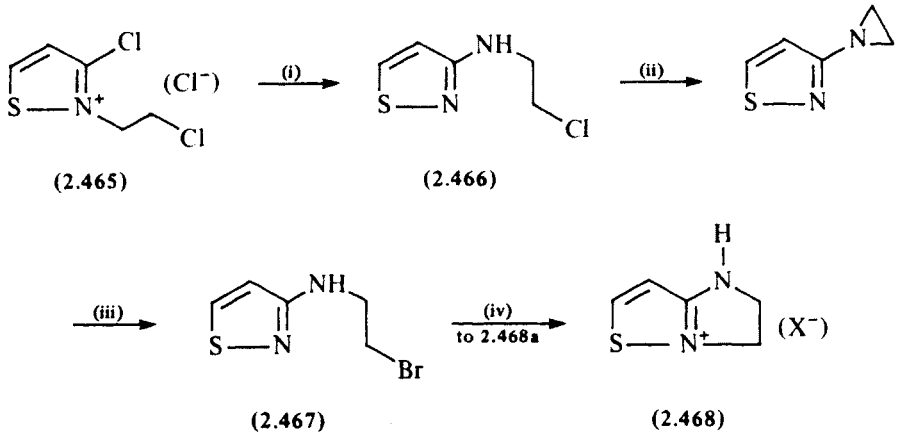
The 2,3-dihydroimidazo[1,2-*b*]isothiazole (**2.464**) has been prepared by oxidative cyclization of the red adduct (**2.463**) formed by treating the imidazolidine derivative (**2.462**) with ethoxycarbonyl isothiocyanate,[248] but the scope of this synthesis has not been evaluated. Compound **2.464** is characterized by the following ^1H nmr spectrum (DMSO-d_6/$CDCl_3$): δ = 1.30 (t, Me); 3.21 (s, Me); 4.05 (s, $2CH_2$); 4.25 (q, CH_2).



(i) EtO_2CNCS, MeCN;
(ii) Br_2, AcOH, 10–15°C

mp 229–231°C (CH_2Cl_2–hexane)

Attempted synthesis of 2,3-dihydroimidazo[1,2-*b*]isothiazolium chloride (**2.468b**) by direct cyclization of the isothiazole derivative (**2.466**) proved difficult:[249] thus **2.466** (available from the intramolecular rearrangement of **2.465**) can be transformed into **2.468b** in only 25% yield after 2 days at 50°C, and some decomposition products are observed. In contrast, the analogous cyclization (**2.467** → **2.468a**) proceeds satisfactorily either at room temperature or for a short period under reflux in methanol (see Scheme 2.45). 2,3-Dihydroimidazo[1,2-*b*]-isothiazolium chloride (**2.468b**) can then be prepared quantitatively from the bromide (**2.468a**) by ion-exchange chromatography.[249]



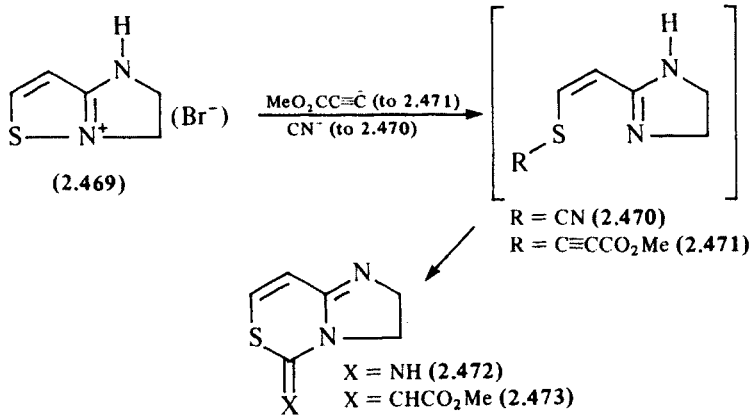
(i) NH_3, MeCN;
(ii) *t*-BuOK, *t*-BuOH;
(iii) HBr, $CHCl_3$;
(iv) room temperature, 2–3 days
or MeOH, reflux, 5 h

	X	MP (°C)
a,	Br	163–165
b,	Cl	164–167

Scheme 2.45

2.16.2. Reactions of 2,3-Dihydroimidazo[1,2-*b*]isothiazoles

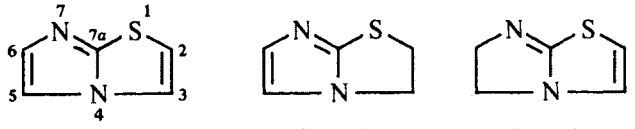
Very little is known about the chemical reactivity of 2,3-dihydroimidazo[1,2-*b*]-isothiazoles, although a brief investigation indicates that such heterocycles might be valuable for the synthesis of condensed imidazoles. Thus attack by nucleophiles (viz., CN^-, $MeO_2CC{\equiv}\bar{C}$) occurs at the sulfur atom of 2,3-dihydroimidazo[1,2-*b*]-isothiazolium bromide (**2.469**) to give intermediates (**2.470**, **2.471**) that recyclize to give imidazothiazines (**2.472** and **2.473**, respectively) in high yield.[250]



(2.469)

2.17. RING SYSTEM C_3N_2–C_3NS: IMIDAZO[2,1-*b*]THIAZOLE

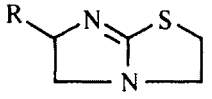
Compounds in the fully unsaturated imidazo[2,1-*b*]thiazole class (**2.474**) are well documented, and there are also many examples of 2,3-dihydro (**2.475**), 5,6-dihydro-(**2.476**), and 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles (**2.477a**); there is only a single citation to a 2,3,5,6,7,7*a*-hexahydro compound (cf. **2.478**) during the literature period covered. Compounds in the 2,3,5,6-tetrahydro category have been extensively investigated because of the commercial success of tetramisole (**2.477b**) as a vetinerary anthelmintic agent (see Section 2.17.4).



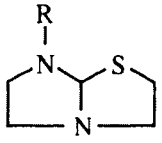
(2.474)

(2.475)

(2.476)



(2.477)
a R = H
b R = Ph

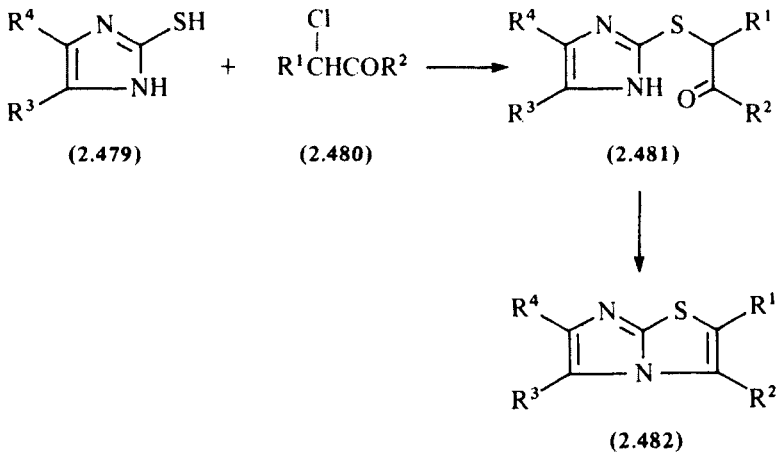


(2.478)
R = e.g., H or alkyl

2.17.1. Imidazo[2,1-*b*]thiazoles

2.17.1.1. Synthesis from Imidazoles

Historical aspects of the synthesis of imidazo[2,1-*b*]thiazoles are covered in Mosby's text on heterocycles with bridgehead nitrogen atoms.[251] A general procedure from 2-mercaptoimidazoles (**2.479**) involves their conversion into 2-(acylalkylthio)-imidazoles (**2.481**) which can be cyclized to substituted imidazo[2,1-*b*]-thiazoles (see Scheme 2.46 and examples collected in Table 2.49). It has been demonstrated that the cyclization of alkyl ketones (**2.481**; R^2 = alkyl) can be effected under reflux in acetic acid or 85% phosphoric acid, but for aryl ketones (**2.481**, R^2 = aryl) the use of phosphorus oxychloride under long reaction times is required.[252] Subsequently it became apparent that for methyl ketones (**2.481**, R^2 = Me) the intermediate need not be isolated and the substrates (**2.479** and **2.480**) can be directly transformed into the bicyclic product (cf. **2.482**) under reflux in butanol.[253] It may be noted that the cyclization of dissymmetrically substituted mercaptoimidazoles (**2.479**, $R^3 \neq R^4$) can, in principle, give rise to two regioisomers of **2.482**. In early work[252] it was shown by unambiguous synthesis that the nitro compound **2.479** (R^3 = H, R^4 = *p*-$O_2NC_6H_4$) was transformed with **2.480** ($R^1 = R^2$ = Me) into the 6-aryl derivative (**2.482**; $R^1 = R^2$ = Me; R^3 = H; R^4 = *p*-$O_2NC_6H_4$) with no evidence for formation of the 5-substituted aryl isomer.



(2.479) (2.480) (2.481)

(2.482)

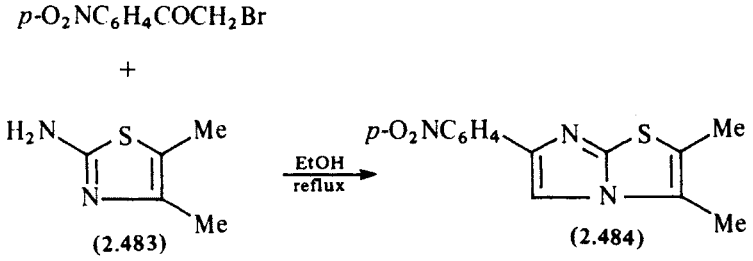
Scheme 2.46

Thus the nitro compound described above was found to be identical to that isolated from the condensation of 2-amino-4,5-dimethylthiazole with *p*-nitrophenacyl bromide (cf. **2.483** → **2.484** and the following section). The structures of many imidazo [2,1-*b*] thiazoles described in Table 2.49 have been assigned by analogy with this result and must be treated with caution.

TABLE 2.49. SYNTHESIS OF IMIDAZO[2,1-*b*]THIAZOLES (**2.482**)[a] FROM 2-MERCAPTOIMIDAZOLES (**2.479**) OR 2-(ACYLALKYLTHIO)IMIDAZOLES (**2.481**)

Product **2.482**							
R^1	R^2	R^3	R^4	Method[b]	Yield (%)	mp (°C)	Reference
H	Me	H	Ph	A	98	113–113.5	252
Me	Me	H	Ph	A	90	157–158	252
H	Ph	H	Ph	B	95	125–125.5[c]	252
H	*p*-$O_2NC_6H_4$	H	Ph	B	96	210.5–211.5	252
H	*m*-$O_2NC_6H_4$	H	Ph	B	80	156.5–157	252
H	Me	H	*p*-$O_2NC_6H_4$	B	98	246	252
Me	Me	H	*p*-$O_2NC_6H_4$	B	86	248–248.5	252
H	Me	H	H	C	73	134–135	253
H	Ph	H	H	B	96	221–223	253
H	*p*-BrC_6H_4	H	H	B	75	125.5–127	253
H	*p*-$O_2NC_6H_4$	H	H	B	88	214–215	253
CH_3CO	Me	H	H	C	55	> 240 (dec.)	253
Ph	Ph	H	H	B	82	153–154	253
H	Ph	H	*p*-$O_2NC_6H_4$	B	99	204–206	253
H	*p*-BrC_6H_4	H	*p*-$O_2NC_6H_4$	B	97	261–262	253
H	Me	Ph	Ph	C	68	243–245	253
CH_3CO	Me	Ph	Ph	C	52	190–191	253
H	*p*-ClC_6H_4	Ph	Ph	D	60	156[d]	254

[a]For patented derivatives (**2.482**; $R^2 = CH_2S_2CNH(CH_2)_nAr$ (n = 1 or 3), see ref. 255.
[b]Preparative method: (A) 85% H_3PO_4, 100°C, 1 h (**2.481** → **2.482**); (B) $POCl_3$, reflux, 1 h (**2.481** → **2.482**); (C) BuOH, reflux, 2–3 h [direct procedure (**2.479** + **2.480**) → **2.482**]; (D) H_3PO_4, 150°C, 3 h (**2.481** → **2.482**).
[c]Melting point of hydrochloride quoted.
[d]Infrared ν_{max} (Nujol) 1600, 1485, and 830 cm^{-1}; nmr ($CDCl_3$) δ = 6.63 (1H, H-2), 6.97–7.68 (14H, Ar–H).



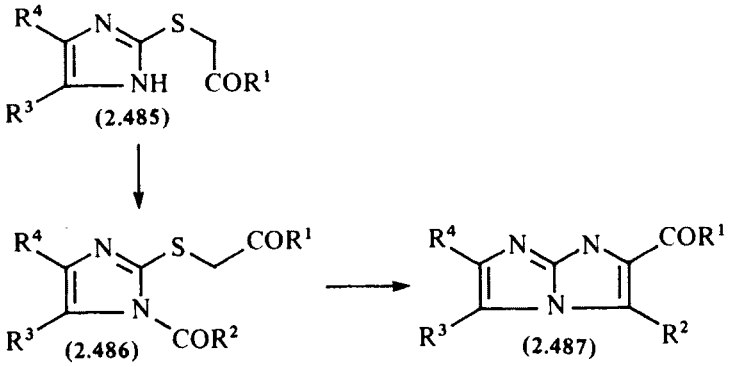
2-(β-Ketoalkylthio)imidazole derivatives (**2.485**) have also been used to prepare 2-acyl derivatives of imidazo[2,1-*b*]thiazole (cf. **2.487**) by means of intermediate 1-acyl imidazoles (cf. **2.486**).[256] The regiochemical problem inherent in this acetic anhydride-mediated cyclization has been solved indirectly. Thus the 5-aryl derivatives (**2.487**, R^3 = Ar; R^4 = H) obtained from such processes have been shown[256] to be isomeric with 6-aryl derivatives of known orientation derived from a different synthetic route (cf. **2.479** + **2.480** → **2.482**). A variety of 2-acyl-5-

TABLE 2.50. SYNTHESIS OF 2-ACYLIMIDAZO[2,1-*b*]THIAZOLE DERIVATIVES (2.487) FROM 2-(ACYLALKYLTHIO)IMIDAZOLES (2.485)

Product 2.487								
R^1	R^2	R^3	R^4	Method	Yield (%)	mp (°C)	ir ν_{max} CO (cm^{-1})	Reference
Me	Me	*p*-$O_2NC_6H_4$	H	A	97	150–151		256
Me	Me	*p*-MeC_6H_4	H	A	97	186–187		256
Ph	H	H	H	B	84	112–113	1633	257
p-$O_2NC_6H_4$	H	H	H	B	68	208–209	1650	257
Ph	H	Ph	H	B	82	126–127	1630	257
p-BrC_6H_4	H	Ph	H	B	96	256–257	1632	257
p-$O_2NC_6H_4$	H	Ph	H	B	85	258–261	1640	257
Me	H	Ph	Ph	B	91	226–227	1675	257
p-BrC_6H_4	H	Ph	Ph	C	93	194–195	1630	257
p-$O_2NC_6H_4$	H	Ph	Ph	C	94	167–169		257
H	Me	Ph	Ph	C	72	228–229	1668	257
Me	Me	Ph	Ph	C	52	190–191	1648	257
p-BrC_6H_4	Me	Ph	Ph	C	94	175–176	1631	257
H	Et	Ph	Ph	C[b]	96	181–183	1671	257
p-BrC_6H_4	Et	Ph	H	C[b]	76–80	161–163	1650	257
Me	Et	*p*-$O_2NC_6H_4$	H	C	63	210–212	1650	257
Ph	Et	*p*-$O_2NC_6H_4$	H	C	42–45	218–220	1639	257
Ph	H	*p*-$O_2NC_6H_4$	H	D	90–93	162–164	1670	257

[a]Preparative method: (A) NaAc, Ac_2O, heat, 0.5 h (direct procedure **2.485** → **2.487**); (B) HCO_2Na, 85% HCO_2H:Ac_2O (1:2), reflux (direct procedure **2.485** → **2.487**); (C) RCO_2Na–$(RCO)_2O$ (R = Me or Et), reflux (direct procedure **2.485** → **2.487**); (D) $EtCO_2Na$–$(EtCO)_2O$, reflux (**2.486** → **2.487**).

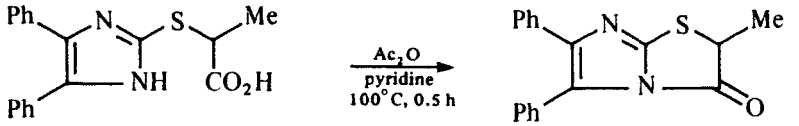
[b]Also obtained by method D (cf. **2.486** → **2.487**).



arylimidazo[2,1-*b*]thiazoles have been synthesized using modified acylation procedures either directly from **2.485** or through intermediate 1-acylimidazoles (cf. **2.486**) (see Table 2.50).[257]

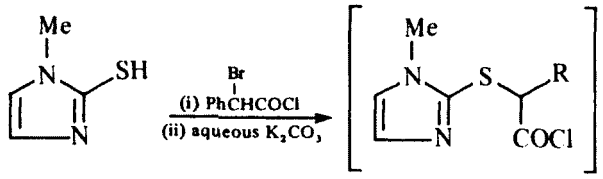
Imidazo[2,1-*b*]thiazoles have also been prepared in reactions closely related to the cyclizations described above (cf. **2.481** → **2.482**). For example, acylative ring closure of the 2-imidazolylthiopropionic acid derivative (**2.488**) provides 2-methyl-

5,6-diphenylimidazo[2,1-*b*]thiazol-3(2*H*)-one (**2.489**),[254] and the mesoionic derivative, anhydro-3-hydroxy-7-methyl-2-phenylimidazo[2,1-*b*]thiazolium hydroxide (**2.492a**), is formed by treating 1-methyl-2-mercaptoimidazole (**2.490**) and with α-bromo(phenylacetyl)chloride followed by alkaline work-up.[258] Interestingly, an attempt[258] to synthesize the 2-unsubstituted mesoionic compound (**2.492b**, through **2.491b** using $BrCH_2COBr$ as coreactant) failed, and the product isolated was actually the 2-substituted compound (**2.492c**); presumably the mesoionic derivative (**2.492b**) is particularly susceptible to electrophilic aromatic substitution at C-2.



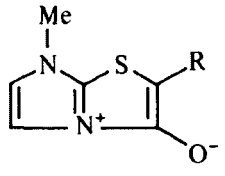
(2.488) (2.489)

mp 160°C (EtOH); 53% yield

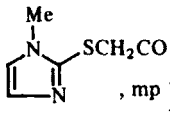


(2.490) (2.491)

a: R = Ph
b: R = H

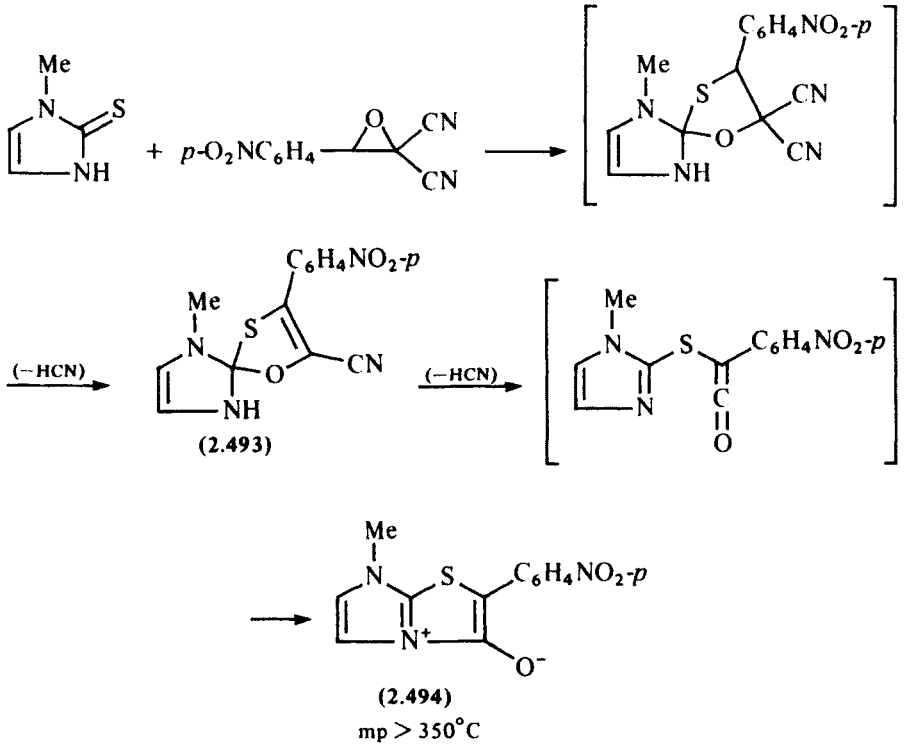


(2.492)

a: R = Ph, mp 188–189°C (EtOAc); 72% yield
b: R = H
c: R = 

, mp 206.5–207.5°C; 23% yield

A 2,7-disubstituted mesoionic imidazo[2,1-*b*]thiazole derivative has also been synthesized in the manner outlined in Scheme 2.47.[259] The spiro imidazoline (**2.493**) can be isolated from this reaction, but it is transformed in hot acetonitrile into the crystalline, violet mesoionic compound (**2.494**).

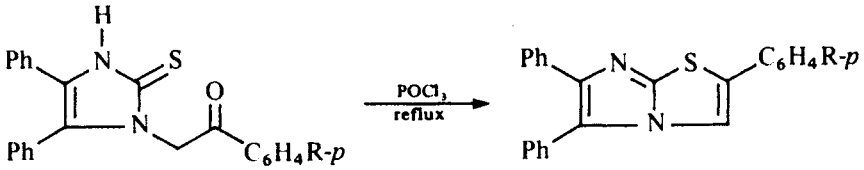


(2.493)

(2.494)
mp > 350°C

Scheme 2.47

The phosphorus oxychloride-induced dehydrative cyclization of 1-phenacyl-4,5-diphenylimidazolin-2-thiones (**2.495**) gives rise to excellent yields of triarylimidazo-[2,1-*b*]thiazoles (**2.496**).[260] Earlier examples of such cyclizations promoted by concentrated hydrochloric acid are given in ref. 261 and are collected in the text by Mosby.[251]



(2.495) (2.496)

R	MP °C (Dec.)	Yield (%)
H	175–177	92
Me	181–182	98
MeO	177–178	98
Cl	214–216	97
Br	236–238	97

TABLE 2.51. SYNTHESIS OF IMIDAZO[2,1-*b*]THIAZOLE DERIVATIVES (**2.500**) FROM 2-AMINOTHIAZOLES

Type(s) of Substrate used	Reaction Conditions	Product **2.500**				Yield (%)	mp (°C) solvent for Recrystallization)	Reference
		R^1	R^2	R^3	R^4			
2.497 + 2.498	EtOH, reflux	Me	Me	H	*p*-$O_2NC_6H_4$	91	248–248.5 (AcOH)	252
2.499	Aqueous NaAc	Me	H	H	Ph	Quant.	129 (EtOH)	262
2.499	Aqueous NaAc	H	H	H	Ph	85	167–168 (MeOH–H_2O)	262
2.497 + 2.498	Heat	H	H	Ph	Ph	58	136 (MeOH)	262
2.497 + 2.498	Heat	Me	H	Ph	Ph	69	189 (EtOH)	262
2.497 + 2.498	Heat	Me	Me	Ph	Ph	33	160–161 (MeOH)	262
2.497 + 2.498	Heat	Ph	Ph	Ph	Ph	59	234–235 (MeOH)	262
2.497 + 2.498	Heat	H	H	Me	Ph	68[a]	126 (EtOH)	262
2.497 + 2.498	Heat	Me	H	Me	Ph	69[a]	114–115 (MeOH)	262
2.499	Aqueous NaAc	Me	H	Me	Me	80	143 (H_2O)	262
2.499	Aqueous NaAc	H	H	H	*p*-BrC_6H_4	Quant.	174 (MeOH)	262
2.497 + 2.498	Heat	H	H	H	3-F-4-$MeOC_6H_3$	70–80	144 (EtOH)	263
2.497 + 2.498	Heat	H	H	H	2-MeO-5-FC_6H_3		100–102 (MeOH)	263
2.497 + 2.498	EtOH, heat	H	H	H	*p*-MeC_6H_4		159 (EtOH)	264
2.497 + 2.498	EtOH, heat	H	H	H	*p*-FC_6H_4		127 (MeOH)	264
2.497 + 2.498	EtOH, heat	H	H	H	*p*-ClC_6H_4		169 (EtOH)	264
2.497 + 2.498	EtOH, heat	H	H	H	*p*-BrC_6H_4		182 (EtOH)	264
2.497 + 2.498	EtOH, heat	H	H	H	*p*-$C_6H_4C_6H_4$		226 (EtOH)	264

2.497 + 2.498	EtOH, heat	H	Me	H	Ph	68	113	265
2.497 + 2.498	EtOH, heat	H	Me	H	p-$O_2NC_6H_4$		257–258	265
2.497 + 2.498	MeCN, 25°C, 18 h	H	H	p-$MeOC_6H_4$	p-$MeOC_6H_4$			266
2.497 + 2.498	Me_2SO, heat	H	H	H	2-Furyl		103–104 (octane)	267
2.497 + 2.498	EtOH, Heat	H	Ph	H	p-BrC_6H_4	75	128 (AcOH)	268[b]
2.497 + 2.498	MeOH, heat	H	H	MeCONH	Ph	55	167–168 (C_6H_6)	269
2.497 + 2.498	MeOH, heat	H	H	MeO_2CNH	Ph	62	175–180 (dec.) (EtOAc)	269
2.497 + 2.498	EtOH, reflux	H	5-[p-BrC_6H_4]-2-furyl	H	Ph	30	303–304 (EtOH)	270
2.497 + 2.498	EtOH, reflux	H	5-[p-ClC_6H_4]-2-furyl	H	Ph	9	293–295 (EtOH)	270
2.497 + 2.498	EtOH, reflux	H	H	H	$CH_2P(O)(EtO)_2$	60	140[c]	271
2.497 + 2.498	EtOH, reflux	H	H	COMe	Me	65	228–230	272
2.497 + 2.498	EtOH, reflux	SO_2NH_2	H	H	H	36	> 305 (dec.) (H_2O)	273
2.497 + 2.498	EtOH, reflux	SO_2NH_2	H	H	Me	20	> 255 (dec.) (H_2O)	273
2.497 + 2.498	EtOH, reflux	SO_2NH_2	H	H	t-Bu	10	197–198 (EtOH)	273
2.497 + 2.498	DMF, reflux	H	H	H	Benzothiazol-2-yl	60	> 260	274
2.497 + 2.498	EtOH, reflux	CH_2CO_2Et	Ph	H	Ph	50	146–148 (EtOH)[d]	275

[a] Yield of the hydrobromide salt quoted.

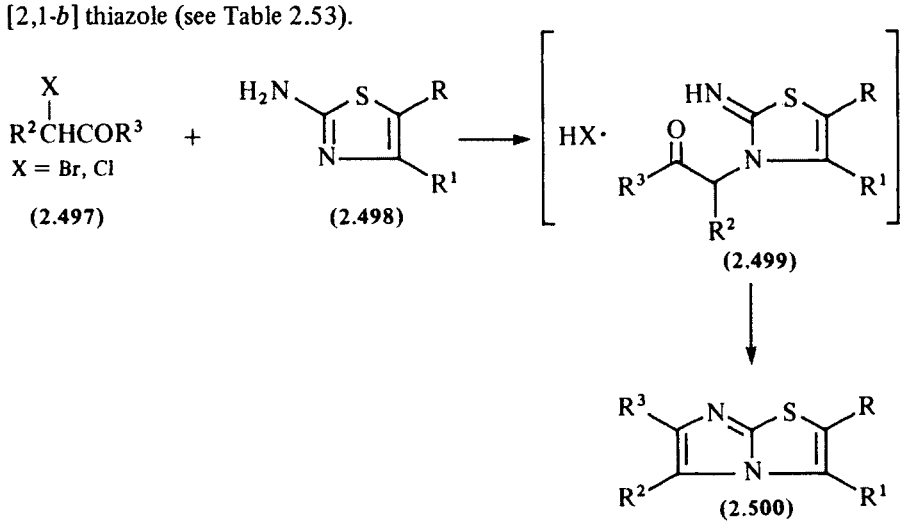
[b] Twenty-seven related 3,6-disubstituted imidazo[2,1-*b*]thiazoles are described in this paper (viz., **2.500**, R = R^2 = H; R^1, R^3 = aryl and 2-thienyl).

[c] Melting point of hydrobromide salt quoted; picrate mp = 154°C.

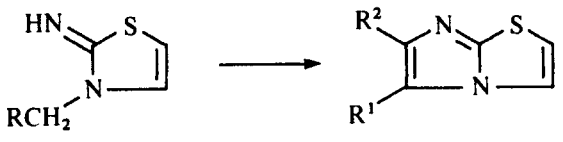
[d] Thirteen related trisubstituted imidazo[2,1-*b*]thiazoles are described in this paper (viz., **2.500**; R = CH_2CO_2Et, R^1 = R^3 = aryl; R^2 = H) in addition to products of hydrolysis of the ester function.

2.17.1.2. Synthesis from Thiazoles

The synthesis of imidazo[2,1-*b*]thiazoles (cf. **2.500**) can be achieved[251] by the dehydrative cyclocondensation of 2-aminothiazoles with α-halogenoketones (cf. **2.497**; X = Cl, Br) through iminothiazoline derivatives (**2.499**). In this type of process, the initial step of alkylation has been shown[261] to occur on the thiazole ring nitrogen, and the procedure has been widely used to give a variety of bicyclic derivatives (**2.500**) of known regiochemistry (see Tables 2.51 and 2.52). In some cases the synthesis has been achieved in a stepwise manner by isolation of the iminothiazoline derivative (**2.499**) and subsequent conversion into the imidazo-[2,1-*b*]thiazole (see Table 2.53).



Variants of the cyclization process (**2.499** → **2.500**) described above include the synthesis[284] of imidazo[2,1-*b*]thiazole (**2.502a**) by acid-induced cyclization of the acetal (**2.501a**) and formation of the 5-acetyl-6-hydroxy derivative (**2.502b**) from acetic anhydride-promoted cyclization of (2-imino-3-thiazolinyl)acetic acid (**2.501b**).[285] The latter cyclization can also be achieved by using phosphorus oxychloride under reflux, but under these conditions the product isolated is actually 6-chloroimidazo[2,1-*b*]thiazole (**2.502c**).[286]



a R = $CH(OMe)_2$
b R = CO_2H

	R^1	R^2	Reaction Conditions	Yield (%)	bp or mp (°C)
a	H	H	H_2SO_4, 90°C	–	106 (bp)
b	Ac	OH	Ac_2O, pyridine, reflux	87	234–235 (mp)
c	H	Cl	$POCl_3$, reflux	87	84–86 (mp)

TABLE 2.52. PATENTED IMIDAZO[2,1-*b*]THIAZOLES (**2.500**) SYNTHESIZED FROM 2-AMINOTHIAZOLES (**2.498**) AND α-HALOGENOKETONES (**2.497**)

Substituents in **2.500**	Area of Commercial Interest	Reference
$R-R^2$ = H, lower alkyl; R^3 = 2-thienyl	Analgesic, antiinflammatory	276
R = H, alkyl; R^1 = H, Me, Ph; R^2 = H, Me, CO_2Et; R^3 = CO_2H, alkoxycarbonyl, etc.	Antidiabetic	277
$R = R^1 = R^2 = H$; R^3 = *p*-$XYCHC_6H_4$ (X = H, Me; Y = CN, CO_2H, CO_2Et, $CONH_2$)	Analgesic, antipyretic, protective agents against uv irradiation	278
R = SO_2NH_2, $R^1 = R^2$ = H; R^3 = H, alkyl, aryl, hetaryl, etc.	Cerebral vasodilator	279[a,b]
$R = R^1 = R^2 = H$; R^3 = *p*-$MeO_2CCH_2OC_6H_4$		280

[a] The α-halogenoketone (cf. **2.497**) is used in the form of a ketal.
[b] See ref. 273.

TABLE 2.53. SYNTHESIS OF IMIDAZO[2,1-*b*]THIAZOLES (**2.500**) BY CYCLIZATION OF THIAZOLIUM SALTS (**2.499**)

Product **2.500**							
R	R^1	R^2	R^3	Cyclization Procedure	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reference
H	Me	H	5-Nitro-2-furyl	H_2O or EtOH, reflux	60	214–215 (EtOH)	281
H	Me	H	2-Furyl	Aqueous $NaHCO_3$, reflux	66	112–113 (EtOH)	281
H	H	H	5-Nitro-2-furyl	H_2O or EtOH, reflux	83	220–221 (C_6H_6–heptane)	281
H	Me	H	5-Bromo-2-furyl	H_2O or EtOH, reflux	42	102–103 (EtOH)[a]	281
H	H	H	2-Furyl	Aqueous $NaHCO_3$, reflux	50	96–98 (aq. EtOH)	281
H	Et	H	2-Furyl	Aqueous $NaHCO_3$	63	128 (EtOH)	282
Me	Me	H	2-Furyl	Aqueous $NaHCO_3$	58	117 (EtOH)	282
H	H	H	2-Thienyl	Aqueous $NaHCO_3$	44	141–143 (petroleum ether–EtOH)	282
H	Me	H	2-Thienyl	Aqueous $NaHCO_3$	80	138–139 (EtOH)	282
H	Et	H	2-Thienyl	Aqueous $NaHCO_3$	71	97–99 (EtOH)	282
Me	Me	H	2-Thienyl	Aqueous $NaHCO_3$	86	170 (EtOH)	282
H	H	H	2-Benzofuryl	Aqueous $NaHCO_3$	47	253–255 (MeOH)	282
H	Me	H	2-Benzofuryl	Aqueous $NaHCO_3$	59	165–166 (EtOH)	282
H	Et	H	2-Benzofuryl	Aqueous $NaHCO_3$	60	168 (EtOH)	282
Me	Me	H	2-Benzofuryl	Aqueous $NaHCO_3$	64	223 (EtOH)	282
H	H	H	3-Me-2-benzothienyl	Aqueous $NaHCO_3$	49	125–127 (Me_2CO)	282
H	Me	H	3-Me-2-benzothienyl	Aqueous $NaHCO_3$	79	186 (EtOH)	282
H	Et	H	3-Me-2-benzothienyl	Aqueous $NaHCO_3$	62	175 (EtOH)	282
Me	Me	H	3-Me-2-benzothienyl	Aqueous $NaHCO_3$	71	240 (Me_2CO)	282
H	CH_2CO_2Et[b]	H	Me	(i) EtOH, reflux; (ii) Aqueous $NaHCO_3$	58	75	283
H	CH_2CO_2Et[b]	H	Ph	(i) EtOH, reflux; (ii) Aqueous $NaHCO_3$	78	85	283
H	CH_2CO_2Et[b]	H	*p*-ClC_6H_4	(i) EtOH, reflux; (ii) Aqueous $NaHCO_3$	80	105	283
H	CH_2CO_2Et[b]	H	*p*-BrC_6H_4	(i) EtOH, reflux; (ii) Aqueous $NaHCO_3$	75	120	283
H	CH_2CO_2Et[b]	H	*p*-MeC_6H_4	(i) EtOH, reflux; (ii) Aqueous $NaHCO_3$	70	122	283
H	CH_2CO_2Et[b]	H	*p*-$MeOC_6H_4$	(i) EtOH, reflux; (ii) Aqueous $NaHCO_3$	65	84	283
H	CH_2CO_2Et[b]	H	*p*-$O_2NC_6H_4$	(i) EtOH, reflux; (ii) Aqueous $NaHCO_3$	78	171	283

[a] Forms a hydrobromide, mp 242–244°C (EtOH).

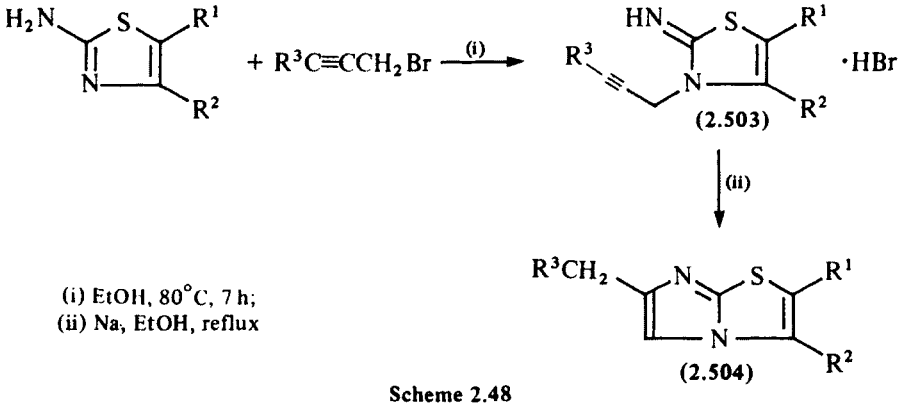
[b] The analogous carboxylic acid derivative has also been prepared by hydrolysis of the ester (20% H_2SO_4, 100°C, 3 h).

TABLE 2.54. SYNTHESIS[a] OF IMIDAZO[2,1-*b*]THIAZOLE DERIVATIVES (**2.504**) FROM 2-AMINOTHIAZOLES AND ALKYNYL BROMIDES[289]

Substituents in **2.504**				
R^1	R^2	R^3	mp (°C) or bp (°C) [torr]	Yield (%)
H	Me	H	96–97 88 (0.35)	80
Me	Me	H	122–123	92
H	H	Ph	144–145	94
H	H	*p*-ClC_6H_4	161–162	96
H	H	*p*-BrC_6H_4	176–177	98
H	Me	Ph	112–113.5	98
H	Me	*p*-ClC_6H_4	122–123.5	98
Me	Me	Ph	154–155	97
Me	Me	*p*-ClC_6H_4	185–186	97
Me	Me	*p*-BrC_6H_4	191–192	98

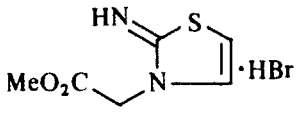
[a]Reaction conditions: 2-aminothiazole derivative, alkynyl bromide, butanol, 115–120°C, 2 h (see Scheme 2.47).

The synthesis of 6-methylimidazo[2,1-*b*]thiazole (**2.504**, $R^1 = R^2 = R^3 = H$); has been achieved from 2-aminothiazole and propargyl bromide in a stepwise manner (see Scheme 2.48),[287,288] but a direct, general synthesis of 6-substituted imidazo[2,1-*b*]thiazoles (**2.504**) has subsequently been achieved by heating 2-aminothiazoles with the alkynyl bromide in butanol[289] (see Table 2.54).

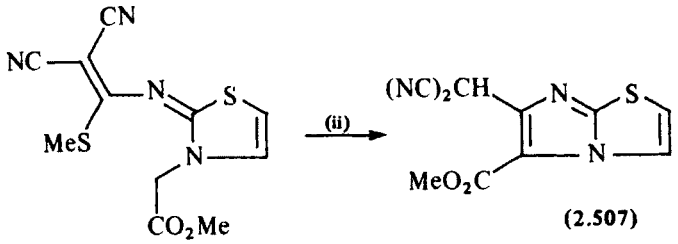


Scheme 2.48

Base-promoted annulation of the iminothiazoline derivative (**2.506**) provides a useful route to 5-methoxycarbonyl derivatives of imidazo[2,1-*b*]thiazoles (e.g., **2.507**; cf. **2.505** → **2.507** in Scheme 2.49),[290] and an effective, high-yielding general synthesis of 6-acetyl derivatives (**2.510**) is illustrated in the sequence **2.508** → **2.509** → **2.510**;[291] it may be noted that the products (**2.509**) of hydrogenolytic fission of the oxazole ring of **2.508** are not isolated and are transformed *in situ* into the imidazo[2,1-*b*]thiazole products.



(2.505)

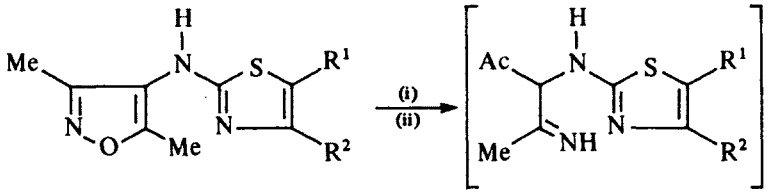


(2.506)

(i) $(MeS)_2C{=}C(CN)_2$; (ii) NaOMe

(2.507)

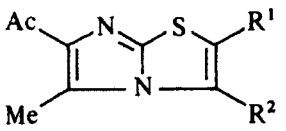
Scheme 2.49



(2.508)

(2.509)

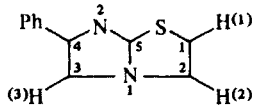
(i) H_2, Raney Ni, EtOH; (ii) AcOH, heat.



(2.510)

R^1	R^2	mp (°C)
H	H	178–179 (EtOH)
H	Me	153–155 (aq. EtOH)
Me	Me	134–135 (MeOH)
Ph	Ph	169–170

TABLE 2.55. BOND DISTANCES AND ANGLES IN 6-PHENYLIMIDAZO[2,1-*b*]-THIAZOLE (**2.511**) FROM X-RAY CRYSTALLOGRAPHIC ANALYSIS[292]



(2.511)

Bond Distance (A)		Bond Angle (°)	
S–C-5	1.725(5)	C-1–S–C-5	92.1(5)
S–C-1	1.735(6)	S–C-1–C-2	112.3(7)
C-1–C-2	1.344(8)	C-1–C-2–N-1	112.0(8)
N-1–C-2	1.420(6)	C-2–N-1–C-3	139.6(13)
N-1–C-3	1.382(6)	C-2–N-1–C-5	114.1(8)
N-1–C-5	1.389(7)	C-3–N-1–C-5	106.3(7)
C-4–C-3	1.389(7)	N-1–C-3–C-4	106.2(7)
C-4–N-2	1.413(6)	C-3–C-4–N-2	109.7(7)
N-2–C-5	1.311(6)	C-4–N-2–C-5	104.9(7)
		S–C-5–N-1	109.5(5)
		S–C-5–N-2	137.6(10)
		N-1–C-5–N-2	112.9(7)

2.17.1.3. Physicochemical Studies

2.17.1.3.1. CRYSTAL AND MOLECULAR STRUCTURE

The molecular structure of 6-phenylimidazo[2,1-*b*]thiazole has been determined by X-ray crystallographic analysis (see Table 2.55 for bond distances and angles relating to structure **2.511**).[292] An interesting feature is the trend toward increasing double bond character (decreasing bond separation) in the series N-1–C-2, N-1–C-3, N-2–C-5.

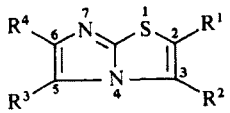
2.17.1.3.2. MASS SPECTRA

The mass spectra of a number of imidazo[2,1-*b*]thiazole derivatives have been recorded.[293,294] At 50 eV, intense molecular ions are formed, and indeed at 12 eV, this ion is the only ion observed in the spectrum of fully unsubstituted imidazo-[2,1-*b*]thiazole. Important fragments in substituted derivatives are exemplified as follows: 2-acetyl-3-methyl ($M^{\cdot+}$–$\dot{C}H_3$); 6-CO_2H ($M^{\cdot+}$–$\dot{O}H$ and $M^{\cdot+}$–CO_2); 6-CO_2Me ($M^{\cdot+}$–$\dot{O}H$).

2.17.1.3.3. NUCLEAR MAGNETIC RESONANCE SPECTRA

Hydrogen-1 nmr chemical shifts and coupling constants for a series of imidazo-[2,1-*b*]thiazoles are collected in Table 2.56.[295] A noticeable feature for 6-unsubstituted derivatives (**2.512a,b**) is a slight broadening of the 6-H resonance, perhaps emanating from the effect of the quadrupole moment of N-7. The chemical shifts fall into two distinct regions with H-2 to higher field than H-3, H-5, and H-6;

TABLE 2.56. ^{1}H NUCLEAR MAGNETIC RESONANCE SPECTRA OF IMIDAZO[2,1-*b*]THIAZOLE DERIVATIVES (2.512)[295]



(2.512)

	R^1	R^2	R^3	R^4
a,	H	H	H	H
b,	H	H	Me	H
c,	H	H	H	Me
d,	H	H	H	Ph
e,	H	H	H	Et
f,	Me	H	H	Ph
g,	H	Me	H	Ph
i,	H	H	Me	Ph
j,	H	H	Me	Me

Compound	Chemical Shifts[a]					Coupling Constants[a]				
	$\delta_{2\text{-H}}$	$\delta_{3\text{-H}}$	$\delta_{5\text{-H}}$	$\delta_{6\text{-H}}$	δ_{CH_3}	$J_{2,3}$ (Hz)	$J_{2,6}$ (Hz)	$J_{5,6}$ (Hz)	Other Couplings (Hz)	
2.512a	6.754	7.405	7.431	7.289		4.47	1.15	1.34		
2.512b	6.736	7.208		6.974	2.340	4.49	1.10		$J_{CH_{3,6}\text{-H}}$	1.06
2.512c	6.640	7.225	7.123		2.313	4.43			$J_{CH_{3,5}\text{-H}}$	1.00
2.512d	6.651	7.236	7.600			4.50				
2.512e	6.683	7.324	7.152		CH_3 1.259 CH_2 2.710	4.41			$J_{CH_{2,5}\text{-H}}$	0.93
									J_{CH_3,CH_2}	7.49
2.512f		7.004	7.459		2.334				$J_{CH_{3,3}\text{-H}}$	1.41
2.512g	6.245		7.482		2.253				$J_{CH_{3,2}\text{-H}}$	1.28
2.512h	6.725	7.216			2.259	4.50				
2.512i	6.623	7.119			2.228	4.47				

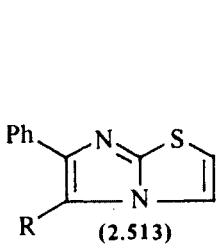
[a]Chemical shifts (ppm) and coupling constants (Hz) are quoted for approximately 0.5 *M* solution in $CDCl_3$ with tetramethylsilane as an internal standard.

the lowest values are observed for H-3 and H-5 in which hydrogen is adjacent to the bridgehead nitrogen. There are two characteristic features in the coupling constant data: a methyl substituent always shows a small coupling (ca. 1.0–1.4 Hz) with the ring proton attached to the adjacent carbon; and a long-range coupling ($J_{2,6}$) of approximately 1.0 Hz has been identified in the spectra of **2.512a** and **b**.

2.17.1.4. Reactions

2.17.1.4.1. REACTIONS WITH ELECTROPHILES

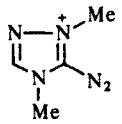
Routine side-chain alkylation of appropriately substituted azo derivatives gives rise to quaternary ammonium compounds (**2.513a**)[296] and triazolium and pyrazolium salts (**2.513b,c**)[297] of value as fast yellow dyestuffs for polyester and acrylic fibers. Electrophilic attack at the ring nitrogen of imidazo[2,1-*b*]thiazoles is exemplified by amination by use of *O*-mesityl sulfonylhydroxylamine from which 7-aminoimidazo[2,1-*b*]thiazolium salts can be isolated in good yield (see **2.514** → **2.515a,b**).[298]

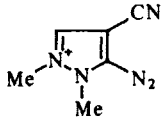


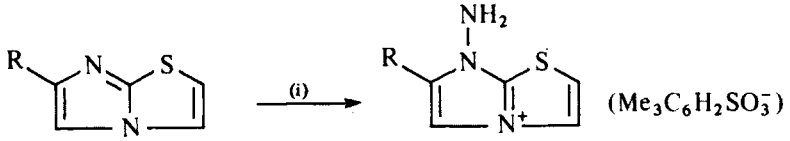
(2.513)

a: R = $R^1_2\overset{+}{N}(Me)(CH_2)_nZ$–C$_6H_3$($R^2$)–$N_2$ (X^-)

R^1 = Me, Et; Z = SO_2, O, CONH; X = $MeSO_4$, Cl, I

b: R =  ($MeSO_4^-$)

c: R =  ($MeSO_4^-$)

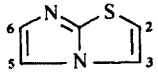


(2.514) (2.515) ($Me_3C_6H_2SO_3^-$)

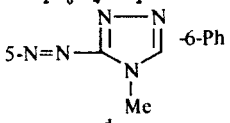
	R	mp (°C)	Yield (%)
a	Me	239–240 (EtOH)	79
b	Ph	181–182 ($MeNO_2$)	74

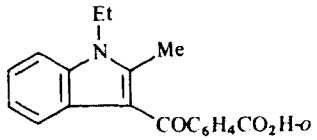
(i) $H_2NOSO_2C_6H_2Me_3$-*s*, CH_2Cl_2, room temperature

TABLE 2.57. ELECTROPHILIC SUBSTITUTION REACTIONS OF IMIDAZO[2,1-*b*]THIAZOLES

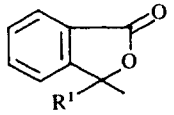


(2.516)

Entry Number	Substituents in Starting Material **2.516**	Substituents in product **2.516**	Reaction Conditions	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reference
1	2,3-Me_2-6-Ph	2,3-Me_2-5-NO-6-Ph	$NaNO_2$, AcOH	62	173 (Me_2CO)	299[a]
2	3-Me-6-Ph	3-Me-5-NO-6-Ph	$NaNO_2$, AcOH	82	174–175 (dec.) (Me_2CO)	299[a]
3	6-Ph	5-NO-6-Ph	$NaNO_2$, aqueous AcOH		180	301
4	6-(2-Furyl)	5-NO-6-(2-furyl)	$NaNO_2$, aqueous AcOH	86	162–163 (C_6H_6–petroleum ether)	302
5	3-Me-6-(2-furyl)	3-Me-5-NO-6-(2-furyl)	$NaNO_2$, aqueous AcOH	81	172–174 (C_6H_6–petroleum ether)	302
6	6-(5-Br-2-furyl)	5-NO-6-(5-Br-2-furyl)	$NaNO_2$, aqueous AcOH	97	250–252 (dec.) (C_6H_6–petroleum ether)	302
7	2-Me-6-(5-Br-2-furyl)	2-Me-5-NO-6-(5-Br-2-furyl)	BuONO, C_6H_6, room temp.	79	> 300 (dec.) (C_6H_6–petroleum ether)	302
8	6-Ph	5-NO_2-6-(*p*-$O_2N C_6H_4$) (A) + 6-(*p*-$O_2N C_6H_4$) (B)	Concentrated HNO_3, conc. H_2SO_4		275–276 (A) 290–300 (B)	301
9	6-Cl	5-NO_2-6-Cl	Concentrated HNO_3, conc. H_2SO_4 5–10°C	86	192–194	286
10	6-Ph	5-N_2Ph-6-Ph	$PhN_2^+X^-$, aqueous pyridine, 2–4°C		161–162	301
11	6-Ph	5-$N_2C_6H_4NO_2$-*o*-6-Ph	*o*-$O_2NC_5H_4N_2^+Cl^-$, aqueous AcOH	60	206 (EtOH)	299[b]
12	6-Ph					297[c]
13	6-Me	5-Br-6-Me[d]				304
14	6-(2-Furyl)	5-Br-6-(2-furyl)	Br_2 (1 equiv.), $CHCl_3$, room temp.	87	150–151 (aq. EtOH) (HBr, 220–221)	302
15	6-(2-Furyl)	5-Br-6-(5-Br-2-furyl)	Br_2(2 equiv.), $CHCl_3$, room temp.	83	163–164 (aq. EtOH) (HBr, 220–224)	302
16	6-(2-Furyl)	5-Br-6-(5-Br-2-furyl)[e]	Br_2 (≥ 3 equiv.) $CHCl_3$, room temp.		178–180	302

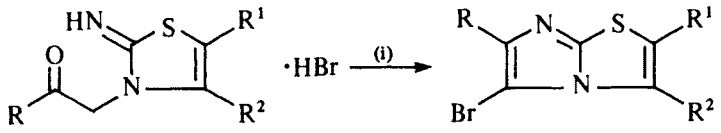
17	3-Me-6-(2-furyl)[f]	3-Me-5-Br-6-(2-furyl)	Br_2 (2 equiv.)	93	145–146 (EtOH) (HBr, 235–236)	302
18	6-Cl	5-CHO-6-Cl	$POCl_3$, $HCONMe_2$, $CHCl_3$, reflux	57	140–142 (EtOH)	286, 305
19	6-Me	5-CHO-6-Me	$POCl_3$, $HCONMe_2$, room temp.	60	140–142 (petroleum ether)	306
20	6-Ph	5-CHO-6-Ph	$POCl_3$, $HCONMe_2$, room temp.	81	133–135	306
21	6-Br	5-CHO-6-Br	$POBr_3$, $HCONMe_2$, 80°C	73	163–165	306
22	6-Cl	5-CH_2NMe_2-6-Cl	*sec*-Amine, CH_2O, AcOH, reflux	14	192–193 (*i*-PrOH)[g]	286
23	6-Cl	5-CH_2NEt_2-6-Cl	*sec*-Amine, CH_2O, AcOH, MeOH, reflux	27	181–183 (*i*-PrOH)[g]	286
24	6-Cl	5-$CH_2N(C_2H_4OH)_2$-6-Cl	*sec*-Amine, CH_2O, AcOH, MeOH, reflux	27	144–146 (MeOH)[g]	286
25	6-Cl	5-[CH_2-1-pyrrolidinyl]-6-Cl	*sec*-Amine, CH_2O, AcOH, MeOH, reflux	70	122–124 (C_7H_{16})	286
26	6-Cl	5-[CH_2-1-piperidinyl]-6-Cl	*sec*-Amine, CH_2O, AcOH, MeOH, reflux	66	110–111 (C_7H_{16})	286
27	6-Cl	5-[CH_2-1-morpholinyl]-6-Cl	*sec*-Amine, CH_2O, AcOH, MeOH, reflux	58	126–128 (PhMe)	286
28	6-(2-furyl)	5-[CH_2-1-piperidinyl]-6-(2-furyl)	*sec*-Amine (1 equiv.), CH_2O, AcOH, heat	79	194–196 (EtOH–Et_2O)[h]	307
29	3-Me-6-(2-furyl)	3-Me-5-[CH_2-1-morpholinyl]-6-(2-furyl)	*sec*-Amine (1 equiv.), CH_2O, AcOH, heat	81	190–192 (EtOH–Et_2O)	307
30	5-C_6H_4OMe-*p*	5-C_6H_4OMe-*p*-6-R[i]				308

[a] For related nitrosation reactions of imidazo[2,1-*b*]thiazoles, see ref. 300.
[b] A number of analogous 5-arylazo-6-aryl derivatives are described in this paper.
[c] Related 5-arylazo-6-phenyl derivatives are described in refs. 297 and 303.
[d] This compound is transformed into the 5-SCN-6-Me derivative by NH_4SCN.
[e] Isolated as the hydrobromide perbromide.
[f] See text for a more detailed description of the bromination of this compound.
[g] Melting point of hydrochloride salt quoted.
[h] Melting point of bisdihydrochloride salt quoted.

[i] R =  (R^1 = 1-ethyl-2-methylindol-3-yl)

Electrophilic substitution reactions of imidazo[2,1-*b*]thiazoles are well explored, although most studies have been performed on 6-substituted derivatives. The collected data in Table 2.57 indicate that nitrosation (entries 1–7), nitration (entries 8 and 9), diazonium coupling (entries 10–12), bromination (entries 13–17), formylation (entries 18–21), and aminomethylation (entries 22–29) of 6-substituted compounds proceeds exclusively at the 5-position and that in an isolated example of alkylation of a 5-substituted derivative, substitution is at the 6-position (see entry 30). As might be expected, a reduction of electron density at the 5-position markedly reduces the reactivity toward electrophiles: thus 6-(2-furyl)imidazo[2,1-*b*]thiazole and the 6-[5-bromo-2-furyl] analog undergo nitrosation at the 5-position (entries 4 and 6), whereas the 6-[5-nitro-2-furyl] analog is unreactive toward nitrosation.[302] Nitration of 6-chloroimidazo[2,1-*b*]thiazole with a mixture of concentrated sulfuric and nitric acids proceeds in high yield to the 5-nitro derivative,[286] but nitration occurs in the phenyl ring as well as in the imidazole ring of 6-phenylimidazo[2,1-*b*]thiazole (see entry 8).[301] The bromination of 6-[2-furyl]imidazo[2,1-*b*]thiazoles has been studied in detail. Through the use of 1 molar equivalent of bromine in chloroform, the 6-(2-furyl) derivative is converted exclusively into 5-bromo-6-(2-furyl)imidazo[2,1-*b*]thiazole, whereas the use of 2 molar equivalents gives rise to formation of the 5-bromo-6-[5-bromo-2-furyl]derivative.[302] In constrast, the initial site of bromination of 6-(2-furyl)-3-methylimidazo[2,1-*b*]thiazole is the 5-position of the furan ring with substitution in the imidazole ring occurring upon use of a second molar equivalent of bromine.[302]

However, bromination (Br_2, $CHCl_3$ or Br_2, AcOH) of the hydrobromide of 6-(2-furyl)imidazo[2,1-*b*]thiazoles, independent of the substitutent (if any) in the thiazole ring, occurs primarily in the furan ring;[309] these results indicate that the reactivity of the imidazole ring toward bromination is reduced by protonation at N-7. 5-Bromo derivatives are also formed by secondary reactions of electrophilic substitution following cyclization of thiazolinium bromides in dimethyl sulfoxide (see **2.517** → **2.518**).[310] It is probable that the bromine required in such processes is provided by dimethyl sulfoxide-mediated oxidation of hydrogen bromide generated in the cyclization step.



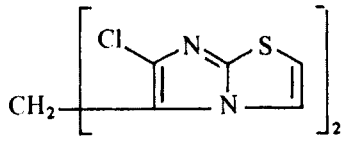
(2.517) (2.518)

(i) Me_2SO, 100°C, 0.5–2 h

R	R^1	R^2	Yield (%)	mp (°C)
p-$O_2NC_6H_4$	H	H	87	231–234
(5-nitro-2-furyl)	H	2-furyl	96	>300

The formation of Mannich bases (entries 22–29 in Table 2.57) occurs in variable yield when imidazo[2,1-*b*]thiazoles are treated with formaldehyde and a secondary amine in acetic acid.[286,307] The acidic nature of the medium is critical to the

success of this type of process: no reaction occurs in the absence of acid, whereas in the presence of hydrochloric acid only the bismethylene imidazo[2,1-*b*]thiazole derivative (**2.519**) is formed.[286]



(**2.519**)

2.17.1.4.2. REACTIONS WITH NUCLEOPHILES

Nucleophilic processes have been employed to effect the following simple functional group interconversions in imidazo[2,1-*b*]thiazoles: 2-CH_2CO_2Et → 2-CH_2CO_2H,[275] 5-CHO → 5CH(OH)R,[311] 5-CHO → 5C(R)=C(R)$CONH_2$,[312] 6-C_6H_4CN → 6-C_6H_4COMe,[313] 6-CO_2Et → 6-CO_2H,[314] 6-CO_2Et → 6-$CONH_2$,[315] and 6-CH_2CO_2Et → 6-CH_2CONH_2[315] (see data in Table 2.58).

2.17.1.4.3. REACTIONS WITH FREE RADICALS

The reactions of 6-chloroimidazo[2,1-*b*]thiazole with *N*-bromosuccinimide and *N*-chlorosuccinimide give the 5-bromo-6-chloro and 5,6-dichloro derivatives, respectively.[305] It is possible, of course, that these processes are electrophilic substitutions, and a systematic study of free radical substitution reactions of imidazo[2,1-*b*]thiazoles is warranted.

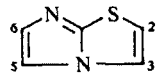
2.17.1.4.4. REDUCTION

There has been no systematic study of the reduction of the imidazo[2,1-*b*]-thiazole nucleus, and reactions in this group are restricted to routine transformations of substituents (see Table 2.59).

2.17.1.4.5. OXIDATION

There has been no report of oxidative cleavage of the imidazo[2,1-*b*]thiazole ring system during the literature period covered. Oxidative functional group transformations include the conversion of 5-formyl derivatives into 5-carboxylic acids (**2.522a–c**) using potassium permanganate in aqueous acetone[319] and the selenium dioxide-promoted conversion of 5-methyl-6-phenylimidazo[2,1-*b*]thiazole into the 5-formyl derivative (**2.522d**).[306] Unfortunately, oxidation processes of the latter type are not generally applicable: thus selenium dioxide oxidation[306] of 6-methylimidazo[2,1-*b*]thiazole gave 5,5′-bis(6-methylimidazo[2,1-*b*]thiazolyl)-selenide (**2.523**), and not a 6-formyl derivative as might have been anticipated. Oxidative coupling of 7-aminoimidazo[2,1-*b*]thiazolium salts (**2.524**) by saturated aqueous bromine gives rise to 7,7′-azo-coupled products (**2.525**).[298] It may be noted that products of the latter type are analogous to commercially successful 1,1′-azoimidazo[1,2-*a*]pyridinium salts of use as neuromuscular blocking agents.[320]

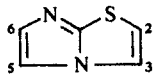
TABLE 2.58. REACTIONS OF IMIDAZO[2,1-*b*]THIAZOLE DERIVATIVES WITH NUCLEOPHILES



(2.520)

Substituents in Starting Material **2.520**	Substituents in Product **2.520**	Reaction Conditions	Yields (%)	Reference
2-EtO_2CCH_2-3,6-diaryl	2-HO_2CCH_2-3,6-diaryl	(i) 7% aq. NaOH, MeOH (ii) AcOH	78–97	275
5-CHO-6-Cl	5-CH(OH)R-6-Cl (R = alkyl, aryl)	RMgBr, Et_2O	40–84	311
2-R-6-R^1-5-CHO (R,R^1 = H, alkyl, aryl)	2-R-6-R^1-5-$C(R^2)$=$C(R^3)CONH_2$ (R^2 = H, CF_3, alkyl; R^3 = H, CN, etc.)	Base-promoted condensations of 5-CHO derivatives		312
6-$C_6H_3R^1R$-2,4 (R^1 = H, Cl; R = CN)	6-$C_6H_3R^1R^2$ (R^1 = H, Cl; R^2 = COMe)	MeMgX		313
2-R^1-3-R^2-6-CO_2Et	2-R^1-3-R^2-6-CO_2H (**2.520a**, R^1 = H, R^2 = Me; **2.520b**, R^1 = Br, R^2 = H)	**2.520a**, 4% NaOH, EtOH, reflux; **2.520b**, dilute HCl, reflux	**2.520a**, 5; **2.520b**, 41	314
3-R-6-R^1 (R = H, Me; R^1 = CO_2Et, CH_2CO_2Et)	3-R-6-$CONH_2$, 3-R-6-CH_2CONH_2	NH_4OH, MeOH	15–46	315

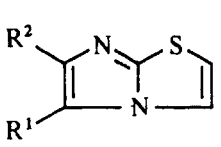
TABLE 2.59. REDUCTION REACTIONS OF IMIDAZO[2,1-*b*]THIAZOLES (**2.251**)



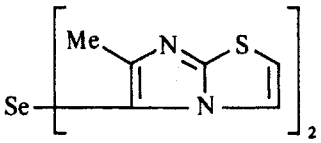
(2.521)

Substituents in Starting Material **2.521**	Substituents in Product **2.521**	Reaction Conditions	Yields (%)	Reference
2-C_6H_3(R) (ZCOR^1) (R = H, halo, alkyl, etc.; Z = bond or alkylene; R^1 = H, alkyl)	2-C_6H_3(R) [ZCH(OH)R^1]	$LiAlH_4$, tetrahydrofuran		316
5-NO_2-6-Cl	5-NHAc-6-Cl[a]	10% Pd–C, Ac_2O, AcOH, room temp.	39	286
5-CHO-6-R (R = Cl, Me, Ph)	5-CH_2OH-6-R[b]	$NaBH_4$, MeOH	70–95	317
5-CHO-6-C_6H_4R-*p* (R = Cl, Me, Ph)	5-CH_2OH-6-C_6H_4R-*p*[c]	$NaBH_4$, MeOH, reflux	70–90	318

[a] Melting point 131–133°C (hexane).
[b] R = Cl, mp not quoted; ir (cm^{-1}) = 3240, 1560, 1230, 995; R = Me, mp 168–171°C ($CHCl_3$); R = Ph, mp 198–200°C ($CHCl_3$).
[c] R = Cl, mp 198–200°C (EtOH) R = Me, mp 188–190°C (EtOH); R = Ph, mp 220–222°C (DMF).

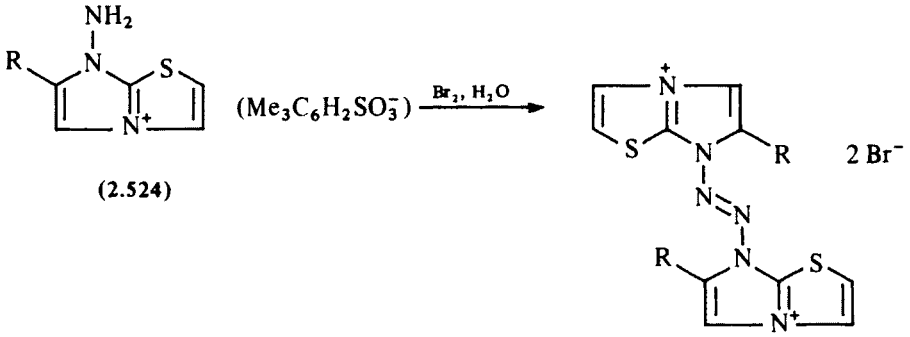


(2.522)



(2.523)

	R^1	R^2	mp (°C)
a	CO_2H	Cl	215 (dec.) (MeOH)
b	CO_2H	Me	205–210 (dec.) (aq. EtOH)
c	CO_2H	Ph	155–156 (dec.) (MeOH)
d	CHO	Ph	133–135



(2.524)

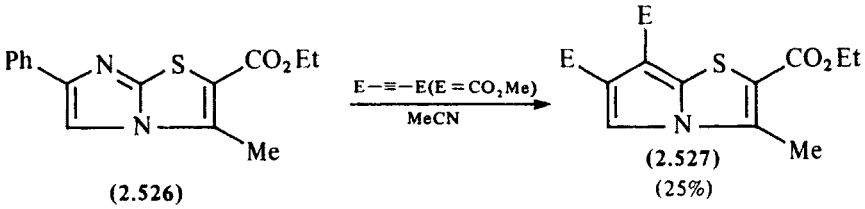
(2.525)

R	mp (°C)	Yield (%)
Me	294–295 (dec.) (MeOH)	63
Ph	272 (dec.) (MeOH)	46

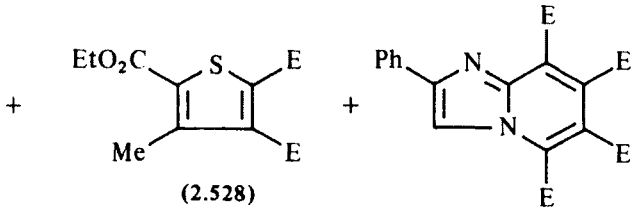
2.17.1.4.6. CYCLOADDITION

Formation of the pyrrolothiazole derivative (**2.527**) by treatment of the imidazo [2,1-*b*] thiazole (**2.526**) with dimethyl acetylene dicarboxylate can be explained by an initial process of cycloaddition followed by extrusion from the adduct of benzonitrile.[321] The course of the reaction is sensitive to the polarity of the solvent: in the polar medium acetonitrile, compounds **2.528** and **2.529** are predominant and probably[321] originate in an initial step **2.530** → **2.531**; in contrast, the product of the Diels–Alder pathway (**2.527**) is the only isolable compound when the reaction is effected in xylene.

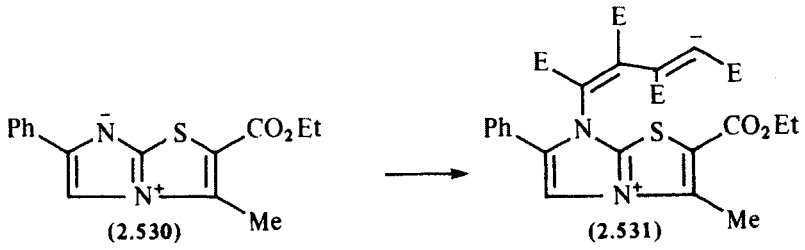
The mesoionic compound, anhydro-3-hydroxy-7-methyl-2-phenylimidazo[2,1-*b*]-thiazolium hydroxide (**2.532**), behaves as a C-2–C-7*a* 1,3-dipole with acetylenic compounds and with methyl isocyanate.[258] In the former case, the initial cycloadducts (**2.534**) lose sulfur to give imidazo[1,2-*a*] pyridines (**2.535**) in poor yield, but in the latter case the primary adduct (**2.536**) is isolated in almost quantitative yield.[258]



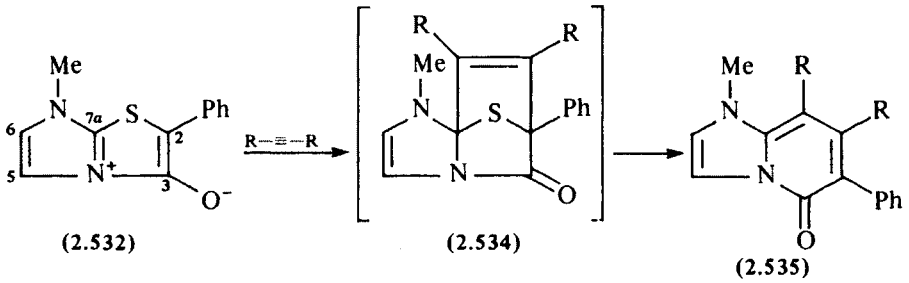
(2.526) (2.527) (25%)



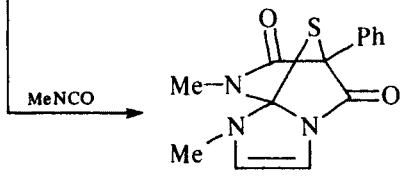
(2.528) (41%) (2.529) (42%)



(2.530) (2.531)



(2.532) (2.534) (2.535)



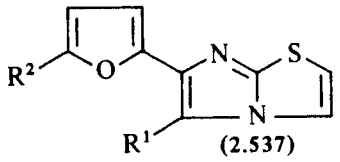
(2.536) (98%)

R	Yield (%)
CO_2Me	28
COPh	19

2.17.1.4.7. MISCELLANEOUS REACTIONS

A 5-aldoxime substituent in the imidazo[2,1-*b*]thiazole ring can be converted by thionyl chloride into a cyano group,[322] and a 5-carboxylic acid substituent can be decarboxylated by heating the substrate in either an acidic or alkaline medium.[323]

The hydrobromide of 5-bromo-6-(2-furyl)imidazo[2,1-*b*]thiazole (**2.537a**) undergoes partial debromination at the 5-position when it is heated in dimethylformamide [cf. **2.537a** → **2.537b** (15%) + **2.537c** (45%) + **2.537d** (8%)[324]]. Two of the isolated products from the reaction (**2.537b,c**) result from a secondary process of bromination in the furan ring. Interestingly, treatment of the dibromide (**2.537c**) with hot dimethylformamide results in selective debromination in the imidazo[2,1-*b*]thiazole nucleus with formation of **2.537b** in 30% yield.[324] The mechanism of this intriguing, selective debromination has not been established.



(2.537)

	R^1	R^2
a	Br	H (hydrobromide)
b	H	Br
c	Br	Br
d	H	H

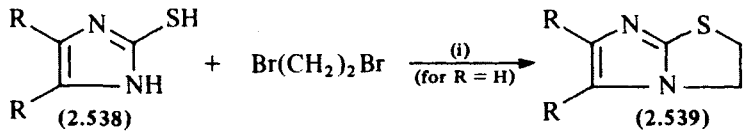
2.17.1.4.8. COMMERCIAL USES

The following imidazo[2,1-*b*]thiazoles have been evaluated for potential commercial interest; 5-azo derivatives (as fast yellow dyestuffs for polyester, acrylic, and nylon fibers);[296,297,303,326] 6-$CONH_2$,[315] 6-CH_2CONH_2[315] and 6-aryl[313,316] (analgesic, antipyretic, antiinflammatory); 5-$C(R^1)$=$C(R^2)CONH_2$ (R^1,R^2 = e.g., H, CF_3, alkyl, etc.) (antihypertensive, diuretic);[312] 2-CH_2CO_2R (R = Et, H) (antiinflammatory);[275] 2-R-5,6-diaryl (R = H, NO_2) (antiinflammatory);[266] 2-$CH_2S_2CNH(CH_2)_n$Ar-7-alkylimidazo[2,1-*b*]thiazolium salts (n = 1 or 3) (antiinflammatory, antimicrobial, anthelmintic);[255] 6-aryl (fungistatic);[325] 5-CH=CHZ$^+$ (Z = quaternized heterocycle, e.g., benzothiazole, imidazo[4,5-*b*]quinoxaline, indole) (spectral sensitizers for silver halide emulsions);[327] and 5- and 6-aryl (anthelmintic).[328,329]

2.17.2. 2,3-Dihydroimidazo[2,1-*b*]thiazoles

2.17.2.1. Synthesis from Imidazoles

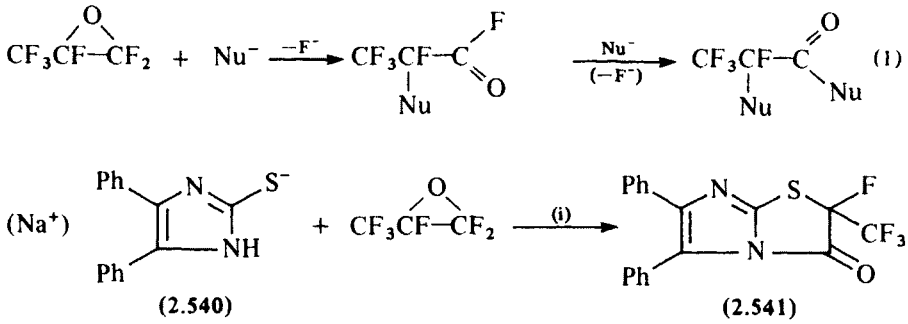
The parent compound, 2,3-dihydroimidazo[2,1-*b*]thiazole (**2.539**, R = H), can be prepared as an oily product by treating a mixture of 1,2-dibromoethane and sodium carbonate with an aqueous solution of the potassium salt of 2-mercaptoimidazole (**2.538**, R = H),[330] and related procedures leading to 5,6-disubstituted analogs (**2.539**, R = e.g., aryl) are covered in the patent



(2.538) (2.539)

(i) Na_2CO_3, *i*-PrOH, 20% aqueous KOH, reflux

literature.[331,334] The unusual mode of reaction of nucleophiles with hexafluoro-1,2-epoxypropane has been harnessed to provide a useful synthesis of a 2,3-dihydroimidazo[2,1-*b*]thiazol-3(2*H*)-one derivative (see reaction 1 and **2.540** → **2.541** in Scheme 2.50).[335]



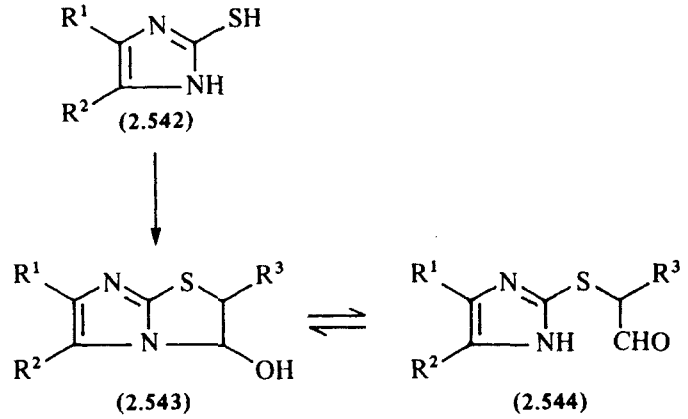
(2.540) (2.541)

(i) MeCN, heat (autoclave), 4 h

mp 115°C (hexane); 60% yield; ir ν_{max} 1175 cm^{-1}

Scheme 2.50

2-Mercaptoimidazole has also been used with α-halogenoacetaldehydes (or equivalents) to provide a synthesis of 3-hydroxy-2,3-dihydroimidazo[2,1-*b*]thiazole derivatives (see **2.542** → **2.543** and Table 2.60).[336–338] The ir spectra of these compounds exhibit bands in the region 3070–3225 cm^{-1} assignable to OH stretching frequency but are able to react in solution in the open-chain aldehyde form (cf. **2.544**); for example, the 5,6-diphenyl derivative (**2.543**, $R^1 = R^2 = Ph$) reacts with *p*-nitrophenylhydrazine to give a *p*-nitrophenylhydrazone, mp 174–175°C (dec.)[338]

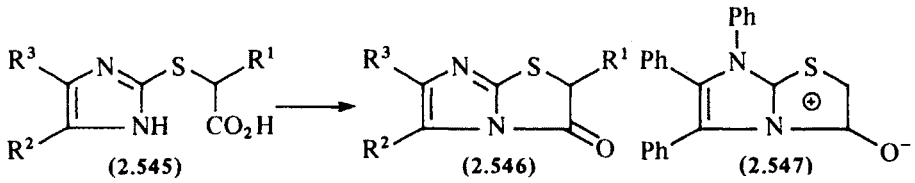


(2.542) (2.543) (2.544)

TABLE 2.60. SYNTHESIS OF 3-HYDROXY-2,3-DIHYDROIMIDAZO[2,1-*b*]THIAZOLES (**2.543**) FROM 2-MERCAPTOIMIDAZOLES

Subsituents in Product **2.543**							
R^1	R^2	R^3	Reaction Conditions	Yield (%)	mp (°C) (Solvent for Recrystallization)	ir [OH Stretching Frequency (cm^{-1})]	Reference
H[a]	CO_2Me[a]	H	$EtOCHBrCH_2Br$, H_2O, reflux	73	172–174 (dec.) (EtOH)		336
Ph	H	H	$EtOCHBrCH_2Br$, H_2O, reflux		160–161		337
H	H	H	$ClCH_2CHO \cdot H_2O$(dimer), EtOH, reflux	87[b]	(Oil) [picrate 143.5–145 (H_2O)]	3410–3225	338
Ph	Ph	H	$ClCH_2CHO$, H_2O (dimer), $HCONMe_2$, 60–65°C	77[b]	187–188 (dec.) ($ClCH_2CH_2Cl$)	3070	338
Ph	Ph	Me	$BrCH(Me)CH(OMe)_2$, aqueous EtOH, reflux	96	172.5–174.5 ($ClCH_2CH_2Cl$)	3070	338

[a]The regiochemical outcome of this cyclization has not been determined.
[b]Yield of hydrochloride salt quoted.



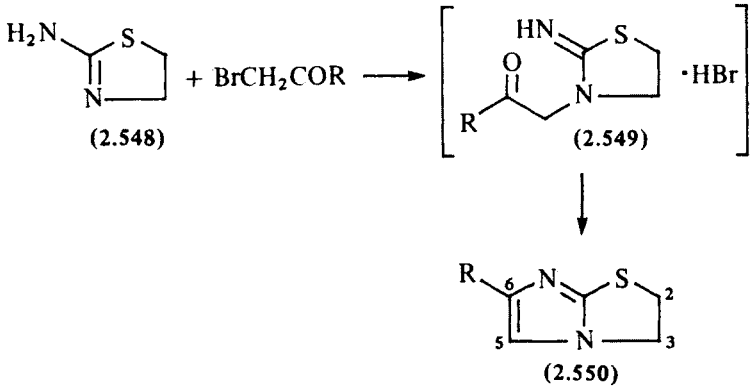
(2.545) (2.546) (2.547)

mp 205–208°C (dec.)
(AcOH–Me_2CO)

The acetic anhydride-mediated dehydrative cyclization of (imidazolythio)acetic and propionic acids gives rise to 2,3-dihydroimidazo[2,1-*b*]thiazol-3-(2*H*)-ones (see **2.545** → **2.546** and Table 2.61),[339–342] although of undefined regiochemistry for the dissymmetrical case where $R^2 \neq R^3$.[339] It is clear from ir spectral data[342] [e.g., $\nu_{max}^{KBr} = 1740\,cm^{-1}$ for **2.546** (R^1 = Me, $R^2 = R^3$ = Ph)] that in the solid state these derivatives exist in the keto form as depicted. In contrast to the cyclization described above, similar treatment of the 1-phenyl imidazole derivative (**2.545**, R^1 = H, $R^2 = R^3$ = Ph, NPh for NH) with acetic anhydride gives a compound believed to be the mesoionic imidazo[2,1-*b*]thiazole (**2.547**).[339]

2.17.2.2. Synthesis from Thiazoles

6-Substituted-2,3-dihydroimidazo[2,1-*b*]thiazoles (**2.550**) have been svnthesized from 2-aminothiazoline (**2.548**) and phenacyl bromides either directly[344] or through subsequent cyclization of the isolable hydrobromide salts of 2-imino-3-phenacylthiazolidines (**2.549**, R = e.g. Ph)[343] (see Table 2.62 for this and related reactions). Processes of this type have analogy in the synthesis of fully unsaturated imidazo[2,1-*b*]thiazoles from 2-aminothiazoles (see Section 2.17.1) and are extensively covered in the patent literature. (See Table 2.63 for compound types and areas of potential commercial interest.) A variant of the cyclization process described above (**2.549** → **2.550**) is the phosphorus oxychloride-mediated cyclization of 2-imino-3-thiazolidinylacetic acid (**2.549** free base, R = OH). Under the forcing conditions required (reflux, 2 h), the product isolated is actually 6-chloro-2,3-dihydroimidazo-[2,1-*b*]thiazole (mp 183–186°C, 52% yield).[286]



(2.548) (2.549) (2.550)

TABLE 2.61. SYNTHESIS OF 2,3-DIHYDROIMIDAZO[2,1-*b*]THIAZOL-3(2*H*)-ONES (**2.546**) FROM (IMIDAZOLYLTHIO)ACETIC ACID DERIVATIVES (**2.545**)

Substituents in Compound **2.546**						
R^1	R^2	R^3	Reaction Conditions	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reference
H	Ph[a]	H	Ac_2O, reflux	97	156–157 (dec.) (EtOH)	339
H	4-$O_2NC_6H_4$[a]	H	Ac_2O, reflux	82	235.5–236 (dec.) (AcOH)	339
H	Ph	Ph	Ac_2O, reflux	99	206–207 (dec.) (AcOH)	339
H	Ph	Ph	Ac_2O, reflux	75	200 (EtOH)	340
H	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Ac_2O, reflux	73	186 (EtOH)	340
H	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Ac_2O, pyridine, reflux	52	188 (EtOH)	341
Me	Ph	Ph	Ac_2O, reflux	88	165 (EtOH)	342

[a]The regiochemistry of this cyclization has not been unequivocally established.

TABLE 2.62. SYNTHESIS OF 2,3-DIHYDROIMIDAZO[2,1-*b*]THIAZOLES (**2.550**) FROM 2-AMINOTHIAZOLINES (**2.548**)

Substituent in **2.550**	Reaction Conditions	mp (°C) (Solvent for Recrystallization)	Reference
Ph	**2.549**, H_2O, heat	149–151 (EtOH) [HBr, 202–204 (EtOH); HCl 203–205]	343
Ph	**2.548**, phenacyl bromide, EtOH	150–151 (EtOH) [picrate, 210–212 (dec.)]	344
p-ClC_6H_4	**2.549**, H_2O, heat	156–159 (EtOH) (HBr, 210–212)	344
p-$O_2NC_6H_4$	**2.549**, H_2O, heat	228–230 (H_2O)	343
$(EtO)_2PO$	**2.548**, acyl bromide derivative, EtOH, reflux	150	271

TABLE 2.63. PATENTED 2,3-DIHYDROIMIDAZO[2,1-*b*]THIAZOLES (**2.550**) PREPARED FROM 2-AMINOTHIAZOLINES AND PHENACYL HALIDE DERIVATIVES

Substituents in **2.550**	Area of Potential Commercial Interest	Reference
2-Ph-3-Me-6-Ph	Antiviral	345
6-C_6H_4R-*p* (R = H, Cl, Br)	–	346
2-R-3-R-5,6-diaryl (R = H, alkyl)	Analgesic, antipyretic	347
5,6-Diaryl	Antiarthritic,[332,350] antiinflammatory,[332,350] immune-enhancing agents[332]	332, 350
6-Aryl	Analgesic, antiinflammatory, antipyretic	348
5,6-Diaryl, 5,6-di(hetaryl)	Antiinflammatory	349

2.17.2.3. Reactions

2.17.2.3.1. REACTIONS WITH ELECTROPHILES

There is little information on electrophilic aromatic substitution in the imidazole ring of 2,3-dihydroimidazo[2,1-*b*]thiazoles. Nitration with concentrated nitric acid at 70–80°C gives a compound believed to be the 5-nitro derivative,[330] although the site of substitution (5- or 6-) has not been unequivocally demonstrated.

The activated methylene position of 2,3-dihydroimidazo[2,1-*b*]thiazol-3(2*H*)-ones couples readily with electrophiles under a variety of conditions to give a series of alkylidene, arylidene, azomethine, and arylhydrazono derivatives (see Table 2.64). The last compounds, formed by use of arene diazonium tetrafluoroborates as electrophiles, apparently exist—in the solid state at least—in the 2-hydrazono-3-keto tautomeric form and not in alternative 2-arylazo-3-keto or 2-arylazo-3-hydroxy forms [cf. ir ν (CO) at 1705–1735 cm^{-1} and ν (NH) at 3230–3270 cm^{-1}].[351]

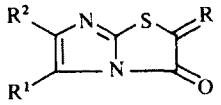
2.17.2.3.2. REACTIONS WITH NUCLEOPHILES

2-Methyl-5,6-diphenylimidazo[2,1-*b*]thiazol-3(2*H*)-one (**2.552**) is cleaved by hydrazine and arylamines to give the hydrazide (**2.553a**) and a series of (imidazol-2-ylthio)propionamides (**2.553b**), respectively.[342] Other reactions with nucleophiles include the addition of Grignard reagents to 2-arylidene derivatives (see **2.551**; R = CH aryl → **2.554**; and see Table 2.65)[340] and the routine conversion of 5-formyl-2,3-dihydroimidazo[2,1-*b*]thiazole derivatives into hydrazones.[353]

2.17.2.3.3. OXIDATION

5-Nitro-2,3-dihydroimidazo[2,1-*b*]thiazole can be oxidised to the sulfone (**2.555a**) by monoperphthalic acid,[330] and this type of oxidation of the thiazole ring sulfur can also be achieved by aqueous potassium permanganate in acetone; in the latter case concomitant oxidation of a 5-formyl substitutent occurs (**2.555**; R^1 = CHO, $n = 0 \rightarrow$ **2.555b–d**).[319] Formation of the 5,6-diaryl sulfone derivative (**2.555e**) is achieved[333] by heating the parent compound with 30% hydrogen peroxide in acetic acid, but the use of this oxidant in ethanol under reflux gives rise to the sulfoxide derivative (**2.555f**).[333]

TABLE 2.64. PREPARATION OF ALKYLIDENE, ARYLIDENE, AZOMETHINE, AND ARYLHYDRAZONO DERIVATIVES (2.551) FROM 2,3-DIHYDROIMIDAZO[2,1-*b*]THIAZOL-3-(2*H*)-ONES



(2.551)

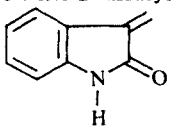
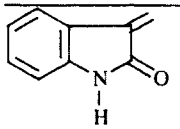
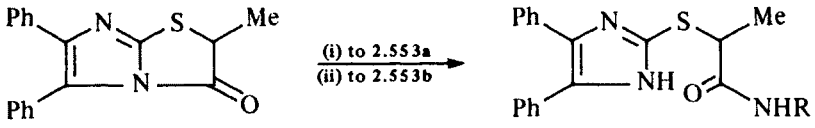
Substituents in 2.551			Reaction Conditions[a]	Yield (%)	mp (°C)	Reference
R	R^1	R^2				
C_4H_9CH	C_6H_5	H	A, B	35	118–119	351
$C_6H_5CH{=}CHCH$	C_6H_5	H	A, B	26	218–219	351
C_6H_5CH	C_6H_5	H	A, B	43	178–179	351
p-$CH_3OC_6H_4CH$	C_6H_5	H	A, B	33	183–184	351
p-$(CH_3)_2CHC_6H_4CH$	C_6H_5	H	A, B	32	143–145	351
o-$O_2NC_6H_4CH$	C_6H_5	H	A, B	36	206–208	351
m-$O_2NC_6H_4CH$	C_6H_5	H	A, B	44	242–244	351
p-$O_2NC_6H_4CH$	C_6H_5	H	A, B	47	261.5–263.5	351
2-Nitrofurfurylidene	C_6H_5	H	A, B	63	192–193	351
5-Nitro-2-furfurylidene	C_6H_5	H	B	63	257–258.5	351
$C_6H_5CH{=}CHCH$	C_6H_5	C_6H_5	B	97	201–202.5	251
C_6H_5CH	C_6H_5	C_6H_5	B	78	195–196	351
p-$CH_3OC_6H_4CH$	C_6H_5	C_6H_5	A	37	200–201	351
p-$(CH_3)_2CHC_6H_4CH$	C_6H_5	C_6H_5	A	36	169.5–171	351
o-$O_2NC_6H_4CH$	C_6H_5	C_6H_5	B	74	195–197	351
m-$O_2NC_6H_4CH$	C_6H_5	C_6H_5	B	49	235.5–237	351
p-$O_2NC_6H_4CH$	C_6H_5	C_6H_5	B	63	242–244	351
2-Nitrofurfurylidene	C_6H_5	C_6H_5	B	42	235–236	351
5-Nitro-2-furfurylidene	C_6H_5	C_6H_5	B	71	270	351
	C_6H_5	H	B	78	334–336	351

TABLE 2.64. (CONTINUED)

Substituents in **2.551**			Reaction			
R	R^1	R^2	Conditions[a]	Yield (%)	mp (°C)	Reference
	C_6H_5	C_6H_5	B	70	340	351
PhCH	Ph	Ph	B, C	82	186	340
p-$MeOC_6H_4CH$	Ph	Ph	C	80	205	340
p-ClC_6H_4CH	Ph	Ph	C	83	215	340
PhCH	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	C	81	185	340
p-$MeOC_6H_4CH$	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	C	78	205	340
PhCH	Ph	H	D	80	125	352
4-$O_2NC_6H_4CH$	Ph	H	D	–[b]	170 (dec.)	352
4-$Me_2NC_6H_4CH$	Ph	H	D	–[b]	150	352
4-OH-3-$MeOC_6H_3CH$	Ph	H	D	–[b]	102	352
4-HOC_6H_4CH	Ph	H	D	–[b]	92	352
4-$O_2NC_6H_4CH$	Ph	H	D	–[b]	85	352
4-$Me_2NC_6H_4CH$	4-$MeOC_6H_4$	4-$MeOC_6H_4$	B	21	229–230	341
4-$Me_2NC_6H_4N$	Ph	H	E	36	180.5–181	351
4-$Me_2NC_6H_4N$	Ph	Ph	E	29	205–205.5	351
4-$Et_2NC_6H_4N$	Ph	Ph	E	25	207–207.5	351
PhNHN	Ph	H	F	58	252.5–253.5	351
PhNHN	Ph	Ph	F	69	227.5–229.5	351
4-$MeOC_6H_4NHN$	Ph	H	G	71	236.5–238	351
4-BrC_6H_4NHN	Ph	H	G	83	252–253	351
4-$MeOC_6H_4NHN$	Ph	Ph	G	70	220–222	351

[a]Reaction conditions: (A) Aldehyde derivative, EtOH, piperidine, heat; (B) aldehyde derivative or isatin, AcOH, heat; (C) compound **2.551** prepared *in situ* from the 2-mercaptoimidazole derivative and chloroacetic acid and treated with the aldehyde, acetic acid, and acetic anhydride under reflux; (D) compound **2.551** (of unclearly defined regiochemistry) prepared *in situ* from 2-mercapto-4-phenylimidazole, $BrCH_2CO_2Et$, pyridine, EtOH, heat, and then treated with ArCHO and piperidine under reflux; (E) nitroso derivative (ArNO), EtOH, reflux; (F) ArN_2^+, BF_4^-, MeOH, 20°C (see ref. 342 for analogous reactions of $ArN_2^+Cl^-$; (G) ArN_2^+, BF_4^-, AcOH, Ac_2O, MeOH, 20°C (see ref. 342 for analogous reactions of $ArN_2^+Cl^-$.

[b]Yield not quoted.

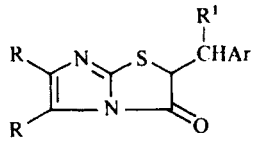


(2.552) (2.553)

(i) N_2H_4, EtOH, heat; (ii) $ArNH_2$, 160–170°C

a: R = NH_2
b: R = aryl

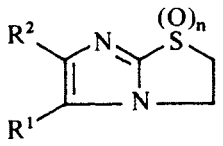
TABLE 2.65. SYNTHESIS[a] OF 2-BENZYHYDRYL-2,3-DIHYDROIMIDAZO[2,1-*b*]-THIAZOL-3(2*H*)-ONES (**2.554**) FROM 2-ARYLIDENE DERIVATIVES (**2.551**, R = CHAr)[340]



(2.554)

Substituents in **2.554**			Yield	mp (°C) (Solvent for
R	Ar	R^1	(%)	Recrystallization)
Ph	Ph	Ph	75	215 (AcOH)
Ph	Ph	C_6H_4Me-*p*	72	223 (dioxan)
Ph	Ph	C_6H_4OMe-*p*	71	190 (EtOH)
Ph	Ph	Et	69	150 (EtOH)
Ph	C_6H_4OMe-*p*	C_6H_4Me-*p*	74	230 (dioxan)
Ph	$C_6H_3(O_2CH_2)$-3,4	C_6H_4Me-*p*	77	235 (dioxan)
C_6H_4OMe-*p*	Ph	Ph	80	200 (dioxan)
C_6H_4OMe-*p*	Ph	C_6H_4Me-*p*	74	222 (dioxan)
C_6H_4OMe-*p*	C_6H_4OMe-*p*	C_6H_4Me-*p*	72	200 (dioxan)
C_6H_4OMe-*p*	$C_6H_3(O_2CH_2)$-3,4	C_6H_4Me-*p*	76	225 (dioxan)

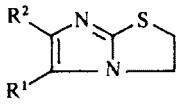
[a]Reaction conditions: 2-arylidene derivative (cf. **2.551**, R = CHAr), R^1MgX, Et_2O, reflux.



(2.555)

	R^1	R^2	*n*	mp (°C)
a	NO_2	H	2	216–217 (EtOH)
b	CO_2H	Cl	2	249–251 (dec.) (MeOH)
c	CO_2H	Me	2	268–270 (dec.) (MeOH)
d	CO_2H	Ph	2	259–260 (dec.) (MeOH)
e	C_6H_4OMe-*p*	C_6H_4OMe-*p*	2	
f	C_6H_4OMe-*p*	C_6H_4OMe-*p*	1	

TABLE 2.66. PRODUCTS FROM REDUCTION OF 2,3-DIHYDROIMIDAZO[2,1-*b*]IMIDAZOLES



(2.556)

Starting Material **2.556**		Product **2.556**		Reaction Conditions[a]	mp (°C) (Solvent for Recrystallization)	Reference
R^1	R^2	R^1	R^2			
CHO	C_6H_4Cl-*p*	CH_2OH	C_6H_4Cl-*p*	A[b]	215–220 (MeOH)	318
CHO	C_6H_4Me-*p*	CH_2OH	C_6H_4Me-*p*	A[b]	227–230 (MeOH)	318
CHO	C_6H_4Ph-*p*	CH_2OH	C_6H_4Ph-*p*	B[b]	259–262 ($HCONMe_2$)	318
H	$C_6H_4NO_2$-*p*	H	$C_6H_4NH_2$-*p*	C	224–226	343

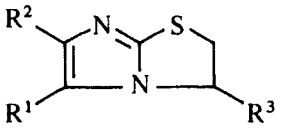
[a]Reaction conditions: (A) $NaBH_4$, MeOH, reflux, 2 h; (B) $LiAlH_4$, tetrahydrofuran; (C) $SnCl_2$, concentrated HCl, MeOH, heat.
[b]Yields in the range 70–90% are quoted for these reactions.

2.17.2.3.4. REDUCTION

There is no information available on reduction of the imidazole ring of 2,3-dihydroimidazo[2,1-*b*]thiazoles during the literature period covered. Products isolated from simple functional group reduction (5-CHO → 5-CH_2OH and 6-$C_6H_4NO_2$-*p* → 6-$C_6N_4NH_2$-*p*) are described in Table 2.66.

2.17.2.3.5. MISCELLANEOUS REACTIONS

6-Chloro-2,3-dihydroimidazo[2,1-*b*]thiazole (**2.557a**) reacts with *N*-chlorosuccinimide in chloroform under reflux to give a high yield of the 5,6-dichloro derivative (**2.557b**),[286] and the oximes (**2.557c** and **d**) are transformed by warm thionyl chloride into nitriles (**2.557e,f**).[322] The 3-hydroxy compound (**2.557g**) is rapidly dehydrated by heating it with phosphorus oxychloride to give the fully aromatic imidazo[2,1-*b*]thiazole derivative.[336]



(2.557)

	R^1	R^2	R^3	mp (°C)
a	H	Cl	H	
b	Cl	Cl	H	86–89 (hexane)
c	CH=NOH	Me	H	
d	CH=NOH	Ph	H	
e	CN	Me	H	100–102 (EtOH)
f	CN	Ph	H	188–192 (EtOH)
g	H	CO_2Me	OH	

2.17.3. 5,6-Dihydroimidazo[2,1-*b*]thiazoles

2.17.3.1. Synthesis from Imidazoles

The most widely used synthetic route to 5,6-dihydroimidazo[2,1-*b*]imidazoles is based on the cyclocondensation of 2-mercaptoimidazolines with α-halogeno ketones (see Scheme 2.51, and cf. related reactions illustrated in Scheme 2.46 leading to imidazo[2,1-*b*]thiazoles). Good yields of 5,6-dihydro derivatives (**2.560**) can be obtained either directly by heating the mercaptoimidazoline (**2.558**) and the α-halogenoketone udner reflux in ethanol or by isolating the intermediate phenacylthioimidazolinium salt (**2.559**) and subsequently effecting its cyclization to the bicyclic product (see examples in Table 2.67 and patented procedures in Table 2.68).

The latter reaction (**2.559** → **2.560**) can usually be effected in ethanol under reflux, but phenacyl derivatives bearing electron withdrawing substituents (cf. **2.559**, R^2 = C_6H_4CN-4, $C_6H_3Cl_2$-2,4) require long reaction times or the use of

TABLE 2.67. SYNTHESIS OF 5,6-DIHYDROIMIDAZO[2,1-*b*]THIAZOLES (**2.560**) FROM 2-MERCAPTOIMIDAZOLINES (**2.558**) AND α-HALOGENOKETONES

Compound **2.560**							
R^1	R^2	R^3	R^4	Method[a]	Yield (%)	mp (°C) (Solvent for Recrystallization)	Reference
H	Ph	H	H	A		110–111; 248–250[b]	354[e]
H	C_6H_4Br-*p*	H	H	A	70	145–146; 290–300[b]	354
H	C_6H_4SMe-*p*	H	H	A	69	118–119; 271–273[b]	354
H	C_6H_4Cl-*p*	H	H	A	73	113–114; 272–274[b]	354
H	$C_6H_4NO_2$-*p*	H	H	A	64	216–218; 287–290[b]	354
H	C_6H_4Br-*p*	H	Me[d]	A	80	270[b]	355
H	$C_6H_4NO_2$-*p*	H	Me[d]	A	88	250 (dec.)[b]	355
H	$C_6H_4C_6H_5$-*p*	H	Me[d]	A	91	265[b]	355
H	Ph	H	Me[d]	A	76	190–191[b]	355
H	$C_6H_3(OH)_2$-3,4	H	Me[d]	A	56	150–155[c]	355
H	$C_6H_2(OH)_3$-2,3,4	H	Me[d]	A	72	241[c]	355
H	Me	H	Me[d]	A	41	206–208[c]	355
H	(5-Nitro-2-furyl)	H	H	A	91	244–245[b]	356
H	(5-Nitro-2-furyl)	H	Me[d]	A	62	253–254[c]	356
H	(5-Nitro-2-furyl)	Me	Me	A	18	211–222[c]	356
H	(5-Nitro-2-furyl)CH=CH	H	H	A	90	245 (dec.) (MeOH)[b]	356
H	1-Adamantyl	H	H	A or B	84	312–314 (dec.)[b]	357
H	1-Naphthyl	H	H	A or B	27	282–284 (dec.)[b]	357
H	2-Naphthyl	H	H	A or B	75	242–248 (dec.)[b]	357
H	2-Furyl	H	H	A or B	58	239–240 (dec.)[b]	357
H	2-Thienyl	H	H	A or B	59	243–244 (dec.)[b]	357
H	2-Pyridyl	H	H	A or B	60	222–225 (dec.)[b]	357
H	3-Pyridyl	H	H	A or B	60	223 (dec.)[b]	357
H	4-Pyridyl	H	H	A or B	20	310–312 (dec.)[f]	357

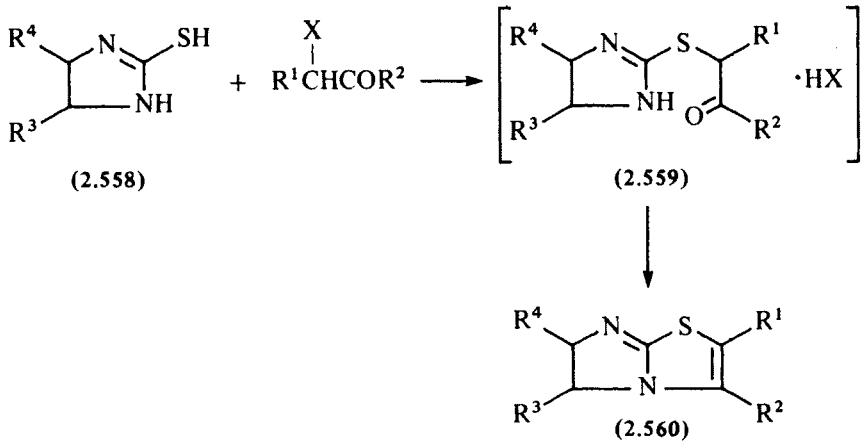
H	(5-Nitro-1-methylpyrrol-2-yl)	H	H	A	52	278[b]	358
H	C_6H_4F-*p*	H	H	A	83	153; 167[b]	359
H	$C_6H_3(F)(Me)$-4,5	H	H	A	63	196–198[b]	359
H	$C_6H_3(F)(Cl)$-4,5	H	H	A	77	192[b]	359
H	$CH_2P(O)(OEt)_2$	H	H	A	85	156	360
COMe	Me	H	H	A		190–192	272
COMe	Ph	H	H	A		171–175	272
COPh	Ph	H	H	A		260–262	272
H	CH_2CO_2Et	H	H	A	88	118; 196[c]	361
H	CH_2CO_2Me	H	H	A	50	180; 199[b]	361
$CONHC_6H_2Me_3$-*s*[g]	Me	H	H	A	36	>280[b]	362
H	$C_6H_4CH_2CO_2Et$-*p*	H	H	A	46	192–195	362
CO_2Et	Me	H	H	A	50	187–188[b]	362
H	Me	H	$(Me)_2$[d]	A	50	220–225[b]	362
H	Ph	H	$(Me)_2$[d]	A	64	260–261[c]	362
$MeSO_2$	Ph	H	H	A	36	183–185	362
Ph	Ph	H	H	A	50	267–268[c]	362
H	CH_2SO_2Ph	H	$(Me)_2$[d]	A	80	> 285 (dec.)[c]	362
H	$CH_2SO_2C_6H_4Me$-*p*	H	$(Me)_2$[d]	A	70	> 280 (dec.)[b]	362
H	CH_2SO_2Me	H	H	A	50	245–250[c]	362
$PhSO_2$	Ph	H	H	A	47	168–170	362

[a] Method: (A) EtOH, reflux (direct procedure **2.558** → **2.560**); (B) AcOH, reflux (indirect procedure **2.559** → **2.560**).
[b] Melting point of hydrobromide salt.
[c] Melting point of hydrochloride salt.
[d] Regiochemistry assigned arbitrarily.
[e] See ref. 357 for synthesis of this and 30 analogous 3-aryl-2,3-dihydroimidazo[2,1-*b*]imidazoles.
[f] Melting point of dihydrobromide salt.
[g] Eight other substituted anilides have been prepared by this method.[362]

TABLE 2.68. PATENTED PROCEDURES[a] LEADING TO 5,6-DIHYDROIMIDAZO[2,1-*b*]-THIAZOLES (cf. **2.558** → **2.560**)

Substituents in **2.560** ($R^3 = R^4 = H$)		Area of Potential Commercial Interest	Reference
R^1	R^2		
Aryl	H	Analgesic, antiinflammatory, antipyretic	348
CH_2CO_2H	Ph		365
Cl	Ph	Antidepressant	366
H	2-Thienyl	Anorexic activity in rats	367
H	Benzimidazol-2-yl	Parasiticide	368
H	CH=CH(5-NO_2-2-furyl)	Antibacterial, antiprotozoal	369
H	3-Aryl	Antiinflammatory, anoretic	370

[a]The compounds (**2.560**) are prepared by the direct process from the 2-mercaptoimidazoline (**2.558**) and the α-halogen ketone.

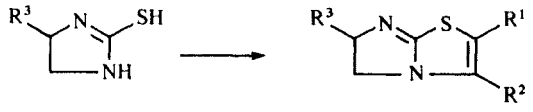


(2.558) (2.559) (2.560)

Scheme 2.51

acetic acid as solvent.[357] The use of unsymmetrically substituted imidazolines (**2.558**; $R^3 \neq R^4$) gives rise to products of unclearly defined regiochemistry [see examples in Table 2.67, R^4 = Me or $(Me)_2$], and further work is warranted on this aspect of the cyclization process. An additional problem associated with the synthesis outlined in Scheme 2.51 is the difficulty occasionally encountered in isolating and purifying requisite α-halogenoketones. A useful modified procedure for such cases involves generation of the latter *in situ* by halogenation of the appropriate ketone using bromine,[355,363] iodine,[355,363] or *N*-bromosuccinimide in the presence of a trace amount of dibenzoyl peroxide.[364] Other reagents that have been used in cyclocondensation reactions with 2-mercaptoimidazolines include α-halogenoaldehyde equivalents,[338,373] α-cyanobenzyl benzene sulfonate[371,372] (see Table 2.69), and 1,2-dibromoethane;[374] the last reagent has been used to prepare 6-(1-methylbenzimidazol-2-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole of potential value as an anthelmintic agent.[374]

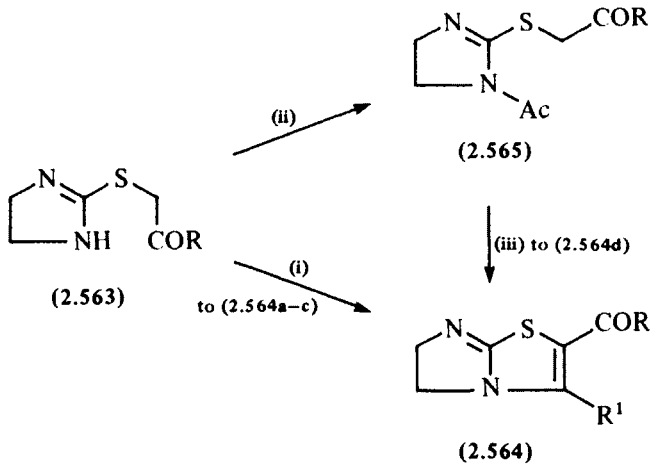
TABLE 2.69. CYCLOCONDENSATION REACTIONS OF 2-MERCAPTOIMIDAZOLINES (**2.561**) LEADING TO 5,6-DIHYDROIMIDAZO[2,1-*b*]-THIAZOLES (**2.562**)



(2.561) (2.562)

Substiuents in **2.562**						
R^1	R^2	R^3	Reaction conditions	Yield (%)	*mp (°C) (Solvent for* Recrystallization)	Reference
Ph	NH_2	H	$PhCH(CN)OSO_2Ph$, EtOH, room temp., 4 h	80	206–207 (dec.) (EtOH[a])	371, 372
H	H	H	$ClCH_2CHO \cdot H_2O$ (dimer), reflux	95	180.5–182.5 (dec.)[b]	338
Me	H	H	$BrCH(Me)CH(OEt)_2$, HBr (cat.), H_2O, reflux	96	104–106 (Me_2CO–petroleum ether)[c]	388
H	H	Ph	$ClCH_2CH(OEt)_2$, NaOEt, EtOH, reflux	41[d]	183–184.5[e]	373

[a] Melting point of benzene sulfonate quoted.
[b] Melting point of hydrochloride quoted.
[c] Melting point of hydrobromide 179–181°C (EtOH); picrate mp 182–183°C (dec.) (EtOH).
[d] Yield of oxalate salt quoted.
[e] Melting point of hydrobromide quoted.



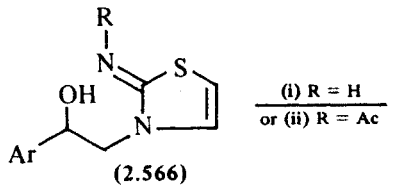
	R	R^1	Yield (%)	mp (°C) (Dec.)
a	Ph	H	86	251–253 (HCl)
b	C_6H_4Br-*p*	H	70	286–287 (HBr)
c	$C_6H_4NO_2$-*p*	H	68	236–238 (HCl)
d	C_6H_4Br-*p*	Me	86	269–270 (HBr)

(i) 85% HCO_2H, HCO_2Na, Ac_2O, reflux;
(ii) Ac_2O, 15–20°C;
(iii) AcONa, Ac_2O, 95–100°C

2-Aroyl derivatives in the 5,6-dihydroimidazo[2,1-*b*]thiazole series (**2.564a–c**) have been prepared by the acylative ring closure of 2-(β-ketoalkylthio)imidazolines (**2.563**) induced by formic acid and sodium formate in acetic anhydride.[257] Reactions of this type proceed by way of 1-acylimidazolines, and the 2-aroyl-3-methyl derivative (**2.564d**) can be synthesized in a stepwise fashion through such an isolable intermediate (**2.565**)[257] (cf. related reactions leading to imidazo[2,1-*b*]-thiazole collected in Table 2.50).

2.17.3.2. Synthesis from Thiazoles

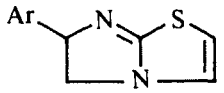
Synthetic procedures leading to 5,6-dihydroimidazo[2,1-*b*]thiazoles from thiazole derivatives have been designed specifically for the preparation of 6-aryl derivatives of interest as potential anthelmintic agents (cf. the properties of 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole described in Section 2.17.4). Alkylation of 2-aminothiazole with a bromomethyl aryl ketone occurs at the ring nitrogen, and borohydride reduction of the ensuing adduct provides 2-imino-3-(β-hydroxyaryl-ethyl)thiazolines (**2.566a**) in good yield.[373] The cyclization process (**2.566** → **2.567**) can then be effected on either the imino derivative[373,375] with thionyl chloride and acetic anhydride or the acetylimino compound (**2.566b**)[373] with thionyl chloride alone. [See also ref. 376 for a patented application of this procedure leading to 6-(aminoaryl)-5,6-dihydroimidazo[2,1-*b*]thiazoles].



(2.566)

a: R = H
b: R = Ac

(i) R = H
or (ii) R = Ac

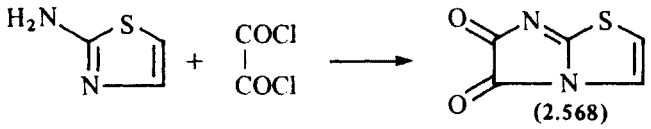


(2.567)

Ar	Yield (%)	mp of Oxalate (°C)	Ref.
Ph	74	175–177	373
C_6H_4Me-*m*	42	160–162	375
2-naphthyl	52	198–199	375

(i) $SOCl_2$, Ac_2O; (ii) $SOCl_2$

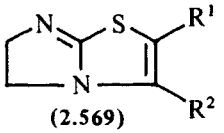
2-Aminothiazole has also been used to prepare 5,6-dihydroimidazo[2,1-*b*]-thiazole-5,6-dione (**2.568**), but this and its condensation products with aldehydes are poorly characterized.[377]



(2.568)

2.17.3.3. *Physicochemical Studies*

The structure of the 2,3-disubstituted-5,6-dihydroimidazo[2,1-*b*]thiazole derivative (**2.569a**) prepared as outlined in Scheme 2.51 has been elucidated X-ray crystallographically, but details of the molecular structure are not provided.[362] The ionization constant (9.30 ± 0.1) of the disubstituted derivative (**2.569b**) has been determined titrimetrically by using 7-(2-hydroxypropyl) theophylline as a solubilizing agent.[378]



(2.569)

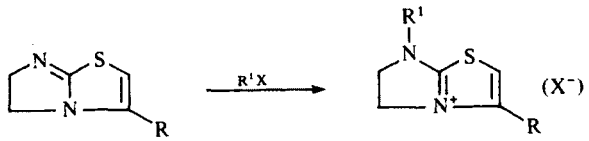
	R^1	R^2
a	SO_2Me	Ph
b	Et	C_6H_4Cl-*p*

2.17.3.4. *Reactions*

2.17.3.4.1. REACTIONS WITH ELECTROPHILES

Electrophilic reagents such as arenesulfonyl halides[379] and alkyl halides[380] react at N-7 of 5,6-dihydroimidazo[2,1-*b*]thiazoles (**2.570**) to give a series of condensed thiazolium compounds (**2.571**) (see Table 2.70). Compounds of the latter type are of interest as antibacterial agents[380] and acaricides,[381] and related compounds [cf. **2.571**; R^1 = acyl,[382] C(Z)NHR^2 (Z = O, S),[383] P(O$^-$) (S)OEt (inner salt)[384]] have been patented for use as anthelmintic[382] and nematocidal[383,384] agents, respectively.

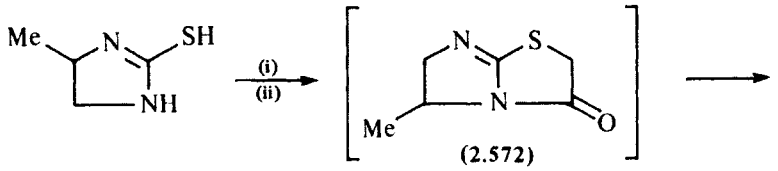
TABLE 2.70. FORMATION OF 7-SUBSTITUTED-5,6-DIHYDROIMIDAZO[2,1-*b*]THIAZOLIUM SALTS (**2.571**) FROM 5,6-DIHYDROIMIDAZO-[2,1-*b*]THIAZOLES (**2.570**)



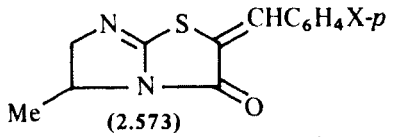
(2.570) (2.571)

Substituents in **2.571**						
R	R^1	X	Reaction Conditions[a]	Yield (%)	mp (°C)	Reference
Me	4-$ClC_6H_4SO_2$	Cl	A	77	140–142	379
Me	4-$O_2NC_6H_4SO_2$	Cl	A	76	191–192	379
Me	4-$MeC_6H_4SO_2$	Cl	A	80	148–150	379
Me	4-$AcNHC_6H_4SO_2$	Cl	A	80	151–152	379
Me	$MeSO_2$	Cl	A		160–161	379
2-(5-Nitrofuryl)	Me	I	B	95	248–249	380
2-(5-Nitrofuryl)	CH_2Ph	Br	B	79	247–247.5	380
2-(5-Nitrofuryl)	$CH_2C_6H_4Cl$-*p*	I	B	80	216–217	380
2-(5-Nitrofuryl)	$CH_2C_6H_3Cl_2$-2,4	I	B	72	222–223	380

[a]Reaction conditions: (A) R^1Cl, MeCN; (B) R^1I or R^1Br, Me_2CO or MeOH, reflux.



(2.572)



(2.573)

	X	Yield (%)	mp (°C)
a	H	49	112–113
b	OH	51	302 (dec.)
c	Me_2N	71	185–187
d	MeO	63	134–135
e	Cl	58	155–156

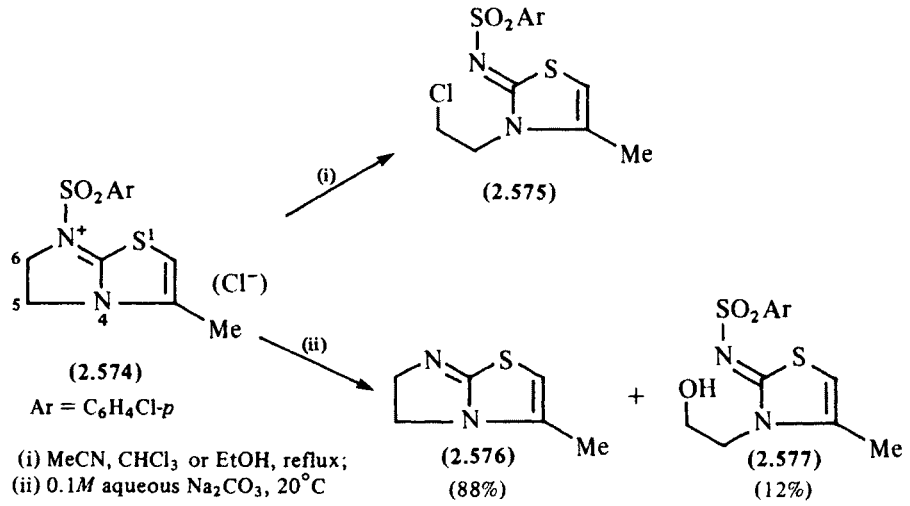
(i) $ClCH_2CO_2Et$, pyridine, reflux;
(ii) *p*-XC_6H_4CHO, piperidine, reflux

Scheme 2.52

Other reactions with electrophilic reagents include the routine acylation of 6-(aminoaryl)-5,6-dihydroimidazo[2,1-*b*]thiazoles[385] and the formation of 2-arylidene-5-methyl-5,6-dihydro compounds (**2.573a–e**) in the manner outlined in Scheme 2.52;[355] the uncertainty in the regiochemical disposition of the methyl group in these products (**2.573**) has been discussed earlier in this section.

2.17.3.4.2. REACTIONS WITH NUCLEOPHILES

The course of reactions of 5,6-dihydroimidazo[2,1-*b*]thiazolium salts is sensitive to the nature of the nucleophile employed. For example, thermal decomposition of the salt (**2.574**) in solution proceeds by attack of chloride ion at C-6 to give the thiazoline derivative (**2.575**); in contrast, reaction with aqueous alkali involves nucleophilic attack at sulfur (cf. **2.574** → **2.576**) with the minor product (**2.577**) arising from attack of hydroxide ion at C-6.[379]



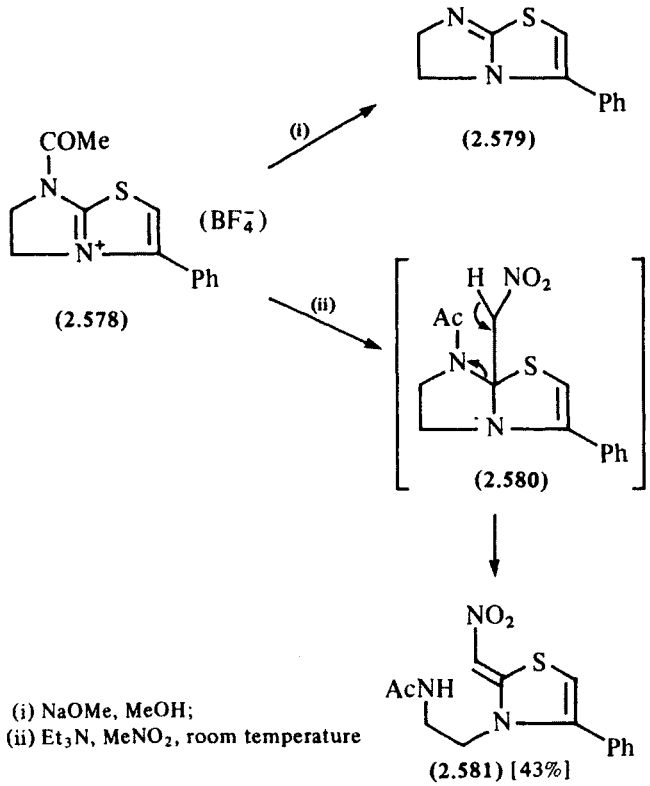
(2.574)
Ar = C_6H_4Cl-*p*

(2.575)

(2.576) (88%)

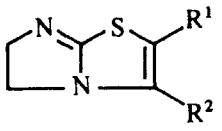
(2.577) (12%)

(i) MeCN, $CHCl_3$ or EtOH, reflux;
(ii) 0.1*M* aqueous Na_2CO_3, 20°C



Removal of a 7-substitutent in the condensed thiazolium salt (**2.578**) is also achieved by sodium methoxide in methanol (see **2.578** → **2.579**), but fission of the imidazoline ring of **2.578** is initiated by attack of nitromethane anion at C-7*a* (see **2.578** → **2.581**, through **2.580**).[386]

Nucleophilic transformations in the 5,6-dihydro series are also exemplified by hydrolysis of an amino substituent at C-3 (**2.582a** → **2.582b**)[371] and displacement of chloride ion implicit in **2.582c** → **2.582d**;[387] compounds of the latter type (**2.582d**) are of interest as potential antidepressant agents.[376]



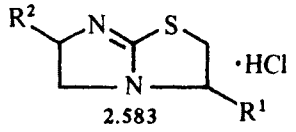
(2.582)

	R^1	R^2
a	Ph	NH_2 (benzene sulfonate)
b	Ph	OH (mp 138–139°C)
c	H	CH_2Cl
d	H	CH_2ZR (Z = O, S, SO_2; R = alkyl, alkoxy, etc.)

2.17.4. 2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazoles

2.17.4.1. Commercial Importance

The wide interest in imidazo[2,1-*b*]thiazole chemistry evident in this compilation (Section 2.17) undoubtedly arises from the commercial success of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride [tetramisole hydrochloride (**2.583a**)] as a broad-spectrum anthelmintic agent, highly active at low doses against gastrointestinal and pulmonary nematodes in a variety of animals and also in humans. The discovery of its activity was disclosed[388] by Janssen Pharmaceutica N.V. (Belgium) in 1966 and its synthesis subsequently described (see later sections on synthesis from thiazoles and imidazoles). The 3-(5-nitro-2-furyl) derivative (furazolium chloride, **2.583b**) is marketed by Norwich and Eaton as Dermafur and Novafur, respectively as a bactericide.



2.583

	R^1	R^2
a	H	Ph
b	(5-NO_2-2-furyl)	H

2.17.4.2. Synthesis from Thiazoles

2,3,5,6-Tetrahydroimidazo[2,1-*b*]thiazole hydrohalides (**2.585**, X = Br[389] and Cl[390]) have been synthesized by base-promoted cyclization of 2-imino-3-(2-halogenoethyl)thiazolidine hydrohalides (**2.584**), and the procedure has been adapted to the preparation of bactericidal 7-substituted-2,3,5,6-tetrahydroimidazo[2,1-*b*]-thiazolium salts (see **2.584** (R ≠ H) → **2.586** and Table 2.71).[391]

TABLE 2.71. SYNTHESIS OF 7-SUBSTITUTED 2,3,5,6-TETRAHYDROIMIDAZO[2,1-*b*]-THIAZOLIUM SALTS (**2.586**)

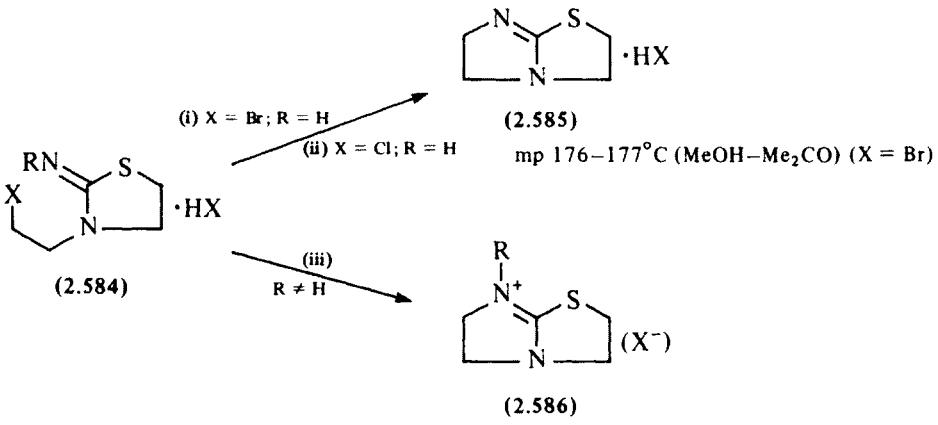
R in Compound **2.586**	X in Compound **2.586**	mp (°C)
tetra-*O*-acetyl-β-D-glucos-1-yl	Cl	173–176
Ph	Cl	75–77[a]
p-Tolyl	Cl	46–48[b]
p-Anisyl	Cl	169–170
1-Naphthyl	Cl	225–227
Ph	HSO_4	168–169
p-Chlorophenyl	Cl	223–225
p-Chlorophenyl	ClO_4	172–173

[a] Hydrate. This resolidifies and remelts at 95–97°C.
[b] Hydrate.

TABLE 2.72. SYNTHESIS OF 2,3,5,6-TETRAHYDRO-6-PHENYLIMIDAZO[2,1-*b*]THIAZOLE (TETRAMISOLE) AND RELATED COMPOUNDS FROM 2-IMINOTHIAZOLIDINES (cf. **2.587** → **2.588**)

Product **2.588** [R (Nature of Salt)]	Reaction Conditions[a]	mp (°C)	Reference
Ph (HCl)	A or B	261.5–264.5	373
2-ClC_6H_4 ($C_2H_2O_4$)	A or B	157–170	373
3-ClC_6H_4 ($C_2H_2O_4$)	A or B	168–172	373
4-ClC_6H_4 ($C_2H_2O_4$)	A or B	192–193	373
3,4-$Cl_2C_6H_3$ (HCl)	A or B	209–214	373
2,3,4-$Cl_3C_6H_2$ (HCl)	A or B	255–256.5	373
3-BrC_6H_4 (HCl)	A or B	194–195.5	373
4-BrC_6H_4 ($C_2H_2O_4$)	A or B	183.5–184	373
4-FC_6H_4 (HCl)	A or B	249–252	373
2-MeO-5-FC_6H_3 (HCl)	A or B	187–190	373
3-F-4-$MeOC_6H_3$ (HCl)	A or B	208–214	373
3-$CF_3C_6H_4$ (HCl)	A or B	173–179	373
4-$MeOC_6H_4$ ($C_2H_2O_4$)	A or B	168–169.5	373
4-MeC_6H_4 (HCl)	A or B	240–242	373
2,4-$Me_2C_6H_3$ (HCl)	A or B	192–196	373
2-$O_2NC_6H_4$ ($C_2H_2O_4$)	A or B	173.5–175.5	373
3-$O_2NC_6H_4$ ($C_2H_2O_4$)	A or B	183–184	373
2-Thienyl (HCl)	A or B	216–220	373
2-Furyl (HCl)	A or B	206.5–209	373
3-MeC_6H_4 ($C_2H_2O_4$)	C	160–162	375
2-Naphthyl ($C_2H_2O_4$)	C	198–199	375
2-(3-Methylbenzofuranyl) (HCl)	D	219–220[b]	392
2-Benzothiazolyl	E	298	274

[a]Reaction conditions: (A) $SOCl_2$, room temperature (R^1 = Ac); (B) concentrated H_2SO_4, room temperature (R^1 = H); (C) $SOCl_2$, Ac_2O, room temperature; (D) $SOCl_2$, Ac_2O, heat, 1 h; (E) $SOCl_2$, $CHCl_3$, reflux, 2 h.
[b]Melting point of free base 93–94°C.

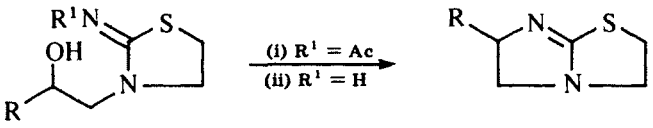


(i) 2*M* KOH; (ii) Et_3N, C_6H_6, 90°C; (iii) heat, or heat in Et_3N

The key compound in the series (tetramisole, **2.588**, R = Ph) can be prepared in good yield by cyclization of readily accessible 2-imino-3-(2-hydroxyphenethyl)-thiazolidine (**2.587a**) or the *N*-acetylimino analog (**2.587b**),[373] and this type of process has been widely used to prepare a variety of tetramisole analogs. [See Table 2.72; patented procedures in Table 2.73; and related cyclization reactions of chloro, bromo, and amino analogs of **2.587** (viz., **2.587**; Cl,[401,403] Br,[404] NH_2,[405] or NH-acyl[406] for OH).] Tetramisole hydrochloride has also been synthesized in the manner outlined in Scheme 2.53, although in this approach the intermediate hydrochloride of 2-imino-3-(2-hydroxyphenethyl)thiazolidine is not isolated.[407] 2-Iminothiazolidine derivatives are probably also intermediates in the reaction of 2-aminothiazoline with an isomer mixture of ethyl-α-bromocinnamate, leading to 5,6-disubstituted 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles (**2.589**, **2.590a** and **2.591**).[408] The stereochemistry of a derivative (**2.590b**) in the series has been elucidated X-ray crystallographically,[408] and the depicted stereochemistry of **2.589** and **2.590a** follow by inference.

TABLE 2.73. PATENTED PROCEDURES LEADING TO TETRAMISOLE AND ITS ANALOGS [cf. **2.587a** → **2.588** (R = Ph)]

Substituent in **2.588**	Reference
Ph	393
Aryl, thienyl, furyl	394
Aminoaryl	395
4- and 5-Thiazolyl	396
3- and 4-Pyridyl	397
2-Thienyl, 2-furyl	398
Phenoxazinyl, phenothiazinyl	399
(3-Methybenzofuran-2-yl)	400



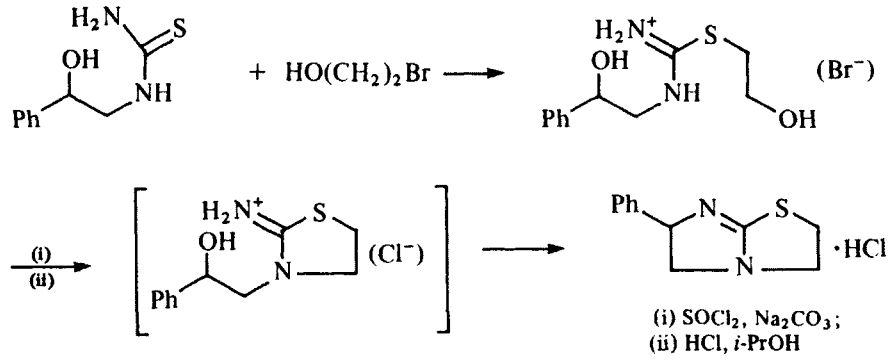
(2.587) (2.588)

	R	R¹
a	Ph	H
b	Ph	Ac

(i) $SOCl_2$, room temperature (R^1 = Ac);
(ii) concentrated H_2SO_4, room temperature (R^1 = H)

2.17.4.3. *Synthesis from Imidazoles*

The cyclizative condensation of 2-mercaptoimidizolines with 1,2-dibromoethane and related compounds provides straightforward access to 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles (see Table 2.74), and this route has been used to prepare the *R*(+) and *S*(−) enantiomers of the commercially successful 6-phenyl derivative in this series (see Section 2.17.4.1, Scheme 2.54, and the physical constants collected in Table 2.75).[409] It may be noted that the *S*(−) enantiomer (levamisole) of tetramisole hydrochloride possesses twice the anthelmintic activity of the racemic mixture and is several times more potent than the *R*(+) enantiomer (dexamisole) (for resolution procedures, see refs. 410–412). Three additional



Scheme 2.53

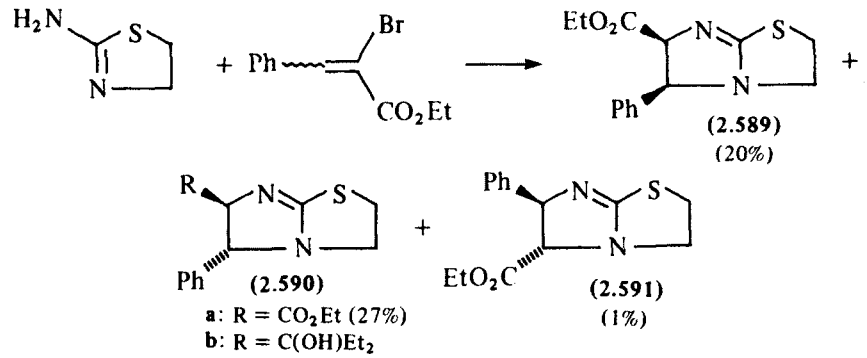
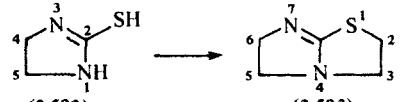


TABLE 2.74. SYNTHESIS OF 2,3,5,6-TETRAHYDROIMIDAZO[2,1-*b*]IMIDAZOLES (2.593) FROM REACTIONS OF 2-MERCAPTOIMIDAZOLINES (2.592) WITH 1,2-DIHALOETHANES, AND RELATED COMPOUNDS

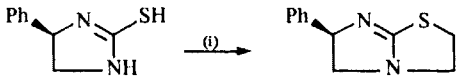


(2.592) (2.593)

Substituents in 2.592	Reaction Conditions	Substituents in 2.593	mp (°C) (Solvent for Recrystallization)	Yield (%)	Reference
4-Ph	$Br(CH_2)_2Br$, Na_2CO_3, NaOH, aqueous *i*-PrOH, reflux	6-Ph	(HCl) 263–265 (EtOH)	63	373
4,5-$(C_6H_4OMe\text{-}p)_2$ (*trans*)	$Br(CH_2)_2Br$, *i*-PrOH, Na_2CO_3	5,6-$(C_6H_4OMe\text{-}p)_2$ (*trans*)			413[a]
None	$Br(CH_2)_2Br$, tributylcetylammonium bromide, C_6H_6, 70°C	None	–[b]	70	414
4,5-Ph_2	$Br(CH_2)_2Br$, tributylcetylammonium bromide, C_6H_6, 70°C	5,6-Ph_2	164–166[c]	96	414
4-oxo-5,5-Ph_2	$Br(CH_2)_2Br$	5-Oxo-6,6-Ph_2 (major) 5,5-Ph_2-6-oxo (minor)[d]			408[g]
4-oxo-5,5-Ph_2	$Br(CH_2)_2Cl$, NaOH, MeOH, reflux	5,5-Ph_2-6-oxo (A) + 5-oxo-6,6-Ph_2 (B)	180–182 ($CHCl_3$–EtOAc) (A)[e] 201–203 ($CHCl_3$) (B)[f]	33 (A) 6 (B)	415[g]
None	$R^1R^2C(Cl)C(Cl)=NOH$, Na_2CO_3, MeOH (R^1, R^2 = e.g., H, alkyl)	2,2-R^1R^2-3-oximino[h]	For 2,2-Me_2-3-oximino, e.g.: 188–191		416
None	$ClCH_2CH(Cl)OEt$, e.g., aqueous HCl, EtOH, reflux[g]	3-*S*-(Imidazolin-2-yl)	246 (EtOH)[i]	24	417
4-R (R = $PhCH_2$, thienyl, furyl, aryl)	$CH_2CH_2OSO_3H$ | OSO_3H	6-*R*			418

[a] 5,6-Diaryl derivatives of this type are of interest as potential antiinflammatory agents.
[b] Compound isolated in a semicrystalline state, uv $\lambda_{max}^{95\%\,EtOH}$ = 205.3 nm (ϵ, 13,000), 227 (6500).
[c] Ultraviolet spectrum: $\lambda_{max}^{95\%\,EtOH}$ = 225.5 nm (ϵ, 19,517), 262.2 (11,574), 296.5 (10,215).
[d] The molecular structure of this compound has been determined X-ray crystallographically.[408]
[e] Ultraviolet spectrum: λ_{max}^{EtOH} = 241 nm (ϵ, 19,135), 263 (6990).
[f] Ultraviolet spectrum: λ_{max}^{EtOH} = 243 nm (ϵ, 7760).
[g] See text.
[h] Compounds of this type are of interest as potential insecticides.
[i] Melting point of hydrochloride salt quoted.

TABLE 2.75. PHYSICAL PROPERTIES OF THE *R*(+) AND *S*(−) ENANTIOMERS OF 2,3,5,6-TETRAHYDRO-6-PHENYLIMIDAZO[2,1-*b*]THIAZOLE (TETRAMISOLE)



R(−) R(+)

(i) $Br(CH_2)_2Br$, alkaline aq. *i*-PrOH

Scheme 2.54

	Enantiomer	
	R(+)	*S*(−)[a]
Melting point of oxalate (°C)	199–202	200–201.5
$[\alpha]_D^{20}$ of oxalate	+ 99 ± 2° (c, 0.5, H_2O)	− 103 ± 2° (c, 0.5, H_2O)
Melting point of HCl salt (°C)	228–230	227–229
$[\alpha]_D^{20}$ of HCl salt	125 ± 2° (c, 0.7, H_2O)	− 124 ± 2° (c, 0.9, H_2O)

[a]The *S*(−) enantiomer was synthesized from the *S*(+) enantiomer of 2-mercapto-4-phenylimidazoline.[409]

features of the data in Table 2.74 are notable. The transformation **2.592** → **2.593** has been effected in two cases in high yield, using tributylacetylammonium bromide as a phase-transfer catalyst.[414] The product distribution from treatment of 5,5-diphenyl-2-thiohydantoin with dihaloalkanes is apparently reversed in changing from 1,2-dibromoethane[408] to 1-bromo-2-chloroethane[415] as coreactant, but full experimental details are unavailable for the former process. Finally, formation of 2,3,5,6-tetrahydro-3-(imidazolin-2-ylthio)imdazo[2,1-*b*]thiazole from the reaction of 2-mercaptoimidazoline and αβ-dichloroethyl ether occurs with the use of a 1 : 1 molar reactant ratio, and no charge is observed when that ratio is modified.[417]

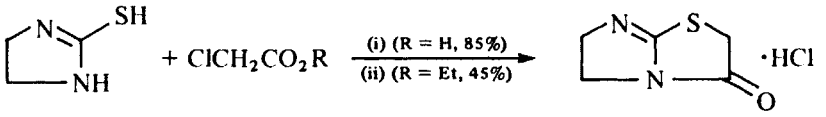
Cyclocondensation reactions of 2-mercaptoimidazoline have also been used to synthesize 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles with a more elaborate pattern of substitution in the thiazole ring. For example, the 3-oxo derivative (**2.594**) can be synthesized with chloroacetic acid[419–421] or ethyl chloroacetate[422] in the manner indicated in Scheme 2.55, and a series of 2,3,5,6-tetrahydro-3-hydroxyimidazo[2,1-*b*]thiazoles has been prepared from 2-mercaptoimidazoline and α-halogeno carbonyl derivatives, typically in acetone[367,427] or isopropanol[424] at room temperature (cf. **2.595** in Scheme 2.55, Table 2.76, and footnotes therein for areas of commercial interest).

The reaction of 2-mercaptoimidazoline (**2.596a**) and its 3-methyl analog (**2.596b**) with acetylene dicarboxylic acid esters gives rise to bicylic derivatives formulated as **2.597a** and **b**, although of undefined regiochemistry in the latter case.[431] It may be noted that alternative isomeric imidazothiazine structures for these products can be excluded on the basis of ^{13}C nmr spectroscopic evidence[432] (see following section) and by analogy with related reactions in the benzimidazole series.[433]

TABLE 2.76. SYNTHESIS OF 2,3,5,6-TETRAHYDRO-3-HYDROXYIMIDAZO[2,1-*b*]-THIAZOLES (2.595) FROM 2-MERCAPTOIMIDAZOLINES AND α-HALOGENOCARBONYL DERIVATIVES

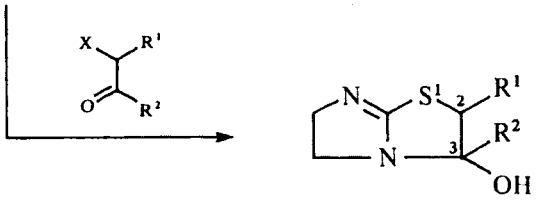
Substituents in Compound 2.595		
R^1	R^2	Reference
$C_6H_3R^1R^2$-2,6 R^1, R^2 = e.g., Me, Me; Cl, CF_3; or Cl, Cl	H	423[a]
H	(4-Methyl-2-thienyl) (5-Methyl-2-thienyl)	367[b]
CH_2CH_2Cl	Ph	424[c]
CH_2CO_2R (R = H, Me, Et)	$C_6H_4R^1$-4 (R^1 = H, Cl)	425[d]
H	$(CH_2)_2NR^1R^2$(R^1, R^2 = alkyl, aralkyl, etc.)	426[e]
H	$CH_2OC_6H_4$Me-2	427[f]
H	C_6H_4R-4 (R = MeO, F, Cl, NO_2)	428
H, Me, Et	$C_6H_3(SO_2NR^1_2)R^2$-3,4 (R^1 = e.g., alkyl; R^2 = H, halogeno, Me, etc.)	429
$CH_2C_6H_4R$ (R = H, halogeno, alkyl, etc.)	$C_6H_4R^1$ (R^1 = H, halogeno, alkyl, etc.)	430

[a] Hypotensive agents.
[b] Anorexic activity in rats.
[c] Antidepressant, anorexigenic agents.
[d] Antitubercular agents.
[e] Vasodilating and hypotensive agents.
[f] Antidepressants.



(2.594)

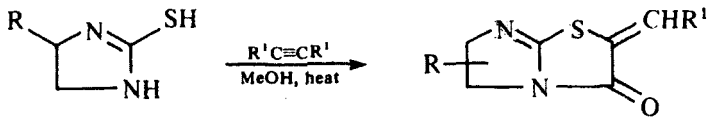
mp. 205°C;[421]
mp 204–206°C (dec.) (EtOH)[422]



(2.595)

(i) AcOH, 60–70°C, 3–4 h; (ii) 150°C, 4 h

Scheme 2.55

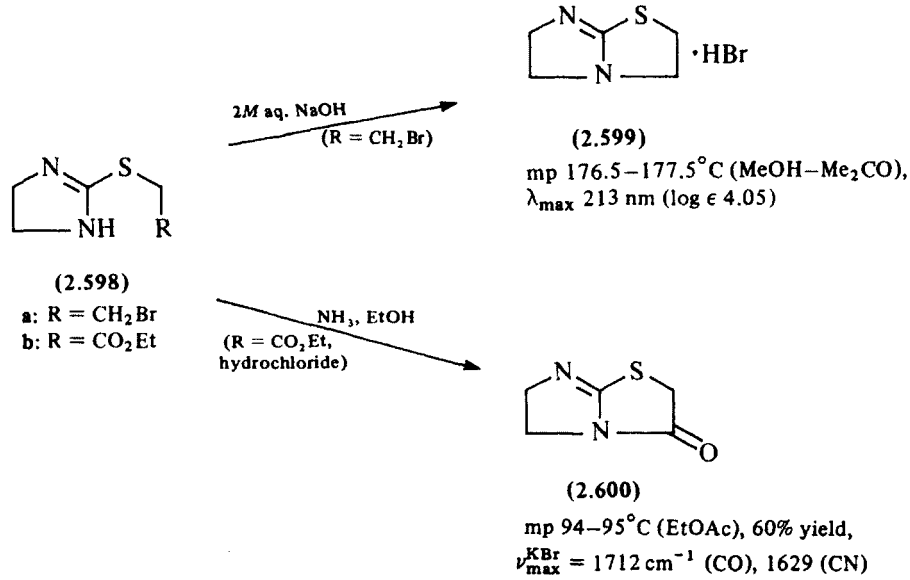


(2.596) (2.597)

a: R = H
b: R = Me

	R	R^1	mp (°C)	Yield (%)	UV λ_{max}^{MeOH} (log ϵ)
a	H	CO_2Et	140–142 (MeOH)	51	218 (3.93) 310 (3.12)
b	Me	CO_2Me	130–133 (MeOH)	70	215 (3.07) 315 (3.39)

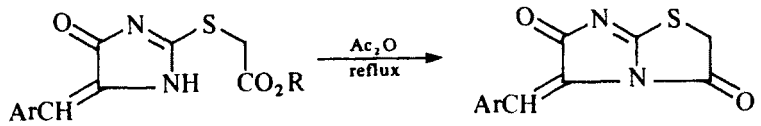
Reactions of the 2-mercaptoimidazoline derivatives described above probably proceed by initial electrophilic attack at sulfur, and such intermediates can be isolated and cyclized to 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles in separate transformations (see, e.g., **2.598a** → **2.599**,[434] **2.598b** → **2.600**,[435] and **2.601** → **2.602**[436]).



(2.599)
mp 176.5–177.5°C (MeOH–Me_2CO), λ_{max} 213 nm (log ϵ 4.05)

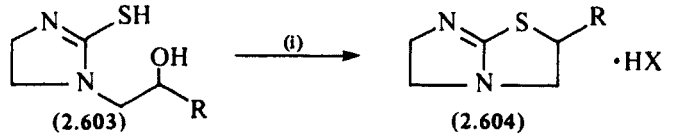
(2.598)
a: R = CH_2Br
b: R = CO_2Et

(2.600)
mp 94–95°C (EtOAc), 60% yield, ν_{max}^{KBr} = 1712 cm^{-1} (CO), 1629 (CN)



(2.601) (2.602)

Ar	mp (°C) (EtOH)	Yield (%)
Ph	152	85
C_6H_4OMe-*p*	183	78
C_6H_4Cl-*o*	141	82
$C_6H_4NO_2$-*m*	205	80



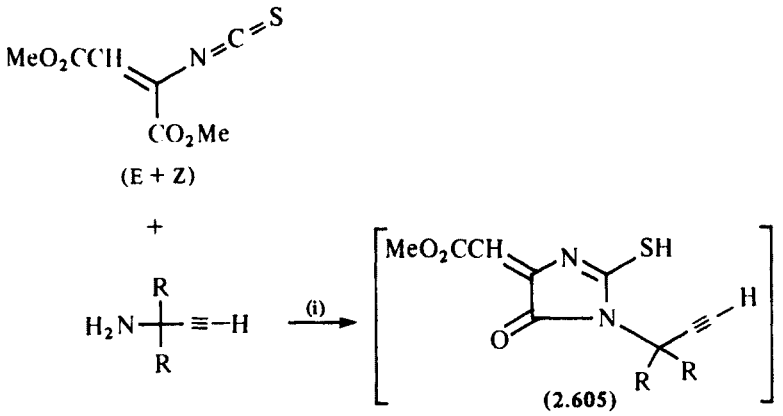
(2.603)

a: R = H
b: R = aryl, hetaryl

(2.604)

	R	X	mp (°C)	Yield (%)
a	H	Cl	185–186	90
b	H	Br	182–183	85
c	Ph			

(i) 6*M* HCl, reflux (R = H); 2*M* HBr, reflux (R = H); conc. HCl, reflux (R = aryl, hetaryl)



(E + Z)

(2.605)

(i) PrOH, reflux

(2.606)

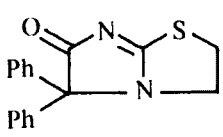
	R	mp (°C)	Yield (%)
a	Me	132	32
b	Et	192–193	21

Scheme 2.56

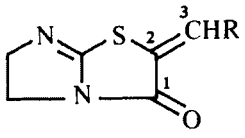
A less common synthetic route to 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles involves the cyclization of 1-[2-hydroxyethyl]-2-mercaptoimidazoline (**2.603a**)[437] and related compounds (cf. **2.603b**)[438] under acidic conditions. This approach has been used to prepare the parent compound in the series (**2.604a**, free base bp 70°C/0.15 torr, mp 27–29°C)[437] as well as an analog (**2.604c**) of tetramisole[438] (cf. Section 2.17.4.1); resolution of the 2-phenyl derivative (**2.640c**) can be effected[438] by using di-4-toluyl-D-tartaric acid to give the (–) and (+) analogs of levamisole and dexamisole, respectively. Finally, the cyclization process illustrated in Scheme 2.56 provides a more complex example in this group in which the highly functionalized 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles (**2.606a,b**) are formed through intermediate thiohydantoins.[439]

2.17.4.4. Physicochemical Studies

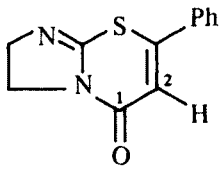
The structure of the minor product (**2.607**) from the reaction of 5,5-diphenyl-2-thiohydantoin and 1,2-dibromoethane has been elucidated X-ray crystallographically,[408] and details of the ^{13}C nmr spectra of compounds **2.608a** and **b** are available (see appended data in Scheme 2.57).[432] It may be noted that the magnitudes of coupling of the lactam carbonyl (C-1) with H on C-3 (ca. 6.3 Hz) serve to differentiate structure **2.608b** from the isomer **2.609** (< 1 Hz for coupling of C-1 to H on C-2).[432]



(2.607)



(2.608)



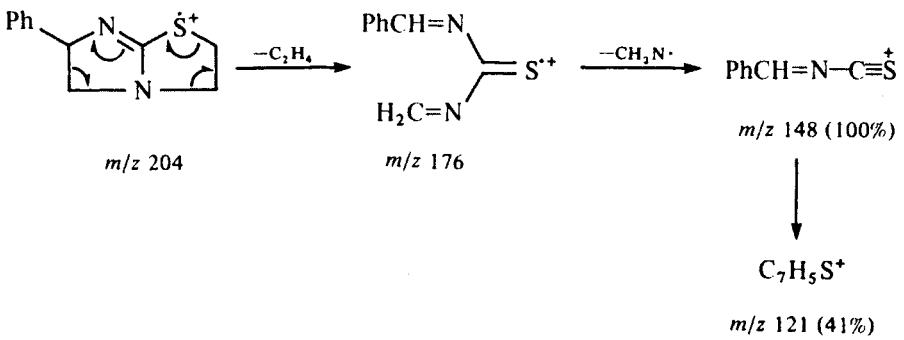
(2.609)

		δ (ppm)		
	R	C_1	C_2	C_3
a	CO_2Me	155.6	146.5	113.6
b	Ph	157.2	125.9	128.2–127.9

Scheme 2.57

The mass spectrum of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole (tetramisole) contains major fragment ions at *m/z* 204, 176, 148, and 121 (see Scheme 2.58).[440] An interesting feature in the proposed[440] fragmentation pattern is formation of the ion at *m/z* 121 (probably $PhC^{+} = S$), which may arise from a phenyl migration within the ion at *m/z* 148 prior to fission.

The kinetics of dehydration of 3-(*p*-chlorophenyl)-2-ethyl-2,3,5,6-tetrahydro-3-hydroxyimidazo[2,1-*b*]thiazole have been shown to be first order in solution, and the influence of temperature and ionic strength on this process have been ascertained.[441]

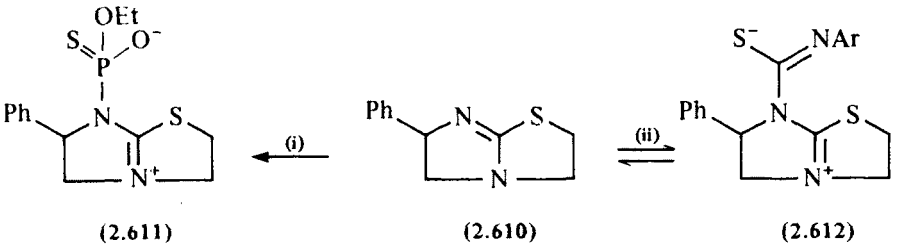


Scheme 2.58

2.17.4.5. Reactions

2.17.4.5.1. REACTIONS WITH ELECTROPHILES

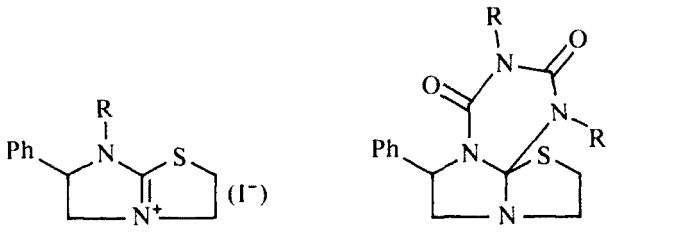
Examples of the formation of betaines by electrophilic attack at N-7 of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole are illustrated in transformations **2.610** → **2.611**[384] and **2.610** → **2.612**.[462] The betaine (**2.612a**) evidently exists in solution as an equilibrium mixture with the starting material (**2.610**) since alkylation with methyl iodide results in formation of a mixture of imidazo[2,1-*b*]-thiazolium salts (**2.613a,b**). 4-Methyl phenylsulfonyl isothiocyanate behaves in similar fashion in this reaction (cf. **2.610** → **2.612**), but aryl- and alkyl isocyanates form spiro[1,3,5]triazine-2,5-dione derivatives (**2.614**) as diastereoisomeric mixtures.[442]



(2.611) (2.610) (2.612)

(i) $(EtO)_2P(S)Cl$, Me_2CO, 50°C;
(ii) ArNCS, MeCN

a: Ar = Ph, 98% yield, mp 86–87°C



(2.613) (2.614)

a: R = C(SMe) = NPh
b: R = Me

e.g., R = Ph, 82% yield, mp 178–180°C

The C-2 position of 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-ones is activated toward electrophilic attack, as exemplified by the formation of a number of arylidene derivatives (see **2.615** → **2.616** and examples collected in Table 2.77). Compounds of this type (**2.616**) can be synthesized by treating the oxo derivative (**2.615**) with the appropriate aldehyde under mildly basic conditions,[435,436] but they can also be prepared directly from 2-mercaptoimidazoline, ethyl chloroacetate, and the aldehyde in a single-step procedure.[422] Other electrophiles used for C-2 attack in this manner include nitrosoarenes[444] and arene diazonium compounds,[445] and the formation of bisarylidenes (**2.618**) from related electrophilic reactions at C-6 is reported (see Table 2.78).[446]

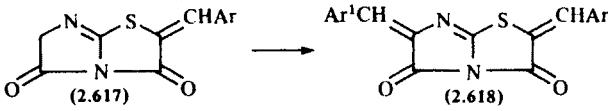
TABLE 2.77. SYNTHESIS OF ARYLIDENE DERIVATIVES (2.616) FROM 2,3,5,6-TETRAHYDROIMIDAZO[2,1-*b*]THIAZOL-3-ONES (2.615)

(2.615) (2.616)

Substituents in 2.616						
Ar	5-Substituent	6-Substituent	Preparative Method	Yield (%)	mp (°C)	Reference
Ph	H	H	A	17	179–180	435
Ph	H	H	A	26	180	421
$C_6H_4NO_2$-*p*	H	H	A	65	268	421
$C_6H_4NMe_2$-*p*	H	H	A	51	270	421
$C_6H_4N(CH_2CH_2SO_3Me)_2$	H	H	A	55	180	421
C_6H_4Cl-*p*	H	H	B	38	228	422
C_6H_4OH-*o*	H	H	B	25	235–236	422
C_6H_4OH-*p*	H	H	B	30	158	422
$C_6H_4NO_2$-*m*	H	H	B	35	233	422
C_6H_4OMe-*p*	H	H	B	20	185	422
C_6H_3(OH) (OMe)-3,4	H	H	B	40	247	422
2-Furyl	H	H	B	35	173–175	422
1-(2-Hydroxynaphthyl)	H	H	B	31	275 (dec.)	422
Ph	=CHPh	=O	C	70	179	436
Ph	$=CHC_6H_4Cl$-*p*	=O	C	60	240	436

[a]Preparative methods: (A) **2.615**, PhCHO, piperidine, EtOH, reflux; (B) 2-mercaptoimidazoline, ethyl chloroacetate, ArCHO, reflux (cf. ref. 443); (C) **2.615** analog, PhCHO, NaAc, AcOH, reflux.

TABLE 2.78. SYNTHESIS[a] OF 2,6-BISARYLIDENE-2,3,5,6-TETRAHYDROIMIDAZO-[2,1-*b*]THIAZOL-3,5-DIONES (**2.618**) FROM MONO ARYLIDENE DERIVATIVES (**2.617**)[446]

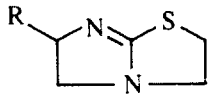


(2.617) (2.618)

Substituents in **2.618**			
Ar	Ar'	Yield (%)	mp (°C)
Ph	Ph	72	242
Ph	C_6H_4OH-*m*	68	258
C_6H_4OH-*m*	C_6H_4OH-*m*	67	263
C_6H_4OH-*m*	Ph	63	254
C_6H_4OH-*m*	$C_6H_4NMe_2$-*p*	69	231
$C_6H_4NMe_2$-*p*	Ph	70	273

[a]Reaction conditions: **2.617**, Ar^1CHO, piperidine, 160°C, 4 h.

Miscellaneous reactions of 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles with electrophiles include transformation of the 6-phenyl derivative (nitrate) in concentrated sulfuric acid into a 6-(*p*-nitrophenyl) derivative (mp 203.5–206°C, 60% yield[373]) and the routine acylation and alkylation of 6-(aminophenyl) derivatives to provide compounds (**2.619a–e**) of interest as anthelmintic agents.

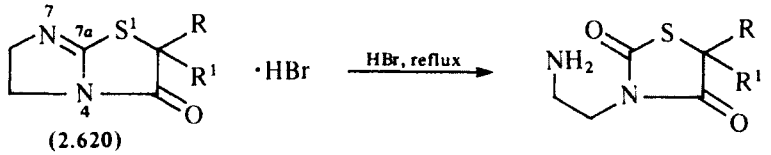


(2.619)

a: R = C_6H_4NHCOR-*p* (R = unsubstituted cycloalkenyl)[385]
b: R = C_6H_4NHCOR-*m* (R = substituted pyridyl)[447]
c: R = C_6H_4NHCOR-*m* (R = substituted pyrazolyl)[448]
d: R = C_6H_4NHCOR-*m* (R = substituted isothiazolyl)[449,450]
e: R = $C_6H_3(R^2)NRR^1$ (R = *i*-Pr, *i*-PrCO, CO_2Me, H, Ac, Me; R^1 = H, Me, CHO; R^2 = Br)[451]

2.17.4.5.2. REACTIONS WITH NUCLEOPHILES

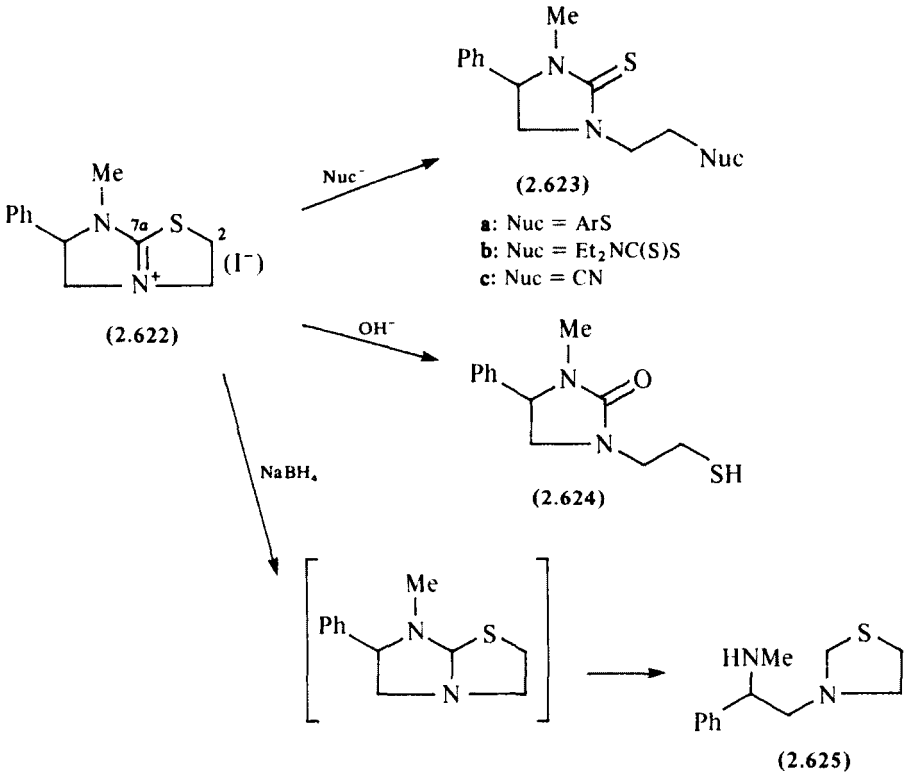
Quaternary salts derived from 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles (**2.620**, **2.622**) behave as ambident electrophiles, and ring fission can occur by nucleophilic attack at C-7*a* or C-2. For example, hydrolysis of **2.620** under acidic conditions gives rise to thiazolidin-2,4-dione derivatives (**2.621**) of interest as anti-



(2.620) (2.621)

R, R^1 = e.g., alkyl, aryl

convulsants and antidepressants,[452] and a thiazolidine derivative (**2.625**) is also formed by attack of hydride ion at C-7*a* of the salt **2.622**.[453] In contrast, attack of hydroxide ion at C-7*a* of the latter is followed by fission of the thiazolidine ring (cf. **2.622** → **2.624**), and attack by sulfur-centered nucleophiles and cyanide occurs at C-2 (see **2.622** → **2.623a–c**). A possible[453] rationale is as follows: if nucleophilic addition at C-7*a* is irreversible (e.g., H^-), or if a secondary reaction can occur (e.g., for OH^-), the observed products result from this mode of attack, but if addition at

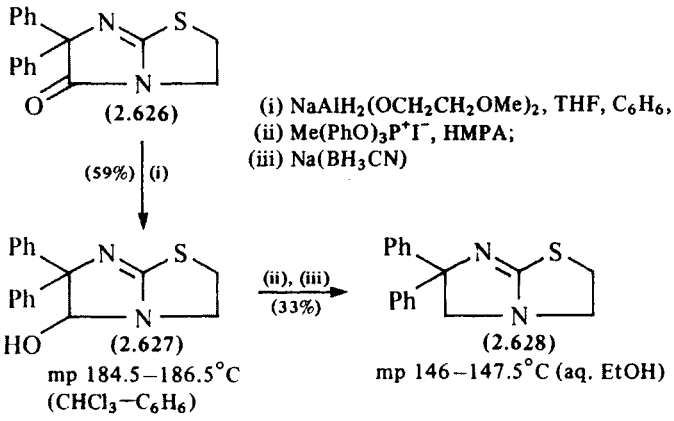


C-7*a* is reversible and there is no possible secondary reaction pathway, then a product of thermodynamic control from C-2 ensues.

Nucleophilic addition of ethyl magnesium bromide to the ester (**2.590a**) to provide the tertiary alcohol (**2.590b**) has been described in Section 2.17.4.2.[408]

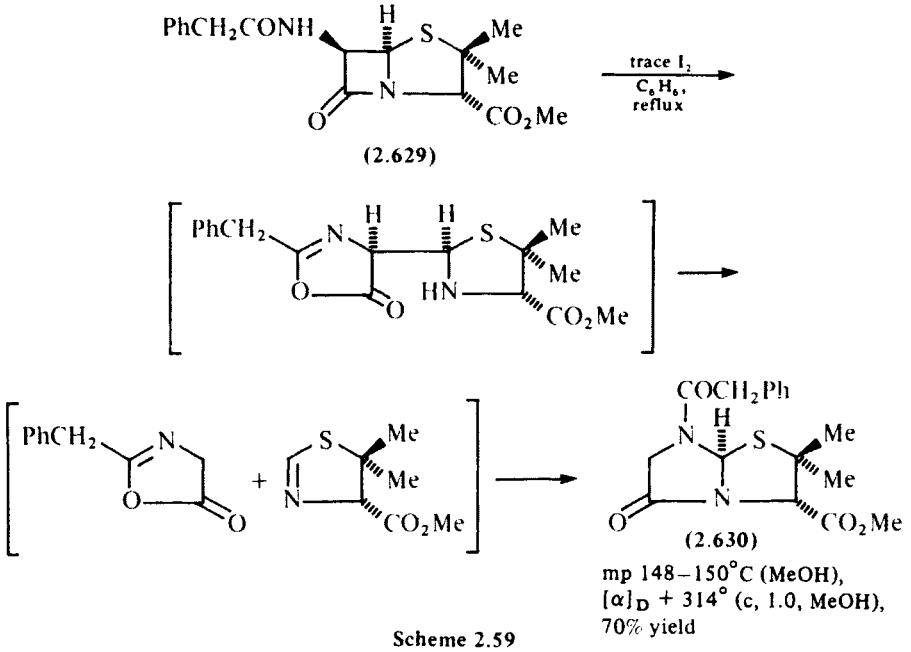
2.17.4.5.3. REDUCTION

Partial reduction of the 5-oxo substituent of **2.626** can be effected by REDAL, and the ensuing 5-hydroxy derivative (**2.627**) can be further reduced, by way of an iodo derivative, with sodium cyanoborohydride (see **2.627** → **2.628**).[415] 2,3,5,6-Tetrahydro-6-(*p*-nitrophenyl)imidazo[2,1-*b*]thiazole can be hydrogenated to the 6-(*p*-aminophenyl) derivative (mp 245–250°C, 42% yield) by 10% palladium on charcoal in *iso*-propanol–methanol containing hydrogen chloride.[373]



2.17.5. 2,3,5,6,7,7*a*-Hexahydroimidazo[2,1-*b*]thiazoles

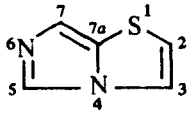
Only one compound in this group has been described during the literature period covered. The transformation of methyl benzyl pencillinate (**2.629**) into methyl benzyl penillonate (**2.630**) can be achieved either thermally or by heating the former with a trace of iodine in toluene.[454] More recently the iodine-promoted process has been reexamined,[455] the structure of the single-product stereoisomer (**2.630**) has been definitively formulated by X-ray diffraction,[456] and a mechanism for its formation postulated (see Scheme 2.59).[455]



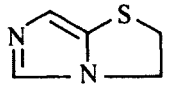
Scheme 2.59

2.18. RING SYSTEM C_3N_2–C_3NS: IMIDAZO[5,1-*b*]THIAZOLE

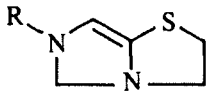
The imidazo[5,1-*b*]thiazole ring system (**2.631**) is less widely studied than the imidazo[2,1-*b*]thiazole nucleus described in Section 2.17. Compounds in the fully unsaturated system have been described in addition to those in the 2,3-dihydro-(**2.632**), 2,3,5,6-tetrahydro-(**2.633**), 2,3,7,7*a*-tetrahydro-(**2.634**), and 2,3,5,6,7,7*a*-hexahydro forms (**2.635**); compounds in the last two categories were among the earliest reported examples in this ring system and are formed by the acid-promoted rearrangement of certain penicillin derivatives (see Sections 2.18.4 and 2.18.5).



(2.631)

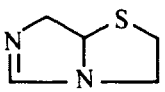


(2.632)

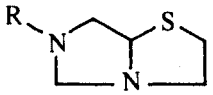


(2.633)

R = e.g., H, alkyl



(2.634)



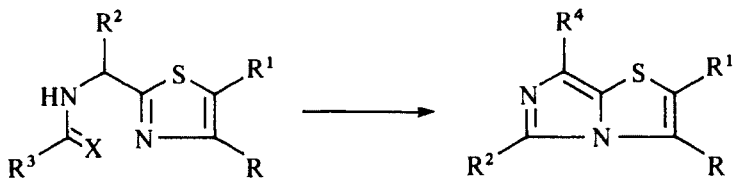
(2.635)

R = e.g., H, alkyl

2.18.1. Imidazo[5,1-*b*]thiazoles

2.18.1.1. Synthesis from Thiazoles

A series of substituted imidazo[5,1-*b*]thiazoles (**2.637**; R^2 = Me or Ph) has been prepared[457] in excellent yield by the phosphorus oxychloride-induced cyclization of 2-(benzoylamino)methyl- and 2-(acylamino)methylthiazoles (cf. **2.636a** and Table 2.79), and 5-mercapto derivatives (**2.637**; R^2 = SH) have been synthesised[458] in a closely related procedure from thiazolylmethyl-substituted thioureas (cf. **2.636b** and Table 2.79). The uv spectrum of the mercapto derivative (**2.637**; R = R^1 = H; R^4 = *p*-$MeOC_6H_4$; R^2 = SH) exhibits absorption maxima at approximately 240 and 335 nm.[458]



(2.636) (2.637)

a: R^3 = Me or Ph; R^2 = H; X = O
b: R^3 = NHC_6H_4OEt-*p*; R = R^1 = H; X = S

TABLE 2.79. SYNTHESIS OF IMIDAZO[5,1-*b*]THIAZOLES (2.637) FROM THIAZOLES (2.636)

Type of Starting Material Used	Reaction Conditions[a]	Substituents in Products 2.637				Yield (%)	mp (°C)	Decomposition of Picrate (°C)	Reference
		R	R^1	R^3	R^4				
2.636a	A	H	Ph	Ph	H	85	147	187	457
2.636a	A	Ph	Ph	Ph	H	85	210	220	457
2.636a	A	Me	Me	Ph	H	81	103	166	457
2.636a	A	H	Me	Ph	H	82	106	212	457
2.636a	A	CO_2Et	Me	Ph	H	81	136	184	457
2.636a	A	H	Ph	Me	H	74	107	198	457
2.636a	A	Ph	Ph	Me	H	72	119	200	457
2.636a	A	Ph	H	Ph	Ph	81	182		457
2.636a	A	Ph	Ph	Ph	Ph	79	183		457
2.636a	A	Me	H	Ph	Ph	83	157		457
2.636a	A	Me	Me	Ph	Ph	83	140		457
2.636a	A	Me	CO_2Et	Ph	Ph	64	181		457
2.636b	B	H	H	SH	3-Pyridyl	70	240–241		458
2.636b	B	H	H	SH	4-Pyridyl	72	273		458
2.636b	B	H	H	SH	*p*-$MeOC_6H_4$	61	224		458

[a]Reaction conditions: (A) $POCl_3$, C_6H_6, reflux; (B) reflux 5 min in dimethylformamide.

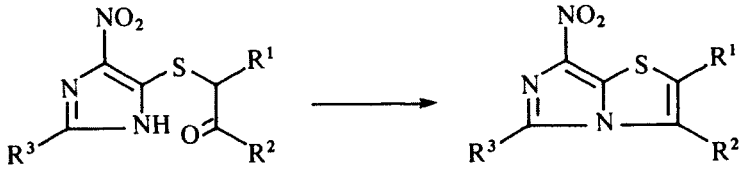
TABLE 2.80. SYNTHESIS OF IMIDAZO[5,1-*b*]THIAZOLES (**2.639**) FROM IMIDAZOLES (**2.638**)[459]

Substituents in **2.639**			Cyclization	Yield	
R^1	R^2	R^3	Method[a]	(%)	mp (°C) (Solvent for Recrystallization)
H	H	Me	A	55	311–312 (dec.) (EtOH, then AcOH)
H	H	Et	A	86	236–237 (dec.) (EtOH)
H	Me	Me	B	85	275–276 (dec.) (EtOH)
H	Me	Et	B	26	239–240 (dec.) (AcOH)
Me	Me	Me	C	93	237–239 (dec.) (EtOH)
Me	Me	Et	C	35	166.5–167 (40% aq. EtOH)

[a]Reaction conditions: (A) $POCl_3$, reflux, 5 h; (B) concentrated H_2SO_4, 30–42°C, 1 h; (C) Ac_2O, reflux.

2.18.1.2. Synthesis from Imidazoles

A series of 7-nitroimidazo[5,1-*b*]thiazoles (**2.639**) has been synthesized[459] by the dehydrative cyclization of 2-alkyl-4-nitro-5-(acylmethyl)mercaptoimidazoles (**2.638**) induced by phosphorus oxychloride, concentrated sulfuric acid, or acetic anhydride (see Table 2.80). Cyclizations of closely related imidazole derivatives have been used to prepare 2,3-dihydro derivatives in the imidazo[5,1-*b*]thiazole series (see Section 2.18.2).



(**2.638**) (**2.639**)

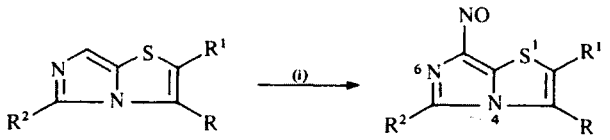
2.18.1.3. Reactions

Very little is known about the reactivity of imidazo[5,1-*b*]thiazoles. It appears that electrophilic nitrosation of 3,5-disubstituted- and 2,3,5-trisubstituted derivatives occurs at the 7-position to give a series of dark-green crystalline nitroso compounds (see **2.640** → **2.641** and Table 2.81).[457]

2.18.1.4. Biological Activity

The 5-mercaptoimidazo[5,1-*b*]thiazole derivatives (**2.637**; R = R^1 = H; R^2 = SH; R^4 = 3- and 4-pyridyl) exhibit weak bacteriostatic action with respect to tuberculosis mycobacteria.[460]

TABLE 2.81. SYNTHESIS OF 7-NITROSOMIDAZO[5,1-*b*]THIAZOLE DERIVATIVES (2.641) BY NITROSATION OF 2.640[457]



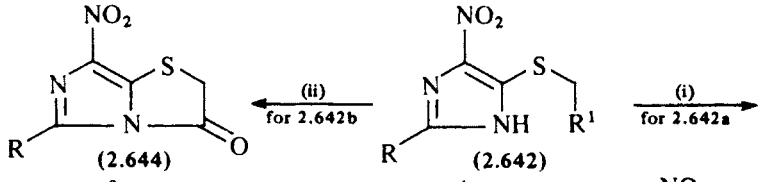
(2.640) (2.641)

(i) $NaNO_2$, AcOH, ice-cooling

Substituents in 2.641				
R	R^1	R^2	Yield (%)	mp (°C) (Dec.)
H	Ph	Ph	65	159
Ph	Ph	Ph	68	184
Me	Me	Ph	54	162
H	Me	Ph	66	166
H	Ph	Me	66	201

2.18.2. 2,3-Dihydroimidazo[5,1-*b*]thiazoles

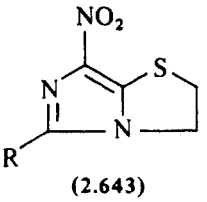
2,3-Dihydro derivatives in the imidazo[5,1-*b*]thiazole series (**2.643a,b** and **2.644a,b**) have been synthesized in moderate to high yield by the dehydrative cyclization of 5-(β-hydroxyethyl)mercapto- and 5-(carboxymethyl)mercapto-imidazoles (**2.642a,b**, respectively).[459] The presence of the 7-nitro group imparts low basic character to these compounds (**2.643**, **2.644**): they are soluble only in concentrated inorganic acids and do not form hydrochlorides, sulfates, or picrates.[459]



(2.644) (2.642)

	R	MP (°C)	Yield (%)
a,	Me	205–205.5 (dec.) (AcOH)	89
b,	Et	162–163 (dec.) (aq. EtOH)	82

a: $R^1 = CH_2OH$
b: $R^1 = CO_2H$



(2.643)

	R	MP (°C)	Yield (%)
a	Me	218–218.5 (EtOH)	64
b	Et	189–190 (EtOH)	42

(i) concentrated H_2SO_4, 30–40°C, 1 h; (ii) Ac_2O, reflux

TABLE 2.82. SYNTHESIS OF 2,3,5,6-TETRAHYDROIMIDAZO[5,1-*b*]THIAZOLE DERIVATIVES (**2.646a**) FROM IMIDAZOLONES (**2.645**)[461]

Ar in **2.646a**	Yield (%)	mp (°C) (EtOH)
Ph	60	257
p-MeC_6H_4	65	218
p-ClC_6H_4	60	160
p-$O_2NC_6H_4$	65	284
o-MeC_6H_4	62	184
m-MeC_6H_4	60	148

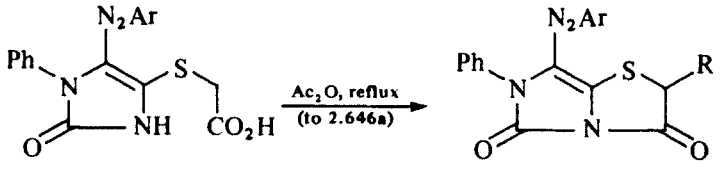
2.18.3. 2,3,5,6-Tetrahydroimidazo[5,1-*b*]thiazoles

A dehydrative cyclization of the type described in the preceding section (cf. **2.642b** → **2.644a,b**)[459] has been used to prepare a series of 3,5-dione derivatives in the 2,3,5,6-tetrahydroimidazo[5,1-*b*]thiazole series (see **2.645** → **2.646a** and Table 2.82).[461] The active methylene group of **2.646a** exhibits the anticipated reactivity pattern with electrophilic reagents as illustrated in reactions with arene diazonium salts, with formaldehyde and primary amines, and with aromatic aldehydes (see conversion of **2.646a** into **2.646b**, **2.646c**, and **2.647**, respectively, and also Table 2.83).[461]

TABLE 2.83. 2,3,5,6-TETRAHYDROIMIDAZO[5,1-*b*]THIAZOLES (**2.646b,c**) PREPARED BY REACTIONS OF **2.646a** WITH ELECTROPHILIC REAGENTS[461]

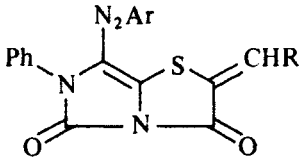
Substituents in **2.646b,c**		Reaction Conditions[a]	Yield (%)	mp (°C)
R	Ar			
N_2Ph	Ph	A	80	267
$N_2C_6H_4Me$-*p*	C_6H_4Me-*p*	A	80	262
$N_2C_6H_4Cl$-*p*	Ph	A	82	311
$N_2C_6H_4NO_2$-*o*	Ph	A	80	171
$N_2C_6H_4Me$-*o*	Ph	A	85	229
$N_2C_6H_4Me$-*p*	Ph	A	80	232
N_2Ph	C_6H_4Me-*p*	A	82	178
$N_2C_6H_4Cl$-*p*	C_6H_4Me-*p*	A	82	205
$N_2C_6H_4NO_2$-*o*	C_6H_4Me-*p*	A	80	227
$N_2C_6H_4Me$-*o*	C_6H_4Me-*p*	A	80	247
CH_2NHPh	Ph	B	72	210
$CH_2NHC_6H_4Me$-*p*	C_6H_4Me-*p*	B	73	223
$CH_2NHC_6H_4Cl$-*p*	Ph	B	76	216
$CH_2NHC_6H_4Me$-*p*	Ph	B	75	235
CH_2NHPh	C_6H_4Me-*p*	B	75	168
$CH_2NHC_6H_4Cl$-*p*	C_6H_4Me-*p*	B	80	230

[a]Reaction conditions: (A) **2.646a**, $Ar^1N_2^+Cl^-$, aqueous EtOH, ice cooling; (B) **2.646a**, 30% aqueous CH_2O, R^1NH_2, EtOH, heat.



(2.645) (2.646)

a: R = H
b: R = N_2Ar^1
c: R = CH_2NHR^1

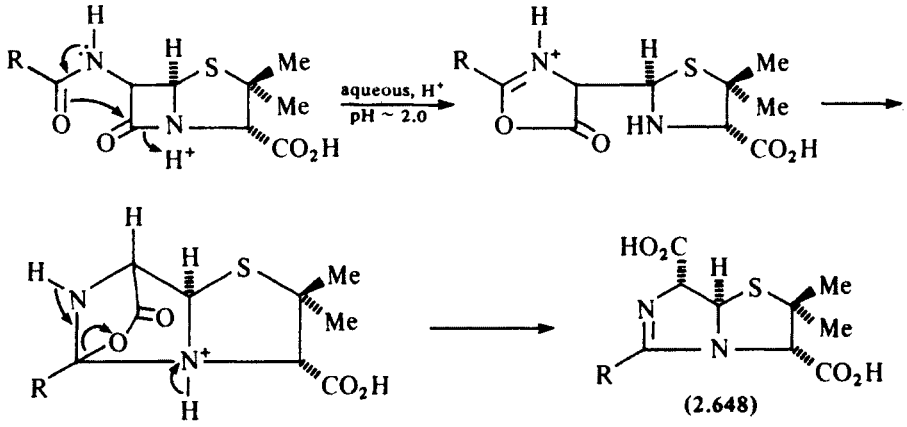


(2.647)

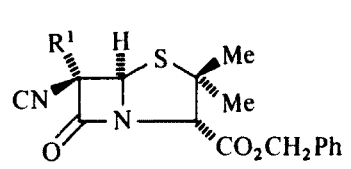
Ar	R	mp (°C)	Yield (%)
Ph	Ph	239	75
p-MeC_6H_4	Ph	188	70
p-MeC_6H_4	*p*-MeC_6H_4	183	70

2.18.4. 2,3,7,7*a*-Tetrahydroimidazo[5,1-*b*]thiazoles

3,7-Dicarboxylic acid derivatives in the 2,3,7,7*a*-tetrahydroimidazo[5,1-*b*]-thiazole group were the first examples of compounds in this ring system. They arise from mild acid hydrolysis (e.g., in aqueous solution at ambient temperature and pH of about 2.0) of penicillins and are commonly referred to as *penillic acids* (cf. **2.648**). The mechanism of this type of process is outlined in Scheme 2.60,[462] and the early literature has been summarized by Mosby.[463]

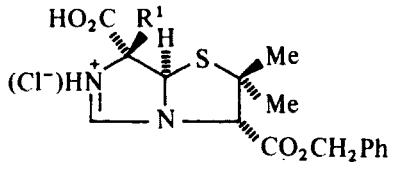


Scheme 2.60



(2.649)

(i) 5*M* aqueous HCl, 0–5°C, 4 h

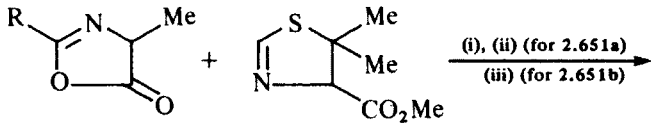


(2.650)

	R^1	MP (°C)	Yield (%)
a	CH_2Ph	156–159	70
b	$(CH_2)_2CO_2CH_2Ph$	155–156	46
c	$C(OH)Me_2$	146–148	55

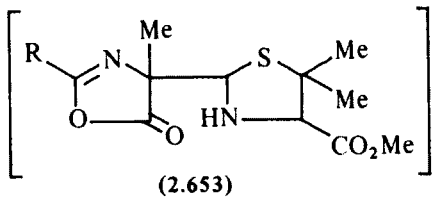
Additional examples of the process are illustrated by the formation of **2.648** (R = CH_2OPh) (mp 182–183°C[464]) and rearrangement of the 6-isocyanopenicillanates (**2.649**) into the penillic acid hydrochloride derivatives (**2.650a–c**).[465]

Compounds closely related to the penillic acids but bearing an additional methyl substituent at C-7 have been prepared as outlined in Scheme 2.61;[466,467] it may be noted that the intermediates in this process (cf. **2.651** + **2.652** → **2.653**) are homologs of the primary intermediate in the mechanism proposed[462] for the penillic acid rearrangement (cf. Scheme 2.60). The intermediate (**2.653a**) has been isolated and characterized,[466] but the phenyloxazolone (**2.651b**) is transformed directly into the penillic acid analog (**2.654b**) under the reaction conditions employed.[467] The carboxylic acid function of **2.654b** is esterified routinely by diazomethane to give a dimethoxycarbonyl derivative [**2.654**; R = Ph; CO_2Me for CO_2H, mp 115°C (Et_2O–hexane)].[467]



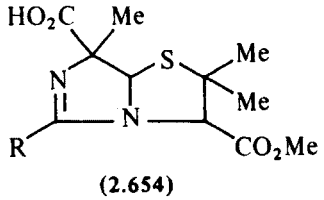
(2.651) (2.652)

a: R = CH_2Ph
b: R = Ph



(2.653)

a: R = CH_2Ph
b: R = Ph



(2.654)

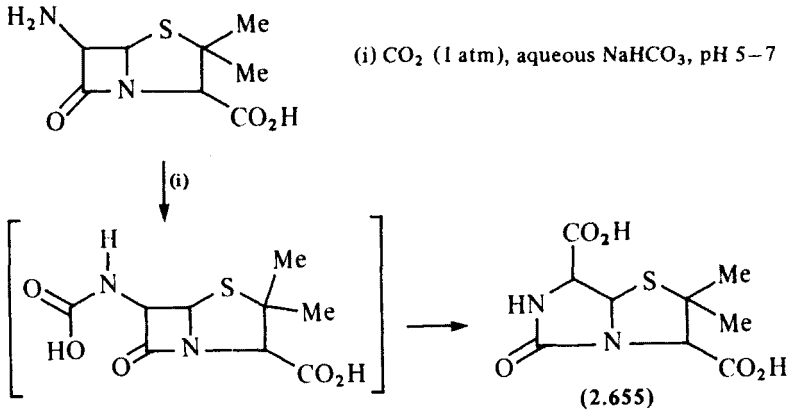
	R	mp (°C)	Yield (%)
a	CH_2Ph	197–199	45
b	Ph	216	98

(i) Pyridine, room temperature, 24 h;
(ii) C_6H_6, reflux, 24 h;
(iii) C_6H_6, reflux, 8 h

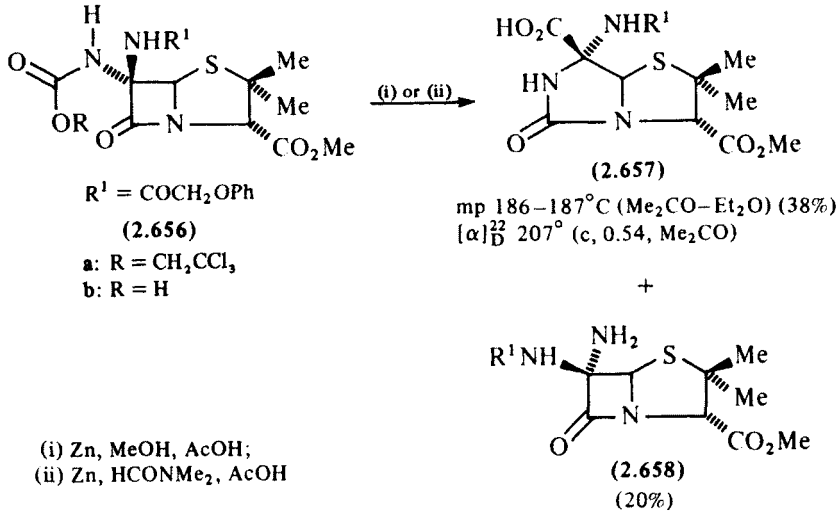
Scheme 2.61

2.18.5. 2,3,5,6,7,7*a*-Hexahydroimidazo[5,1-*b*]thiazoles

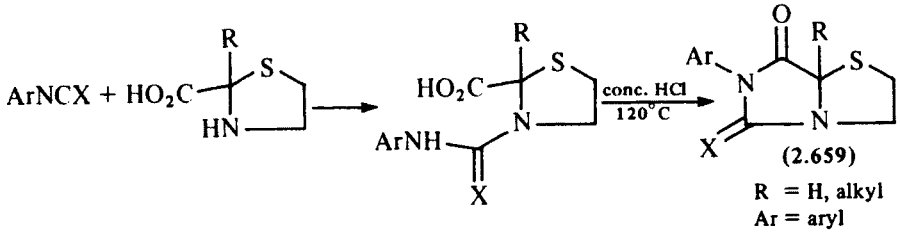
The 2,3,5,6,7,7*a*-hexahydro-2,2-dimethyl-5-oxoimidazo[5,1-*b*]thiazole derivative (**2.655**) has been isolated from aerated culture media of *P. crysogenum* by extraction with butyl acetate[468] and has also been synthesized from 6-aminopenicillanic acid and carbon dioxide in a penillic acid type of rearrangement (see Scheme 2.62,[469] and cf. Section 2.18.4). Compound **2.655** forms a disodium salt, mp 250–251°C (dec.), $[\alpha]_D^{25}$ +277° (c, 1.0, H_2O) and a dimethyl ester, mp 170–171°C, $[\alpha]_D^{25}$ + 238 (c, 1.0, MeOH).[469] A more elaborate product (**2.657**) of penillic acid rearrangement is formed together with the desired penicillanate (**2.658**) during deprotection of the 6,6-disubstituted penicillin derivative (**2.656**).[470] (See **2.656a** → **2.656b** → **2.657**).



Scheme 2.62



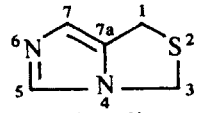
A more conventional synthesis of hexahydroimidazo[5,1-*b*]thiazoles from thiazolidines has provided compounds of interest as fungicides (see **2.659** in Scheme 2.63).[471]



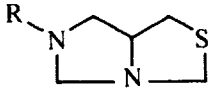
Scheme 2.63

2.19. RING SYSTEM C_3N_2–C_3NS: 1*H*,3*H*-IMIDAZO[1,5-*c*]THIAZOLE

Compounds in the unsaturated 1*H*,3*H*-imidazo[1,5-*c*]thiazole group (**2.660**) are not cited during the literature period covered, and this section is concerned solely with derivatives of the 5,6,7,7*a*-tetrahydro type (cf. **2.661**).



(2.660)



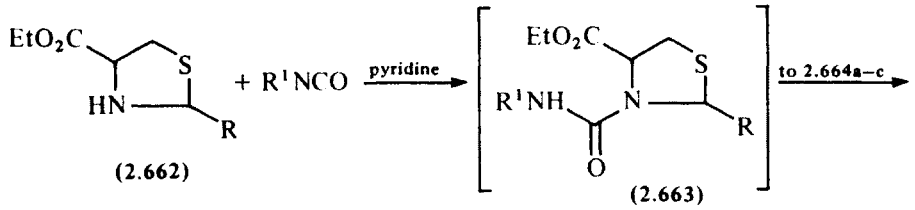
(2.661)

R = H, alkyl, aryl

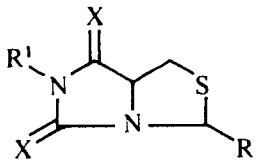
2.19.1. 5,6,7,7*a*-Tetrahydro-1*H*,3*H*-imidazo[1,5-*c*]thiazoles

2.19.1.1. Synthesis from Thiazolidines

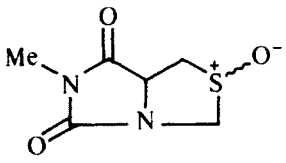
1*H*,3*H*-Imidazo[1,5-*c*]thiazole-5,7(6*H*,7*aH*) diones (**2.664a–c**) have been synthesized by treatment of the ethyl ester of L-thiazolidine-4-carboxylic acid (**2.662**) with methyl and phenyl isocyanate;[472] the intermediate *N*-carbamoyl derivative (**2.663**; R = H; R^1 = Me) is isolated from the first type of reaction and can be transformed into the bicyclic product by ethanolic potassium hydroxide.[472] The dione derivatives (**2.664a–c**) can be reduced ($LiAlX_4$, X = H or D) to give fully saturated compounds (**2.664d–g**)[472] and can also be oxidized (viz., for **2.664c**) by sodium metaperiodate in aqueous methanol to give an isomeric mixture (*cis:trans* = 7.3) of bicyclic sulfoxides (**2.665**).[473] The pure *cis* isomer (mp 125–127°C) can be obtained by crystallization of the product from chloroform-hexane, and trituration of the mother liquor with benzene gives a mixture that contains predominantly the *trans* compound.[473]



(2.662) (2.663)



(2.664)

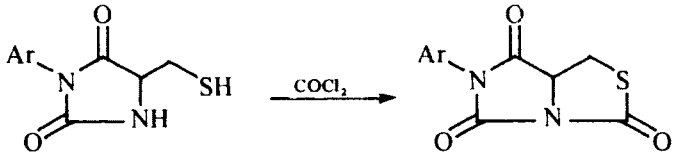


(2.665)

	X	R	R^1	mp (°C) or bp (°C/torr)
a	O	H	Ph	149–150
b	O	Me	Ph	136–137
c	O	H	Me	50–51
d	H, H	H	Ph	118
e	H, H	Me	Ph	230 (dec.)
f	D, D	H	Ph	117
g	H, H	H	Me	74–76/3.5

2.19.1.2. Synthesis from Imidazolidin-2,4-diones

Treatment of the 3-arylimidazolidin-2,4-diones (**2.666**) with phosgene gives a series of 6-aryl-1*H*,3*H*-imidazo[1,5-*c*]thiazole-3,5,7(6*H*,7*aH*) triones (**2.667**) of interest as fungicides.[474]

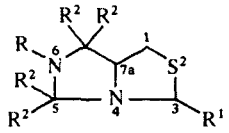


(2.666) (2.667)
Ar = aryl

2.19.1.3. Synthesis from Penicillins

The bicyclic sulfoxide (**2.669**) has been isolated in trace quantitites from treatment of benzyl penicillin sulfoxide trichloroethylester (**2.668**) with *t*-butyl hypochlorite.[475] The former product (**2.669**) probably arises from a process including fission of the 5,6-bond of **2.668**.

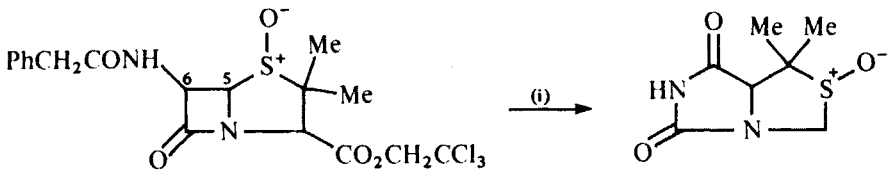
TABLE 2.84. ^{1}H NMR SPECTRA OF PERHYDROIMIDAZO[1,5-*c*]THIAZOLES (**2.670**)[472]



(2.670)

Substituents in **2.670**				Chemical Shifts and Coupling Constants[a]											
R	R^1	R^2	Solvent	H_3	$H_{3'}$	$J_{3,3'}$	H_5	$H_{5'}$	$J_{5,5'}$	H_1	$H_{1'}$	$J_{1,1'}$	H_{7a}	$J_{7a,1}$	$J_{7a,1'}$
Ph	H	H	C_6H_6	4.09	3.76	−10.0	4.09	3.75	−3.7	2.67	2.28	−10.0	–	7.5	6.5
			$CDCl_3$	4.37	4.14	−9.8	4.38	4.01	−3.8	3.06	2.72	−10.4	–	7.8	6.6
Ph	H	D	C_6H_6	4.11	3.78	−9.9	–	–	–	2.72	2.32	−10.2	3.34	7.9	6.9
Ph	Me	H	$CDCl_3$	–	4.59	–	4.41	4.02	−4.1	3.28	2.80	−10.7	–	8.1	6.9
Me	H	H	$CDCl_3$	4.31	4.13	−10.1	3.68	3.56	−3.8	3.02	2.67	−10.2	–	7.6	6.6

[a]Chemical shifts are δ values (ppm from tetramethylsilane as internal standard), and coupling constants are in hertz.



(2.668) (2.669)

(trace)

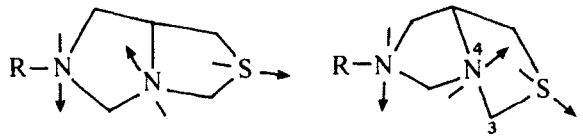
mp 213–215°C (dec.)

(i) *t*-BuOCl (3 equiv.), sodium borate, MeOH, 25°C

2.19.1.4. Nuclear Magnetic Resonance Studies

The ^{1}H nmr spectra of perhydroimidazo[1,5-*c*]thiazoles (**2.670**) have been analyzed in detail (see Table 2.84).[472] By evaluation of the geminal coupling constants $J_{3,3'}$ and $J_{5,5'}$ (ca. − 10.0 Hz and ca. − 3.7 Hz, respectively) and comparison of the latter value with those of related molecules,[476] it has been concluded that compounds of this type (**2.670**) exist preferentially in conformation (**2.671**). It may be noted that in this conformation, and in contrast to an alternative arrangement with the N-4–C-3 bond pseudoaxial (**2.672**), the unfavorable dipolar forces between the bridgehead nitrogen and sulfur are avoided.

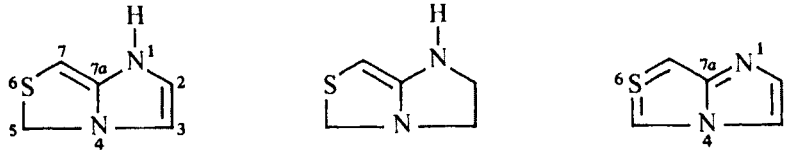
The stereochemistry (*cis* and *trans*) and solution conformational behavior of the sulfoxide derivatives (cf. **2.665**) have also been adduced from ^{1}H nmr spectral data.[473]



(2.671) (2.672)

2.20. RING SYSTEM C_3N_2–C_3NS: IMIDAZO[1,2-*c*]THIAZOLE

Compounds in the imidazo[1,2-*c*]thiazole category are not extensively cited, and there are no examples in the parent 1*H*,5*H*-imidazo[1,2-*c*]thiazole group (**2.673**) during the literature period covered. This section is concerned with 2,3-dihydro-1*H*,5*H*-imidazo[1,2-*c*]thiazoles (**2.674**) and with more recent derivatives in the imidazo[1,2-*c*]thiazole-6-*S* (IV) group (**2.675**).

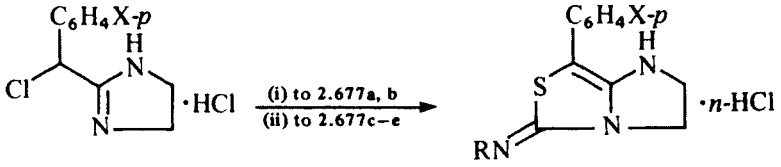


(2.673) (2.674) (2.675)

2.20.1. 2,3-Dihydro-1*H*,5*H*-imidazo[1,2-*c*]thiazoles

2.20.1.1. Synthesis from Imidazolines

7-Aryl-2,3-dihydro-5-imino-1*H*,5*H*-imidazo[1,2-*c*]thiazoles (**2.677a,b** and **c–e**) have been prepared by the cyclizative condensation of α-chlorobenzylimidazolines (**2.676**) with ammonium thiocyanate[477] and imidazolinethione,[478] respectively. Compounds of the former type (**2.677**) are of interest as hypotensive agents and as central nervous system stimulants.



(2.676) (2.677)

	R	X	n	mp (°C) [dec.]
a	H	H	1	224–227
b	H	Cl	1	230–232
c	$(CH_2)_2NH_2$	H	2	219–222
d	$(CH_2)_2NH_2$	Cl	2	225–228
e	$(CH_2)_2NH_2$	MeO	2	216–222

(i) NH_4SCN, MeOH, Me_2CO, reflux;
(ii) imidazolinethione, EtOH, reflux

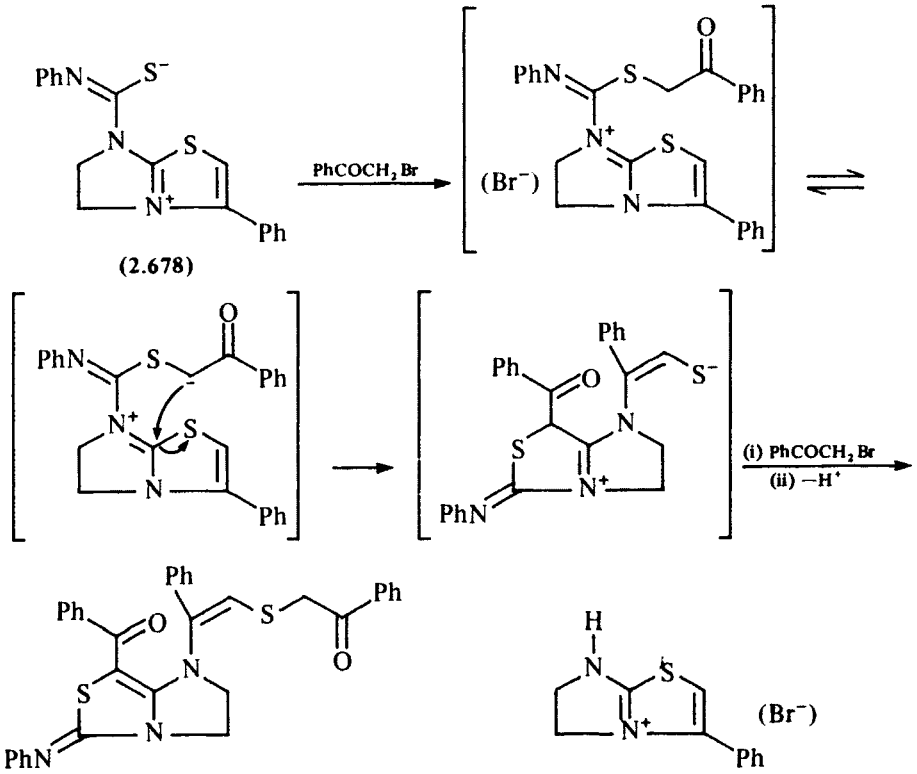
2.20.1.2. Synthesis from Imidazo[2,1-b]thiazoles

Methylation of the zwitterionic imidazo[2,1-*b*]thiazole derivative (**2.678**) by methyl iodide proceeds in anticipated fashion at the exocyclic sulfur, but a more complex reaction pathway has been observed during reaction with phenacyl bromide (see Scheme 2.64).[479] The major product (**2.679**) is formed together with the imidazo[2,1-*b*]thiazolium salt (**2.680**) in a mechanism assumed[479] to involve scission of the thiazole ring of the imidazo[2,1-*b*]thiazole system. The molecular structure of the bicyclic product (**2.679**) has been determined by X-ray crystallographic methods.[479]

2.20.2. Imidazo[1,2-*c*]thiazole-6-S(IV)

2.20.2.1. Synthesis

2,5,7-Triphenylimidazo[1,2-*c*]thiazole-6-S(IV) [**2.682**] has been obtained in good overall yield through the salt (**2.681**) in the manner outlined in Scheme 2.65.[480] The orange, crystalline tetravalent sulfur compound (**2.682**) can be recovered unchanged after heating under reflux in xylene for 6 h. It is characterized by the following spectral data: uv λ_{max}^{EtOH} = 487 nm (log ε 3.92), 310 (3.85), and 255 (4.04); ir 1585 cm^{-1}; and ^1H nmr ($CDCl_3$) δ = 6.80–8.50 (m).



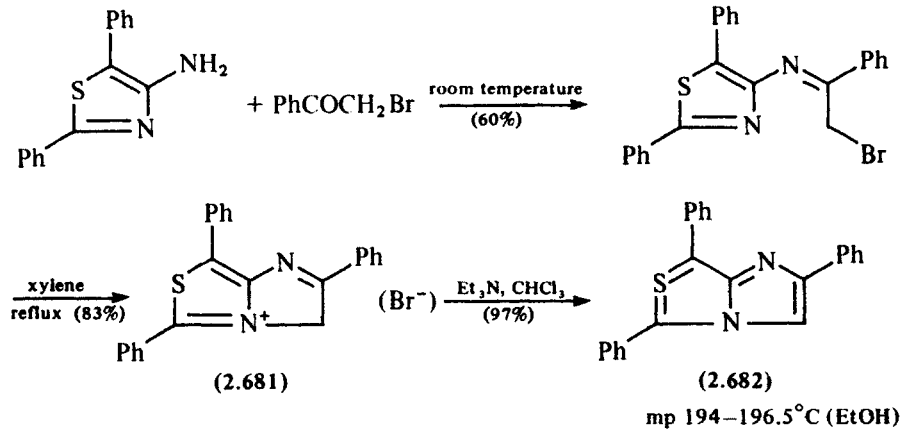
(2.678)

(2.679)

mp 197°C (Me_2CO),
40% yield,
ir ν_{max} = 3060, 1680 cm^{-1}

(2.680)

Scheme 2.64



(2.681)

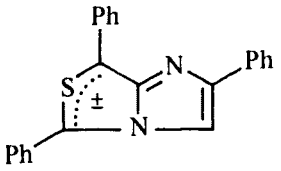
(2.682)

mp 194–196.5°C (EtOH)

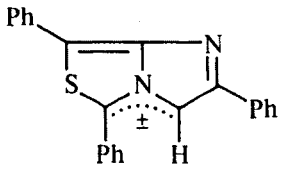
Scheme 2.65

2.20.2.2. Reactions

The imidazo[1,2-*c*]thiazole product (**2.682**) is capable of functioning as a thiocarbonyl ylide (cf. **2.682A**) and also as an azomethine ylide 1,3-dipole (cf. **2.682B**). In principle, two modes of 1,3-dipolar cycloaddition should exist, and the term "biperifunctional" has been proposed[480] to describe the reactivity of such



(**2.682A**)

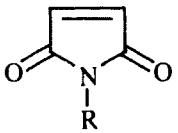


(**2.682B**)

unusual substrates. Such peripheral cycloaddition to the heterocycle (**2.682**) is demonstrated in reactions with *N*-(*p*-tolyl)maleimide (**2.683**) in which behavior in the azomethine ylide (see **2.682** → **2.684** + **2.685**) and thiocarbonyl ylide (see **2.682** → **2.686** + **2.687**) forms is manifested.[480] From a wider study[480] of the interconversion of (**2.684**–**2.687**) by retro-1,3-dipolar cycloaddition, it is apparent that the adducts are in thermal equilibrium. It has been concluded that the adduct (**2.684**) is the initial kinetically controlled product and that **2.687** is the ultimate product of thermodynamic control. The structures of adducts of the bicyclic compound (**2.682**) with other symmetrical dipolarophiles (e.g., dimethylmaleate and dimethylfumarate) have since been evaluated,[481] and the regiochemical outcome of reactions with unsymmetrical dipolarophiles has been determined.[482] [See Scheme 2.66 for an interesting example where the imidazo[1,2-*c*]thiazole (**2.682**) participates in a 1,3-dipolar cycloaddition regioselectively as depicted from canonical form **2.688**.]

(**2.682**)

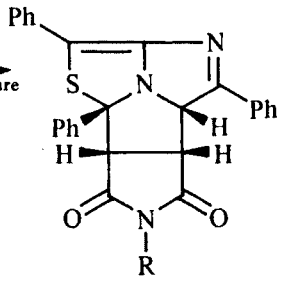
+



R = *p*-tolyl

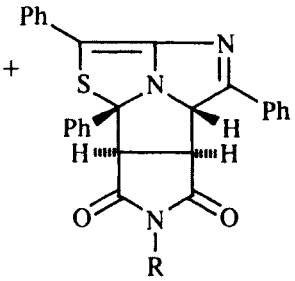
(**2.683**)

C_6H_6, room temperature

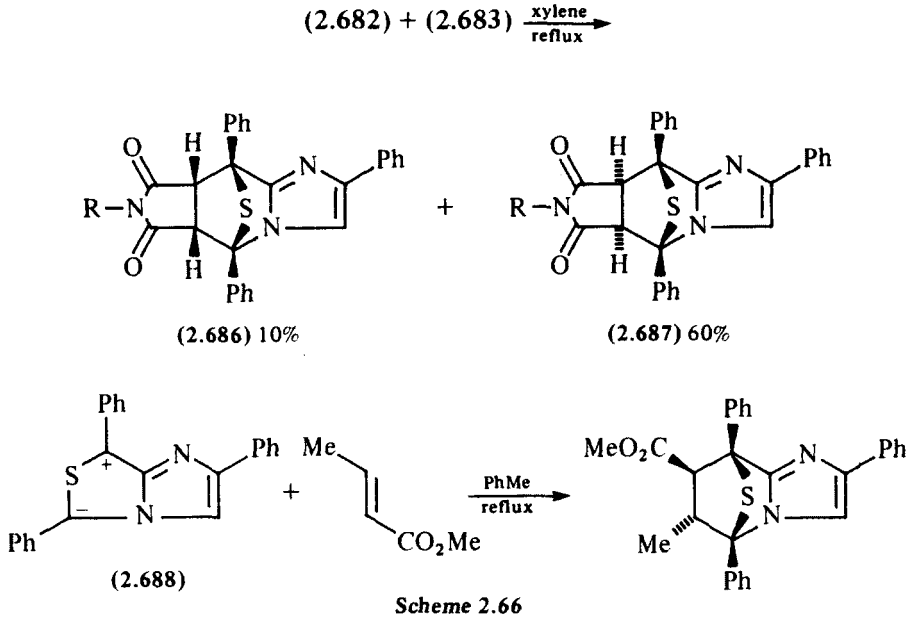


(**2.684**) 26%

+



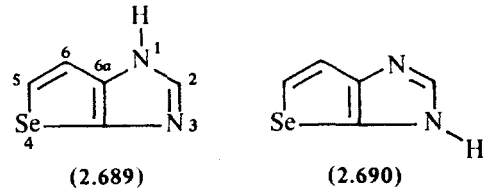
(**2.685**) 47%



Scheme 2.66

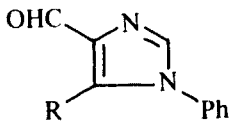
2.21. RING SYSTEM C_3N_2–C_4Se: SELENOLO[2,3-*d*]IMIDAZOLE

In principle, compounds in this group may belong to the 1*H*- (**2.689**) or 3*H*-selenolo[2,3-*d*]imidazole types (**2.690**); three compounds in the latter group have been characterized, but there are no examples of the former type during the literature period covered.



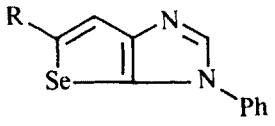
(**2.689**) (**2.690**)

The 3-phenyl-3*H*-selenolo[2,3-*d*]imidazoles (**2.692a,b**) have been prepared by base-promoted cyclization of 5-imidazolylselenologycolic ester and carboxylic acid derivatives, respectively (**2.691b,c**);[148] the latter are readily available from the potassium selenide salt (**2.691a**). The carboxylic acid (**2.692b**) is decarboxylated by heating it above its melting point to give the 5-unsubstituted compound (**2.692c**) and in this sense parallels the behavior of carboxylic acids in the thieno[2,3-*d*]imidazole series (see Section 2.14.2).



(2.691)

a: R = SeK
b: R = $SeCH_2CO_2Me$
c: R = $SeCH_2CO_2H$

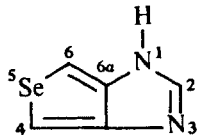


(2.692)

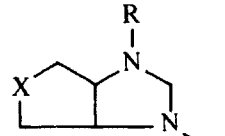
	R	mp (°C)	uv Spectrum λ_{max} (log ϵ)
a	CO_2Me	153 (aq. EtOH)	242 (4.17)
			283 (3.89)
			312 (4.14)
b	CO_2H	247–249 (BuOH)	248 (4.17)
			306 (4.03)
c	H	110–111 (hexane)	238 (4.34)
			264 (sh)

2.22. RING SYSTEM C_3N_2–C_4Se: 1*H*-SELENOLO[3,4-*d*] IMIDAZOLE

There are no examples of fully unsaturated 1*H*-selenolo[3,4-*d*]imidazoles (**2.693**) during the literature period covered. Interest in related 2,3,3*a*,4,6,6*a*-hexahydro derivatives (cf. **2.694a**) has been stimulated by the isosteric relationship of such compounds to the nucleus of biotin (cf. **2.694b** and Section 2.15.5).



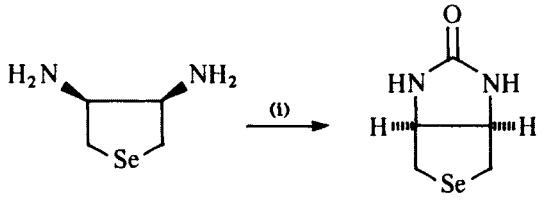
(2.693)



(2.694)

R = e.g., H, alkyl
a: X = Se
b: X = S

Hexahydro-2-oxo-1*H*-selenolo[3,4-*d*]imidazole (**2.696**) has been obtained[483] in moderate yield by reaction of phosgene with *cis*-3,4-diaminoselenolophane (**2.695**), but the latter is rather tedious to synthesize (seven steps from 1,4-dihydroxybut-2-ene).



(2.695)

(2.696)

mp 256–258°C (sealed tube) (EtOH)
ir 3200, 1690, 1260 cm^{-1}.

(i) $COCl_2$, C_6H_6, pyridine, reflux

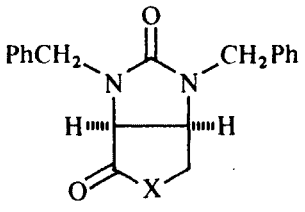
TABLE 2.85. ^{1}H NMR SPECTRA[a] OF METHYL ESTER OF SELENOLOBIOTIN (2.698b) AND BIOTIN METHYL ESTER (2.698c)[484]

	Chemical Shifts and Coupling Constants			
Compound	H_A, H_B	H_X	H_Y	Other Protons
2.698b	$H_A = 3.0$			
	$H_B = 2.75$			2.3 (t), $J = 6$; CH_2CO_2Me
		4.5 (m)	4.35 (m)	
	$J_{AB} = 12$			3.65 (s); CO_2Me
	$J_{AX} = 4.5$		$J_{XY} = 7–8$	
	$J_{BX} = 0–1$			3.5; H_c
2.698c	$H_A = 2.9$			
	$H_B = 2.66$			2.3 (t) $J = 6$; CH_2CO_2Me
	$J_{AB} = 12.5$	4.45 (m)	4.25 (m)	3.64, CO_2Me
	$J_{AX} = 4.5$		$J_{XY} = 8–9$	3.16, H_c
	$J_{BX} = 0–1$			

[a]Chemical shifts are δ values quoted in ppm from tetramethylsilane as an internal standard with coupling constants quoted in hertz (solvent $CDCl_3$).

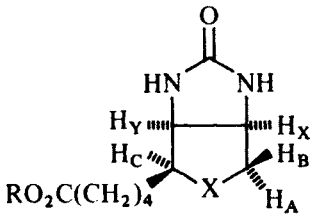
The selenium analog of biotin (**2.698a**) has been synthesized[484,485] from the selenolo lactone (**2.697b**) by a procedure identical to that devised by Goldberg and Sternbach[183] for the preparation of biotin (see Scheme 2.34 in Section 2.15.5). The key intermediate (**2.697b**) can be prepared by treating the lactone (**2.697a**) with bis(methoxymagnesium)diselenide followed by hypophosphorus acid. A comparative study of the ^{1}H nmr spectra of the methyl esters of selenolobiotin (**2.698b**) and biotin (**2.698c**) (Table 2.85) indicates small chemical shift differences in the protons H_A, H_B, H_C, H_X, and H_Y but more importantly illustrates that the coupling constants J_{AX}, J_{BX}, and J_{XY} are almost identical; from the latter data it has been concluded[484,485] that the solution conformations of the two molecules are very similar.

Selenolobiotin (**2.698a**) has also been identified as an excretion product of the fungus *Physomyces blakesleeanus.*[486]



(**2.697**)

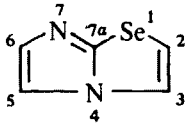
(+) a: X = O
(+) b: X = Se



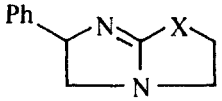
(**2.698**)

(+) a: R = H; X = Se, mp 234°C, $[\alpha]_D^{25}$ + 80.5 (c, 1.0, 0.1*M* NaOH)
b: R = Me, X = Se
c: R = Me, X = S

2.23. RING SYSTEM C_3N_2–C_3NSe: IMIDAZO[2,1-*b*] SELENAZOLE



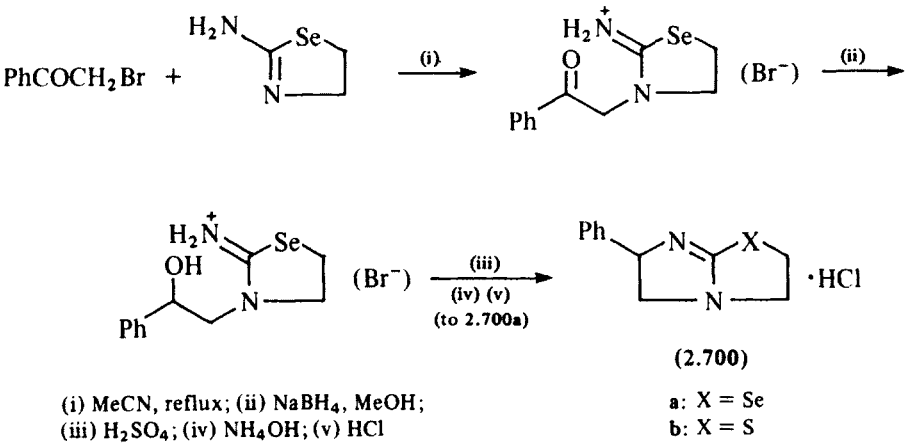
(2.699)



(2.700)

a: X = Se
b: X = S

Compounds in the fully unsaturated imidazo[2,1-*b*]selenazole ring system (**2.699**) are not cited during the literature period covered, and this section describes an isolated publication concerning the synthesis (Scheme 2.67) of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]selenazole (**2.700a**)[487] of interest as a potential anthelmintic agent [cf. synthesis of the sulfur analog (**2.700b**, tetramisole) by a related procedure (**2.587a** → **2.588**) outlined in Section 2.17.4]. The product, selenotetramisole (**2.700a**), has been resolved by means of (+)-10-camphor sulfonate salts to give the (+) and (−) enantiomers as hydrochloride salts with the following physical properties, respectively: mp 237–238.5°C, $[\alpha]_D^{25}$ + 112.8° (c, 0.9, H_2O); mp 236.5–238.5°C, $[\alpha]_D^{25}$ − 110.0° (c, 0.5, H_2O).



(i) MeCN, reflux; (ii) $NaBH_4$, MeOH;
(iii) H_2SO_4; (iv) NH_4OH; (v) HCl

(2.700)

a: X = Se
b: X = S

Scheme 2.67

It is notable that (−)tetramisole and (−)selenotetramisole exhibit similar behavior as inhibitors of alkaline phosphatase isoenzymes, and the possibility exists that ^{75}Se-radiolabeled (−)selenotetramisole can be used to provide information on tetramisole biodistribution.[487]

REFERENCES

1. J. W. Lown and B. E. Landberg, *Can. J. Chem.*, **52**, 798 (1974).
2. H. von Dobeneck, E. Weil, E. Brunner, H. Deubel and D. Wolkenstein, *Justus Liebigs Ann. Chem.*, **1978**, 1424.
3. H. C. Wormser, *J. Pharm. Sci.*, **58**, 1038 (1969).
4. H. C. Wormser, *J. Pharm. Sci.*, **59**, 1732 (1970).
5. H. C. Wormser and H. N. Abramson, *J. Pharm. Sci.*, **64**, 1514 (1975).
6. H. C. Wormser and H. N. Abramson, *J. Pharm. Sci.*, **64**, 1882 (1975).
7. Y. Aoki, H. Suzuki, H. Akiyama, and S. Okano, German Patent 2,331,244 (1974); *Chem. Abstr.*, **80**, 95951z; see also British Patents 1,420,509 and 1,420,510.
8. M. D. Glick, H. C. Wormser, and H. N. Abramson, *Acta Crystallogr., Sect. B*, **33**, 1095 (1977).
9. H. von Euler and H. Hasselquist, *Arkiv. Kemi*, **13**, 185 (1958); *Chem. Abstr.*, **53**, 11351g.
10. M. Tomita, M. Irie, and T. Ukita, *Tetrahedron Lett.*, **1968**, 4933.
11. H. H. Wasserman, K. Stiller, and M. B. Floyd, *Tetrahedron Lett.*, **1968**, 3277.
12. H. C. Wormser and W. H. Chin, *J. Heterocycl. Chem.*, **12**, 595 (1975).
13. A. Lawson, *J. Chem. Soc.*, **1956**, 307.
14. B. A. Priimenko and P. M. Kochergin, *Khim. Geterotsikl. Soedin*, 7, 1243 (1971); *Chem. Abstr.*, **76**, 59530v; Engl. transl. in. *Chem. Heterocycl. Compd.*, **1971**, 1168.
15. P. M. Kochergin, B. A. Priimenko, V. S. Ponomar, M. V. Povstyanoi, A. A. Tkachenko, I. A. Mazur, A. N. Krasovskii, E. G. Knysh, and M. I. Yurchenko, *Khim. Geterotsikl. Soedin*, **1969**, 177; *Chem. Abstr.*, **71**, 13065r; Engl. transl. in *Chem. Heterocycl. Compd.*, **1969**, 135.
16. A. Hetzheim and H. Pusch, *Z. Chem.*, **10**, 385 (1970); *Chem. Abstr.*, **74**, 13068f.
17. P. M. Kochergin and B. A. Priimenko, *Khim. Geterosikl. Soedin*, **1969**, 176; *Chem. Abstr.*, **71**, 3325m; Eng. Transl. in *Chem. Heterocycl. Compd.*, **1969**, 134.
18. L. F. Miller and R. E. Bambury, *J. Med. Chem.*, **15**, 415 (1972).
19. B. A. Priimenko and P. M. Kochergin, *Khim. Geterotsikl. Soedin*, **1971**, 1692; *Chem. Abstr.*, **77**, 5404j; Engl. Transl. in *Chem. Heterocycl. Compd.*, **1971**, 1574.
20. L. F. Miller and R. E. Bambury, *J. Org. Chem.*, **38**, 1955 (1973).
21. A. M. Simonov, V. A. Anisimova, and N. I. Avdyunina, USSR Patent 562,544 (1977); *Chem. Abstr.*, **87**, 152204d.
22. A. V. Ivaschenko, V. T. Lazareva, L. V. Shmelev, and R. V. Poponova, *Khim. Geterotsikl. Soedin*, **1982**, 384; *Chem. Abstr.*, **97**, 6220w; Engl. Transl. in *Chem. Heterocycl. Compd.*, **1982**, 290.
23. V. M. Dziomko and A. V. Ivashchenko, *Khim. Geterotsikl. Soedin*, **1973**, 1190; *Chem. Abstr.*, **79**, 146458h; Engl. Transl. in *Chem. Heterocycl. Compd.*, **1973**, 1082.
24. T. Muro, T. Nakao, and K. Ogawa, Japanese Patent 76 11,784 (1976); *Chem. Abstr.*, **84**, 180225t.
25. V. P. Arya, K. Nagajaran, J. David, S. J. Shenoy, and N. G. Gokhale, *Indian J. Chem., Sect. B*, **16B**, 226 (1978); *Chem. Abstr.*, **89**, 109233s.
26. D. L. Trepanier, S. Wang, and C. E. Moppett, *J. Chem. Soc., Chem. Commun.*, **1973**, 642.
27. V. M. Dziomko and A. V. Ivashchenko, *Zh. Org. Khim.*, **9**, 2193 (1973); *Chem. Abstr.*, **80**, 27154s; *J. Org. Chem.* (USSR), **1973**, 2206.

28. P. M. Kochergin, M. V. Povstyanoi, B. A. Priimenko, and V. S. Ponomar, *Khim. Geterotsikl. Soedin*, **1970**, 129; *Chem. Abstr.*, **72**, 90370j; Engl. Transl. in *Chem. Heterocycl. Compd.*, **1970**, 125
29. P. K. Martin, H. R. Matthews, H. Rapoport, and G. Thyagarajan, *J. Org. Chem.*, **33**, 3758 (1968).
30. V. M. Dziomko, O. V. Ivanov, V. N. Avilina, A. V. Ivashchenko, and S. T. Kazakova, *Proc. Internatl. Solvent Extract. Conf.*, **2**, 1893 (1974); *Chem. Abstr.*, **83**, 121574n.
31. H. Staehle, H. Koeppe, W. Kummer, W. Kobinger, L. Pichler, and C. Lillie, Eur. Pat. Appl. EP 51,809 (1980); *Chem. Abstr.*, **97**, 162278e; see also idem, German Patent 2,827,617 (1980); *Chem. Abstr.*, **92**, 181192g.
32. F. Khuong, J. P. Le Forestier, and R. Gontarel, *Tetrahedron*, **28**, 5207 (1972).
33. A. F. McKay, M. E. Kreling, G. Y. Paris, R. O. Braun, and D. J. Whittingham, *Can. J. Chem.*, **35**, 843 (1957).
34. A. F. McKay, R. O. Braun, and G. Y. Paris, U.S. Patent 2,816,896 (1957); *Chem. Abstr.*, **52**, 14701e.
35. (a) A. F. McKay and D. L. Garmaise, *Can. J. Chem.*, **35**, 8 (1957); (b) A. F. McKay and D. L. Garmaise, U.S. Patent 2,782,205 (1957); *Chem. Abstr.*, **52**, 445i.
36. B. Rouot and G. Leclerc, *Bull Soc. Chim. Fr.*, **1979**, 520.
37. J. L. H. Van Gelder, A. H. M. Raeymaekers, L. F. C. Roevens, and W. J. Van Laerhoven, U.S. Patent 3,963,718 (1976); *Chem. Abstr.*, **85**, 177422v, see also idem, U.S. Patent 3,983,133 (1976); *Chem. Abstr.*, **86**, 55482q; idem, German Patent 2,361,188 (1974); *Chem. Abstr.*, **81**, 77962v.
38. A. Kosayama, T. Konno, K. Higashi, and F. Ishikawa. *Chem. Pharm. Bull.* (Japan), **27**, 848 (1979).
39. A. F. McKay and M. E, Kreling, *Can. J. Chem.*, **40**, 205 (1962).
40. C. G. Freeman, J. V. Turner, and D. A. Ward, *Aust. J. Chem.*, **31**, 179 (1978).
41. M. Pinza, G. LiBassi, G. Broccali, and G. Pifferi, *Heterocycles*, **4**, 1699 (1976).
42. H. Staehle, H. Koeppe, W. Kummer, and P. Dannenberg, German Patent 2,109,524 (1972); *Chem. Abstr.*, **77**, 164750k.
43. E. V. Dehmlow and H. J. Westendorf, *Z. Naturf. B*, **25**, 1191 (1970).
44. P. Lambert, G. Evrard, and F. Durant, *Acta. Crystallogr., Sect. B*, **B34**, 2654 (1978).
45. A. F. McKay and M. E. Kreling, *Can. J. Chem.*, **40**, 1160 (1962).
46. A. Kosasayama and F. Ishikawa, *Chem. Pharm. Bull.* (Japan), **27**, 1596 (1979).
47. (a) A. F. McKay and M. E. Kreling, U.S. Patent 2,865,913 (1958); *Chem. Abstr.*, **53**, 8180e; (b) A. F. McKay and M. E. Kreling, *Can. J. Chem.*, **36**, 775 (1958).
48. F. Ishikawa, A. Kosasayama, and T. Konno, *Chem. Pharm. Bull.* (Japan), **26**, 3666 (1978).
49. J. E. Richman and H. E. Simmons, *Tetrahedron*, **30**, 1769 (1974).
50. A. F. McKay and M. E. Kreling, British Patent 801,413 (1958); *Chem. Abstr.*, **53**, 14125c.
51. F. Ishikawa, T. Imano, and Y. Abiko, Japanese Patent 78, 79,890 (1978); *Chem. Abstr.*, **90**, 23133t; F. Ishikawa, T. Imano, K. Higashi, and Y. Abiko, Japanese Patent 78 79,888 (1978); *Chem. Abstr.*, **90**, 23095g; F. Ishikawa and Y. Abiko, Japanese Patent 78 82,796 (1978); *Chem. Abstr.*, **89**, 197549c.
52. H. Staehle, H. Koeppe, W. Kummer, and H. W. Samtleben, German Patent 2,118,261 (1972), *Chem. Abstr.*, **78**, 29773a; see also U.S. Patent 3,769,288 (1973).
53. Daiichi Seiyaku Co Ltd., Japanese Patent 81 08,385 (1981); *Chem. Abstr.*, **95**, 43112s.
54. J. C. Harris, U.S. Patent 2,992,996 (1956); *Chem. Abstr.*, **56**, 10314f.
55. (a) J. L. H. Van Gelder, A. H. M. Raeymaekers, L. F. C. Roevens, and W. J. Van Laer-

hoven, U.S. Patent 3,923,808 (1975); *Chem. Abstr.*, **84**, 180261b; (b) W. Rohr, R. Swoboda, and H. A. Staab, *Chem. Ber.*, **101**, 3491 (1968).

56. E. P. Papadopoulos and H. S. Habiby, *J. Org. Chem.*, **31**, 327 (1966).
57. E. P. Papadopoulos and S. B. Bedrosian, *J. Org. Chem.*, **33**, 4551 (1968).
58. E. P. Papadopoulos, P. Eleftherios, and M. C. Schupbach, *J. Org. Chem.*, **42**, 3925 (1977).
59. L. Capuano, M. Welter, and R. Zander, *Chem. Ber.*, **103**, 2394 (1970).
60. L. Capuano, W. Lazik, and R. Zander, *Chem. Ber.*, **107**, 3237 (1974).
61. F. H. McMillan, U.S. Patent 3,395,154 (1968); *Chem. Abstr.*, **70**, 4108j; see also idem, French Patent M4501; *Chem. Abstr.*, **64**, 16151q, idem, British Patent 1,060, 194 (1967); *Chem. Abstr.*, **67**, 21913y.
62. G. Satzinger, W. Herrmann, and F. Zimmerman, *Arzneim Forsch.*, **25**, 1849 (1975); *Chem. Abstr.*, **84**, 111531c.
63. H. Koga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* (Japan), **22**, 482 (1974).
64. J. Elguero, R. Jacquier, and S. Mignonac-Mondon, *J. Heterocycl. Chem.*, **10**, 411 (1973).
65. L. Knutsson and J. Elguero, *An. Quim.*, **74**, 795 (1978); *Chem. Abstr.*, **91**, 56912v.
66. H. A. Elfahham, K. V. Sadek, G. E. H. Elgemeie, and M. H. Elnagdi, *Chem. Lett.*, **1982**, 119.
67. A. S. Shawali, M. Sami, S. M. Sherif, and C. Parkanyi, *J. Heterocycl. Chem.*, **17**, 877 (1980).
68. M. H. Elnagdi, E. A. E. Hafez, H. A. El-Fahham, and E. M. Kandeel, *J. Heterocycl. Chem.*, **17**, 73 (1980).
69. R. Faure, E. J. Vincent, and J. Elguero, *Tetrahedron Lett.*, **1973**, 2703.
70. J. P. Fayet, M. C. Vertut, R. M. Claremunt, J. M. Fabrega, and L. Knutsson, *Bull. Soc. Chim. Fr.*, **1975**, 393.
71. J. Elguero, A. Fruchier, L. Knutsson, R. Lazaro, and J. Sandstrom, *Can. J. Chem.*, **52**, 2744 (1974).
72. R. Faure, E. J. Vincent, and J. Elguero, *Org. Magn. Res.*, **9**, 508 (1977).
73. J. Druey, P. Schmidt, and K. Eichenberger, U.S. Patent 2,989,537 (1961); *Chem. Abstr.*, **55**, 25990i.
74. J. Elguero, L. Knutsson, and S. Migonac-Mondon, *Bull. Soc. Chim. Fr.*, **1975**, 255.
75. W. Schulze and H. Willitzer, *Chem. Ber.*, **100**, 3460 (1967).
76. K. Pilgram, *J. Heterocycl. Chem.*, **17**, 1413 (1980).
77. L. H. Ennis, L. Moeller, J. J. Wang, and O. S. Selawry, *Biochem. Pharmacol.*, **20**, 2539 (1971).
78. L. Lantos, H. Ho, C. Razgaitis, and B. Loev, *J. Org. Chem.*, **43**, 4841 (1978).
79. J. G. Michels and G. C. Wright, *J. Org. Chem.*, **34**, 3213 (1969).
80. H. Gnichtel, L. Belkien, W. Totz, and L. Wawretschek, *Liebigs Ann. Chem.*, **1980**, 1016.
81. R. J. Garay, A. Lopez-Castro, and R. Marquez, *Acta Crystallogr., Sect. B*, **30**, 1801, (1974); *Chem. Abstr.*, **81**, 69637c.
82. A. Conde, F. Bernier, and R. Marquez, *Acta Crystallogr., Sect. B*, **36**, 3048 (1980); *Chem. Abstr.*, **94**, 75049x.
83. G. A. Ellestad, D. B. Cosulich, R. W. Broschard, J. H. Martin, M. P. Kunstmann, G. O. Morton, J. E. Lancaster, W. Fulmor, and F. M. Lovell, *J. Am. Chem. Soc.*, **100**, 2515 (1978).
84. P. F. Wiley, R. R. Herr, H. K. Jahnke, C. D. Chidester, S. A. Mizsak, L. B. Spaulding, and A. D. Argondelis, *J. Org. Chem.*, **44**, 9 (1979).

85. (a) R. R. Herr, H. K. Jaknke, and A. D. Argondelis, *J. Am. Chem. Soc.*, **89**, 4808 (1967); (b) A. D. Argondelis, S. A. Mizsak, and P. A. Meulman, *J. Antibiotics*, **27**, 564 (1974).
86. R. A. Whitney, *Can. J. Chem.*, **59**, 2650 (1981).
87. C. J. Morel, *Helv. Chim. Acta*, **44**, 403 (1961).
88. F. Micheel and E. Drescher, *Chem. Ber.*, **91**, 668 (1958).
89. J. Fernandez-Bolanos, F. Garcia Gonzalez, J. Gasch-Gomez, and M. Menendez Gallego, *Tetrahedron*, **19**, 1883 (1963).
90. F. Krueger and H. Rudy, *Liebigs Ann. Chem.*, **669**, 146 (1963).
91. H. Fritz, C. J. Morel, and O. Wacker, *Helv. Chim. Acta*, **51**, 569 (1968).
92. J. Fernandez-Bolanos and J. Fuentes Mota, *An. Quim*, **72**, 79 (1976); *Chem. Abstr.*, **86**, 121657d.
93. J. Yoshimura, T. Sekiya, and T. Iida, *Bull. Chem. Soc. Japan*, **45**, 1227 (1972).
94. F. Garcia-Gonzalez, J. A. Galbis Perez, J. I. Fernandez Garcia-Hierro, and J. Fernandez-Bolanos, *An. Quim*, **75**, 1002 (1979); *Chem. Abstr.*, **93**, 47045d.
95. R. Vega and A. Lopez-Castro, *An. Fiz*, **67**, 331 (1971); *Chem. Abstr.*, **76**, 132759h.
96. R. J. Garay, A. Lopez-Castro, and R. Marquez, *An. Fiz*, **67**, 333 (1971); *Chem. Abstr.*, **76**, 132760b.
97. R. J. Garay, R. Vega, and A. Lopez-Castro, *Crystal Struct. Commun.*, **5**, 353 (1976).
98. R. Vega, V. Hernandez-Montis and A. Lopez-Castro, *Acta Crystallogr., Sect. B*, **32**, 1363 (1976).
99. R. Jiminez-Garay, A. Lopez-Castro, and R. Marquez, *Acta Crystallogr., Sect. B*, **32**, 2115 (1976).
100. M. A. Pradera de Fuentes, M. Yruela Antinolo, J. Fuentes Mota, and J. Fernandez-Bolanos, *An. Quim*, **74**, 945 (1978); *Chem. Abstr.*, **91**, 91891j.
101. Ciba Geigy AG, British Patent 1,040,732 (1970); *Chem. Abstr.*, **75**, 151799s; see also British Patent 1,105,151 (1970); *Chem. Abstr.*, **75**, 151795n and British Patent 1,108, 179 (1970); *Chem. Abstr.*, **75**, 151796p.
102. M. V. Alvarez, M. D. Astudillo, F. Bolanos, E. Ramos, and F. Sanz, *Arch. Inst. Farmacol. Exp. Madrid*, **21**, 101 (1969); *Chem. Abstr.*, **75**, 137296u.
103. B. R. Baker and T. L. Hullar, *J. Org. Chem.*, **30**, 4053 (1965).
104. I. K. Korobitsyna, Yu. K. Yur'ev and O. I. Nefedova, *Zh. Obshch. Khim.*, **24**, 188 (1954); *Chem. Abstr.*, **49**, 3197a. Engl. transl. in *J. Gen. Chem. USSR*, **24**, 191 (1954).
105. I. K. Korobitsyna, I. G. Zhukova and Yu. K. Yur'ev, *Zh. Obshch. Khim.*, **29**, 2190 (1959); *Chem. Abstr.*, **54**, 10989b. Engl. transl. in *J. Gen. Chem., USSR*, **29**, 2157 (1959).
106. I. K. Korobitsyna, Yu K. Yur'ev, and I. G. Zurova, *Zh. Obshch. Khim.*, **27**, 1582 (1957); *Chem. Abstr.*, **52**, 3783h; Engl. Transl. in *J. Gen. Chem. USSR.*, **27**, 1654 (1957).
107. B. Gross, M. El Sekily, S. Mancy, and H. S. El Khadem, *Carbohydr. Res.*, **37**, 384 (1974).
108. M. Gerecke, J. P. Zimmermann, and W. Aschwanden, *Helv. Chim. Acta*, **53**, 991 (1970).
109. Y. Aoki, H. Suzuki, H. Akiyama, and S. Okano, German Patent 2,331,244 (1974); *Chem. Abstr.*, **80**, 95951z.
110. Y. Aoki, H. Suzuki, H. Akiyama, and S. Okano, German Patent 2,446,256 (1975); *Chem. Abstr.*, **83**, 58826d.
111. Y. Aoki, H. Suzuki, H. Akiyama, and S. Okano, Swiss Patent 605,968 (1978); *Chem. Abstr.*, **90**, 38925b.

112. M. Hazama, T. Aratani, G. Suzukamo, and T. Takahashi, European Patent Application EP44,158 (1982); *Chem. Abstr.*, **96**, 162445h.

113. Y. Aoki, H. Suzuki, H. Akiyama, and S. Okano, Japanese Patent 75 19,766 (1975); *Chem. Abstr.*, **83**, 114401a.

114. K. Kogure, I. Yoshimura, H. Fukawa, and T. Shimizu, *Agric. Biol. Chem.*, **40**, 1657 (1976); see also K. Kogure, I. Yoshimura, and H. Fukawa, Japanese Patent 72 42,793 (1972); *Chem. Abstr.*, **78**, 97660m.

115. D. F. Kutepov, A. A. Potashnik, D. N. Khokhlov and V. A. Tuzhilkina, *Zh. Obshch. Khim.*, **29**, 855 (1959); *Chem. Abstr.*, **54**, 1481f; Engl. transl. in *J. Gen. Chem. USSR.*, **29**, 840 (1959).

116. K. Hofmann, *J. Am. Chem. Soc.*, **67**, 1459 (1945).

117. K. Hofmann, C. Chen, A. Bridgwater, and A. E. Axelrod, *J. Am. Chem. Soc.*, **60**, 191 (1947).

118. (a) K. Hofmann, A. Bridgwater, and A. E. Axelrod, *J. Am. Chem. Soc.*, **69**, 1550 (1947); (b) ibid., **71**, 1253 (1949); (c) K. Hofmann, U.S. Patent 2,506,594 (1950); *Chem. Abstr.*, **44**, 7885h.

119. K. Hofmann and A. E. Axelrod, *J. Biol. Chem.*, **187**, 29 (1950).

120. W. M. zu Reckendorf, *Chem. Ber.*, **101**, 3802 (1968).

121. H. Ohrui, H. Kuzuhara, and S. Emoto, *Agric. Biol. Chem.*, **34**, 375 (1970).

122. H. Ohrui, H. Kuzuhara, and S. Emoto, *Agric. Biol. Chem.*, **35**, 750 (1971).

123. H. Ohrui, N. Sueda, and S. Emoto, *Agric. Biol. Chem.*, **42**, 865 (1978); see also Institute of Physical and Chemical Research, Japanese Patent 81 59,790 (1981); *Chem. Abstr.*, **95**, 169704e; S. Emoto, H. Ohrui, and K. Sueta, Japanese Patent 79 109,972 (1979); *Chem. Abstr.*, **92**, 164251h; S. Emoto, H. Ohrui, and K. Sueta, Japanese Patent 79 109,971 (1979); *Chem. Abstr.*, **92**, 59176q.

124. T. Sasaki, K. Minamoto, T. Sugiura, and M. Niwa, *J. Org. Chem.*, **41**, 3138 (1976).

125. D. Lednicer, U.S. Patent 3,455,924 (1969); *Chem. Abstr.*, **71**, 101878p.

126. A. Hetzheim and H. Pusch, *Z. Chem.*, **15**, 267 (1975).

127. K. C. Agrawal, K. B. Bears, R. K. Sehgal, J. N. Brown, P. E. Rist, and W. D. Rupp, *J. Med. Chem.*, **22**, 583 (1979).

128. R. K. Sehgal, M. W. Webb, and K. C. Agrawal, *J. Med. Chem.*, **24**, 601 (1981); see also R. K. Sehgal and K. C. Agrawal, *J. Heterocycl. Chem.*, **16**, 1499 (1979).

129. J. N. Brown, P. E. Rist, and K. C. Agrawal, *Crystal Struct. Commun.*, **8**, 761 (1979).

130. V. E. Marquez, L.-M. Twanmoh, H. B. Wood, and J. S. Driscoll, *J. Org. Chem.*, **37**, 2558 (1972).

131. K. Okada, J. A. Kelley, and J. S. Driscoll, *J. Heterocycl. Chem.*, **14**, 511 (1977).

132. V. E. Marquez, T. Hirata, L.-M. Twanmoh, H. B. Wood, and J. S. Driscoll, *J. Heterocycl. Chem.*, **9**, 1145 (1972).

133. A. F. Mackay and M. E. Kreling, *Can. J. Chem.*, **37**, 427 (1959); A. F. Mackay, G. Y. Paris, and M. E. Kreling, *J. Am. Chem. Soc.*, **79**, 5276 (1957).

134. K. H. Magosch and R. Feinauer, *Justus Liebigs Ann. Chem.*, **742**, 128 (1970); R. Feinauer, *Angew. Chem. Internatl. Ed. Engl.*, **5**, 894 (1966).

135. J. W. Cornforth, in *The Chemistry of Penicillin*, Princeton University Press, Princeton, NJ, 1949.

136. M. J. S. Dewar and I. J. Turchi, *J. Org. Chem.*, **40**, 1521 (1975).

137. E. I. Ivanov, A. V. Bogatskii, and A. E. Abramovich, *Dokl. Akad. Nauk SSSR.*, **255**, 359 (1980); *Chem. Abstr.*, **94**, 156062y; Engl. transl. **255**, 516 (1980).

138. A. C. Davis and A. L. Levy, *J. Chem. Soc.*, **1951**, 3479.

139. V. A. J. Clark, T. J. Evans, and R. G. Simmonds, *J. Chem. Soc., Perkin Trans. I*, **1975**, 1803.

140. H. Gnichtel, R. Walentowski, and K. E. Schuster, *Chem. Ber.*, **105**, 1701 (1972).

141. H. Gnichtel and K. E. Schuster, *Chem. Ber.*, **111**, 1171 (1978).

142. D. R. Hoff and L. H. Peterson, British Patent, 1,197,691 (1968); see also South African Patent 68,00,904 (1969); *Chem. Abstr.*, **72**, 100702k.

143. P. N. Preston, in *Benzimidazoles and Congeneric Tricyclic Compounds* (P. N. Preston, Ed.), Wiley-Interscience, New York, 1981, Part 1, p. 28.

144. See ref. 143, Part 2, Chapter 10.

145. V. G. Zhiryakov, P. I. Abramenko, and G. I. Priklonskikh, *Zh. Vses, Khim. O-Va*, **23**, 345 (1978); *Chem. Abstr.*, **89**, 164916s.

146. D. Binder, F. Hillesbrand, and C. R. Noe, *J. Chem. Res. Synop.*, **1979**, 96; *J. Chem. Res.* (M), **1979**, 1146–1154.

147. D. Binder, C. R. Noe, and F. Hillesbrand, *Arch. Pharm.* (Weinheim), **312**, 845 (1979).

148. R. V. Khozeeva, L. Ya Kvitko, E. L. Baramov, and A. V. El'tsov, *Zh. Org. Khim.*, **13**, 232 (1977); *Chem. Abstr.*, **86**, 121254v; Engl. transl. in *J. Org. Chem. USSR.*, **13**, 215 (1977).

149. H. Berner and H. Reinshagen, *Monatsh. Chem.*, **107**, 299 (1976).

150. D. G. O'Sullivan and A. K. Wallis, *J. Med. Chem.*, **15**, 103 (1972).

151. D. G. O'Sullivan, D. Pantic, and A. K. Wallis, *Experientia*, **24**, 661 (1968).

152. See ref. 143, Part 2, Chapter 10.

153. S. Nishimura and E. Imoto, *Bull. Chem. Soc. Japan*, **35**, 432 (1962).

154. P. A. Rossy and F. Vogel, German Patent DE 3,018,134 (1981); *Chem. Abstr.*, **96**, 68721y.

155. S. I. Zav'yalov, N. A. Rodionova, O. V. Dorofeeva and L. L. Zheleznaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1975**, 2892; *Chem. Abstr.*, **84**, 105481v; Engl. transl. in *Bull. Acad. Sci. USSR-Div. Chem. Sci.*, **1975**, 2720; see also S. I. Zav'yalov, N. A. Rodionova and O. V. Dorofeeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1975**, 1679 *Chem. Abstr.*, **83**, 147428t; Engl. transl. in *Bull. Acad. Sci. USSR Div. Chem. Sci.*, **1975**, 1641; S. I. Zav'yalov, I. A. Rubtsov, L. L. Zheleznaya, A. B. Pavlova, and N. A. Rodionova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1973**, 1679, *Chem. Abstr.*, **79**, 105143h; Engl. transl. in *Bull. Acad. Sci. USSR Div. Chem. Sci.*, **1973**, 1573; S. I. Zav'yalov, L. B. Kochanova, and O. V. Dorofeeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1980**, 1943; *Chem. Abstr.*, **94**, 15640y; S. I. Zav'yalov and O. V. Dorofeeva, *Izv. Akad Nauk SSSR, Ser. Khim.*, **1979**, 225; *Chem. Abstr.*, **90**, 137731s; Engl. transl. in *Bull. Acad. Sci. USSR Div. Chem. Sci.*, **1979**, 210.

156. S. I. Zav'yalov, N. A. Rodionova, I. V. Scherbak, O. V. Dorofeeva, Z. S. Volkova, A. Kh. Zitmanis, and V. S. Ragovska, *Izv. Akad. Nauk SSSR, Ser Khim.*, **1975**, 1895; *Chem. Abstr.*, **83**, 206165e, Eng. transl. in *Bull. Acad. Sci. USSR Div. Chem. Sci.*, **1975**, 1780.

157. S. I. Zav'yalov, N. A. Rodionova, L. L. Zheleznaya, G. I. Bolestova, V. V. Filippov, Z. N. Parnes, and D. N. Kursanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1975**, 1643; *Chem. Abstr.*, **83**, 164075t; Engl. transl. in *Bull. Acad. Sci. USSR. Div. Chem. Sci.*, **1975**, 1533; see also idem, German Patent 2,417,992 (1975); *Chem. Abstr.*, **84**, 31076t; idem, British Patent 1,419,927.

158. S. I. Zav'yalov and O. V. Dorofeeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1980**, 1634; *Chem. Abstr.*, **94**, 3963t; Engl. transl. in *Bull. Acad. Sci. USSR. Div. Chem. Sci.*, **1980**, 1178.

159. S. Kanthamani. *Proc. Indian Acad. Sci.*, **47A**, 175 (1958); *Chem. Abstr.*, **52**, 18381h; see also G. B. Brown, S. R. Safir, B. R. Baker, S. Bernstein, and L. Dorfman, *J. Org. Chem.*, **12**, 483 (1947).

160. T. Makaiyama, Y. Sato, T. Taguchi, and K. Watanabe, Japanese Patent 76 138,692 (1976); *Chem. Abstr.*, 87, 53292z.

161. T. Takaya, H. Yoshimoto, and E. Imoto, *Bull. Chem. Soc. Japan*, **40**, 2636 (1967).

162. F. Ellis, P. G. Sammes, M. B. Hursthouse, and S. Neidle, *J. Chem. Soc., Perkin Trans. I*, **1972**, 1560.

163. K. Ohba, K. Mori, T. Kitahara, S. Kitamura, and M. Matsui, *Agric. Biol. Chem.*, **38**, 1679 (1974).

164. G. I. Khaskin, T. E. Bezemonova, and P. G. Dul'nev, *Khim. Geterotsikl. Soedin*, **1982**, 328; *Chem. Abstr.*, **96**, 217766w; Engl. transl. in *Chem. Heterocycl. Compd.*, **1982**, 246.

165. H. Kotaka, K. Inomata, Y. Murata, H. Kinoshita, and M. Katsuragawa, *Chem. Lett.*, **1976**, 1073.

166. F. Ellis and P. G. Sammes, *J. Chem. Soc., Perkin Trans. I*, **1972**, 2866.

167. K. Ohba, T. Kitahara, K. Mori, and M. Matsui, *Agric. Biol. Chem.*, **38**, 2431 (1974); see also idem, German Patent 2,534,962 (1976); *Chem. Abstr.*, **85**, 33009t; U.S. Patent 3,983,134 (1976).

168. K. Shimaji, Y. Aoki, K. Maejima, and T. Takahashi, Japanese Patent 79 112,886 (1979); *Chem. Abstr.*, **92**, 41955h.

169. A. F. Wagner and K. Folkers, *Vitamins and Coenzymes*, Wiley-Interscience, New York, 1964, Chapter 8.

170. T. Terrione, in *Vitamins and Hormones*, Vol. 18 (R. S. Harris and D. J. Ingle, Eds.), Academic Press, 1960, pp. 1–42.

171. L. D. Greenberg, *Ann. Rev. Biochem.*, **26**, 181 (1957).

172. J. J. Burns and A. H. Conney, *Ann. Rev. Biochem.*, **29**, 413 (1960).

173. P. Gyorgy, F. W. Zilliken, in *Fermente Horm., Vitam. Beziehungen Wirkstoffe Zueinander, Dritte Erweiterte Aufl.*, Vol. 3, (R. Ammon and W. Dirscherl, Eds.), Thieme, Stuttgart, West Germany, 1974, Part 1, pp. 766–807.

174. F. Lynen, J. Knappe, E. Lorch, G. Jütting, and E. Ringelmann, *Angew. Chem.*, **71**, 481 (1959).

175. D. B. McCormick, R. Grisser, and H. Sigel, *Met. Ions Biol. Syst.*, **1**, 213 (1974).

176. A. A. Poznanskaya and V. Z. Gorkin, *Vopr. Med. Khim.*, **8**, 115 (1962); *Chem. Abstr.*, **57**, 7776g.

177. M. J. Cravey and H. Kohn, *J. Am. Chem. Soc.*, **102**, 3928 (1980); see also references cited therein.

178. W. C. Stallings, C. T. Monti, M. D. Lane, and G. T. De Titta, *Proc. Natl. Acad. Sci.* (USA), **77**, 1260 (1980); see also references cited therein.

179. M. A. Boas, *Biochem. J.*, **21**, 712 (1927).

180. R. Blair and C. Whitehead, *Feedstuffs*, **48**, 30 (1976).

181. D. B. McCormick, *Nutr. Rev.*, **33**, 97 (1975).

182. J. O. Anderson and R. E. Warwick, *Poult. Sci.*, **49**, 569 (1970).

183. M. W. Goldberg and L. H. Sternbach, U.S. Patent 2,489,235 (1949); *Chem. Abstr.*, **45**, 187d; idem, U.S. Patent 2,489,233 (1949); *Chem. Abstr.*, **45**, 185d; idem., U.S. Patent 2,489,232 (1949); *Chem. Abstr.*, **45**, 186h; see also I. Isaka, K. Kubo, M. Takashima, and M. Murahashi, *Yakugaku Zasshi*, **88**, 964 (1968); *Chem. Abstr.*, **70**, 19984r; M. Murakami, K. Kubo, and I. Isaka, Japanese Patent 70 31.669 (1970); *Chem. Abstr.*, **74**, 100018h; I. Isaka, K. Kubo, M. Takeshima, and M. Murakami, Yakugaku Zasshi, **88**, 1062 (1968); *Chem. Abstr.*, **70**, 11632d; idem, Japanese Patent 70 37,775 (1970); *Chem. Abstr.*, **74**, 87976x; idem, Japanese Patent 70 37,776 (1970); *Chem. Abstr.*, **74**, 100055t; idem, Japanese Patent 71 03,580 (1971); *Chem. Abstr.*, **74**, 125694p.

184. M. Gerecke, J. P. Zimmermann, and W. Aschwanden, *Helv. Chim. Acta*, **53**, 991 (1970).

185. T. Takahashi, K. Shimago, and K. Maeshima, European Patent Application EP 36,030 (1981); *Chem. Abstr.*, **96**, 85557s.

186. S. Lavielle, S. Bory, B. Moreau, M. J. Luche, and A. Marquet, *J. Am. Chem. Soc.*, **100**, 1558 (1978); idem, German Patent 2,508,831 (1975); *Chem. Abstr.*, **84**, 59463r.

187. S. Bory, R. Lett, B. Moreau, and A. Marquet, *Tetrahedron Lett.*, **1972**, 4921; S. Bory and A. Marquet, ibid., **1973**, 4155.

188. T. Ogawa, T. Kawano, and M. Mutsui, *Carbohydr. Res.*, **57**, C31 (1977); M. Matsui, T. Ogawa, T. Kono, and S. Kitamura, Japanese Patent 78 73,589 (1978); *Chem. Abstr.*, **90**, 23050p.

189. R. J. Parry and M. G. Kunitani, *J. Am. Chem. Soc.*, **98**, 4024 (1976).

190. A. Fliri and K. Hohenlohe-Öhringen, *Chem. Ber.*, **113**, 607 (1980).

191. P. N. Confalone, M. R. Uskokovic, and G. Pizzolato, *J. Org. Chem.*, **42**, 135 (1977), idem, U.S. Patent 3,978,084 (1976); *Chem. Abstr.*, **86**, 5465r.

192. P. Rossy, F. G. M. Vogel, W. Hoffmann, J. Paust, and A. Nuerrenbach, *Tetrahedon Lett.*, **22**, 3493 (1981); P. Rossy and F. G. M. Vogel, German Patent 3,018,109 (1981); *Chem. Abstr.*, **96**, 67822z.

193. P. N. Confalone, G. Pizzolato, and M. R. Uskokovic, *J. Org. Chem.*, **42**, 1630 (1977).

194. J. Vasilevskis, J. A. Gualtieri, S. D. Hutchings, R. C. West, J. W. Scott, D. R. Parrish, F. T. Bizzaro, and G. F. Field, *J. Am. Chem. Soc.*, **100**, 7423 (1978); G. F. Field, German Patent 2,558,356 (1976); *Chem. Abstr.*, **86**, 29809g; J. Vasilevskis, German Patent 2,730,341 (1978).

195. H. Ohrui and S. Emoto, *Tetrahedron Lett.*, **1975**, 2765.

196. F. G. M. Vogel, J. Paust, and A. Nuerrenbach, *Justus Liebigs Ann. Chem.*, **1980**, 1972.

197. P. N. Confalone, E. D. Lollar, G. Pizzolato, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **100**, 6291 (1978).

198. P. N. Confalone, E. D. Lollar, G. Pizzolato, and M. R. Uskokovic, U.S. Patent 4,062, 868 (1977); *Chem. Abstr.*, **88**, 190823h; see also H. J. Monteiro, *An. Acad. Bras. Cienc*, **52**, 493 (1980); *Chem. Abstr.*, **94**, 208767d.

199. P. N. Confalone, G. Pizzolato, E. G. Baggiolini, E. D. Lollar, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **99**, 7020 (1977).

200. E. G. Baggiolini, H. L. Lee, and M. R. Uskokovic, U.S. Patent 4,247,704 (1981); *Chem. Abstr.*, **95**, 115543h.

201. E. G. Baggiolini, H. L. Lee, and M. R. Uskokovic, U.S. Patent 4,245,104 (1981); *Chem. Abstr.*, **95**, 80929j.

202. C. Bonnemere, J. A. Hamilton, L. K. Steinrauf, and J. Knappe, *Biochemistry*, **4**, 240 (1965).

203. W. F. Paton, Fu-Tong Liu, and I. C. Paul, *J. Am. Chem. Soc.*, **101**, 1005 (1979).

204. G. T. De Titta, J. W. Edmonds, W. Stallings, and J. Donohue, *J. Am. Chem. Soc.*, **98**, 1920 (1976); see also W. C. Stallings, *Arch. Biochem. Biophys.*, **183**, 189 (1977).

205. B. M. Craven, C. Cusatis, G. L. Gartland, and E. A. Vizzini, *J. Molec. Struct.*, **16**, 331 (1973).

206. A. Caron and J. Donohue, *Acta Crystallogr., Sect. B*, **25**, 404 (1969).

207. N. M. Green, W. P. Mose, and P. M. Scopes, *J. Chem. Soc.* (C), **1970**, 1330.

208. J. A. Glasel, *Biochemistry*, **5**, 1851 (1966).

209. R. Griesser, H. Siegel, L. D. Wright, and D. B. McCormick, *Biochemistry*, **12**, 1917 (1973).

210. H. Flaster and H. Kohn, *J. Heterocycl. Chem.*, **18**, 1425 (1981); see also J. H. Bradbury and R. N. Johnson, *J. Magn. Resonance*, **35**, 217 (1979).

211. A. Abe, M. Nee, J. D. Roberts, W. L. Wittenberg, and N. J. Leonard, *J. Am. Chem. Soc.*, **103**, 4954 (1981).

212. M. Wit and G. A. Webb, *Annu. Rep. NMR Spectrosc.*, 7, 117 (1977).

213. G. M. Maggiora, *J. Theor. Biol.*, **43**, 51 (1974).

214. H. Janecke and H. Voege, *Fresenius Z. Anal. Chem.*, **254**, 355 (1971); *Chem. Abstr.*, **75**, 67528v.

215. R. N. Johnson and G. R. Boyden, *J. Pharm. Sci.*, **66**, 1212 (1977).

216. S. Ahuja, *J. Pharm. Sci.*, **65**, 163 (1976).

217. H. Kohn, Y. Gopichand, and P. Charumilind, *J. Org. Chem.*, **43**, 4955 (1978).

218. J. Knappe, K. Biederbick, and W. Bruemmer, *Angew. Chem., Internatl. Ed. Engl.*, **1**, 400 (1962).

219. A. B. A. Jansen and P. J. Stokes, *J. Chem. Soc.*, **1962**, 4909.

220. A. B. A. Jansen and P. J. Stokes, *J. Chem. Soc.*, **1964**, 1530.

221. G. F. Field, *J. Org. Chem.*, **43**, 1084 (1978).

222. S. Ochoa and Y. Kaziro, in *Comprehensive Biochemistry*, Vol. 16 (F. Florkin and E. H. Stotz, Eds.) Elsevier, New York, 1965, p. 210.

223. D. B. McCormick, *J. Heterocycl. Chem.*, **10**, 235 (1973).

224. N. M. Green, L. Konieczny, E. J. Toms, and R. C. Valentine, *Biochem. J.*, **125**, 781 (1971).

225. K. E. Meier and A. E. Ruoho, *J. Supramolec. Struct.* **9**, 243 (1978); *Chem. Abstr.*, **90**, 164312n.

226. J. M. Becker, M. Wilchek, and E. Katchalski, *Proc. Natl. Acad. Sci.* (USA), **68**, 2604 (1971).

227. M. Bodansky and D. T. Fagan, *J. Am. Chem. Soc.*, **99**, 235 (1977).

228. (a) B. K. Sinha and C. F. Chignell, *J. Med. Chem.*, **18**, 669 (1975); (b) idem, *Methods Enzymol.*, **62**, 295 (1979); (c) C. F. Chignell, D. K. Starkweather, and B. K. Sinha, *J. Biol. Chem.*, **250**, 5622 (1975).

229. K. Hofmann, F. M. Finn, and Y. Kiso, *J. Am. Chem. Soc.*, **100**, 3585 (1978).

230. K. Hofmann, G. Titus, J. A. Montibeller, and F. M. Finn, *Biochemistry*, **21**, 978 (1982).

231. E. A. Bayer, B. Rivnay, and E. Skutelsky, *Biochim. Biophys. Acta*, **550**, 464 (1979).

232. M. E. Wilson and G. M. Whitesides, *J. Am. Chem. Soc.*, **100**, 306 (1978); see also M. E. Wilson and R. G. Nuzzo, *J. Am. Chem. Soc.*, **100**, 2269 (1978); R. G. Nuzzo, S. L. Haynie, M. E. Wilson, and G. M. Whitesides, *J. Org. Chem.*, **46**, 2861 (1981).

233. L. J. Hanka, M. B. Bergy, and R. B. Kelly, *Science*, **154**, 1667 (1967); L. J. Hanka, L. M. Reineke, and D. G. Martin, *J. Bacteriol.*, **100**, 42 (1969).

234. G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Am. Chem. Soc.*, **92**, 3520 (1970); G. F. Field, W. J. Zally, L. H. Sternbach, and J. F. Blovnt, *J. Org. Chem.*, **41**, 3853 (1976).

235. A. Piffeteau, M. N. Dufour, M. Zamboni, M. Gaudry, and A. Marquet, *Biochemistry*, **19**, 3069 (1980).

236. Fu-Tong Liu and N. J. Leonard, *J. Am. Chem. Soc.*, **101**, 996 (1979).

237. L. J. Hanka, D. G. Martin, and L. M. Reineke, *Antimicrob. Agents Chemoth.*, **1**, 135 (1972); *Chem. Abstr.*, 77, 3765d; L. J. Hanka and D. G. Martin, German Patent 2,023,047 (1970).

238. Y. Aoki, H. Suzuki, H. Akiyama, and S. Okano, Japanese Patent 74 87,691 (1974); *Chem. Abstr.*, **82**, 156300b.

239. H. Akiyama, H. Suzuki, K. Maejima, and Y. Aoki, Japanese Patent 74 15,277 (1974).

240. K. Enoki, T. Yao, K. Ishimitsu, K. Tsukashima, and E. Ikari, German Patent 2,364,744 (1974); *Chem. Abstr.*, **81**, 105506v.

241. Y. Aoki, H. Suzuki, and T. Nakagome, Japanese Patent 76 08,289 (1976); *Chem. Abstr.*, **85**, 33013q.

242. A. D. Landman, *J. Vitam. Nutr. Res.*, **46**, 310 (1976); *Chem. Abstr.*, **86**, 39700d.

243. M. N. Kazarinoff, W. B. Im, J. A. Roth, D. B. McCormick, and L. D. Wright, *J. Biol. Chem.*, **247**, 75 (1972).

244. J. A. Roth and D. B. McCormick, *J. Biol. Chem.*, **245**, 6264 (1970).

245. F. Frappier, M. Jouany, A, Marquet, A. Olesker, and J. C. Tabet, *J. Org. Chem.*, **47**, 2257 (1982).

246. W. B. Im, D. B. McCormick, and L. D. Wright, *J. Biol. Chem.*, **248**, 7798 (1973).

247. S. D. Mikhno, T. M. Filippova, N. S. Kulachkima, I. G. Suchkova and V. M. Berezovskii, *Zh. Org. Khim.*, **14**, 1706 (1978); *Chem. Abstr.*, **89**, 197247c. Engl transl. in *J. Org. Chem. USSR.*, **14**, 1591 (1978).

248. S. Rajappa, B. G. Advani, and R. Srienivasan, *Indian J. Chem., Sect. B*, **15B**, 886 (1977); *Chem. Abstr.*, **88**, 121038u.

249. J. Rokach, P. Hamel, Y. Girard, and G. Reader, *J. Org. Chem.*, **44**, 1118 (1979).

250. J. Rokach, P. Hamel, Y. Girard, and G. Reader, *Tetrahedron Lett.*, **1979**, 1281.

251. W. L. Mosby, *Heterocyclic Systems with Bridgehead Nitrogen Atoms*, Interscience, New York, 1961, p. 157.

252. P. M. Kochergin, *Zh. Obshch. Khim.*, **26**, 2493 (1956); *Chem. Abstr.*, **51**, 5050b; *J. Gen. Chem. USSR.*, **26**, 2785 (1956).

253. I. A. Mazur and P. M. Kochergin, *Khim. Geterotsikl. Soedin*, **1970**, 512; *Chem. Abstr.*, **73**, 87855 m; Engl. transl. in *Chem. Heterocycl. Compd.*, **1970**, 434.

254. J. Mohan, V. K. Chadha, and H. K. Pujari, *Indian J. Chem.*, **11**, 747 (1973).

255. R. C. Tweit, U.S. Patent 3,542,802 (1970); *Chem. Abstr.*, **74**, 112042z.

256. P. M. Kochergin, *Zh. Obshch. Khim.*, **26**, 2916 (1956); *Chem. Abstr.*, **51**, 8078f; Engl. trans. in *J. Gen. Chem. USSR.*, **26**, 3243 (1956).

257. I. A. Mazur, P. M. Kochergin, and V. G. Tromsa, *Khim. Geterotsikl. Soedin*, **7**, 389 (1971), *Chem. Abstr.* **76**, 14434a; Engl. transl. in *Chem. Heterocycl. Compd.*, **1971**, 359.

258. K. T. Potts and S. Kanemasa, *J. Org. Chem.*, **44**, 3803 (1979).

259. M. Bandy and A. Robert, *Tetrahedron Lett.*, **21**, 2517 (1980).

260. I. A. Mazur and P. M. Kochergin, *Khim. Geterotsikl. Soedin*, **1970**, 824; *Chem. Abstr.*, **73**, 120565s; Engl. transl. in *Chem. Heterocycl. Compd.*, **1970**, 763; see also P. M. Kochergin, B. A. Priimenko, V. S. Ponomar, M. V. Povstyanoi, A. A. Tkachenko, I. A. Mazur, A. N. Krasovskii, E. G. Knysh, and M. I. Yurchenko, *Khim. Geterotsikl. Soedin*, **1969**, 177; *Chem. Abstr.*, **71**, 13065r; Engl. transl. in *Chem. Heterocycl. Compd.*, **1969**, 135.

261. B. Kickhofen and F. Krohnke, *Chem. Ber.* **88**, 1109 (1955).

262. T. Pyl, R. Girbelmann, and H. Beyer, *Justus Liebigs Ann. Chem.*, **643**, 145 (1961).

263. N. Maziere, N. P. Buu-Hoi, and N. Dat Xuong, *Bull. Soc. Chim. Fr.*, **1963**, 1000.

264. N. P. Buu-Hoi, Nguyen-Dat-Xuong, and Ta-Thu-Cuc, *Bull. Soc. Chim. Fr.* **1966**, 1277.

265. L. Pentimalli and A. M. Guerra, *Gazz. Chim. Ital.*, **97**, 1286 (1967); *Chem. Abstr.*, **68**, 95754q.

266. D. Lednicer, U.S. Patent 3,455,924 (1969); *Chem. Abstr.*, **71**, 101878p.

267. N. Saldapols, J. Popelis, and E. Liepins, *Zh. Org. Khim.*, **16**, 1494 (1980); *Chem. Abstr.*, **94**, 3551g, *J. Org. Chem. USSR*, **16**, 1285 (1980); N. Saldabols, L. N. Alekseeva, B. Brizga, L. Kruzmetra, and S. Hillers, *Khim-Farm. Zh.*, **1970**, 20; *Chem. Abstr.*, **73**,

77136p; N. Saldabols and O. E. Lando, USSR Patent 600,143 (1978); *Chem. Abstr.*, 89, 59885h.

268. M. Patra, S. K. Mahapatra, and B. Dash, *J. Indian Chem. Soc.*, **51**, 1031 (1974); *Chem. Abstr.*, 83, 164112c.

269. B. S. Drach, I. Yu Dolgushina, and A. D. Sinitsa, *Khim. Geterosikl. Soedin*, **1974**, 928; *Chem. Abstr.*, 81, 105382b; Engl. transl. in *Chem. Heterocycl. Compd.*, **1974**, 810.

270. A. F. Oleinik, G. A. Modnikova, K. Yu. Nivitskii, T. A. Gus'kova, and G. N. Pershin, *Khim. Farm. Zh.*, **1974**, 7; *Chem. Abstr.*, 81, 63554b.

271. M. Baboulene and G. Sturz, *C. R. Hebd. Seances Acad. Sci. Ser. C*, **284**, 799 (1977); *Chem. Abstr.*, 87, 117807f.

272. J. F. Robert and J. J. Panouse, *J. Heterocycl. Chem.*, **16**, 1201 (1979).

273. I. T. Barnish, P. E. Cross, R. P. Dickinson, B. Gadsby, M. J. Parry, M. J. Randall, and I. W. Sinclair, *J. Med. Chem.*, **23**, 117 (1980).

274. S. K. Dubey, R. Rastogi, and S. Sharma, *Monatsh. Chem.*, **112**, 1387 (1981).

275. S. N. Sawhney, R. D. Kodali, G. S. Dindsa, and S. P. Singh, *Indian J. Chem., Sect. B*, **21**, 134 (1982); *Chem. Abstr.*, 96, 217763t.

276. M. Tanaka, K. Otsuka, M. Obata, T. Tanabe, T. Saida, K. Nomura, K. Amemiya, K. Saga, and S. Kano, Japanese Patent 74 70, 986 (1974); *Chem. Abstr.*, 81, 136142c.

277. E. Tedeschi, German Patent 2,505,068 (1975); Chem. Abstr., 83, 206269s.

278. M. Nakanishi, T. Muro, O. Nakatsu, T. Nakao, and K. Ogawa, German Patent 2,432, 410 (1975); *Chem. Abstr.*, 83, 43367f.

279. I. T. Barnish, P. E. Cross, R. P. Dickinson, and B. Gadsby, British Patent 1,464,259 (1977); *Chem. Abstr.*, 87, 102336c.

280. Yamanouchi Pharmaceutical Co. Ltd., Japanese Patent 81 115,780 (1981); *Chem. Abstr.*, 96, 35323s.

281. N. Saldabols, G. Zarina, and S. Hillers, *Khim. Geterotsikl. Soedin*, **1968**, 178; *Chem. Abstr.*, 69, 96550c; Engl. transl. in *Chem. Heterocycl. Compd.*, **1968**, 137.

282. G. Kempter, J. Spindler, H. J. Fiebig, and G. Sarodnick, *J. Prakt. Chem.*, **313**, 977 (1971).

283. S. N. Sawhney, S. K. Arora, and S. P. Singh, *Indian J. Chem. Soc., Sect. B*, **16**, 523 (1978); *Chem. Abstr.*, 89, 215300w.

284. L. Almiranti, A. Mugnaini, L. Polo Fritz, and E. Provinciali, *Boll. Chim. Pharm.*, **105**, 32 (1966); *Chem. Abstr.*, 65, 700b.

285. A. N. Krasovskii, N. Grins, A. K. Sheinkman, N. A. Klyuev, and A. B. Belikov, *Khim. Geterotsikl. Soedin*, **1978**, 476; *Chem. Abstr.*, 89, 43217f; Engl. transl. in *Chem. Heterocycl. Compd.*, **1978**, 388.

286. J. P. Paolini and L. J. Lendvay, *J. Med. Chem.*, **12**, 1031 (1969).

287. I. Iwai and T. Hiraoka, *Chem. Pharm. Bull.* (Tokyo), **12**, 813 (1964).

288. Sankyo Co. Ltd, Belgian Patent 660,274 (1965); *Chem. Abstr.*, 63, 18103b.

289. S. Kano and T. Noguchi, Japanese Patent 69 32,793 (1969); *Chem. Abstr.*, 72, 79041g.

290. K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **101**, 991 (1981); *Chem. Abstr.*, 96, 104144y.

291. V. Spiro, O. Migliari, and E. Ajello, *J. Heterocycl. Chem.*, **11**, 91 (1974).

292. L. Cavalca, P. Domiano, and A. Musatti, *Cryst. Struct. Commun.*, **1**, 345 (1972); *Chem. Abstr.*, 78, 21234e.

293. O. S. Anisimova, Yu. N. Sheinker, P. M. Kochergin, and I. A. Mazur, *Khim. Geterotsikl. Soedin*, **1974**, 935; *Chem. Abstr.*, 81, 104149u; Engl. transl. in *Chem. Heterocycl. Compd.*, **1974**, 816.

294. O. S. Anisimova, Yu. N. Sheinker, P. M. Kochergin, and A. N. Krasovskii, *Khim. Geterotsikl. Soedin*, **1974**, 778; *Chem. Abstr.*, **81**, 151141v; Engl. transl. in *Chem. Heterocycl. Compd.*, **1974**, 674.

295. L. Marchetti, L. Pentimalli, P. Lazzeretti, L. Schenetti, and F. Taddei, *J. Chem. Soc., Perkin Trans. II*, **1973**, 1926.

296. J. G. Fisher and G. T. Clark, U.S. Patent 3,804,823 (1974); *Chem. Abstr.*, **81**, 5119a.

297. J. G. Fisher and J. M. Straley, British Patent, 1,236,656 (1971); *Chem. Abstr.*, **75**, 119193d; see also idem, U.S. Patent 3,928,311 (1975); *Chem. Abstr.*, **84**, 91634h.

298. E. E. Glover and K. D. Vaughan, *J. Chem. Soc., Perkin Trans. I*, **1974**, 1137.

299. T. Pyl, K. H. Wuensch, and H. Beyer, *Justus Liebigs Ann. Chem.*, **657**, 108 (1962).

300. T. Pyl, R. Giebelmann and H. Beyer, *Justus Liebigs Ann. Chem.*, **643**, 145 (1961).

301. L. Pentimalli, G. Cogo, and A. M. Guerra, *Gazz. Chim. Ital.*, **98**, 488 (1967); *Chem. Abstr.*, **67**, 116850q.

302. N. O. Saldabol, L. L. Zeligman, S. A. Giller, Y. Y. Popelis, A. Abele, and L. N. Alekseeva, *Khim. Geterotsikl. Soedin*, **1972**, 1353; *Chem. Abstr.*, **78**, 43341q; Engl. transl. in *Chem. Heterocyl. Compd.*, **1972**, 1223.

303. J. F. Dawson and E. Teal, British Patent, 1,401,968 (1971); *Chem. Abstr.*, **84**, 19161j.

304. S. Kano, D. Takiguchi, and T. Noguchi, Japanese Patent 68 24,187 (1968); *Chem. Abstr.*, **70**, 57839e.

305. J. P. Paolini and L. J. Lendvay, U.S. Patent, 3,632,816 (1972); *Chem. Abstr.*, **76**, 126987q.

306. A. Andreani, D. Bonazzi, M. Rambaldi, and L. Greci, *Boll. Chim. Farm.*, **118**, 694 (1979); *Chem. Abstr.*, **93**, 150175v.

307. N. Saldabol, L. L. Zeligman, and L. A. Ritevskaya, *Khim. Geterotsikl. Soedin*, **1975**, 1208; *Chem. Abstr.*, **84**, 30960q; Engl. transl. in *Chem. Heterocycl. Compd.*, **1975**, 1051.

308. T. E. Hoover, S. Farber, and W. J. Becker, German Patent 2,008,494 (1980); *Chem. Abstr.*, **95**, 25057y.

309. N. O. Saldabol, L. L. Zeligman, Y. Y. Popelis, and S. A. Giller, *Khim. Geterotsikl. Soedin*, **1975**, 55; *Chem. Abstr.*, **83**, 9898v; Engl. transl. in *Chem. Heterocycl. Compd.*, **1975**, 45.

310. N. O. Saldabol and O. E. Lando, *Khim. Geterosikl. Soedin*, **1978**, 258; *Chem. Abstr.*, **88**, 190733d; Engl. transl. in *Chem. Heterocycl. Compd.*, **1978**, 211.

311. E. Costakis, M. Hamogeorgakis, and G. Tsatsas, *Chimica Chronika, New Series*, **7**, 171 (1978); *Chem. Abstr.*, **91**, 20398t.

312. H. Meyer, H. Horstmann, E. Moeller, and B. Garthoff, German Patent DE 3,020,421 (1981); *Chem. Abstr.*, **96**, 85561p.

313. T. Muro, T. Nakao, and K. Ogawa, Japanese Patent 76 11,784 (1976); *Chem. Abstr.*, **84**, 180225t.

314. E. Abigenti, F. Arena, P. De Caprariis, C. Ferreri, E. Marmo, R. Ottavo, F. Rossi, and M. Giasi, *Farmaco Ed. Sci.*, **36**, 893 (1981); *Chem. Abstr.*, **96**, 52258s.

315. (a) E. Abigenti, F. Arena, M. Arena, M. Carola, P. De Caprariis, A. P. Caputi, F. Rossi, L. Giordano, C. Vacca, E. Lampa, and E. Marmo, *Farmaco Ed. Sci.*, **34**, 417 (1979); *Chem. Abstr.*, **91**, 39390f; (*b*) E. Abigenti, F. Arena, P. De Caprariis, and L. Parenti, *Farmaco Ed. Sci.*, **31**, 880 (1976); *Chem. Abstr.*, **86**, 106472w.

316. T. Muro, K. Ogawa, and T. Nakao, Japanese Patent 76 125,097 (1976); *Chem. Abstr.*, **87**, 23271z.

317. A. Andreani, D. Bonazzi, and M. Rambaldi, *Farmaco Ed. Sci.*, **35**, 896 (1980); *Chem. Abstr.*, **94**, 139689r.

318. A. Andreani, D. Bonazzi, and M. Rambaldi, *Arch. Pharm.* (Weinheim), **315**, 451 (1982); *Chem. Abstr.*, 97, 72289b.

319. A. Andreani, M. Rambaldi, D. Bonazzi, and L. Greci, *Boll. Chim. Farm.*, **119**, 647 (1980); *Chem. Abstr.*, **94**, 19226p.

320. E. E. Glover and M. Yorke, *J. Chem. Soc.* (C), **1971**, 3280.

321. N. Abe, T. Nishikawa, and N. Komoto, *Bull. Chem. Soc. Japan.*, **53**, 3308 (1980); idem, *Chem. Lett.*, **1980**, 223; see also N. Abe, T. Nishikawa, T. Omori, and E. Harada, *Bull. Chem. Soc. Japan*, **55**, 200 (1982).

322. A. Andreani, D. Bonazzi, M. Rambaldi, G. Fabbri, and K. D. Rainsford, *Eur. J. Med. Chem–Chim. Ther.*, 17, 271 (1982); *Chem. Abstr.*, 97, 162885x.

323. S. Ordzhonikidze All-Union Scientific Research Chemical–Pharmaceutical Institute (P. M. Kochergin and T. A. Mazur); USSR Patent 196,868 (1967); *Chem. Abstr.*, 68, 95819q.

324. N. O. Saldabol and O. E. Lando, *Zh. Org. Khim.*, **13**, 2626 (1977); *Chem. Abstr.*, 88, 136573p; *Russ. J. Org. Chem.*, 13, 2438 (1977).

325. G. Tartler and W. Weuffen, *Pharmazie*, **21**, 425 (1966); *Chem. Abstr.*, **65**, 17418c.

326. L. Pentimalli and V. Passalacqua, *Boll. Sci. Fac. Chim. Ind. Bologna*, **24**, 205 (1966); *Chem. Abstr.*, **66**, 105869f.

327. J. W. Carpenter, J. D. Mee, and D. W. Heseltine, U.S. Patent 3,615,639 (1971); *Chem. Abstr.*, 77, 103346m; idem, German Patent 1,804,465 (1969); *Chem. Abstr.*, 74, 100620y.

328. Y. Hashimoto and S. Kano, Japanese Patent 74 06,099 (1974); *Chem. Abstr.*, **82**, 11375v.

329. Y. Hashimoto and S. Kano, Japanese Patent 73 19,715 (1973); *Chem. Abstr.*, 79, 61794q.

330. K. Nagarajan, V. P. Arya, S. J. Shenoy, R. K. Shah, A. N. Goud, and G. A. Bhat, *Indian J. Chem., Sect. B*, **15**, 629 (1977); *Chem. Abstr.*, 88, 37693w.

331. P. M. Kochergin, I. A. Mazur, and V. I. Fomenko, USSR Patent 226,622 (1968); *Chem. Abstr.*, **70**, 57844c.

332. P. E. Bender, German Patent 2,742,725 (1978); *Chem. Abstr.*, **89**, 24305s.

333. R. Goeschke and P. G. Ferrini, British Patent Application 2,039,882 (1980); *Chem. Abstr.*, 95, 43104r.

334. P. E. Bender and I. Lantos, U.S. Patent 4,175,127 (1979); *Chem. Abstr.*, **92**, 94397j.

335. H. A. Hammouda and N. Ishikawa, *Bull. Chem. Soc. Japan*, **51**, 3091 (1978).

336. P. M. Kochergin, *Zh. Obshch. Khim.*, **30**, 1529 (1960); *Chem. Abstr.*, **55**, 1586b; Engl. transl. in *J. Org. Chem. USSR*, **30**, 1542 (1960).

337. P. M. Kochergin and M. N. Shchukina, *Zh. Obshch. Khim.*, **26**, 2905 (1956); *Chem. Abstr.*, **51**, 8077g, *J. Gen. Chem. USSR*, **26**, 3233 (1956).

338. I. A. Mazur and P. M. Kochergin, *Khim. Geterotsikl. Soedin*, **1970**, 508; *Chem. Abstr.*, 73, 66501c; Engl. transl. in *Chem. Heterocycl. Compd.*, **1970**, 470.

339. P. M. Kochergin, *Zh. Obshch. Khim.*, **31**, 3267 (1961); *Chem. Abstr.*, **57**, 2208i; Engl. transl. in *J. Gen. Chem. USSR*, **31**, 3048 (1961).

340. A. Mustafa, M. I. Ali, M. A. Abou-State, and Abou-Elfotooh G. Hamman, *J. Prakt. Chem.*, **314**, 785 (1972); *Chem. Abstr.*, 78, 72002k.

341. R. P. Gupta and H. K. Pujari, *Indian J. Chem. Soc., Sect. B*, **16B**, 329 (1978); *Chem. Abstr.*, 89, 129450p.

342. M. I. Ali, M. A. Abou-State, and A. Fouad Ibrahim, *J. Prakt. Chem.*, **316**, 147 (1974); *Chem. Abstr.*, **81**, 49638a.

343. Yu. V. Markova, K. K. Kuz'mina, E. M. Peresleni, and M. N. Shchukina, *Zh. Org.*

Khim., **1**, 1475 (1965); *Chem. Abstr.*, **64**, 2080h; Engl. transl. in *J. Org. Chem. USSR*, **1**, 1494 (1965).

344. I. A. Mazur, P. M. Kochergin, and V. I. Fomenko, *Khim. Farm. Zh.*, **3**, 11 (1969); *Chem. Abstr.*, **72**, 12645p.

345. C. Jeanmart, M. N. Messer, and P. E. Simon, German Patent 1,900,974 (1969); *Chem. Abstr.*, **71**, 91483q; Societé des Usines Chimiques Rhone-Poulenc, French Patent M7391 (1969); *Chem. Abstr.*, **78**, 43477p.

346. S. Kano and T. Taniguchi, Japanese Patent 73 19, 592 (1973); *Chem. Abstr.*, **78**, 147964m.

347. Metabio, German Patent 2,709,639 (1977); *Chem. Abstr.*, **88**, 22910r.

348. K. Noda, A. Nakagawa, S. Miyata, and H. Ide, Japanese Patent 79 12,393 (1979), *Chem. Abstr.*, **91**, 52265.

349. Ciba-Geigy A. G., Japanese Patent 79 16,470 (1979); *Chem. Abstr.*, **91**, 57003m.

350. P. E. Bender, U.S. Patent 4,263,311 (1981); *Chem. Abstr.*, **95**, 97797n.

351. I. A. Mazur and P. M. Kochergin, *Khim. Geterotsikl. Soedin*, **1967**, 894; *Chem. Abstr.*, **68**, 105109z; Engl. transl. in *Chem. Heterocycl. Compd.*, **1967**, 706.

352. A. Ali and R. K. Saksena, *Indian J. Chem. Soc.*, **58**, 1117 (1981); *Chem. Abstr.*, **96**, 104145z.

353. A. Andreani, M. Rambaldi, and D. Bonazzi, *Farmaco Ed. Sci.*, **35**, 573 (1980); *Chem. Abstr.*, **93**, 186243e.

354. M. Fefer and L. C. King, *J. Org. Chem.*, **26**, 828 (1961).

355. V. K. Chadha, H. S. Chaudhari, and H. K. Pujari, *Indian J. Chem.*, **8**, 885 (1970); *Chem. Abstr.*, **74**, 13059d.

356. H. R. Snyder and L. E. Benjamin, *J. Med. Chem.*, **9**, 402 (1966).

357. C. J. Sharpe, R. S. Shadbolt, A. Ashford, and J. W. Ross, *J. Med. Chem.*, **14**, 977 (1971).

358. V. P. Arya and V. Honkan, *Indian J. Chem., Sect. B*, **14**, 752 (1976); *Chem. Abstr.*, **87**, 39210q.

359. K. C. Joshi, V. N. Pathak, and P. Arya, *Agric. Biol. Chem.*, **41**, 543 (1977); *Chem. Abstr.*, **87**, 53140y.

360. M. Baboulene and G. Sturz, *Phosphorus and Sulfur*, **5**, 87 (1978); *Chem. Abstr.*, **90**, 168672c.

361. E. Campaigne and T. P. Selby, *J. Heterocycl. Chem.*, **17**, 1255 (1980).

362. L. J. Powers, S. W. Fogt, Z. S. Ariyan, D. J. Rippin, R. D. Heilman, and R. J. Matthews, *J. Med. Chem.*, **24**, 604 (1981).

363. V. K. Chadha and H. K. Pujari, *Can. J. Chem.*, **47**, 2843 (1969).

364. K. S. Dhaka, V. K. Chadha, and H. K. Pujari, *Aust. J. Chem.*, **26**, 435 (1973).

365. R. E. Moser, L. J. Powers, and Z. S. Ariyan, German Patent 2,701,853 (1977); *Chem. Abstr.*, **87**, 135310t.

366. R. F. Manning, U.S. Patent 3,551,426 (1970); *Chem. Abstr.*, **74**, 88042b.

367. P. L. Anderson and R. E. Manning, U.S. Patent 3,557,110 (1971); *Chem. Abstr.*, **74**, 100086d.

368. Chimetron S.a.r.l., French Patent 1,488,314 (1967); *Chem. Abstr.*, **69**, 59238m.

369. J. K. Landquist, British Patent 1,072,579 (1967); *Chem. Abstr.*, **68**, 59568y.

370. C. P. Krimmel, U.S. Patent 2,969,369 (1961); *Chem. Abstr.*, **55**, 15513d.

371. E. C. Taylor, G. A. Berchtold, N. A. Goeckner, and F. G. Stroehmann, *J. Org. Chem.*, **26**, 2715 (1961).

372. R. M. Dodson, U.S. Patent 2,933,497 (1960); *Chem. Abstr.*, **54**, 24805e.

373. A. H. M. Raeymakers, F. T. N. Allewijn, J. Vandenberk, P. J. A. Demoen, T. T. T. Offenwert, and P. A. J. Janssen, *J. Med. Chem.*, **9**, 545 (1966).

374. Chimetron S.a.r.l., French Patent 1,565,320 (1969); *Chem. Abstr.*, **72**, 79039n.

375. K. K. Bhargava, M. H. Lee, Y.-M. Huang, L. D. Cunningham, K. C. Agrawal, and A. C. Sartorelli, *J. Med. Chem.*, **20**, 563 (1977).

376. American Cyanamide Co., Japanese Patent 75 76,084 (1975); *Chem. Abstr.*, **85**, 123904k.

377. E. K. Dora, B. Dash, and C. S. Panda, *J. Indian Chem. Soc.*, **56**, 620 (1979); *Chem. Abstr.*, **93**, 8081t.

378. H. V. Maudling and M. A. Zoglio, *J. Pharm. Sci.*, **60**, 309 (1971); *Chem. Abstr.*, **74**, 80440j.

379. R. M. Acheson, M. W. Cooper, and I. R. Cox, *J. Chem. Soc., Perkin Trans I*, **1980**, 1773.

380. H. R. Snyder and L. E. Benjamin, *J. Med. Chem.*, **13**, 164 (1970).

381. R. M. Acheson, I. R. Cox, J. K. Stubbs, and A. B. Penrose, South African Patent 76 06,646 (1976); *Chem. Abstr.*, **88**, 84595a; idem, German Patent 2,650,428 (1977); *Chem. Abstr.*, **87**, 102316w; R. M. Acheson, J. K. Stubbs, C. A. R. Baxter, and D. E. Kuhla, German Patent 2,444,890 (1975); *Chem. Abstr.*, **83**, 79230v; D. E. Kuhla, U.S. Patent 3,860,718 (1975); *Chem. Abstr.*, **82**, 140133p.

382. L. D. Spicer and J. J. Hand, South African Patent 70 07,849 (1970); *Chem. Abstr.*, **76**, 140815p.

383. Y. Miki and M. Koshi, Japanese Patent 78 147,086 (1978); *Chem. Abstr.*, **91**, 20500v.

384. Y. Miki and M. Koshi, Japanese Patent 78 144,595 (1978); *Chem. Abstr.*, **91**, 20502x.

385. R. J. Dorgan, European Patent Application EP 46,377 (1982); *Chem. Abstr.*, **96**, 217845w.

386. H. Kohn and R. E. Davis, *J. Org. Chem.*, **42**, 72 (1977); see also H. Kohn, *J. Am. Chem. Soc.*, **98**, 3690 (1976).

387. D. C. Bigg, European Patent Application 2,400 (1979); *Chem. Abstr.*, **92**, 22501r.

388. D. Thienpont, O. F. J. Vanparijis, A. H. M. Raeymaekers, J. Vandenberk, P. J. A. Demoen, F. T. N. Allewijn, R. P. H. Marsboom, C. J. E. Niemegeers, K. H. L. Schellekens, and P. A. J. Janssen, Nature, **209**, 1084 (1966).

389. L. A. Cott, *J. Chem. Soc.* (C), **1966**, 1226.

390. H. Dorn and H. Welfe, *Chem. Ber.*, **100**, 3246 (1967).

391. H. Dorn, M. Schuett, and H. Welfe, East German Patent 34,860 (1964); *Chem. Abstr.*, **63**, 11570h; W. Weuffen and H. Dorn, *Pharmazie*, **22**, 580 (1967); *Chem. Abstr.*, **68**, 10568j.

392. S. Nielek and T. Lesiak, *Chem. Ber.*, **115**, 1247 (1982).

393. J. Kreidl, G. Visky, L. Czibula, J. Felmeri, and B. Benko, Hungarian Patent 21,679; *Chem. Abstr.*, **97**, 127639y.

394. Janssen Pharmaceutica N.V., Netherlands Patent 6,505,806; *Chem. Abstr.*, **64**, 11213f.

395. L. D. Spicer and J. J. Hand, U.S. Patent 3,989,835 (1970); *Chem. Abstr.*, **86**, 72644m; French Patent 2,199,979 (1974); *Chem. Abstr.*, **82**, 16835e; German Patent 2,147,857 (1973); *Chem. Abstr.*, **79**, 53326y; South African Patent 71 05,803 (1972); *Chem. Abstr.*, **78**, 72151h; German Patent 2,114,563 (1971); *Chem. Abstr.*, **77**, 19650y; U.S. Patent 4,014,892 (1977).

396. Chimetron S.a.r.l., French Patent 1,488,271 (1967); *Chem. Abstr.*, **69**, 43909v.

397. Chimetron S.a.r.l., French Patent 1,483,322 (1967); *Chem. Abstr.*, **69**, 43914t.

398. Chimetron S.a.r.l., French Patent 1,488,268 (1967); *Chem. Abstr.*, **69**, 59243j.

399. Chimetron S.a.r.l., French Patent 1,488,269 (1967); *Chem. Abstr.*, **69**, 59262q.

400. S. Nielek and T. Lesiak, *Collect. Lect. – Internatl. Symp. Furan Chem. 3rd.*, 224 (1979); *Chem. Abstr.*, **92**, 163900g.

401. A. Balien and J. Koln, Australian Patent 413,243 (1971); *Chem. Abstr.*, **76**, 59626f.

402. Imperial Chemical Industries of Australia and New Zealand, Netherlands Patent Application 6,610,166 (1967); *Chem. Abstr.*, **68**, 49591m.

403. Americal Cyanamid Co., British Patent 1,076,109 (1967); *Chem. Abstr.*, **68**, 78276t.

404. K. Horsanyi, R. Szebeni, P. Kiss, D. Korobnits, K. Takacs, G. Heja, and G. Kormoczy, German Patent 2,065,854 (1976); *Chem. Abstr.*, **85**, 123925t; German Patent 2.034,081 (1971); *Chem. Abstr.*, **75**, 36037e.

405. M. E. McMenim, USSR Patent SU 847,915 (1981); *Chem. Abstr.*, **96**, 6727w.

406. M. E. McMenim, German Patent 2,236,970 (1973); *Chem. Abstr.*, **78**, 124588c.

407. O. Maruyama, T. Kawashima, and M. Yokoyama, Japanese Patent 79 114,393 (1979); *Chem. Abstr.*, **92**, 181186h.

408. A. Forbes Cameron, I. R. Cameron, and F. D. Duncanson, *J. Chem. Soc., Perkin Trans. II*, **1981**, 789.

409. A. H. M. Raeymaekers, L. F. C. Roevens, and P. A. J. Janssen, *Tetrahedron Lett.*, **1967**, 1467.

410. Imperial Chemical Industries (Australia and New Zealand) Ltd., British Patent 1,169,310 (1969); *Chem. Abstr.*, **72**, 55453s.

411. T. Leigh, *Chem. Ind.* (London), **1970**, 1016.

412. E. Fogassy, M. Acs, J. Felmeri, and Z. Aracs, *Period Polytech. Chem. Eng.*, **20**, 247 (1976); *Chem. Abstr.*, **87**, 68233e.

413. R. Goschke and P. G. Ferrini, European Patent Application 13,560 (1980); *Chem. Abstr.*, **94**, 47329v.

414. H. J. M. Dou, M. Ludwikow, P. Hassanaly, J. Kister, and J. Metzger, *J. Heterocycl. Chem.*, **17**, 393 (1980).

415. K. Okada, J. A. Kelly, and J. S. Driscoll, *J. Org. Chem.*, **42**, 2594 (1977).

416. D. F. Bushey and T. D. J. D'Silva, European Patent Application EP 43,263 (1982); *Chem. Abstr.*, **96**, 199666g.

417. J. Ashby and D. Griffiths, *J. Chem. Soc., Perkin Trans. I*, **1975**, 657.

418. A. H. M. Raeymaekers, D. C. A. Cornil, and P. J. A. W. Demoen, USSR Patent 588,921 (1978); *Chem. Abstr.*, **88**, 152619p.

419. Deutsche Advance Produktion G.m.b.h., Belgian Patent 622,292 (1962); *Chem. Abstr.*, **59**, 15446f.

420. I. I. Chizhevskaya and M. I. Zavadskaya, *Zh. Org. Khim.*, **4**, 1116 (1968); *Chem. Abstr.*, **69**, 52071t.

421. I. I. Chizhevskaya and M. I. Zavadskaya, *Khim. Geterotsikl. Soedin*, **1971**, 93; *Chem. Abstr.*, **77**, 164592k.

422. H. S. Chaudhari and H. K. Pujari, *J. Indian Chem. Soc.*, **45**, 710 (1968); *Chem. Abstr.*, **70**, 3936r.

423. R. E. Manning, German Patent 2,000,788 (1970); *Chem. Abstr.*, **73**, 66600j.

424. W. J. Houlihan and R. E. Manning, Swiss Patent 507,290 (1971); *Chem. Abstr.*, **75**, 118334p.

425. P. H. L. Wei and C. Bell, U.S. Patent 3,853,872 (1974); *Chem. Abstr.*, **82**, 140202k.

426. G. Ferrand, French Patent 2,414,510 (1979); *Chem. Abstr.*, **92**, 215470p.

427. Synthelabo S. A., Japanese Patent 80 111,492 (1980); *Chem. Abstr.*, **94**, 103411e.

428. M. A. Iradyan, V. S. Mirzoyan, and R. A. Aroyan, *Arm. Khim. Zh.*, **33**, 506 (1980); *Chem. Abstr.*, **94**, 14661u.

429. H. J. Lang and R. Muschaweck, Patent Specifications (Aust.), AV 514,406 (1981); *Chem. Abstr.*, **96**, 142843h.

430. D. Bigg, French Patent 2,479,831 (1981); *Chem. Abstr.*, **96**, 162715z.

431. K.-C. Liu, J. Y. Tuan, and B. J. Shih, *J. Chim. Chem. Soc.* (Taipei), **24**, 65 (1977); *Chem. Abstr.*, **87**, 135200g.

432. U. Voegeli, W. Von Philipsborn, K. Nagarajan, and M. D. Nair, *Helv. Chim. Acta*, **61**, 607 (1978).

433. A. McKillop, G. C. A. Bellinger, P. N. Preston, A. Davidson, and T. J. King, *Tetrahedron Lett.*, **1978**, 2621.

434. L. A. Cort, *J. Chem. Soc.*, **1965**, 3456.

435. E. Campaigne and M. C. Wani, *J. Org. Chem.*, **29**, 1715 (1964).

436. A. F. A. Shalaby, H. A. Daboun, and M. A. Abdel Aziz, *Z. Naturf.*, **31B**, 111 (1976); *Chem. Abstr.*, **84**, 121725h.

437. Z. Olszenko-Piontkowa and T. Urbanski, *Bull. Acad. Pol. Sci. Ser. Sci. Chim.*, **17**, 351 (1969); *Chem. Abstr.*, **72**, 31692t.

438. F. DeBarre, C. Jeanmart, and P. E. Simon, German Patent 2,359,864 (1972); *Chem. Abstr.*, **81**, 91520f.

439. P. C. Thieme and E. Haedicke, *Justus Liebigs Ann. Chem.*, **1978**, 227; *Chem. Abstr.*, **89**, 109234t.

440. B. R. Webster, *J. Chem. Soc., Chem. Commun.*, **1966**, 124.

441. H. V. Maudling and M. A. Zoglio, *J. Pharm. Sci.*, **66**, 1175 (1977); *Chem. Abstr.*, **87**, 172796b.

442. D. C. H. Bigg, A. W. Faull, and R. S. Purvis, *J. Heterocycl. Chem.*, **14**, 989 (1977).

443. J. A. van Allen, *J. Org. Chem.*, **21**, 24 (1956).

444. I. I. Chizheviskaya, L. I. Gopanovich, and R. S. Kharchenko, *Zh. Khim.*, **1968**, Abstr. No. 8Zh 381; *Chem. Abstr.*, **70**, 106421y.

445. I. I. Chizhevskaya and M. I. Zavadskaya, *Vesti Akad. Navuk Belarus SSR, Ser. Khim. Navuk*, **1970**, 77; *Chem. Abstr.*, **74**, 52890n.

446. A. H. Harhash, M. H. Elnagdi, S. Ezz-el-Din, and K. M. Foda, *Indian J. Chem.*, **13**, 238 (1975); *Chem. Abstr.*, **83**, 131513f.

447. J. E. Thorpe, German Patent 2,718,976 (1977); *Chem. Abstr.*, **88**, 50866z.

448. R. J. Dorgan and R. A. Webster, European Patent Application EP 41,322 (1981); *Chem. Abstr.*, **96**, 142847n.

449. M. R. G. Leeming and J. K. Stubbs, German Patent 2,747,121 (1978); *Chem. Abstr.*, **89**, 24311r.

450. Pfizer Corporation, French Patent, 2,368,492 (1978); *Chem. Abstr.*, **90**, 152182g.

451. American Cyanamide Co., French Patent 2,153,206 (1973); *Chem. Abstr.*, **79**, 92223g.

452. D. C. H. Bigg, European Patent Application 2,978 (1979); *Chem. Abstr.*, **92**, 163956e.

453. D. C. H. Bigg, A. W. Faull, and S. R. Purvis, *J. Heterocycl. Chem.*, **14**, 603 (1977).

454. A. B. A. Jansen and R. Robinson, *Monatsh. Chem.*, **98**, 1017 (1967); *Chem. Abstr.*, **67**, 73546a.

455. R. Sharma and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. I*, **1980**, 2001.

456. W. Clegg, *Acta Crystallogr., Sect. B*, **B34**, 3460 (1978); *Chem. Abstr.*, **90**, 32299d.

457. T. Pyl, O. Sietz, and K. Staege, *Justus Liebigs Ann. Chem.*, **679**, 144 (1964).

458. V. G. Ermolaeva and M. N. Shchukina, *Khim. Geterotsikl. Soedin*, **1967**, 84; *Chem. Abstr.*, **67**, 540649; Engl. transl. in *Chem. Heterocycl. Compd.*, **1967**, 59.

459. P. M. Kochergin, A. M. Tsyganova, and L. M. Viktorova, *Khim. Geterotsikl. Soedin*,

1967, 93: *Chem. Abstr.*, **67**, 64298u; Engl. transl. in *Chem. Heterocycl. Compd.* **1967**, 66.

460. V. G. Ermolaeva, T. N. Zykova, G. N. Pershin, and M. N. Shchukina, *Khim. Farm. Zh.*, **1**, 19 (1967); *Chem. Abstr.*, **67**, 64288r; Engl. transl. in *Pharm. Chem. J.*, **1**, 17 (1967).

461. A. F. A. Shalaby, M. A. Abdel Aziz, and S. S. M. Boghdadi, *Z. Naturf.*, **36B**, 501 (1981).

462. R. B. Woodward, in *The Chemistry of Penicillin* (H. T. Clarke, J. R. Johnson, and R. Robinson, Eds.), Princeton University Press, Princeton, NJ, 1949, pp. 445, 453.

463. W. L. Mosby, *Heterocyclic Compounds with Bridgehead Nitrogen, Part 1*, Interscience, New York, 1961, pp. 151–156.

464. I. N. Blinova and A. S. Khokhlov, *Antibiotik*, **12**, 275 (1967); *Chem. Abstr.*, **67**, 64289s.

465. P. H. Bentley, J. P. Clayton, M. O. Boles, and R. J. Girven, *J. Chem. Soc., Perkin Trans. I*, **1979**, 2455.

466. M. R. Bell, S. D. Clemans, R. Oesterlin, and J. A. Carlson, *J. Heterocycl. Chem.*, **11**, 823 (1974).

467. K. P. Prasad and T. Petrzilka, *Helv. Chim. Acta*, **58**, 2504 (1975).

468. A. Ballio, E. B. Chain, F. Dentice Di Accadia, M. Mauri, K. Rauer, M. J. Schlesinger, and S. Schlesinger, *Nature*, **191**, 909 (1961).

469. D. A. Johnson and G. A. Hardcastle, *J. Am. Chem. Soc.*, **83**, 3534 (1961); idem, French Patent 1,320,530 (1963); *Chem. Abstr.*, **60**, 2938f; see also F. R. Batchelor, D. Gazzard, and J. H. C. Nayler, *Nature*, **191**, 910 (1961).

470. D. H. Bremner, M. M. Campbell, and G. Johnson, *J. Chem. Soc., Perkin Trans. I*, **1976**, 1918; idem, *J. Chem. Soc. Chem. Commun.*, **1976**, 293.

471. Mitsubishi Chemical Industries Co. Ltd., Japanese Patent 81 61,390 (1981); *Chem. Abstr.*, **95**, 115553m; see also Japanese Patent 79 157,590 (1979); *Chem. Abstr.*, **93**, 46682x; European Patent Application 6,663 (1980); *Chem. Abstr.*, **93**, 114517z.

472. T. A. Crabb, M. J. Hall, and R. O. Williams, *Tetrahedron*, **29**, 3389 (1973).

473. M. J. O. Anteunis, W. A. Nachtergaele, and M. Budesinsky, *Bull. Soc. Chim. Belg.*, **88**, 233 (1979); *Chem. Abstr.*, **91**, 81317n.

474. Mitsubishi Chemical Industries Co. Ltd., Japanese Patent 81 61,391 (1981); *Chem. Abstr.*, **95**, 115554n.

475. J. Nakano, H. Kanda, Y. Nakamura, M. Nakata, and M. Tomita, *Tetrahedron Lett.*, **1976**, 2797.

476. P. J. Chivers and T. A. Crabb, *Tetrahedron*, **26**, 3389 (1970).

477. R. E. Manning, U.S. Patent 3,555,039 (1971); *Chem. Abstr.*, **74**, 100057v.

478. R. E. Manning, U.S. Patent 3,547,939 (1970); *Chem. Abstr.*, **74**, 141805c.

479. S.-W. Park, W. Reid, and W. Schuckmann, *Angew. Chem., Internatl. Ed. Engl.*, **15**, 494 (1976).

480. O. Tsuge, S. Kanemasa, and T. Hamamoto, *Chem. Lett.*, **1982**, 1491.

481. O. Tsuge, S. Kanemasa, and T. Hamamoto, *Chem. Lett.*, **1983**, 85.

482. O. Tsuge, S. Kanemasa, and T. Hamamoto, *Heterocycles*, **20**, 647 (1983).

483. R. L. Martin and B. E. Norcross, *J. Org. Chem.*, **40**, 523 (1975).

484. S. Bory and A. Marquet, *Tetrahedron Lett.*, **1976**, 2033.

485. A. Marquet, *Pure Appl. Chem.*, **49**, 183 (1977).

486. C. Lindblow-Kull, F. J. Kull, and A. Shrift, *Biochem. Biophys. Res. Commun.*, **93**, 572 (1980); *Chem. Abstr.*, **92**, 194157z.

487. R. N. Hanson, R. W. Giese, M. A. Davis, and S. M. Costello, *J. Med. Chem.*, **21**, 496 (1978).

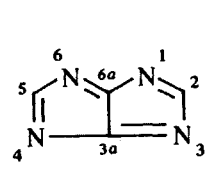
Chemistry of Heterocyclic Compounds, Volume 46
P. N. Preston

CHAPTER 3

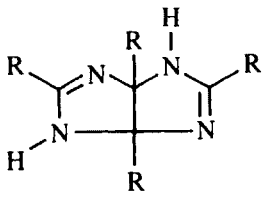
Condensed Imidazoles of Type 5-5 with Two Additional Heteroatoms

3.1. RING SYSTEM C_3N_2–C_3N_2: IMIDAZO[4,5-*d*]IMIDAZOLE

Compounds in the fully unsaturated imidazo[4,5-*d*]imidazole ring system (**3.1**) are unusual, and this section is concerned almost entirely with tetrahydro compounds (**3.2**–**3.4**). The latter group contains isolated examples of 1,3*a*,4,6*a* (**3.2**) and 3,3*a*,4,6*a*-tetrahydro (**3.3**) derivatives but is dominated by the chemistry of tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)dione ("glycoluril," **3.4**; R = H) and related compounds.

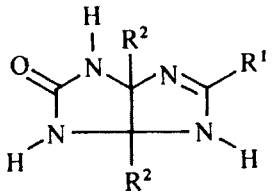


(3.1)



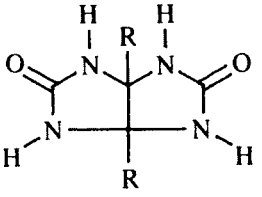
(3.2)

R = Ph



(3.3)

R^1 = hetaryl;
R^2 = Me, aryl

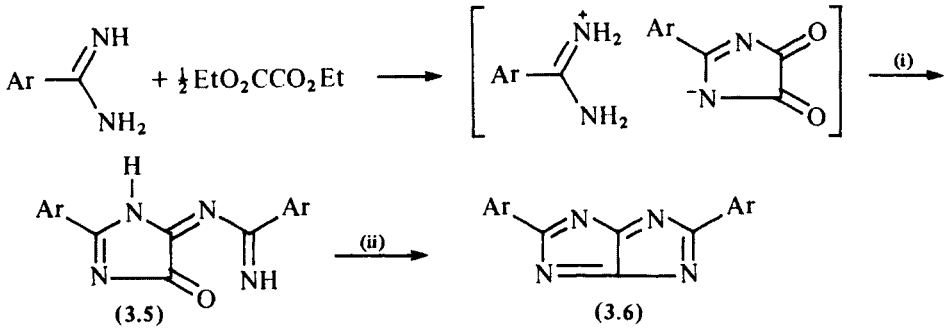


(3.4)

R = e.g., H, alkyl, aryl

3.1.1. Imidazo[4,5-*d*]imidazoles

2,5-Diarylimidazo[4,5-*d*]imidazoles (**3.6**) have been synthesized[1] by means of imidazolinylidenebenzamidines (**3.5**) in the manner outlined in Scheme 3.1. The uv spectrum of the phenyl derivative (**3.6**; Ar = Ph) exhibits λ_{max} = 278 mm (ϵ, 500), and the ir spectra of all the aryl compounds (cf. **3.6**) contain characteristic ir bands at 1590, 1530, 1505, 1370, and 1170 cm^{-1}. Several attempts[1] to reduce the diaryl derivatives (**3.6**) (e.g., using Li–NH_3, Li–THF, $NaBH_4$–DMF) resulted in the formation of complex mixtures, and no pure compounds could be isolated.



(3.5) (3.6)

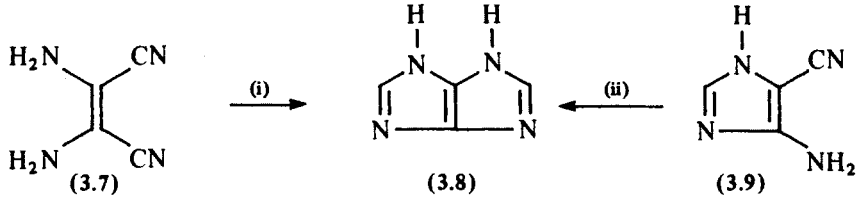
Ar	mp (°C)	Yield (%)
Ph	181.5–183 (EtOAc)	50
p-MeC_6H_4	236.5–239 (DMF)	47
p-$MeOC_6H_4$	175 ($MeCN$–$CHCl_3$)	41
3,4,5-$(MeO)_3C_6H_2$	236–238 ($CHCl_3$)	22

(i) 200°C, 20 min (neat); (ii) $POCl_3$, pyridine, 90°C, 3 h

Scheme 3.1

3.1.2. 1,6-Dihydroimidazo[4,5-*d*]imidazoles

The parent, unsubstituted compound in this group (**3.8**) is formed in 20% yield by uv photolysis of 1,2-diamino-1,2-dicyanoethene (**3.7**) in tetrahydrofuran;[2] 4-aminoimidazole-5-carbonitrile (**3.9**) is an intermediate in this transformation and can also be converted rapidly by photolysis into the bicyclic product. The 1,6-dihydro compound (**3.8**) exhibits the following spectral properties: uv λ_{max}^{MeOH} = 210 nm (log ϵ 3.64), 242 (3.79); ^{1}H nmr (DMSO-d_6) δ = 3.70 (br, 2H, exch., NH), 7.72 (s, 2H, CH).

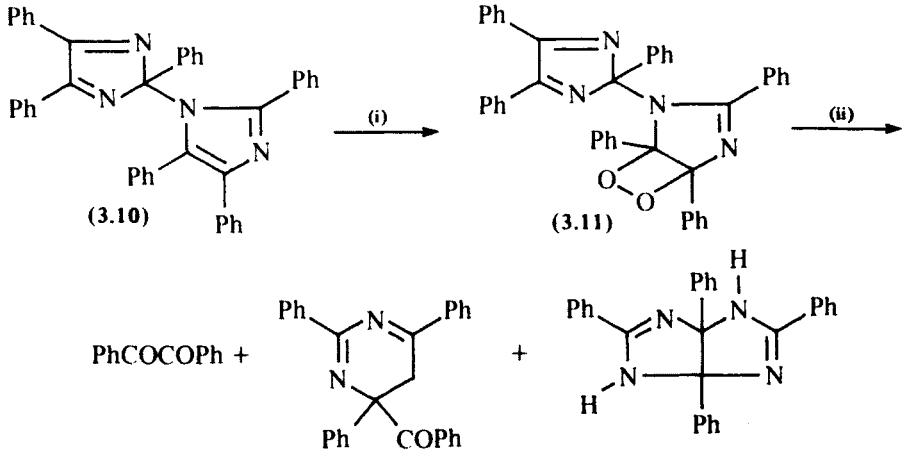


(3.7) (3.8) (3.9)

(i) uv light (254 nm), THF, 35 h; mp 265°C (EtOH);
(ii) uv light (254 nm), MeCN, 10 min bistosylate salt, mp 260°C (dec.)

3.1.3. 1,3*a*,4,6*a*-Tetrahydroimidazo[4,5-*d*]imidazoles

It is claimed[3] that 1,3*a*,4,6*a*-tetrahydro-2,3*a*,5,6*a*-tetraphenylimidazo[4,5-*d*]-imidazole (**3.12**) is formed reductively from the photooxidation product (**3.11**) of the lophyl radical dimer (**3.10**) (see Scheme 3.2); the relative yield of the bicyclic product (**3.12**) is increased when the reduction is effected in acidic conditions. There are no published spectroscopic data available to support the structural formulation (**3.12**).



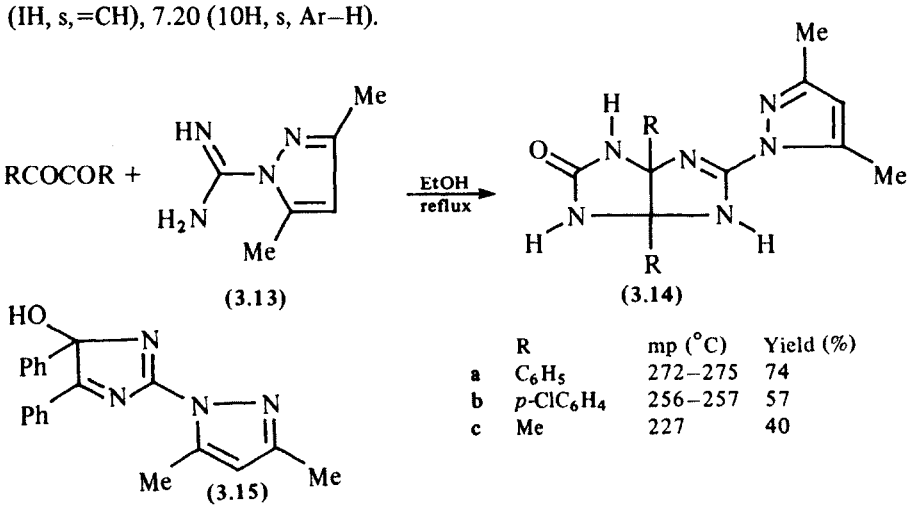
(3.12)

(i) uv light, methylene blue, CH_2Cl_2—MeOH, −50°C; mp 378–380°C
(ii) NaI, −50°C

Scheme 3.2

3.1.4. 3,3*a*,4,6*a*-Tetrahydroimidazo[4,5-*d*]imidazoles

Treatment of benzils and butan-2,3-dione with 1-amidino-3,5-dimethylpyrazole (**3.13**) gives reasonable yields of pyrazol-1-yl derivatives of 3,3*a*,4,6*a*-tetrahydroimidazo[4,5-*d*]imidazoles (**3.14**), and not the pyrazole derivative (e.g., **3.15**) as might have been anticipated;[4] the mechanism of this process has not been elucidated, but the formulation (cf. **3.14**) has been established by transforming **3.14a** by acidic hydrolysis into tetrahydro-3*a*,6*a*-diphenylimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*) dione. The following spectral data have been described[4] for **3.14a**: ir ν_{CO} = 1705 cm^{-1}; ^{1}H nmr (CF_3CO_2D) δ = 2.42 and 2.75 (3H, 3H, s, Me), 6.45 (IH, s, =CH), 7.20 (10H, s, Ar–H).



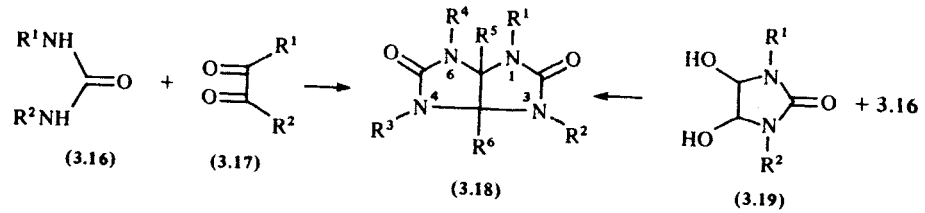
	R	mp (°C)	Yield (%)
a	C_6H_5	272–275	74
b	*p*-ClC_6H_4	256–257	57
c	Me	227	40

3.1.5. Synthesis and Reactions of Glycoluril [Tetrahydroimidazo[4,5-*d*]-imidazole-2,5(1*H*,3*H*)dione] and Related Compounds

3.1.5.1. Synthesis from Ureas

Condensed imidazolidinones of the glycoluril type (**3.18**) are inexpensive to prepare and have attracted considerable attention from a commercial viewpoint (see Section 3.1.5.7). They were first prepared over 100 years ago by the acid-promoted condensation of glyoxal (**3.17**; $R^1 = R^2 = H$) with urea and its derivatives (**3.16**), or with glyoxal monoureide (4,5-dihydroxyimidazolidin-2-one, **3.19**). The early literature is summarized in ref. 5, patented procedures are covered in refs. 11 and 12, and examples of these and related processes are collected in Table 3.1. The parent, unsubstituted derivative (**3.18**, R^1–R^6 = H) is obtained by heating 30% glyoxal and urea in dilute hydrochloric acid; it is a high-melting solid, insoluble in most solvents, including dimethylformamide and dimethylsulfoxide, and exhibits ir spectral bands at 1680 and 3200 cm^{-1}.[5] The regiochemical outcome of condensations of unsymmetrical ureas with glyoxal has been studied in detail.[5,7]

TABLE 3.1. SYNTHESIS OF TETRAHYDROIMIDAZO[4,5-*d*]IMIDAZOLES (**3.18**) ("GLYCOLURILS") FROM UREA DERIVATIVES (**3.16**) AND IMIDAZOLIDINONES (**3.19**)



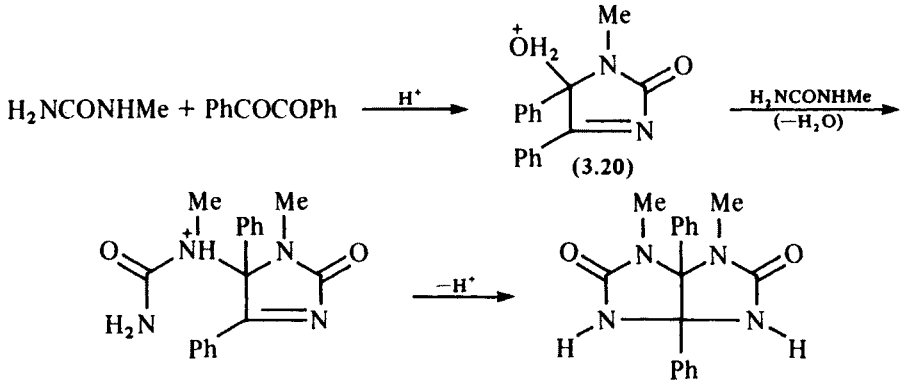
Starting Materials	Product (**3.18**) R¹	R²	R³	R⁴	R⁵	R⁶	Reaction Conditions[a]	mp (°C) (Solvent for Recrystallization)	Yield (%)	Reference
3.16 + **3.17**	H	H	H	H	H	H	A	300 (dec.)	78	5
3.16 + **3.19**	*i*-Pr	H	H	H	H	H	A	248–249	51	6
3.16 + **3.19**	*n*-Bu	H	H	H	H	H	A	267–268	32	6
3.16 + **3.19**	Ph	H	H	H	H	H	A	300	82	6
3.16 + **3.19**	CH_2Ph	H	H	H	H	H	A	283–284	65	6
3.16 + **3.17**	Me	H	Me	H	H	H	A	268–270 (MeOH)	–[b]	5,7
3.16 + **3.17**	Me	H	H	Me	H	H	A	298–300 (MeOH)	–[c]	5,7

3.16 + 3.17	Ph	H	H	Ph	H	H	A	375–380 (cyclohexanone)	22	5,7
3.16 + 3.17	*i*-Pr	H	*i*-Pr	H	H	H	A	291–293 (C_6H_6–MeOH)	20	7
3.16[c] **+ 3.17**	Me	H	Ph	H	H	H	A	283–285 (C_6H_6–MeOH)	22	7
3.16[c] **+ 3.17**	C_6H_{11}	H	Ph	H	H	H	A	> 300 (cyclohexanone)	18	7
3.16[c] **+ 3.17**	*i*-Pr	H	Ph	H	H	H	A	> 300 (EtOH)	15	7
3.16[d] **+ 3.17**	Ph	Me	Me	H	H	H	A	252–254 (C_6H_6–MeOH)	24	7
3.16 + 3.19	Me	Me	H	H	H	H	A	254–256	27	6
3.16 + 3.19	*i*-Pr	*i*-Pr	H	H	H	H	A	248–249	51	6
3.16 + 3.17	H	H	H	H	Ph	Ph	B	300		8
3.16 + 3.17	Me	H	H	Me	Ph	Ph	B	300 (EtOH)		8
3.16 + 3.17	H	H	H	H	Me	Ph	B	348		9
3.16 + 3.17	Me	H	Me	H	Me	Me	B	305[e]		10
3.16 + 3.17	Me	H	H	Me	Me	Me	B	305[e]		10

[a] Reaction conditions: (A) reflux in aqueous hydrochloric acid; (B) CF_3CO_2H, C_6H_6, reflux with continuous removal of water (Dean–Stark apparatus).
[b] Formed together with the 1,6-dimethyl isomer, combined yield 62%.
[c] Formed together with 1,3-dimethyl isomer, combined yield 62%.
[d] Two urea derivatives are used in this condensation.
[e] Melting point of mixture with the 1,6-isomer quoted, combined yield 62%.
[f] mp of mixture with the 1,3-isomer quoted, combined yield 62%.

Thus 1-methylurea is transformed[5] into a 7:4 mixture of 1,4- and 1,6-dimethyl derivatives (cf. **3.18**), whereas 1-isopropylurea and 1-phenylurea afford single bicyclic products of 1,4-disubstitution; surprisingly, the condensation of glyoxal with an equimolar mixture of 1-methylurea and 1-phenylurea gives the 1,4-dissymmetrically substituted derivative (**3.18**; R^1 = Ph, R^3 = Me, R^2 = R^4 = R^5 = R^6 = H) as the major product in 22% yield when six compounds could possibly arise.[7]

Formation of the 1,6-dimethyl bicyclic adduct (**3.21**) as the sole product from 1-methlyurea and benzil has been rationalized[8] according to the mechanism outlined in Scheme 3.3; a key step in this process is attack at the protonated intermediate (**3.20**) by the more nucleophilic alkylated nitrogen of 1-methylurea.

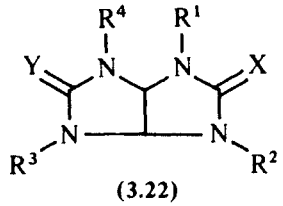


Scheme 3.3

(3.20)

(3.21)

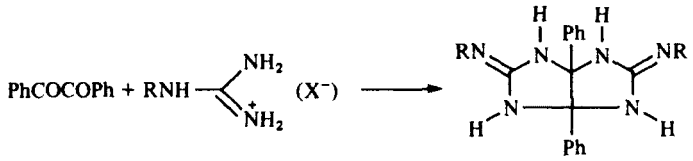
Preparation of sulfur analogs of tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*, 3*H*) diones (**3.22a,b**) has been achieved,[6,13] although in poor yield, by condensing 4,5-dihydroxyimidazolidin-2-one (**3.19**) with thiourea or 1-*n*-butylthiourea. A superior complementary route to **3.22b** involves the condensation of 4,5-dihydroxy-imidazolidin-2-thione with urea, and this approach has been employed to prepare 1,3-dialkyl-5-thiono derivatives of this type (**3.22c–e**).[13] Characteristic ir bands in such compounds are exemplified as follows for **3.22b**: 1515 cm^{-1} (C=S), 1700 (C=O), and 3200 (N–H).[13]



(3.22)

	X	Y	R^1	R^2	R^3	R^4	mp (°C)	Yield (%)
a	S	O	*n*-Bu	H	H	H	171 (dec.) (EtOH)	–
b	S	O	H	H	H	H	300 (H_2O)	24
c	O	S	Me	Me	H	H	247–249 (MeOH)	71
d	O	S	H	*i*-Pr	H	H	260–261 (MeOH)	52
e	O	S	Me	Bu	H	H	213–214 (H_2O)	77

TABLE 3.2. SYNTHESIS OF BISIMINO ANALOGS (3.24) OF TETRAHYDROIMIDAZO[4,5-*d*]IMIDAZOLE-2,5(1*H*,3*H*) DIONES (3.18) FROM BENZIL AND GUANIDINES



(3.23) (3.24)

Starting Materials (3.23)		Product (3.24)				
R	X	R	Reaction Conditions	mp (°C) (Solvent for Recrystallization)	Yield (%)	Reference
H	NO_2	H[a]	EtOH, heat	–[a]	–	14
H	HSO_4	H	KOH, Et_3N, room temp.	360 (DMF)[b]	–	15
CH_2Ph	Cl	CH_2Ph	KOH, aqueous EtOH, reflux	218–219 (dec.) MeOH–DMF[c]	–	16
$C(OCH_3)$=NH	Cl	$C(OCH_3)$=NH	NaOEt, EtOH, room temp.	219 (EtOH)	18	17
C(OEt)=NH	Cl	C(OEt)=NH	NaOEt, EtOH, room temp.	208 (EtOH)	30	17
C(O*n*-Pr)=NH	Cl	C(O*n*-Pr)=NH	NaOEt, EtOH, room temp.	233 (EtOH)	23	17
C(O*i*-Pr)=NH	Cl	C(O*i*-Pr)=NH	NaOEt, EtOH, room temp.	229 (EtOH)	41	17
C(O*n*-Bu)NH	Cl	C(O-*n*-Bu)=NH	NaOEt, EtOH, room temp.	228 (EtOH)	50	17

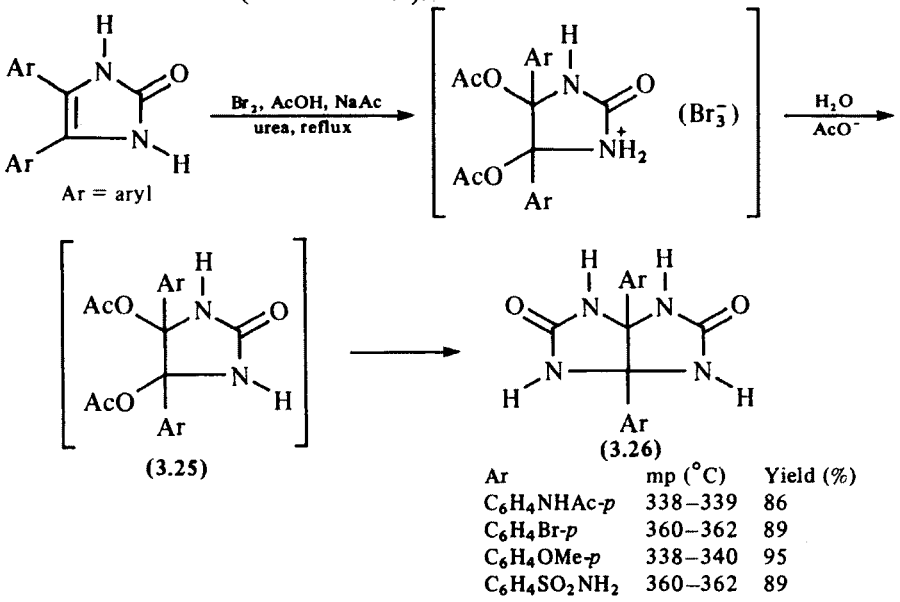
[a]The product is isolated as a salt and can be converted into a 1,3,4,6-tetrachloro derivative of value as an antivesicant.
[b]Forms a diacetate, mp 247°C (dec.).
[c]Ultraviolet spectrum λ_{max}^{EtOH} = 220.5 nm (ϵ, 13,900), 222 (13,700). Forms a dihydrochloride, mp 280°C (dec.).

3.1.5.2. *Synthesis from Guanidines*

Procedures closely related to those described in the previous section [cf. (**3.16** + **3.17**) → **3.18**] have been used to prepare bisimino analogs of tetrahydroimidazo-[4,5-*d*]imidazole-2,5(1*H*,3*H*) diones (see **3.23** → **3.24** and Table 3.2). The 3*a*,6*a*-diphenyl-2,5-bis(alkoxyimidoylimide) derivatives [(**3.24**; R = C (*O*-alkyl)=NH] are characterized by ir absorption bands at approximate values of 3420 (NH), 3260 (=NH), and 1100 cm^{-1} (C–O–C).[17]

3.1.5.3. *Synthesis from Imidazolones*

Excellent yields of 3*a*,6*a*-diaryltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones (**3.26**) are formed by treating 4,5-diphenylimidazolin-2-one with bromine in acetic acid containing an excess of anhydrous sodium acetate and urea;[18] it is likely that 4,5-diacetoxy-4,5-diarylimidazolidin-2-ones (**3.25**) are intermediates in these transformations (see Scheme 3.4).



Ar	mp (°C)	Yield (%)
C_6H_4NHAc-*p*	338–339	86
C_6H_4Br-*p*	360–362	89
C_6H_4OMe-*p*	338–340	95
$C_6H_4SO_2NH_2$	360–362	89

Scheme 3.4

3.1.5.4. *Physicochemical Studies: X-Ray Crystallographic Analysis*

The molecular structure of 3*a*,6*a*-dimethyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)dione (**3.27**; $R^1 = R^2 = Me$; R^3–R^6 = H) has been determined X-ray crystallographically [see Fig. 3.1 for bond lengths (Å) and angles (°) (standard deviations in parentheses)].[19]

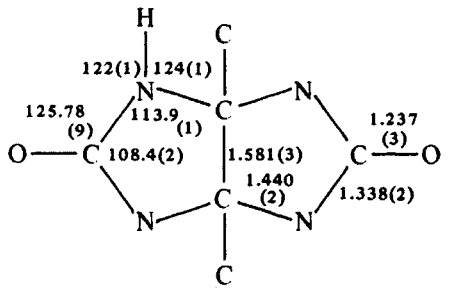


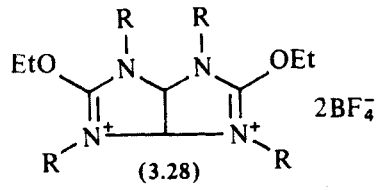
Figure 3.1. Molecular structure of 3*a*, 6*a*-dimethyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*, 3*H*)dione.

There are two planar five-membered rings with a 65.0° angle between the plane normals of the rings. Each molecule is hydrogen-bonded to four neighboring molecules by eight N–H···O hydrogen bonds [$d_{N\ldots O} = 2.869(2)$ Å]. It is interesting to note that the C=O bond length (1.237 Å) is slightly longer than the C=O of a series of barbiturates (1.21 Å) and shorter than that of urea (1.27 Å). [See discussion of the crystallographically determined bond lengths in biotin (**2.430e**) in Section 2.15.5 of Chapter 2.]

3.1.5.5. Reactions with Electrophiles

3.1.5.5.1. ALKYLATION

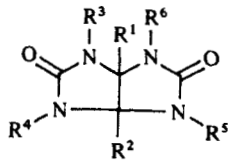
The *N*-alkylation of mono, di, and trialkyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)diones (cf. **3.27**; R^3–R^6 = H, alkyl) can be achieved in variable yields by using alkyl iodides in the presence of sodium amide in liquid ammonia (see Table 3.3[20]). The reaction rate decreases in passing from methyl iodide to higher alkyl iodides such as *n*-propyl and *n*-butyl iodides. In contrast, alkylation of the diones (**3.27**, R^1–R^6 = H and **3.27**, R^1, R^2 = H, R^3–R^6 = Me) with triethyloxonium tetrafluoroborate gives products **3.28a** and **b** of *O*-alkylation, respectively,[21] but no reaction occurs with higher homologs of the tetramethyl diones. The *N*-unsubstituted bis salt (**3.28a**) is very hygroscopic and easily reverts to the starting material by hydrolysis. In contrast, the tetramethyl analog (**3.28b**) is stable in air for several days: it is hydrolyzed at 100°C to the starting material but also to products of ring fission, including *N*,*N*′-dimethylurea and *N*,*N*′-dimethylhydantoin.[21]



(3.28)

	R	Yield (%)	mp (°C)
a	H	100	–
b	Me	90	115–120

TABLE 3.3. ALKYLATION[a] OF TETRAHYDROIMIDAZO[4,5-*d*]IMIDAZOLE-2,5(1*H*,3*H*)DIONES (3.27)



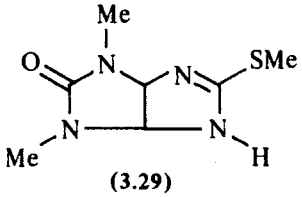
(3.27)

Alkylation Product (3.27)	Compound Alkylated (3.27)	Yield (%)	mp (°C)	ir Spectrum ν (cm^{-1})	
$R^1 = R^2 = H$, R^3–$R^6 = CH_3$	R^1 –$R^6 = H$	50	228 (from ethanol) 225–227	1735 2945 2900	(C=O) (*N*-CH_3)
$R^1 = R^2 = H$, R^3–$R^6 = C_2H_5$	R^1–$R^6 = H$	49	107–109 (from cyclohexane)	1702 1685 2970 2925 2875	(C=O) (*N*-C_2H_5)
R^1–$R^6 = CH_3$	$R^1 = R^2 = CH_3$, R^3–$R^6 = H$	35	211–213 (from octane)	1735 1715 2972 2910	(C=O) (*N*-CH_3)
$R^1 = R^3$–$R^6 = CH_3$, $R^2 = H$	$R^1 = CH_3$, R^2–$R^6 = H$	48	148–150 (from octane)	1700 2960 2900	(C=O) (*N*-CH_3)
$R^1 = CH_3$, $R^2 = H$, R^3–$R^6 = C_2H_5$	$R^1 = CH_3$, R^2–$R^6 = H$	20	78–80 (from cyclohexane)	1702 2986 2949 2890	(C=O) (*N*-C_2H_5)
$R^1 = R^2 = H$,	R^1–$R^4 = R^6 = H$,	50	118–119 (from cyclohexane)	1700	(C=O)

$R^3 = R^4 = R^6 = CH_3$, $R^5 = t$-Bu	$R^5 = t$-C_4H_9			2978	(*N*-Alk)
$R^1 = R^2 = H$	R^1–R^5 = H,	35	138–140 (from cyclohexane)	1707	(C=O)
R^3–$R^5 = CH_3$, R^6 = Ph	R^6 = Ph			1609, 1596	(Ph)
				2945	(*N*-Alk)
$R^1 = R^2 = H$, $R^3 = R^5 = C_2H_5$, $R^4 = R^6 = CH_3$	$R^1 = R^2 = R^3 = R^5 = H$, $R^4 = R^6 = CH_3$	31	108–110 (from isooctane)	1698	(C=O)
				2980, 2945, 2885	(*N*-Alk)
$R^1 = R^2 = H$, $R^3 = R^6 = C_2H_5$, $R^4 = R^5 = CH_3$	$R^1 = R^2 = R^3 = R^6 = H$, $R^4 = R^5 = CH_3$	70	89–90 (from isooctane)	1720, 1705	(C=O)
				2995, 2950, 2895	(*N*-Alk)
$R^1 = R^2 = H$, $R^4 = R^6 = CH_3$, $R^3 = R^5 = n$-C_3H_7	$R^1 = R^2 = R^3 = R^5 = H$, $R^4 = R^6 = CH_3$	50	114–116 (from isooctane)	1704	(C=O)
				3395, 2976, 2945, 2885	(*N*-Alk)
$R^1 = R^2 = H$, $R^4 = R^6 = CH_3$, $R^3 = R^5 = n$-C_4H_9	$R^1 = R^2 = R^3 = R^5 = H$, $R^4 = R^6 = CH_3$	56	68–70 (from isooctane)	1700	(C=O)
				2970, 2941, 2882	(*N*-Alk)
$R^1 = R^2$ = Ph, $R^3 - R^6 = CH_3$	$R^1 = R^2$ = Ph, $R^3 = R^4 = R^5 = CH_3$, $R^6 = H$	58	286–288 (from benzene)	1718	(C=O)
				1591	(Ph)
				3082, 2968	(*N*-CH_3)
$R^1 = R^2$ = Ph, R^3–$R^5 = CH_3$, $R^6 = C_2H_5$		21	236–237 (from 1:10 toluene–ether)	1719	(C=O)
				1592	(Ph)
				3080, 2953	(*N*-Alk)

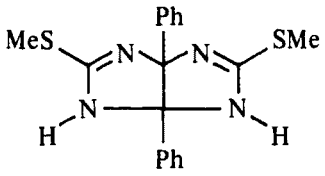
[a]Reaction conditions: $NaNH_2$, liquid NH_3, Et_2O, alkyl iodide −40 to −45°C, then warm to room temperature.

The reaction of thiono and bisthiono analogs of tetrahydroimidazo[4,5-*d*]-imidazole-2,5(1*H*,3*H*)diones with methyl iodide in basic media affords products (**3.29**[20], **3.30**[16]) of alkylation at sulfur.



(3.29)

mp 127–128°C



(3.30)

mp 242°C

3.1.5.5.2. ACYLATION

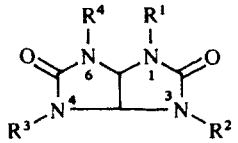
The acylation of tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)dione (**3.31**, R^1–R^4 = H) with carboxylic acid anhydrides affords 1,3,4,6-tetraacyl- or 1,4-diacyl derivatives depending on the molar ratios used (see Table 3.4).[22] Reactions of this type are most efficiently carried out in 70% perchloric acid at room temperature (for **3.31**, R^1–R^4 = H → tetraacyl derivatives), 90–110°C (for **3.31**, R^1–R^4 = H → 1,3-diacyl derivatives), and 40–45°C for the synthesis of diacyl derivatives derived from 1,3- and 1,6-dimethyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*) diones.

N-Acetylation reactions of the unsubstituted dione (**3.31**, R^1–R^4 = H) have also been achieved by using ketene in γ-butyrolactone containing perchloric acid.[23]

3.1.5.5.3. OTHER REACTIONS WITH ELECTROPHILES

Reactions of tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)diones with formaldehyde,[24] epoxides,[25,26] and chlorinating[27,28] and nitrating agents[29,30] are summarized in Table 3.5. Treatment of the dione (**3.32**, R^1–R^6 = H) with formaldehyde under aqueous alkaline conditions gives the tetramethylol derivative,[24] but when the reaction is conducted in the presence of a primary amine, the products are tetracyclic condensed imidazo[4,5-*d*]imidazoles (**3.33**).[31] In contrast, condensation of the dione (**3.32**, R^1–R^6 = H) with formaldehyde in hydrochloric acid affords an amorphous cross-linked aminal-type polymer; the latter undergoes an interesting rearrangement in concentrated sulfuric acid at 110°C to give a cyclic hexamer of dimethanotetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)dione (see Fig. 3.2), formed presumably by cleavage and rearrangement of the polymer under conditions of thermodynamic control.[32]

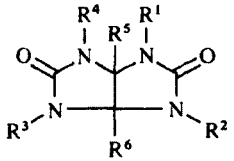
TABLE 3.4. ACYLATION PRODUCTS (3.31) OF TETRAHYDROIMIDAZO[4,5-*d*]IMIDAZOLE-2,5(1*H*,3*H*) DIONES[22]



(3.31)

Starting Material (3.31; R^4 = H)			Product (3.31)				Yield	mp (°C) (Solvent for	^{1}H nmr Spectrum [δ
R^1	R^2	R^3	R^1	R^2	R^3	R^4	(%)	Recrystallization	(Ring Proton) from TMS]
H	H	H	COMe	COMe	COMe	COMe	93	234–238 (dioxan)	6.64
H	H	H	COEt	COEt	COEt	COEt	63	148–150 (*i*-PrOH)	6.67
H	H	H	CO*n*-Pr	CO*n*-Pr	CO*n*-Pr	CO*n*-Pr	77	145–146 (*i*-PrOH)	6.65
H	H	H	CO*n*-C_5H_{11}	CO*n*-C_5H_{11}	CO*n*-C_5H_{11}	CO*n*-C_5H_{11}	30	70–70.5 (*i*-PrOH)	6.67
H	H	H	$COCH_2Cl$	$COCH_2Cl$	$COCH_2Cl$	$COCH_2Cl$	–	262–265 (*i*-PrOH)	–
H	H	H	H	COMe	H	COMe	81	328–330 (DMF)	5.74
H	H	H	H	COEt	H	COEt	100	249–252 (DMF–Me_2CO)	5.75
H	H	H	H	CO*n*-Pr	H	CO*n*-Pr	56	228–230 (DMF)	5.72
H	H	H	H	CO*n*-C_5H_{11}	H	CO*n*-C_5H_{11}	40	198–200 (*i*-PrOH)	–
H	H	H	H	CO*n*-C_7H_{15}	H	CO*n*-C_7H_{15}	38	186 (*i*-PrOH)	5.79
H	H	H	H	COPh	H	COPh	64	294–296 (DMF–dioxan)	6.01
H	H	H	H	$COCH_2Cl$	H	$COCH_2Cl$	74	> 360	–
Me	Me	H	Me	Me	COMe	COMe	18	235–236	5.71
Me	Me	H	Me	Me	COEt	COEt	52	183–184	5.72
Me	H	Me	Me	COMe	Me	COMe	69	216–218	–
Me	H	Me	Me	COEt	Me	COEt	59	172–173	–

TABLE 3.5. PRODUCTS FORMED FROM TETRAHYDROIMIDAZO[4,5-*d*]IMIDAZOLE-2,5(1*H*,3*H*)DIONES (**3.22**) WITH MISCELLANEOUS ELECTROPHILIC REAGENTS



(3.32)

Reaction conditions	Product	Reference
3.32 (R^1–R^6 = H), CH_2O, aqueous alkali	R^1–R^4 = CH_2OH; R^5 = R^6 = H	24
3.32 (R^1–R^5 = H; R^6 = Me), PhCH(O)CH_2, DMF, 100°C	R^1 = R^2 = R^3 = R^5 = H; R^4 = $CH_2CH(OH)Ph$; R^6 = Me	25
3.32 (R^1, R^2 = Me; R^3–R^6 = H): (i) $CH_2(O)CH_2$, $Me_3\overset{+}{N}CH_2Ph(\bar{O}H)$, DMF, 60°C; (ii) Me_3SiCl	R^1 = R^2 = Me; R^3 = R^4 = $(CH_2)_2OSiMe_3$, R^5 = R^6 = H	26
3.32 (R^1–R^4 = H; R^5 = R^6 = Ph), NaOCl, HCl (pH = 7–7.5)	R^1–R^4 = Cl; R^5 = R^6 = Ph	27
3.32 (R^1–R^4 = H; R^5 = R^6 = aryl), Cl_2, 10% aqueous NaOH (pH = 6–8)	R^1–R^4 = H, Cl, R^5 = R^6 = aryl	28
3.32 (R^1–R^6 = H), HNO_3, N_2O_5	R^1–R^4 = NO_2, R^5 = R^6 = H	29
3.32 (R^1–R^6 = H), HNO_3	R^1–R^4 = H, H, NO_2, NO_2; R^5 = R^6 = H	30

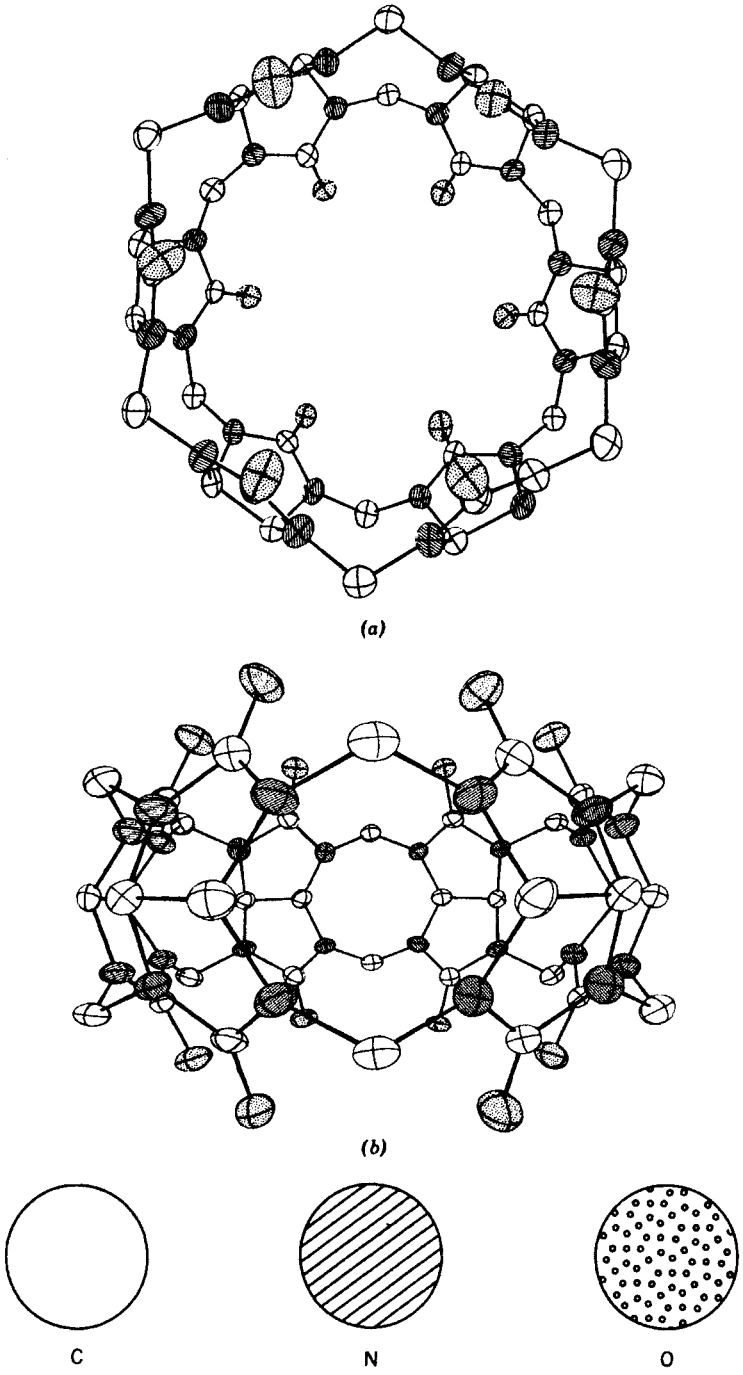
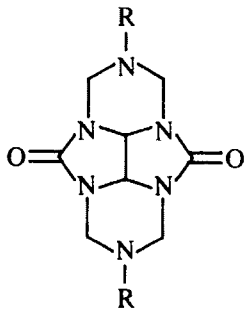


Figure 3.2. Top (*a*) and edge-on view (*b*) of the molecular structure of the cyclic hexamer of dimethanoglycoluril.

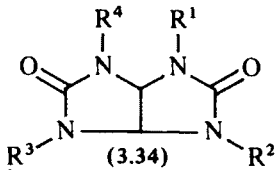


(3.33)

R = alkyl, cycloalkyl, etc.

3.1.5.6. Reactions with Nucleophiles

1,3,4,6 - Tetraacetyl – tetrahydroimidazo [4,5-*d*] imidazole - 2,5 (1*H*,3*H*) dione (**3.34a**) transfers four acetyl groups in two stages through **3.34b** to **3.34c** when reacting with nucleophilic compounds (e.g., amines, alcohols, thiols) under basic conditions (e.g., K_2CO_3, MeCN), and the first stage provides a useful preparative procedure for the synthesis of acetylated substrates of the types exemplified;[33] the selectivity of the method is illustrated by acetylation at the primary, but not secondary, amino group of 3(ethylamino)propylamine.[33]



(3.34)

a: R^1–R^4 = Ac
b: $R^1 = R^3$ = Ac; $R^2 = R^4$ = H
c: R^1–R^4 = H

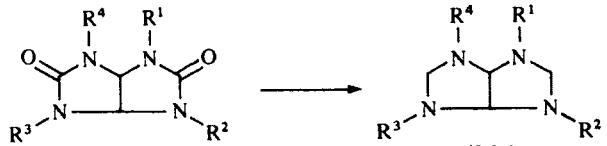
3.1.5.7. Reduction

Tetraalkyltetrahydroimidazo[4,5-*d*] imidazole-2,5(1*H*,3*H*)diones (**3.35**) are reduced by lithium aluminum hydride (LAH) in dioxan[34] or ether[35] to give fully saturated derivatives (see **3.36** and Table 3.6) in processes that have analogy in the reduction of 1,3-dimethylbenzimidazolone to 2,3-dihydro-1,3-dimethylbenzimidazole.[36] The octahydro derivatives (cf. **3.36**) are liquids that can be stored for extended periods at −20°C.[34]

3.1.5.8. Commercial Applications

The straightforward synthesis and low cost of tetrahydroimidazo[4,5-*d*]-imidazole-2,5(1*H*,3*H*)dione and its derivatives (cf. **3.37**) make them attractive from a commercial viewpoint, and their applications in a wide variety of areas are

TABLE 3.6. SYNTHESIS OF 1,3,4,6-TETRAALKYLOCTAHYDROIMIDAZO[4,5-*d*]IMIDAZOLES (**3.36**) BY REDUCTION[a] OF TETRAHYDRO-IMIDAZO-[4,5-*d*]IMIDAZOLE-2,5(1*H*,3*H*)DIONES[34]



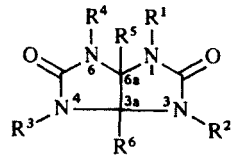
(3.35) (3.36)

Product (**3.36**)				Yield			
R^1	R^2	R^3	R^4	(%)	bp (°C) [torr]	n_D^{20}	^{1}H nmr Spectrum [Solvent, (ppm), *J* (Hz)]
Me	Me	Me	Me	66	44–46 [3][b]	1.4800	C_6H_{12}: 3.71 (s, CH), 2.35 (s, NMe), 3.1 and 3.4 (CH_2, $J = 5$)
Et	Et	Et	Et	31	67–68 [2]	1.4739	CCl_4: 1.04 (t, Me, $J = 7.2$), 2.56 (*q*, NCH_2, $J = 7.2$), 3.22 and 3.34 (CH_2, $J = 6.6$), 4.04 (s, CH)
Me	Et	Me	Et	46	55–56 [1]	–	CCl_4: 1.04 (t, CMe, $J = 7.2$), 2.28 (s, NMe), 2.52 (*q*, NCH_2, $J = 7.2$), 3.13 and 3.41 (CH_2, $J = 6$), 3.87 (s, CH)
Me	Bu	Me	Bu	40	92–93 [1]	1.4736	CCl_4: 0.92 (CH_3[Bu], $J = 6$), 1.37 (m, CH_2[Bu]), 2.29 (s, NMe), 2.53 (t, CH_2[Bu], $J = 6$), 3.12 and 3.42 (CH_2, $J = 6$), 3.84 (s, CH)

[a] Reaction conditions: $LiAlH_4$, dioxan, 95°C, 24 h.

[b] This compound, bp 107–111°C (42 torr), has also been prepared by using $LiAlH_4$ in Et_2O under reflux (see ref. 35).

TABLE 3.7. DERIVATIVES OF TETRAHYDROIMIDAZO[4,5-*d*]IMIDAZOLE 2,5(1*H*,3*H*)DIONE (**3.37**) OF COMMERCIAL INTEREST



(3.37)

Substituents in **3.37**	Area of Commercial Interest	Reference
R^1–R^4 = NO_2, NO_2, H, H; R^5 = R^6 = H	Explosives	30,37
R^1–R^4 = NO_2; R^5, R^6 = H	Explosives	29
R^1–R^4 = $COCH_3$; R^5 = R^6 = H	Bleaching agents	38–41
R^1 = R^3 = Cl, Br; R^2 = R^4 = acyl; R^5 = R^6 = H, Me, Ph	Bleaching agents	42,43
R^1 = e.g., alkyl, aryl; R^2 = R^4 = CH_2OH; R^3 = e.g., $HOCH_2$, *p*-ClC_6H_4; R^5 = R^6 = H	Bactericides	44
R^1–R^4 = Cl; R^5 = R^6 = H	Bactericides	45
R^1–R^4 = H, Cl; R^5 = R^6 = aryl	Bactericides[a]	28
R^1–R^4 = H	(With CH_2O) resins	47

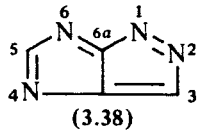
R^1–R^4 = CH_2OH; R^5 = H; R^6 = Me	Cross-linking agents	48,49
R^1–R^4 = CH_2O–alkyl; R^5 = R^6 = H	(With acid catalyst) cross-linking agents	50
R^1–R^4 = CH_2NHCO_2Ph; R^5 = R^6 = H	Cross-linking agent	51
R^1 = $CH_2CH(OH)Ph$; R^2–R^5 = H; R^6 = Me	(With isocyanates) polyurethane foams	25
R^1 = R^2 = Me; R^3, R^4 = H, CH_2CH_2OH; R^5 = R^6 = H	(With isocyanates) polyurethanes	52
R^1–R^4 = $(CH_2)_2CO_2(CH_2)_2SC_{12}H_{25}$	Antioxidants for polymers and lard	53
R^1–R^4 = Me; R^5 = R^6 = H	Antiepileptic agent	54
R^1–R^4 = H, alkyl, $CH_2\overset{O}{\diagdown\diagup}CHCH_2$; R^5 = R^6 = H, alkyl	Antineoplastic agents	55
R^1–R^4 = CH_2OMe; R^5 = R^6 = H	(With stearic acid) detergents	56
R^1–R^4 = CH_2OR (R = H, alkyl, alkoxy); R^5 = R^6 = H	Fabric finishes	57–59
R^1 = p-$C_6H_4SO_2NHX$ (X = azo or anthraquinone residue); R^2–R^4 = H, CH_2OH	Dyestuffs for cotton	60
R^1–R^4 = H, Me; R^5 = R^6 = H	Slow-nitrogen-release fertilizers	61
R^1–R^4 = Cl; R^5 = R^6 = Ph ("iodogen")	(With ^{125}I) labeling of biological materials for radioimmunoassay	62
R^1–R^4 = Cl; R^5 = R^6 = Ph	Removal of SH from proteins prior to analysis	63
R^1 = R^4 = Cl; R^5 = R^6 = Ph	(With Na ^{131}I) synthesis of ^{131}iodo-2-thiouracil derivatives	64

[a]For closely related bactericidal compositions in the 2,5-diimino series (cf. **3.37**, C=NH for C=O), see ref. 46.

protected in a number of patents (see Table 3.7). Tetrachloro derivatives (cf. **3.37**; R^1–R^4 = Cl) are particularly useful and have found application as bleaching agents, as bactericides, and as a valuable reagent (viz., **3.37**; R^1–R^4 = Cl, R^5 = R^6 = Ph) with ^{125}I for labeling of biological materials for radioimmunoassay.

3.2. RING SYSTEM C_3N_2–C_3N_2: IMIDAZO[4,5-*c*]PYRAZOLE

The imidazo[4,5-*c*]pyrazole ring system (**3.38**) can be constructed from cyclization of pyrazoles or imidazoles, but very little is known about the properties and reactions of compounds in this group.



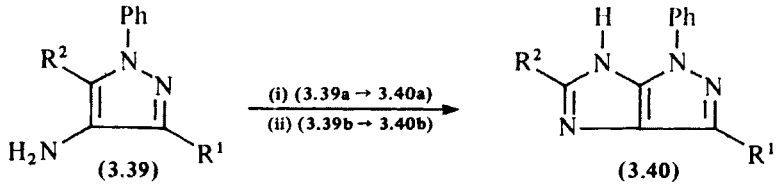
(3.38)

3.2.1. Synthesis from Pyrazoles

1,6-Dihydro-1-phenylimidazo[4,5-*c*]pyrazol-5-ol (**3.40a**) has been prepared[65] from **3.39a** by means of a product of Curtius rearrangement, but the scope of this approach and the potential tautomeric nature of **3.40a** have not been evaluated. An isolated example of a mercapto analog (**3.40b**) of **3.40a** has been synthesized from the 4,5-diaminopyrazole (**3.39b**) and carbon disulfide,[66] but a wider variety of 1,6-dihydro derivatives (**3.43**) is available[67] by the deoxygenation of condensed imidazole *N*-oxides (**3.42**) with the use of triethyl phosphite or titanium trichloride (see Table 3.8); the *N*-oxides (**3.42**) are accessible in reasonable yields by base-promoted cyclization of easily prepared 5-benzylaminopyrazole derivatives (**3.41**). The potential tautomeric nature of the *N*-oxides (**3.42**) is recognized,[67] but there are no spectral data reported to establish the position of such equilibria.

TABLE 3.8. PHYSICAL PROPERTIES OF 1,6-DIHYDROIMIDAZO[4,5-*c*]PYRAZOLES (**3.42** AND **3.43**)[67]

	Compound **3.42**		Compound **3.43**	
R in **3.42** and **3.43**	mp (°C)	Yield (%)	mp (°C)	Yield (%)
C_6H_5	195	75	338	82
4-$CH_3C_6H_4$	260	68	312	87
4-ClC_6H_4	240	62	350	82
4-BrC_6H_4	242	65	360	84
4-$H_2NC_6H_4$	200	53	205	86
3-$HOOCC_6H_4$	140	50	216	79
2,4-$(CH_3)_2C_6H_3$	226	68	239	79
2-HO-4-$NO_2C_6H_3$	190	61	218	80



(3.39)

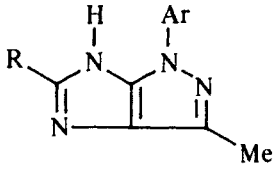
(i) (3.39a → 3.40a)
(ii) (3.39b → 3.40b)

(3.40)

	R^1	R^2
a	H	CON_3
b	Me	NH_2

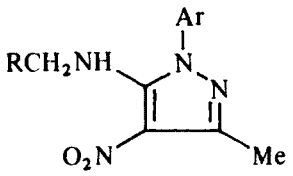
(i) xylene, 100°C, 0.5 h; (ii) CS_2, EtOH, heat

	R^1	R^2	MP (°C)
a	H	OH	209 (MeOH)
b	Me	SH	269 (dioxan–EtOH)



(3.43)

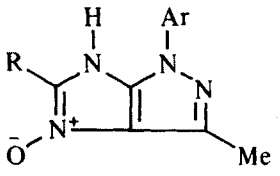
(ii)



(3.41)

Ar = $C_6H_4NO_2$-*p*

(i)

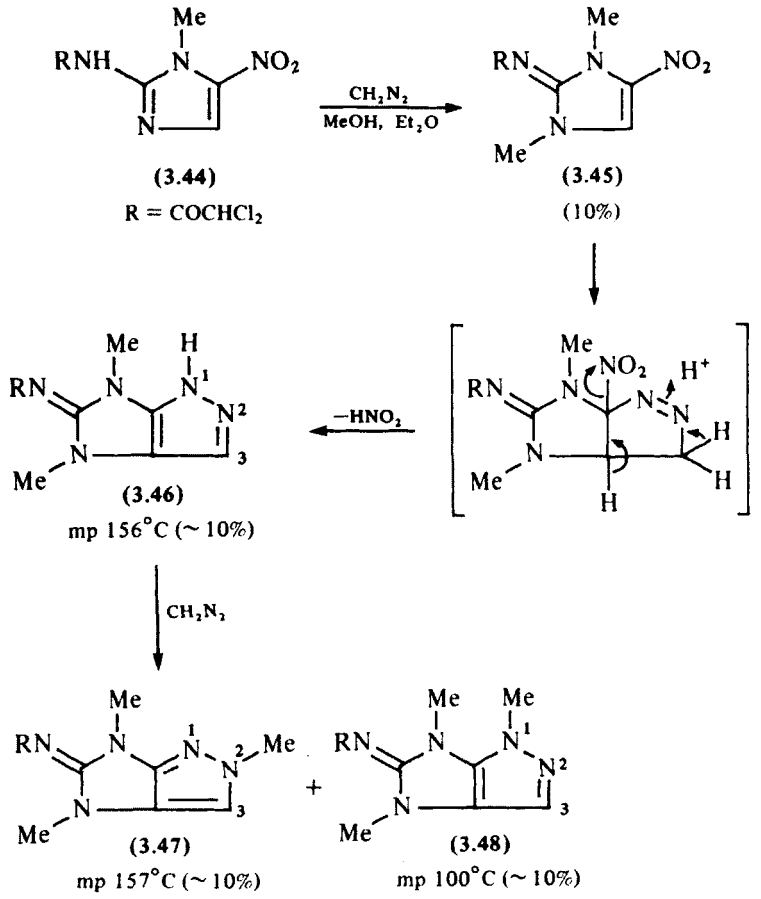


(3.42)

(i) NaOH, MeOH, DMF, reflux, 3–4 h;
(ii) $P(OEt)_3$, heat, or $TiCl_3$, DMF, THF

3.2.2. Synthesis from Imidazoles

2-(2,2-Dichloroacetamido)-1-methyl-5-nitroimidazole (**3.44**) reacts with diazomethane to afford the anticipated product of *N*-methylation (**3.45**) but also gives an imidazo[4,5-*c*]pyrazole derivative (**3.46**), through an adduct of 1,3-dipolar cycloaddition (see Scheme 3.5).[68] Ensuing methylation of **3.46** gives rise to the isomeric products (**3.47** and **3.48**), and one of these (**3.47**) has been prepared in a separate reaction of the nitro compound (**3.45**) with diazomethane.[68] In the ^{13}C nmr spectra of **3.46**–**3.48**, the C-3 resonances appear at δ = 110.4, 111.6, and 120 ppm (from TMS) respectively, and the multiplicity of this signal at 111.6 ppm for **3.47** ($^1J_{CH}$ = 194 Hz; $^3J_{CH}$ = 1.5 Hz) serves to unambiguously differentiate it structurally from **3.48**, where such three bond coupling is absent.



Scheme 3.5

3.3. RING SYSTEM C_3N_2–C_2N_3: IMIDAZO[2,1-*c*][1,2,4]-TRIAZOLE

Compounds of the fully unsaturated type in this group can belong to either the 1*H*-(**3.49**) or the 7*H*-imidazo[2,1-*c*][1,2,4]triazole systems (**3.50**). A few compounds in this class are known, and there is an isolated reference to the synthesis of 5,6-dihydroimidazo[2,1-*c*][1,2,4]triazoles (cf. **3.51**).

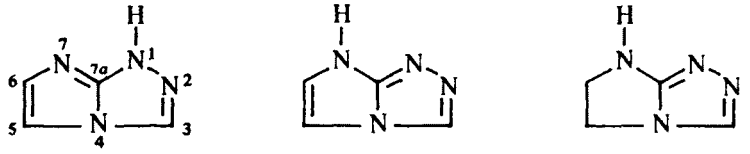
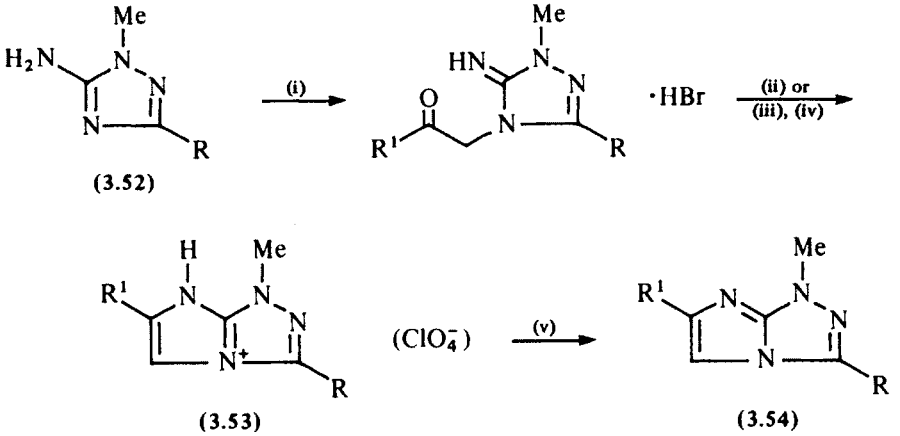


TABLE 3 9. PHYSICAL PROPERTIES OF IMIDAZO[2,1-*c*][1,2,4]TRIAZOLIUM SALTS (**3.53**) AND THEIR FREE BASES (**3.54**)[69]

		Compound **3.53**		Compound **3.54**	
R	R^1	mp (°C)	Yield (%)	mp (°C)	Yield (%)
H	Ph	205	73	143	71
H	4-BrC_6H_4	270	65	220	98
H	4-$O_2NC_6H_4$	223	81	205	78
Me	Ph	258	74	–	–
Me	4-$O_2NC_6H_4$	225	90	218	97
Et	Ph	242	77	60	56
Et	4-BrC_6H_4	260	87	129	92
Et	4-$O_2NC_6H_4$	196	67	127	96

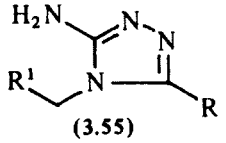
3.3.1. 1*H*-Imidazo[2,1-*c*][1,2,4]triazoles

A series of crystalline 1-methyl-1*H*-imidazo[2,1-*c*][1,2,4]triazoles (**3.54**) and their perchlorates (**3.53**) have been synthesized by means of isolable triazolium compounds derived from 5-aminotriazoles (**3.52**) (see Scheme 3.6 and Table 3.9).[69,70] Dehydrative ring closure of the triazolium salts is best achieved by heating them in a mixture of anhydrous perchloric and acetic acids, and the free bases (**3.54**) are liberated in alkali. As might be anticipated, the ^1H nmr chemical shift (in CF_3CO_2H) of H-3 (δ = 8.67) and H-5 (7.77) of the salt (**3.53**; R = H, R^1 = 4-BrC_6H_4) are both at low field relative to those (in $CDCl_3$) of H-3 (7.87) and H-5 (7.28) of the free base (cf. **3.54**). Reactions related to those in Scheme 3.6 are illustrated in the transformations **3.55a** → **3.56a**[71,72] and **3.55b** → **3.56b**[73]. The



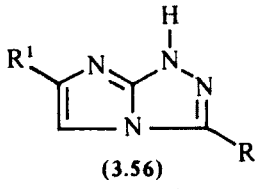
(i) R^1COCH_2Br, Me_2CO, heat; (ii) $HClO_4$, CH_3CO_2H; (iii) $NaHCO_3$, EtOH; (iv) $HClO_4$; (v) NaOH, MeOH, 100°C, 18 h

Scheme 3.6



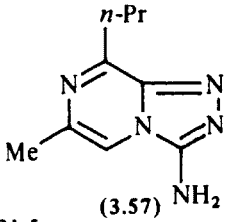
(3.55)

a: R = CO*n*-Pr; R^1 = COMe
b: R = H; R^1 = $CH(OEt)_2$



(3.56)

	R	R^1
a:	CO*n*-Pr	Me
b:	H	H (sulfate)



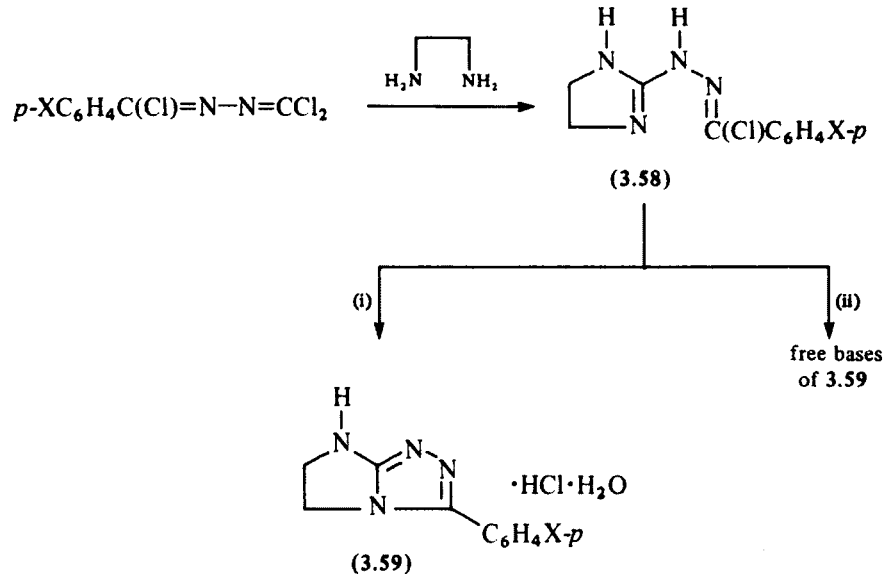
(3.57)

mp (°C)
220.5–221.5
–

triazole derivative (**3.55a**) has been isolated as a product of acidic degradation of the triazolo[4,3-*a*]pyrazine (**3.57**) and is transformed into the imidazo[2,1-*c*]-[1,2,4]triazole (**3.56a**) by heating it in the solid state.

3.3.2. 5,6-Dihydroimidazo[2,1-*c*][1,2,4]triazoles

The bicyclic framework of 5,6-dihydroimidazo[2,1-*c*][1,2,4]triazoles has been constructed by cyclization of the hydrazonyl chlorides (**3.58**) either in an unbuffered medium to give the hydrochloride hydrates (**3.59**) or under alkaline conditions to give their free bases (see Scheme 3.7 and Table 3.10).[74] Characteristic ir spectral bands of these derivatives are as follows: **3.59**, 3570 (OH); 2800–2700 (3 bands, $\overset{+}{N}H_2$); 1760, 1675 (C=N); **3.59** (free bases), 3300 (NH); and 1645 (C=N) cm^{-1}.



(i) dioxan : H_2O (4 : 1), room temperature
(ii) dioxan–H_2O, Na_2CO_3

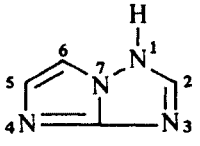
Scheme 3.7

TABLE 3.10. PHYSICAL PROPERTIES OF 5,6-DIHYDROIMIDAZO[2,1-*c*][1,2,4]-TRIAZOLIUM SALTS (**3.59**) AND THEIR FREE BASES[74]

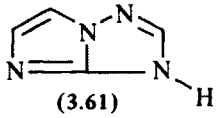
	Compound **3.59**		Free Base of **3.59**	
X	mp (°C)	Yield (%)	mp (°C)	Yield (%)
H	242–244	85	184–185	87
i-Pr	230–232	88	–	–
Me	235–236	90	184–185	87
Cl	245–247	92	214–216	85
Br	230–232	95	229–230	88
NO_2	256–258	92	242–243	85

3.4. RING SYSTEM C_3N_2–C_2N_3: IMIDAZO[1,2-*b*][1,2,4]-TRIAZOLE

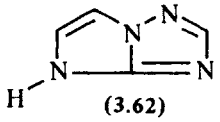
Fully unsaturated imidazo[1,2-*b*][1,2,4]triazoles may exist in the 1*H*- (**3.60**), 3*H*- (**3.61**), 4*H*- (**3.62**), and 6*H*-tautomeric forms (**3.63**). A few compounds in this group are known (see Section 3.4.1), but in most cases the nature of such tautomeric equilibria have not been rigorously ascertained; therefore, they are formulated as 1*H* derivatives (cf. **3.60**) unless there are spectroscopic data to indicate the preponderance of a different tautomeric structure. 2,3-Dihydro- (**3.64**) and 5,6-dihydro compounds (**3.65**) in the imidazo[1,2-*b*][1,2,4]triazole group are also known.



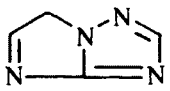
(**3.60**)



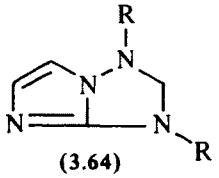
(**3.61**)



(**3.62**)

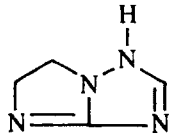


(**3.63**)



(**3.64**)

R = e.g., H, alkyl



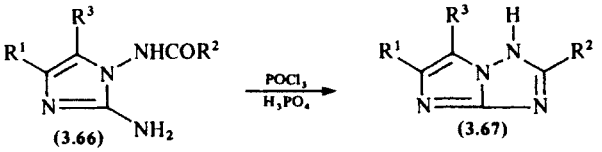
(**3.65**)

3.4.1. Imidazo[1,2-*b*][1,2,4]triazoles

3.4.1.1. Synthesis from Imidazoles

A series of disubstituted imidazo[1,2-*b*][1,2,4]triazoles and one trisubstituted imidazo[1,2-*b*][1,2,4]triazole (**3.67**) have been prepared by the phosphorus

TABLE 3.11. SYNTHESIS OF IMIDAZO[1,2-*b*][1,2,4]TRIAZOLES (3.67) BY CYCLIZATION OF 2-AMINO-1-ACYLAMINO-4-ARYLIMIDAZOLES (3.66)[75,76]



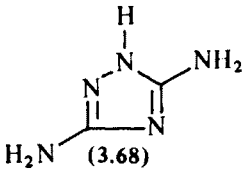
Substituents in 3.67						
R^1	R^2	R^3	Yield (%)	mp (°C)	Solvent for Recrystallization	Reference
Ph	Me	H	91	302–303[a]	Pyridine	75
Ph	Et	H	61	289–291	EtOH	75
Ph	*n*-Pr	H	56	279–280	EtOH–pyridine	75
Ph	*i*-Pr	H	59	267–268	EtOH	75
Ph	CH_2Ph	H	89	277–278	EtOH–pyridine	75
Ph	Me	Ph	85	280	EtOH–pyridine	75
p-BrC_6H_4	Me	H	83	245–247	Pyridine	75
p-ClC_6H_4	Me	H	71	241–243	Pyridine	75
p-$MeOC_6H_4$	Me	H	49	307–308	Pyridine	75
p-$O_2NC_6H_4$	Ph	H	30	310 (dec.)[b]	MeCN	76

[a]Forms a hydrochloride, mp 282–283°C (EtOH), and a nitrate, mp 182–183°C (EtOH).
[b]Infrared spectrum ν_{max} = 3100, 1600, 1515, 1345, and 1110 cm^{-1}.

oxychloride-promoted dehydrative cyclization of 2-amino-1-acylamino-4-arylimidazoles (**3.66**) (see Table 3.11).[75,76] The latter are available from ring cleavage of substituted 1,3,4-oxadiazolium salts with ammonia or by the acylation of 1,2-diamino-4-arylimidazoles.[75]

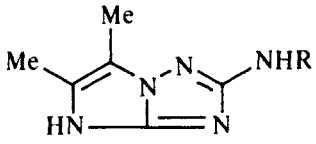
3.4.1.2. Synthesis from Triazoles

Treatment of 3,5-diamino-*s*-triazole (**3.68**) with acetoin and acetic acid in the presence of *p*-toluene sulfonic acid gives a product formulated[77] as the 4*H*-imidazo-[1,2-*b*][1,2,4]triazole derivative (**3.69**), but the possible dominance of other tautomeric forms (see, e.g., **3.69** ⇌ **3.70a**) has not been definitely excluded by spectroscopic measurements; the 2-amino derivative (**3.70b**) is formed, as a hydrochloride salt, by deacylation of **3.70a** with concentrated hydrochloric acid.[77] The imidazo[1,2-*b*][1,2,4]triazole framework has also been constructed from 1-substituted-5-aminotriazoles either preformed (see **3.71a,b** → **3.72a,b**[78] and **3.71c** → **3.74**[73]) or generated *in situ* (see **3.71d** → **3.73c**).[79] The tautomeric nature of the 2,5-disubstituted derivatives has not been determined (see, e.g., **3.72** ⇌ **3.73**), but the parent compound of the series (**3.74**) is considered[73] to exist predominantly as structure **3.74** with alternative tautomers (e.g., **3.75**) excluded on the basis of ^1H nmr spectral analysis.



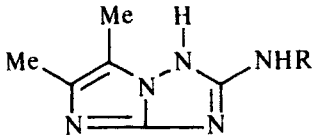
(3.68)

(i)



(3.69)

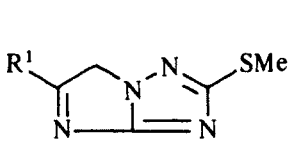
(R = Ac)



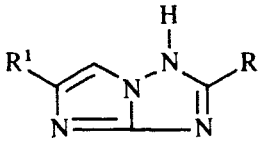
(3.70)

(i) $MeCH(OH)COMe$, AcOH, p-$MeC_6H_4SO_3H$

	R	mp (°C)	Yield (%)
a	Ac	293–294 (EtOH)	36
b	H	246–247	85 (HCl salt)

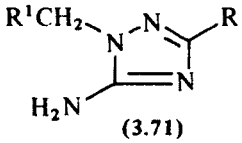


(3.72)



(3.73)

(i) for 3.71a, b



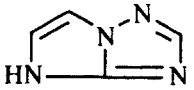
(3.71)

	R	R^1
a	SMe	COPh
b	SMe	COC_6H_4Me-p
c	H	$CH(OMe)_2$
d	H	$COC_6H_4SO_2Me$-p

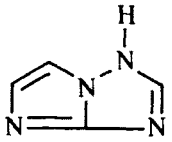
(ii) for 3.71c

	R^1	R	mp (°C)	Yield (%)
a	Ph	SMe	276–279 (DMF)	87
b	C_6H_4Me-p	SMe	295–298 (DMF)	84
c	$C_6H_4SO_2Me$-p	H	286–291 (AcOH)	35

(i) 40% HBr, reflux;
(ii) concentrated H_2SO_4, 1 h



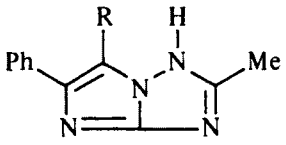
(3.74)



(3.75)

3.4.1.3. Reactions

Very little is known about the reactivity of the imidazo[1,2-*b*] [1,2,4] triazole nucleus. The 2,5-disubstituted derivative (**3.76a**) undergoes electrophilic substitution at the 6-position [see **3.76a** → **3.76b** (conc. HNO_3, conc. H_2SO_4, 0°C) and **3.76a** → **3.76c** (Br_2, AcOH)],[75] but the preferred site of substitution in the parent system has not been determined.

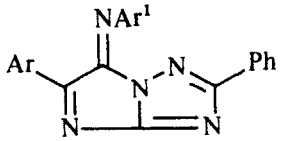


(3.76)

	R	mp (°C)	Yield (%)
a	H	–	–
b	NO_2	273–275	65
c	Br	182 (EtOH) (free base 235)	83 (as HBr salt)

3.4.1.4. Practical Applications

A series of 1*H*-imidazo[1,2-*b*] [1,2,4] triazoles containing a 6-substituent of the type $C(R^1)=C(R^2)COR^3$ (R^1,R^2 = e.g., H, alkyl; R^3 = e.g., amino) have been assessed for diuretic activity,[80] and compounds of type **3.77** are of interest for use as image dyes in color photography.[76]

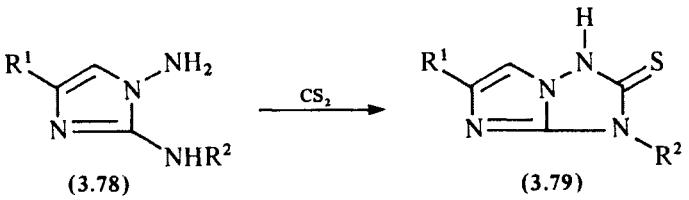


(3.77)

Ar = aryl; Ar^1 = aryl containing OH or NEt_2

3.4.2. 2,3-Dihydro-1*H*-imidazo[1,2-*b*] [1,2,4] triazoles

Compounds in this class are restricted to two thiono derivatives (**3.79**) derived from treatment of 1,2-diamino-4-arylimidazoles (**3.78**) with carbon disulfide.[75]

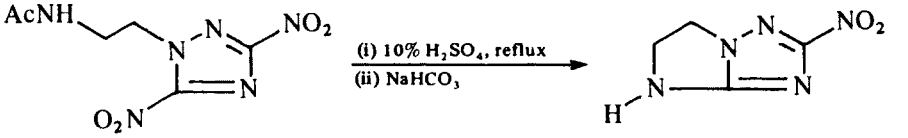


(3.78) (3.79)

R^1	R^2	mp (°C)	Yield (%)
Ph	H	248–250 (DMF–Et_2O)	83
p-BrC_6H_4	*n*-Pr	134–135 (DMF–Et_2O)	63

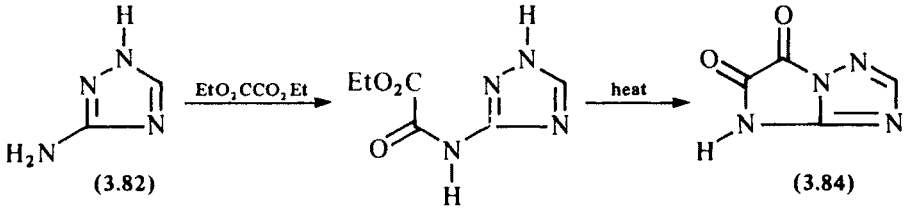
3.4.3. 5,6-Dihydroimidazo[1,2-*b*][1,2,4]triazoles

5,6-Dihydro-2-nitroimidazo[1,2-*b*][1,2,4]triazole (**3.81**) has been synthesized by an unusual process of intramolecular nucleophilic displacement of nitrite ion in the triazole derivative (**3.80**, NH_2 for NHAc),[81] and the 5,6-dihydro-5,6-dioxo compound (**3.84**) has been prepared by the sequence **3.82** → **3.83** → **3.84**.[82] The nature and position of possible tautomeric equilibria in these compounds (**3.81**, **3.84**) has not been ascertained.



(3.80) (3.81)

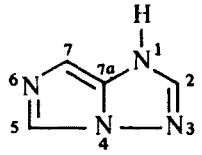
mp 177–178°C (EtOH) (51%)



(3.82) (3.83) (3.84)

3.5. RING SYSTEM $C_3N_2-C_2N_3$: 1*H*-IMIDAZO[1,5-*b*][1,2,4]-TRIAZOLE

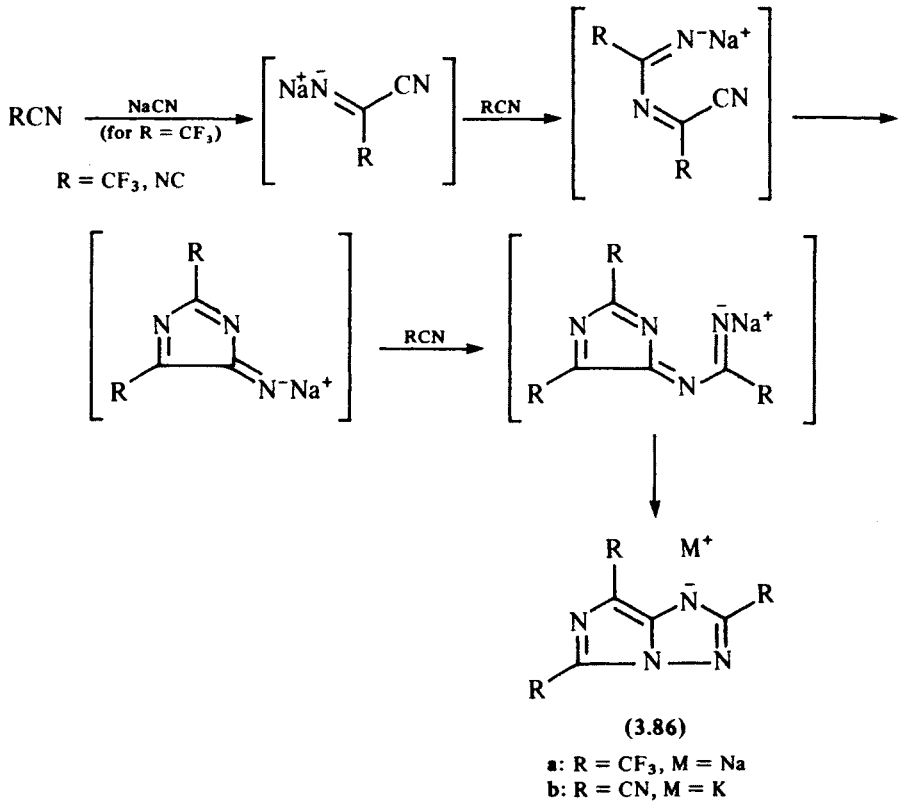
The bicyclic framework of the 1*H*-imidazo[1,5-*b*][1,2,4]triazole system (**3.85**) can be constructed from triazole derivatives, but the simplest route involves the cyclooligomerization of nitriles.



(3.85)

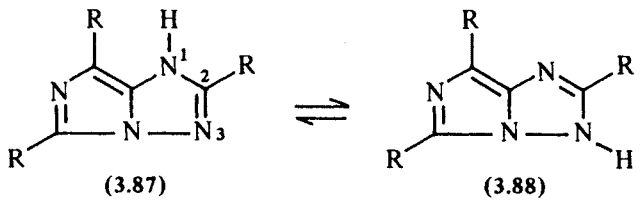
3.5.1. Synthesis from Nitriles

Treatment of trifluoroacetonitrile or cyanogen with sodium cyanide[83] or potassium cyanide[84] gives salts of 2,5,7-trisubstituted-1*H*-imidazo[1,5-*b*][1,2,4]-



Scheme 3.8

triazoles **3.86a** and **b**, respectively, probably by the mechanism depicted in Scheme 3.8.[83] Acidification of the salts (**3.86a,b**) gives the products **3.87a** and **b**, which exist, at least for **3.87a**, in the 1*H* and not the 3*H*-tautomeric form as evidenced by ^{1}H nmr spectral analysis of a 3-^{15}N-labeled derivative.[83]

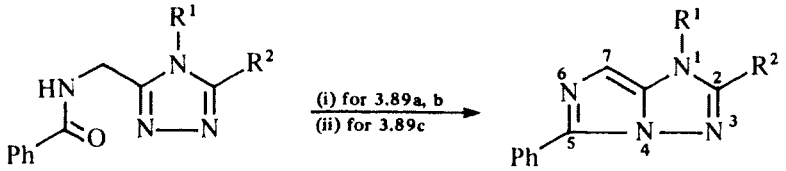


(3.87) (3.88)

	R	mp (°C)	Yield (%)
a	CF_3	180–195 (C_6H_6)	70
b	CN	200 (darkens) 250 (blackens)	–

3.5.2. Synthesis from Triazoles

Dehydrative cyclization[85,86] of 3-benzamido-4*H*-1,2,4-triazole derivatives (**3.89a–c**) gives rise to moderate yields of 5-phenylimidazo[1,5-*b*][1,2,4]triazoles (**3.90a–c**), and not condensed benzodiazepins as might be expected from a Bischler–Napieralski type of process. The ^{1}H nmr spectrum (DMSO-d_6) of **3.90a** is as follows: δ = 7.08 (s, 1H, H-7), 7.2–8.4 (m, 10H, Ar–H), 9.32 (s, 1H, H-2).[85a]

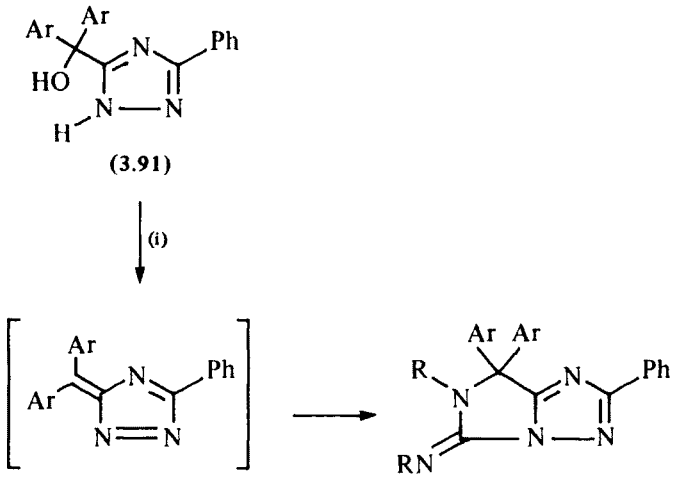


(3.89) (3.90)

	R^1	R^2	mp (°C)	Yield (%)
a	C_6H_5	H	225–226	62
b	C_6H_4Cl-*p*	H	232–233	76
c	2-thienyl	Me	190	57

(i) Polyphosphate ester, 150°C, 0.5 h;
(ii) P_2O_5, $POCl_3$, 90–100°C

Imidazo[1,5-*b*][1,2,4]triazoles formulated[87] as **3.93a–c** are also formed, perhaps through triazafulvenes (**3.92**), when the triazoles (**3.91**) are heated with an excess of dicyclohexylcarbodiimide.[87]

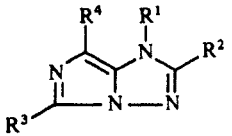


R = cyclohexyl

	Ar	MP (°C)	Yield (%)
a	Ph	173–175 (EtOH)	12
b	*p*-$MeOC_6H_4$	158–162 (EtOH)	38
c	*p*-$O_2NC_6H_4$	165–170	34

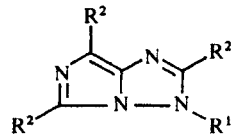
(i) $C_6H_{11}N{=}C{=}NC_6H_{11}$; $MeO(CH_2)_2OMe$, reflux

TABLE 3.12. PHYSICAL AND SPECTRAL PROPERTIES OF MISCELLANEOUS 1*H*- AND 3*H*-IMIDAZO[1,5-*b*][1,2,4]TRIAZOLES



(3.94)

	R^1	R^2	R^3	R^4
a,	H	CF_3	CF_3	CF_3
b,	Me	CF_3	CF_3	CF_3
c,	H	CN	CN	CN
d,	Me	CN	CN	CN
e,	H	$CONH_2$	$CONH_2$	$CONH_2$
f,	H	$CONH_2$	$CONH_2$	CN
g,	H	CO_2H	CO_2H	$CONH_2$
h,	Me	CO_2H	CO_2H	$CONH_2$
i,	Me	H	H	$CONH_2$
j,	Me	H	H	CN



(3.95)

	R^1	R^2
a,	Me	CF_3
b,	Me	CN

Starting Material	Reaction Conditions	Product(s)	Yield (%)	mp (°C) (Solvent for Recrystallization	uv Spectrum λ_{max} (nm) (Extinction Coefficient)	Reference
3.94a	CH_2N_2, Et_2O	**3.94b** + **3.95a** (93:7)	–	43–45.5 (pentane)[a]	λ_{max}^{EtOH} = 266 (ϵ, 3800), 226 (5500)	83

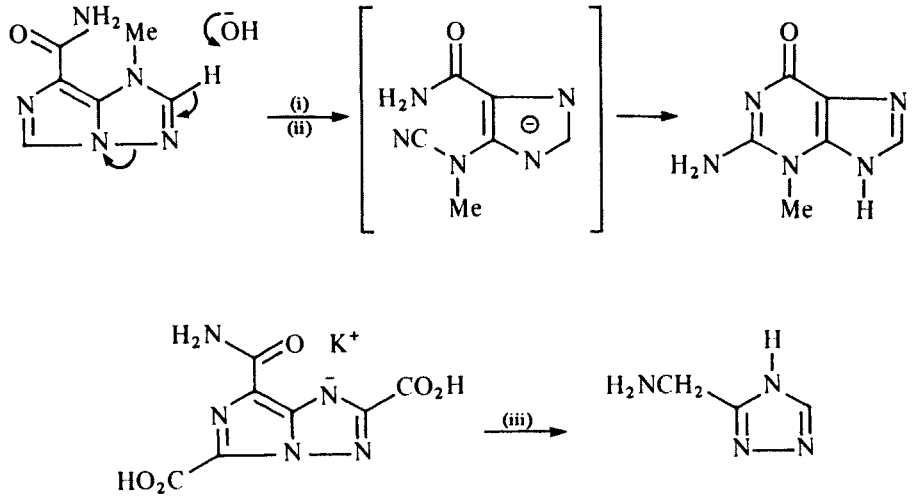
3.94c	Me_2SO_4, MeCN, reflux	**3.94c** + **3.95b** (3:1)	97	234–235 (MeCOEt) **(3.94c)** 182–183 ($CHCl_3$–EtOAc) **(3.95b)**	λ_{max}^{EtOH} = 298 (6600), 264 (12,500), 221 (22,400)	84
3.94c	30% H_2SO_4, room temp.	**3.94e**	95	Not quoted	(pH 13) λ_{max} = 335 (20,600), 295 (8400), 238 (24,400)	84
3.94c	1 *M* NaOH, room temp.	**3.94f**[b]	–	> 400	(pH 12) λ_{max} = 323 (17,700), 290 (8700), 234 (29,600)	84
3.94c[c]	KOH, dioxan, H_2O, heat	**3.94g**[c]	96	Darkens 210		84
3.94g[b]	(i) Me_2SO_4; 6 *M* NaOH (ii) 2 *M* HCl	**3.94h**	69	280–283[d]	(2 *M* HCl) λ_{max} = 313 (12,300), 278 (9900), 245 (sh, 12,900), 224 (17,900)	
3.94h	Sublime *in vacuo*, 180–240°C	**3.94i**	71	289–292 (H_2O)	(pH 1) 273 (15,200), 232 (6900)	84
3.94i	$POCl_3$, reflux	**3.94j**	53	219–220 ($ClCH_2CH_2Cl$)	(2 *M* HCl) λ_{max} = 265 (21,000), 227 (7000)	84

[a] Melting point of the major product (**3.94b**) quoted.
[b] Sodium salt.
[c] Potassium salt.
[d] Gas evolution occurs at 180°C.

3.5.3. Reactions

The products of alkylation and of hydrolytic reactions of the trisubstituted 1*H*-imidazo[1,5-*b*][1,2,4]triazoles (**3.94a** and **c**) are summarized in Table 3.12.[83,84] Methylation of both substrates occurs predominantly at *N*-1 with a minor component formed from alkylation at *N*-3; a similar preference for methylation at *N*-1 is observed when the sodium salt of **3.94g** is treated with dimethyl sulfate under basic conditions (see **3.94g** → **3.94h**). Hydrolytic reactions of **3.94c** provide access to valuable acyl derivatives of 1*H*-imidazo[1,5-*b*][1,2,4]triazoles (viz., **3.94e–g**), and the routine functional group interconversion ($CONH_2$ → CN) can be achieved by using phosphorus oxychloride (see **3.94i** → **3.94j**).[84]

Ring fission of the triazole ring and the imidazole rings of 1*H*-imidazo[1,5-*b*]-[1,2,4]triazoles can be induced by alkali and acid, respectively (see Scheme 3.9).[84]

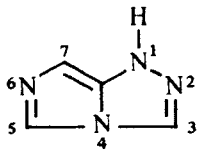


(i) 0.5 *M* NaOH, reflux (ii) 1 *M* HCl; (iii) 6 *M* H_2SO_4, room temperature

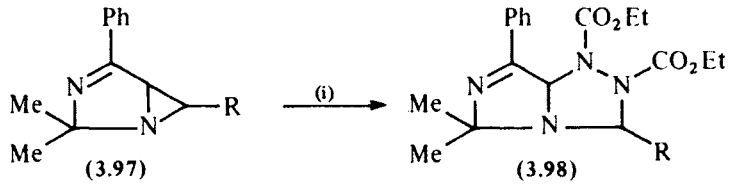
Scheme 3.9

3.6. RING SYSTEM C_3N_2–C_2N_3: IMIDAZO[5,1-*c*][1,2,4]-TRIAZOLE

Compounds in the fully unsaturated 1*H*-imidazo[5,1-*c*][1,2,4]triazole ring system (**3.96**) are not described during the literature period covered, and there is an isolated example of a derivative of the 2,3,5,7*a*-tetrahydro type. Thus the aziridino-imidazole (**3.97**) reacts with diethylazodicarboxylate to give the adduct (**3.98**)[88] in a process with analogy in an earlier described synthetic route leading to pyrrolo-[1,2-*c*]imidazoles (see Section 1.3.6 in Chapter 1).



(3.96)



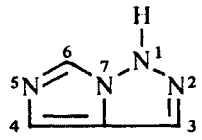
(3.97) (3.98)

R = *p*-$O_2NC_6H_4$ mp 119–120°C, 76% yield

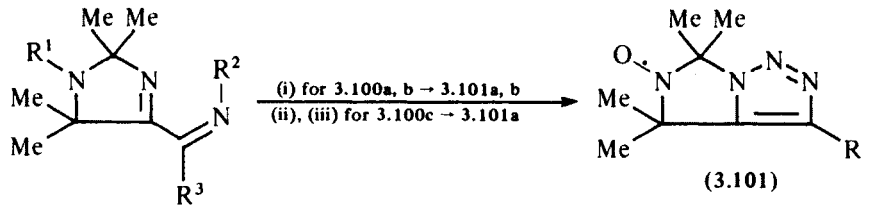
(i) $EtO_2CN{=}NCO_2Et$, decane, reflux

3.7. RING SYSTEM C_3N_2–C_2N_3: IMIDAZO[1,5-*c*][1,2,3]-TRIAZOLE

Compounds in the parent, unsaturated imidazo[1,5-*c*][1,2,3]triazole system (**3.99**) are unknown, and examples in this group are restricted to the bicyclic nitroxide free radicals, formally 4*H*-imidazo[1,5-*c*][1,2,3]triazol-5(6*H*)-yloxy derivatives (**3.101a,b**).[89,90] They can be prepared either by oxidation of the hydrazones (**3.100a,b**) with manganese dioxide or lead dioxide in benzene[89] or from the cyclic nitroxide (**3.100c**) with tosyl hydrazine followed by treatment with alkali.[90] The esr spectra of the bicyclic nitroxides (**3.101a,b**) exhibit characteristic triplets with a_N = 1.40 and 1.46 mT, respectively (EtOH solvent).[89]



(3.99)



(3.100) (3.101)

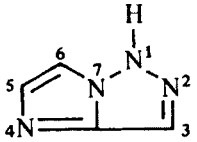
	R^1	R^2	R^3
a	OH	NH_2	H
b	OH	NH_2	Me
c	—O·	*t*-Bu	H

	R	mp (°C)	Yield (%)
a	H	99–101 (hexane)	96
b	Me	92–94 (hexane)	91

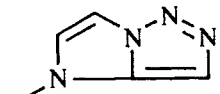
(i) MnO_2, C_6H_6, 6 h; (ii) *p*-$MeC_6H_4SO_2NHNH_2$; (iii) NaOH

3.8. RING SYSTEM C_3N_2–C_2N_3:IMIDAZO[1,2-*c*][1,2,3]-TRIAZOLE

Compounds in the imidazo[1,2-*c*][1,2,3]triazole system can exist in 1*H*- (**3.102**), 4*H*- (**3.103**) and 6*H*-tautomeric forms, but only two compounds have been synthesized in this class.



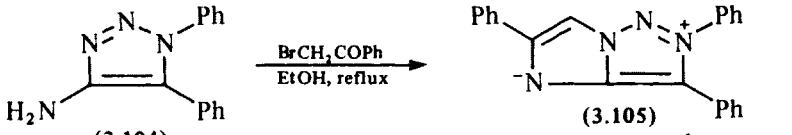
(3.102)



(3.103)

3.8.1. Imidazo[1,2-*c*][1,2,3]triazolium Betaines

A variety of bicyclic heteroaromatic betaines, including anhydro-2,3,5-triphenyl-4*H*-imidazo[1,2-*c*][1,2,3]triazolium hydroxide (**3.105**), have been synthesized in the manner outlined in **3.104** → **3.105**.[91]



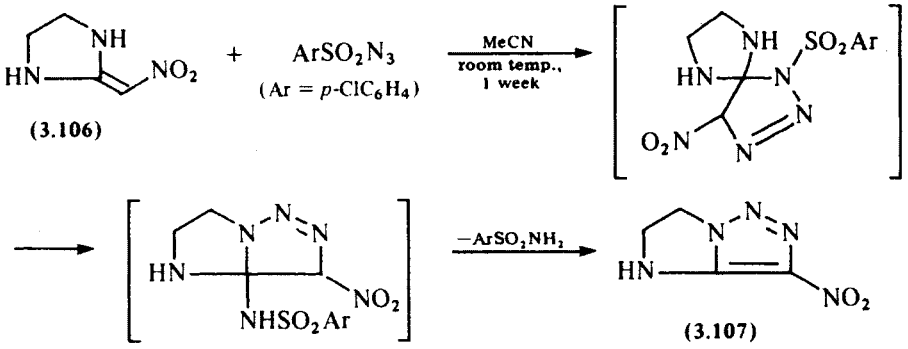
(3.104)

(3.105)

mp 214–216°C (26% yield)

3.8.2. 5,6-Dihydro-4*H*-imidazo[1,2-*c*][1,2,3]triazoles

A 3-nitro compound in this group (**3.107**) has been prepared from the imidazoline derivative (**3.106**) by a process of 1,3-dipolar cycloaddition with concomitant Dimroth rearrangement (see Scheme 3.10).[92] The reactivity of compounds in the imidazo[1,2-*c*][1,2,3]triazole system has not been studied.



(3.107)

mp 215°C (dec.) (MeCN) (65% yield);
uv λ_{max}^{EtOH} 255 (12,600), 332 (7600)

Scheme 3.10

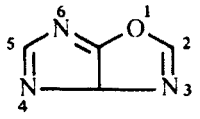
TABLE 3.13. PHYSICAL PROPERTIES OF TETRAHYDROIMIDAZO[4,5-*d*]OXAZOL-2-ONES (3.111)[94]

Compound 3.111			
R^1	Ar	mp (°C) (Solvent for Recrystallization)	Yield (%)
4-$MeOC_6H_4$	Ph	216–218 (Me_2CO)[a]	69
4-$MeOC_6H_4$	2-ClC_6H_4	190–191 (Et_2O)	79
4-$MeOC_6H_4$	4-ClC_6H_4	222–224 (Me_2CO)	86
Ph	Ph	189–190 (Me_2CO)	61
Ph	2-ClC_6H_4	232–233 (Me_2CO)	49
Ph	4-ClC_6H_4	205–206 (Me_2CO)	72

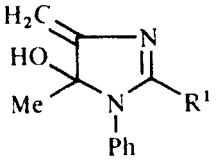
[a]Spectral properties: ir $\nu_{max}^{KBr} = 1760\,cm^{-1}$ (C=O), 1615 (C=N).

3.9. RING SYSTEM C_3N_2–C_3NO: IMIDAZO[4,5-*d*]OXAZOLE

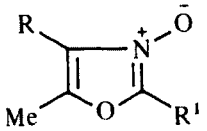
There are no citations to the fully unsaturated imidazo[4,5-*d*]oxazole system (**3.108**) during the literature period covered, and there is an isolated reference dealing with the synthesis of tetrahydroimidazo[4,5-*d*]oxazol-2-ones. In contrast to the reaction of phenyl isocyanate with 4-methyl-substituted oxazole-*N*-oxides (**3.109a**), which gives dihydroimidazoles (**3.110**),[93] the reaction of 4-phenyloxazole *N*-oxides (**3.109b**) provides[94] condensed imidazoles (**3.111**) by a complex pathway involving incorporation of 2 mol of aryl isocyanate. (See the proposed[94] mechanism in Scheme 3.11 and Table 3.13 for physical properties of compounds **3.111**.) The



(3.108)



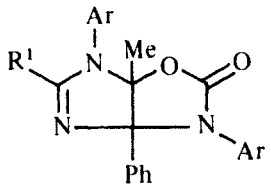
(3.110)



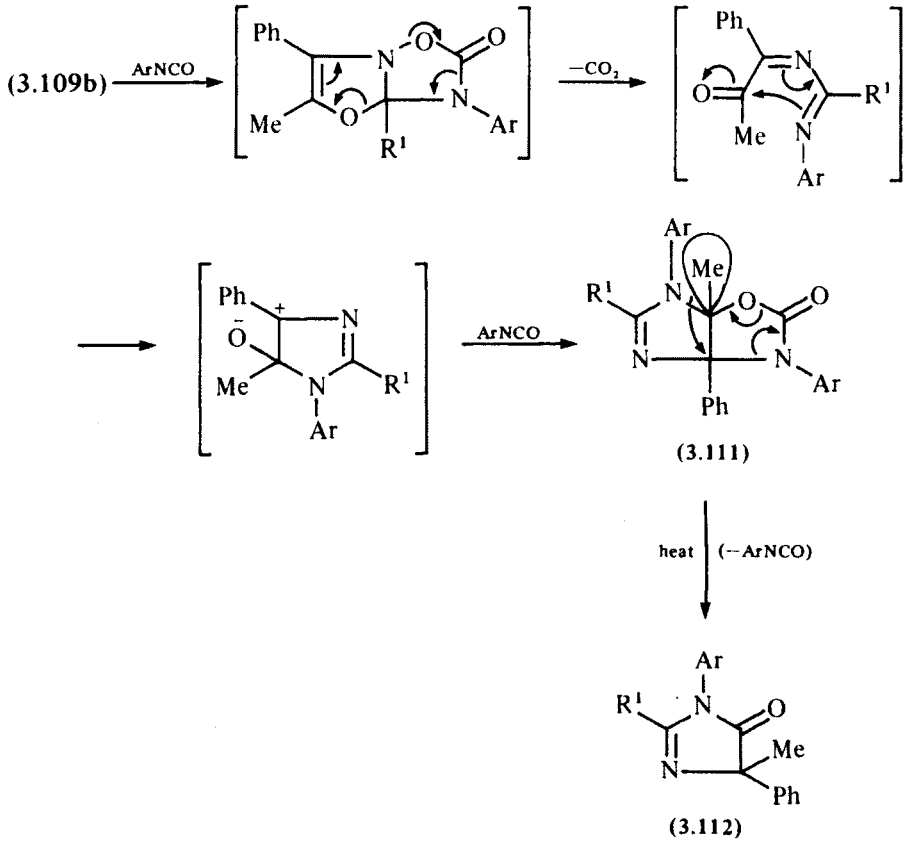
(3.109)

a: R = Me
b: R = Ph

(i) PhNCO;
(ii) 2 ArNCO, $CHCl_3$, room temperature



(3.111)

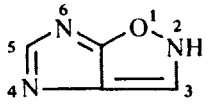


Scheme 3.11

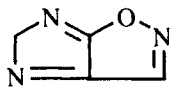
bicyclic derivatives (**3.111**) are stable toward acids and bases and do not react with organic bases such as aniline and morpholine; they undergo pyrolysis (ca. 50–60°C beyond mp) with fission of the oxazole ring to give imidazolones (cf. **3.112** in Scheme 3.11).[94]

3.10. RING SYSTEM C_3N_2–C_3NO: IMIDAZO[4,5-*d*]ISOXAZOLE

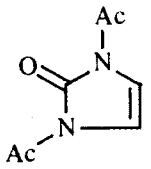
Derivatives in the fully unsaturated 2*H*- (**3.113**) or 5*H*-imidazo[4,5-*d*]isoxazole (**3.114**) are not cited during the literature period covered. 1,3-Dipolar cycloaddition of diphenyl nitrone to 1,3-diacetylimidazolone (**3.115**) is claimed[95] to provide the diastereoisomeric hexahydroimidazo[4,5-*d*]isoxazol-5-ones (**3.116a,b**), but the relative stereochemistry of each adduct is unassigned. The ir spectra (KBr) of **3.116a** and **b** exhibit maxima at 1690, 1710, and 1770 cm^{-1} and 1710 and 1775 cm^{-1}, respectively.[95]



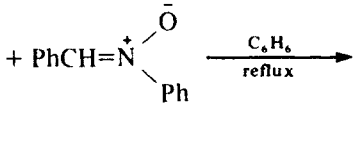
(3.113)

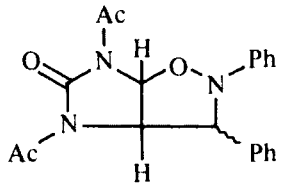


(3.114)



(3.115)



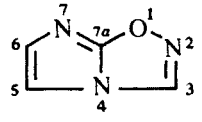


(3.116)

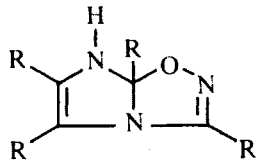
	mp (°C)	Yield (%)
a	165–166 ($CHCl_3$)	23
b	136–138 (Et_2O)	9

3.11. RING SYSTEM $C_3N_2-C_2N_2O$: IMIDAZO[1,2-*d*][1,2,4]-OXADIAZOLE

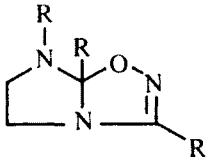
Compounds in the parent imidazo[1,2-*d*][1,2,4]oxadiazole ring system (**3.117**) have not been synthesized, and this section is concerned with 7,7*a*-dihydro (**3.118**) and 5,6,7,7*a*-tetrahydro derivatives (**3.119**).



(3.117)



(3.118)
R = Ph, alkyl



(3.119)
R = Ph, alkyl

3.11.1. 7,7*a*-Dihydroimidazo[1,2-*d*][1,2,4]oxadiazoles

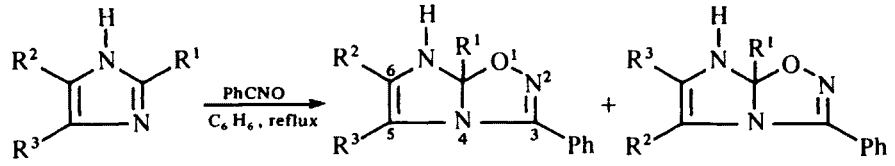
1,3-Dipolar cycloaddition of imidazoles (**3.120**) occurs readily with excess benzonitrile oxide in benzene to give a valuable general synthesis of 7,7*a*-dihydro-imidazo[1,2-*d*][1,2,4]oxadiazoles.[96] Because of the tautomeric nature of the starting materials, symmetrically substituted ($R^2 = R^3$) and unsymmetrically substituted ($R^2 \neq R^3$) compounds give rise to either a single product (e.g., **3.121a–c**) or a mixture of two regioisomers (e.g., **3.121d–f** + **3.122d–f**, respectively) (see Table 3.14).

TABLE 3.14. PHYSICAL PROPERTIES OF 7,7*a*-DIHYDROIMIDAZO[1,2-*d*][1,2,4]-OXADIAZOLES (**3.121** and **3.122**)[96a]

Product **3.121** or **3.122**	mp (°C) (THF)	Yield (%)
3.121a	194[a]	73
3.121b	224	62
3.121c	215	91
3.121d	205	24
3.122d	164	40
3.121e	205	77
3.122e	195	6
3.121f	208	40
3.122f	230	22

[a]Spectroscopic properties of **3.121a**: ir ν_{max} (Nujol) = 2800–2500 (NH), 1625, 1510, 1500, 1330, 1260 1210, 1110, 1080, 1060, 1035, 995, 935, 830, 780, 740, 700, and 685 cm^{-1}; ^1H nmr (DMSO-d_6) δ = 7.14 (H-6), 7.30 (H-5), 7.93 (H-7*a*), 12.21 (NH), 7.44 (Ar–H), J_{56} = 1 Hz, $J_{5,7a}$ = 0.7 Hz, $J_{6,7a}$ = 0.7 Hz.

Very little is known about the reactivity of these derivatives except that reductive cleavage (Sn, conc. HCl, reflux) occurs in the oxadiazole ring to form the starting imidazole and benzoic acid [e.g., **3.121a** → **3.120** (R^1–R^3 = H)].[96a]

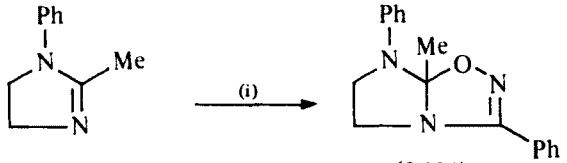


(3.120) (3.121) (3.122)

	R^1	R^2	R^3		R^1	R^2	R^3
a	H	H	H	d	H	Me	H
b	Me	H	H	e	H	Ph	H
c	H	Ph	Ph	f	Et	Me	H

3.11.2. 5,6,7,7*a*-Tetrahydroimidazo[1,2-*d*][1,2,4]oxadiazoles

1,3-Dipolar cycloaddition of benzonitrile oxide to the imidazoline derivative (**3.123**) affords a product formulated[97] as the tetrahydroimidazo[1,2-*d*][1,2,4]-oxadiazole (**3.124**), but the efficiency and scope of such reactions has not been assessed.

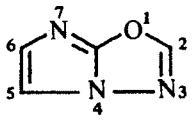


(3.123) (3.124)
mp 132°C

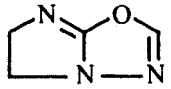
(i) PhC(Cl)=NOH, Et_3N, Et_2O, reflux (≡PhCNO)

3.12. RING SYSTEM C_3N_2–C_2N_2O: IMIDAZO[2,1-*b*][1,3,4]-OXADIAZOLE

Compounds in the fully aromatic imidazo[2,1-*b*][1,3,4]oxadiazole ring system (**3.125**) are known in addition to 5-oxo and 5,6-dioxo derivatives of the 5,6-dihydro type (cf. **3.126**).



(3.125)



(3.126)

3.12.1. Imidazo[2,1-*b*][1,3,4]oxadiazoles

3.12.1.1. Synthesis

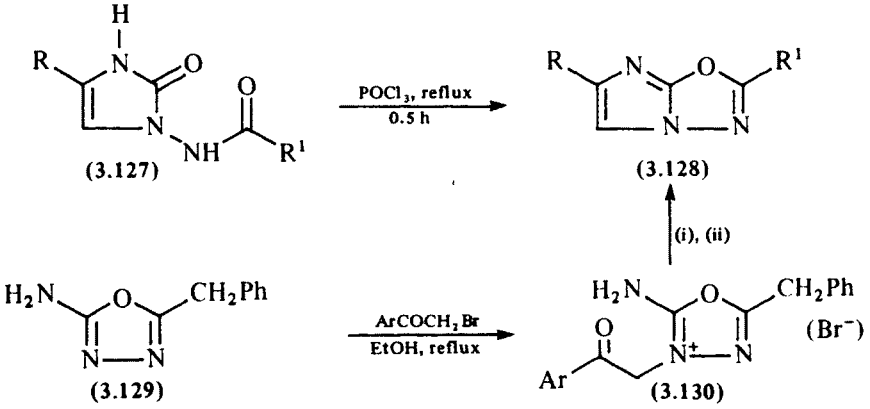
Fully unsaturated imidazo[2,1-*b*][1,3,4]oxadiazoles can be constructed from either imidazoles or oxadiazoles. For example, dehydrative cyclization of 1-acylamino-4-arylimidazolones (**3.127**) by phosphorus oxychloride affords an efficient general synthesis of 2,6-disubstituted derivatives in the series (see **3.128** and Table 3.15).[98] The alternative route involves the synthesis of 2-amino-3-

TABLE 3.15. SYNTHESIS OF IMIDAZO[2,1-*b*][1,3,4]OXADIAZOLES (**3.128**) FROM 1-ACYLAMINO-4-ARYLIMIDAZOLONES (**3.127**)[98]

Compound **3.128**			
R	R^1	mp (°C) (Solvent for Recrystallization)	Yield (%)
Ph	Me	136–137 (aq. MeOH)	76
p-BrC_6H_4	Me	172 (EtOH)	95
p-ClC_6H_4	Me	175 (EtOH)	76
p-$H_3CC_6H_4$	Me	168–169 (EtOH)	72
Ph	*i*-Pr	128 (aq. EtOH)	64
P-BrC_6H_4	*i*-Pr	146 (EtOH)	82
Ph	$PhCH_2$	157–158 (EtOH)	91
p-BrC_6H_4	$PhCH_2$	191 (EtOH)	90
p-ClC_6H_4	$PhCH_2$	177–178 (EtOH)	96
p-$H_3CC_6H_4$	$PhCH_2$	143–144 (EtOH)	78
p-$MeOC_6H_4$	$PhCH_2$	155–156 (EtOH)	80
Ph	Ph	201 (EtOH)	90
p-BrC_6H_4	Ph	224–225 (*n*-BuOH)	100
p-ClC_6H_4	Ph	217–218 (*n*-PrOH)	95
p-$H_3CC_6H_4$	Ph	183–184 (EtOH)	81
p-$MeOC_6H_4$	Ph	193–194 (EtOH)	86

TABLE 3.16. SYNTHESIS OF IMIDAZO[2,1-*b*][1,3,4]OXADIAZOLES (**3.128**) FROM 2-AMINO-3-PHENACYL-1,3,4-OXADIAZOLIUM BROMIDES (**3.130**)[99]

Compound **3.128** ($R^1 = CH_2Ph$) R	mp (°C) (EtOH)	Yield (%)
Ph	244–246	76
p-BrC_6H_4	274–276	89
p-$O_2NC_6H_4$	280–284	87
p-$MeOC_6H_4$	237–239	80
p-MeC_6H_4	257–259	76
o-HOC_6H_4	244–246	68



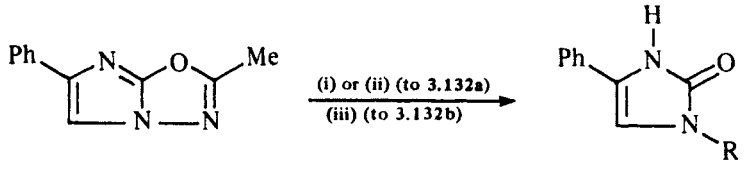
(3.127) (3.128) (3.129) (3.130)

(i) Reflux, H_2O; (ii) NH_3 (to **3.128**; $R^1 = CH_2Ph$, R = aryl)

phenacyl-1,3,4-oxadiazolium salts (cf. **3.129** → **3.130**) and their subsequent cyclization in hot water (cf. **3.130** → **3.128** and Table 3.16).[99]

3.12.1.2. Reactions

Treatment of imidazo[2,1-*b*][1,3,4]oxadiazoles with hot concentrated hydrochloric acid or hot aqueous potassium hydroxide results in cleavage of the oxadiazole ring to give a 1-acylaminoimidazolone derivative (see, e.g., **3.131** → **3.132a**);[98] cleavage can also be effected by using hot 48% hydrobromic acid to afford 4-phenylimidazolone (**3.132b**).[98]



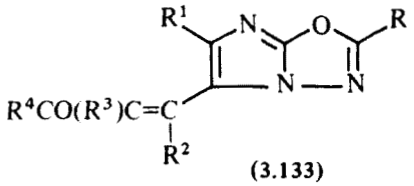
(3.131) (3.132)

a R = NHCOMe
b R = H

(i) Concentrated HCl, reflux; (ii) 8% aqueous KOH, reflux; (iii) 48% HBr, reflux

3.12.1.3. Commerical Applications

Alkenyl amides of type **3.133** have been patented for use as diuretics, antihypertensives, and uricosurics.[100]



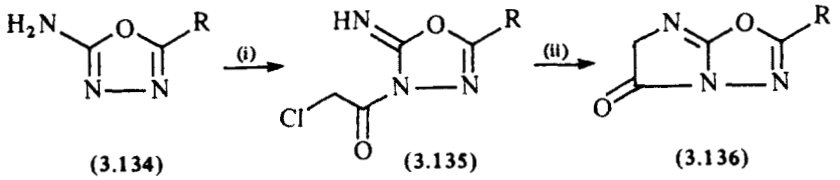
(3.133)

R, R^1 = H, alkyl, aryl, etc.
R^2 = H, alkyl, CF_3
R^3 = H, CN, halogeno, etc.
R^4 = NH_2

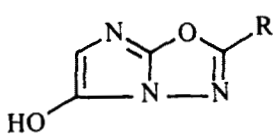
3.12.2. 5,6-Dihydroimidazo[2,1-*b*][1,3,4]oxadiazoles

3.12.2.1. Synthesis

A series of 2-arylimidazo[2,1-*b*][1,3,4]oxadiazol-5(6*H*)-ones (**3.136**) has been prepared in good yield in stepwise fashion from 2-amino-5-substituted-1,3,4-oxadiazoles (see **3.134** → **3.135** → **3.136** and Table 3.17).[101] The existence of a tautomeric equilibrium (**3.136** ⇌ **3.137**) is apparent from ir spectral measurements that indicate the presence of an O–H stretching frequency in addition to a band attributable to the 5-oxo substituent (see Table 3.17).



(3.134) **(3.135)** **(3.136)**



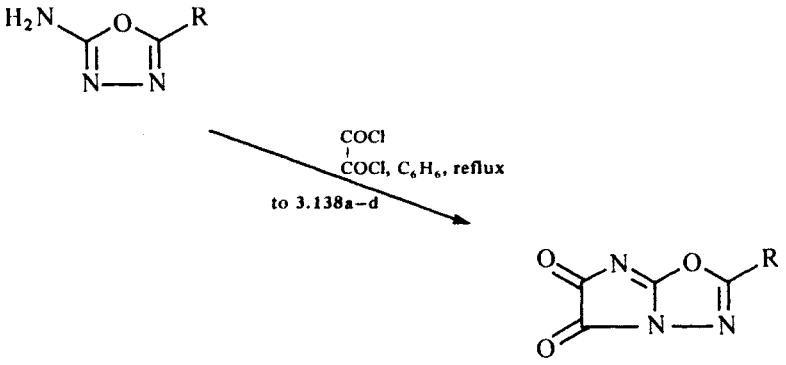
(3.137)

(i) $ClCOCH_2Cl$, 0°C,
(ii) pyridine, room temperature, 0.5 h

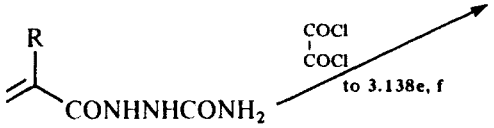
TABLE 3.17. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF IMIDAZO[2,1-*b*][1,3,4]OXADIAZOL-5(6*H*)-ONES (**3.136**)[101]

Compound **3.136** R	Yield (%)	mp (°C) (Solvent for Recrystallization)	uv Spectrum[a] λ_{max}^{EtOH} (log ϵ)	ir Spectral Bands ν_{max}^{Nujol} (cm^{-1})
Ph	77	235–236 (EtOH)	275 (4.30) (acid solution) 268 (4.26) (alkaline solution)	3425 (OH), 1662 (CO)
p-$MeOC_6H_4$	82	220 (EtOH)	286 (4.16) 278 (4.20) (acid solution) 291 (4.20) (alkaline solution)	3534 (OH), 1733 (CO)
p-ClC_6H_4	84	220 (MeOH)	294 (4.09) 268 (4.19) (acid solution) 305 (4.35) (alkaline solution)	3703 (OH), 1739 (CO)
2,4-$Cl_2C_6H_3$	82	172 (Me_2CO)	295 (4.23) 285 (4.12) (acid solution) 299 (4.33) (alkaline solution)	3597 (OH), 1697 (CO)
$PhCH_2$[b]	40	95 (dec.) (Et_2O)	234 (4.19), 259 (3.40), 410 (4.06); 302 (3.91), 410 (4.09) (alkaline solution)	–

[a] Data from acid and alkaline solutions refer to ethanol solutions containing a trace of acid and alkali, respectively.
[b] Data given are for the hydrochloride.



(3.138)



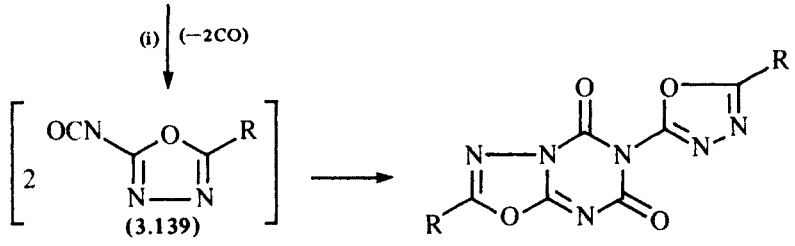
	R	mp (°C) (dec.)
a	Ph	180–193
b	CH_2Ph	110–120
c	*p*-ClC_6H_4	209–220
d	*p*-$O_2NC_6H_4$	215–225
e	$CH{=}CH_2$	–
f	$C(Me){=}CH_2$	135

2-Amino-1,3,4-oxadiazoles have also been used, with oxalyl chloride, to synthesize 2-aryl-5,6-dioxoimidazo[2,1-*b*][1,3,4]oxadiazoles (**3.138a–d**),[102] and compounds of this type (**3.138e,f**) have also been prepared by treating oxalyl chloride with acryloyl- and methylacryloylsemicarbazides.[103] The diones (**3.138a–d**) exhibit[102] the following prominent ir spectral bands: ν_{max}^{KBr} 1030 (C–O–C), 1680 (C=N), 1749, and 1786 (C=O) cm^{-1} and characteristic oxadiazole bands at 1420, 1290, 1180, 1090, and 740 cm^{-1}.

3.12.2.2. Reactions

Pyrolysis of the 5,6-dioxo derivatives (**3.138a–d**) in dichlorobenzene proceeds with loss of carbon monoxide to afford dimers (**3.140**) of the isocyanate (**3.139**).[102] The vinyl derivatives (**3.138e,f**) are useful monomers for the preparation of cross-linked polymers.[103]

2 (3.138a–d)



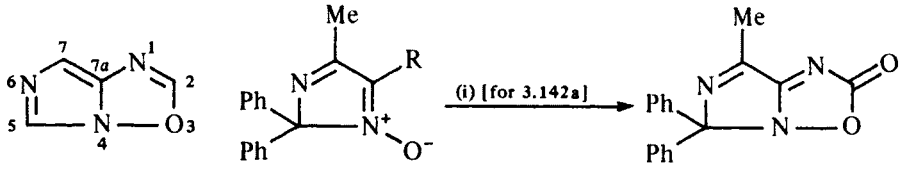
(3.139)

(i) Heat in $Cl_2C_6H_4$

(3.140)

3.13. RING SYSTEM C_3N_2–C_2N_2O: IMIDAZO[1,5-*b*][1,2,4]-OXADIAZOLE

Compounds in the fully unsaturated imidazo[1,5-*b*][1,2,4]oxadiazole ring system (**3.141**) are unknown. The partially reduced derivative, 7-methyl-5,5-diphenylimidazo[1,5-*b*][1,2,4]oxadiazol-2(5*H*)-one (**3.143**), has been prepared by way of a nonisolable intermediate product of Curtius rearrangement (**3.142b**) of the *N*-oxide derivative (**3.142a**).[104] The presence of a strong carbonyl band at 1770 cm^{-1} in the ir spectrum of **3.143** is assigned[104] to the δ-lactam function [see Section 2.13 in Chapter 2 for additional reactions of *N*-oxides (cf. **3.142**) leading to imidazo[1,5-*b*]isoxazoles].

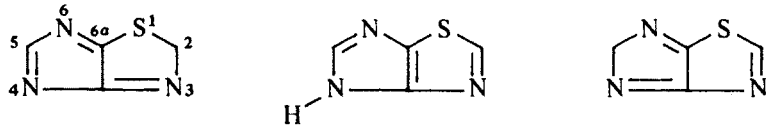


(**3.141**) (**3.142**) (**3.143**)

a: R = CON_3
b: R = NCO
(i) Heat in EtOH, C_6H_6, or H_2O

3.14. RING SYSTEM C_3N_2–C_3NS: IMIDAZO[4,5-*d*]THIAZOLE

In principle, compounds in the imidazo[4,5-*d*]thiazole ring system can belong to the 2*H* (**3.144**), 4*H* (**3.145**) or 5*H* (**3.146**) categories, but the only known compounds in this class are 4,6-dihydro-5*H*-imidazo[4,5-*d*]thiazol-5-ones and -thiones.



(**3.144**) (**3.145**) (**3.146**)

3.14.1. 4,6-Dihydro-5*H*-imidazo[4,5-*d*]thiazoles

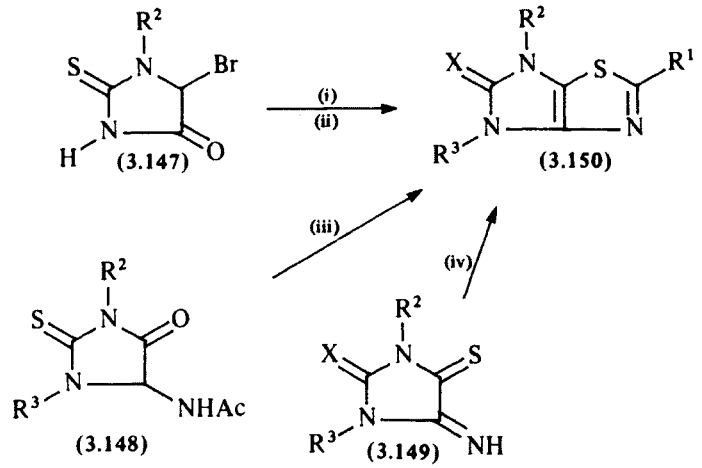
3.14.1.1. Synthesis from Thiohydantoins

Thiohydantoin substrates (**3.147–3.149**) have been used in a variety of cyclization procedures to construct the bicyclic framework of 4,6-dihydro-5*H*-imidazo[4,5-*d*]thiazol-5-thiones (**3.150**, X = S) and a 5-oxo analog (**3.150**, X = O) (see Table 3.18).[105–107] Aspects of the chemical reactivity of these products (cf. **3.150**, X = S) are described in Section 3.14.3.

TABLE 3.18. SYNTHESIS OF 4,6-DIHYDRO-5*H*-IMIDAZO[4,5-*d*]THIAZOL-5-THIONES (**3.150**, X = S) AND A RELATED COMPOUND (**3.150**, X = O) FROM THIOHYDANTOINS (**3.147–3.149**)

	Product (**3.150**)						
Type of Starting Material	R^1	R^2	R^3	X	Yield (%)	mp (°C)	Reference
3.147	NH_2	Ph	H	S	55	>250	105
3.147	NH_2	*o*-MeC_6H_4	H	S	55	173	105
3.147	NH_2	*p*-MeC_6H_4	H	S	60	178–182	105
3.147	NH_2	*p*-ClC_6H_4	H	S	65	170–172	105
3.147	NH_2	*o*-$MeOC_6H_4$	H	S	70	>250	105
3.147	NH_2	*p*-$MeOC_6H_4$	H	S	65	157	105
3.147	NH_2	*p*-$EtOC_6H_4$	H	S	70	>250	105
3.147	Me	*p*-MeC_6H_4	H	S	60	174	105
3.147	Me	*p*-ClC_6H_4	H	S	50	180	105
3.148	Me	Me	Me	S	33	150	106
3.149	Ph	Ph	Ph	S	61	261–263[a]	107
3.149	Ph	Ph	Ph	O	38	157–161[b]	107

[a] Recrystallized from $CHCl_3$–petroleum ether. Infrared spectral bands (KBr): 1595 and 1496 cm^{-1}.
[b] Recrystallized from $CHCl_3$–petroleum ether. Infrared spectral bands (KBr): 1598 and 1500 cm^{-1}.



(i) H_2NCSNH_2 [to **3.150** ($R^1 = NH_2$)] or $MeCSNH_2$ [to **3.150** ($R^1 = Me$)];
(ii) NH_4OH; (iii) P_2S_5, PhMe, 110°C; (iv) PhCHO, dioxan, trace $BF_3 \cdot Me_2O$, reflux

3.14.1.2. Synthesis from Thiazoles

An unorthodox synthesis of 4,6-dihydro-5*H*-imidazo[4,5-*d*]thiazoles (**3.154**) has been achieved from thiazolium salts (**3.151**) by way of thiazolium ylides (**3.152**) and condensed spirothiazolidines (**3.153**) (see data collected in Table 3.19).[108-110] A key intermediate in the proposed[108] acid-promoted degradation of

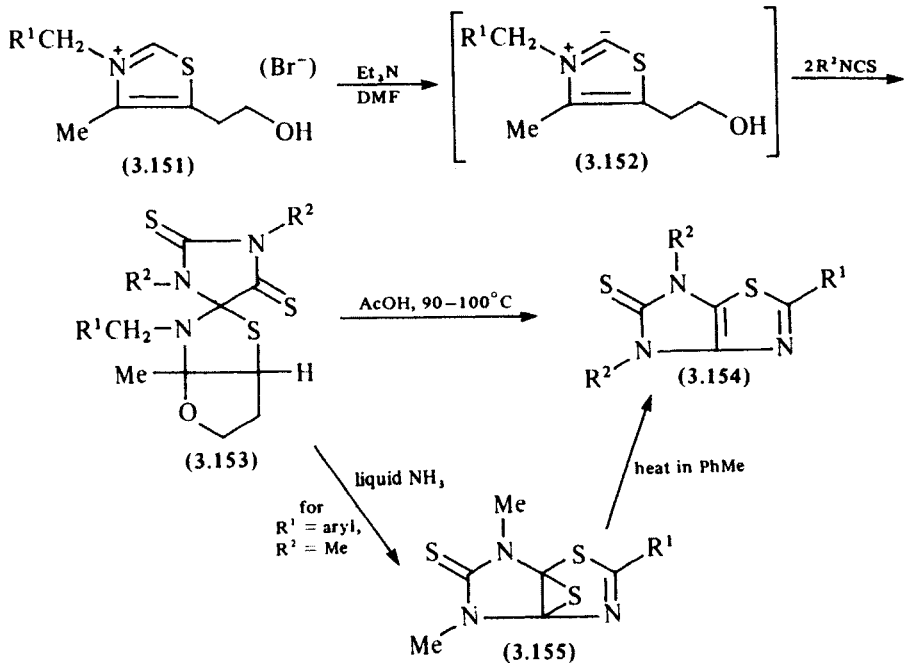
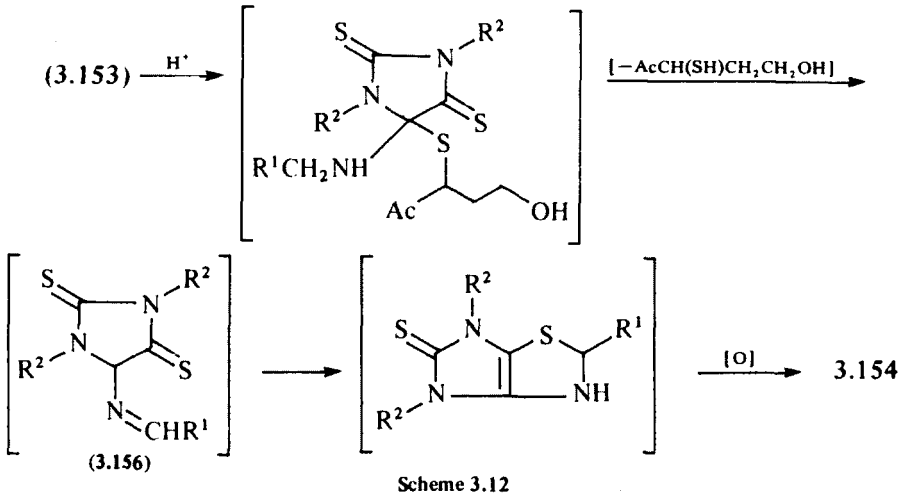


TABLE 3.19. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF 4,6-DIHYDRO-5*H*-IMIDAZO[4,5-*d*]THIAZOL-5-THIONES (**3.154**)

Compound **3.154**					
R^1	R^2	mp (°C)	Yield (%)	uv Spectrum λ_{max}^{EtOH} nm (log ϵ)	Reference
C_6H_5	CH_3	201–202	63	249 (4.07), 280 (4.15), 375 (4.32)	108
$C_6H_4NO_2$-*p*	CH_3	>270	42	282.5 (4.17), 442 (4.26)	108
Pym[a]	CH_3	>270	50	225 (4.11), 283 (4.15), 400 (4.31)	108
Pym[a]	$CH_2CH{=}CH_2$	259–260	50	225 (4.09), 287 (4.08), 399 (4.25)	108
C_6H_4Me-*p*	Me	240–243	20	281 (4.12), 3.74 (4.32)	110

[a]Pym = 2-methyl-4-aminopyrimidin-5-yl.

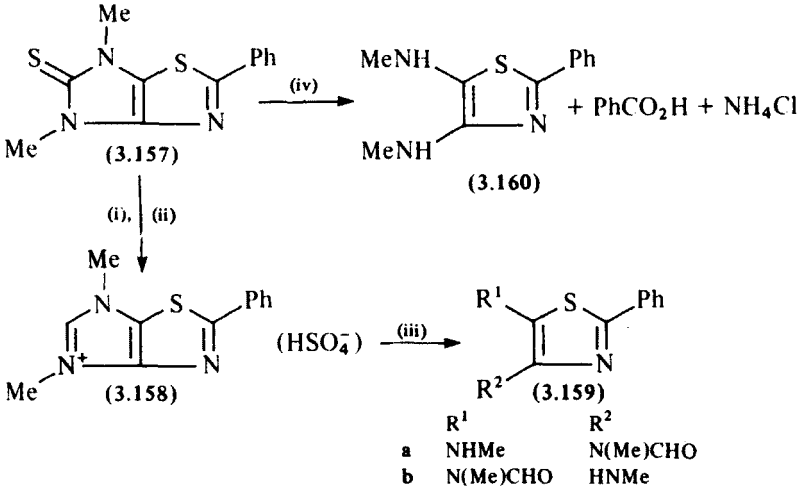


Scheme 3.12

the spiro compound (**3.153**) is a thiohydantoin (**3.156** in Scheme 3.12), and analogies with a synthetic approach (cf. **3.149** → **3.150**) described in the previous section are apparent. The 4,6-dihydro-5*H*-imidazo[4,5-*d*]thiazoles (cf. **3.154**) can also be prepared[110] from the spiro compounds (**3.153**) by means of condensed thiirans (**3.155**), but little synthetic value can be anticipated from this approach.

3.14.1.3. Reactions

The 5-thiono substituent of the 4,6-dihydro compound (**3.157**) is removed oxidatively by hydrogen peroxide in acetic acid,[108] and the ensuing quaternary salt (**3.158**) can be cleaved by aqueous alkali to give a 1:1 mixture of the regio-

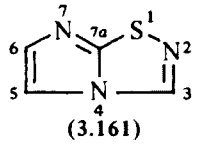


(i) 35% H_2O_2, AcOH, room temperature; (ii) H_2SO_4;
(iii) 10% aqueous NaOH; (iv) 20% HCl, room temperature

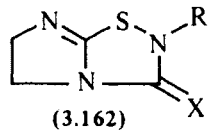
isomers (**3.159a** and **b**).[108] Cleavage of the imidazoline ring of **3.157** can also be effected[108] by 20% aqueous hydrochloric acid at room temperature (see **3.157** → **3.160**), but this process is also accompanied by decomposition of the thiazole ring. It may be noted that the thiazole derivative (**3.160**) can be reconverted into the bicyclic product (**3.157**) by treating it with thiophosgene, but the efficiency and scope of this synthetic approach have not been determined.

3.15. RING SYSTEM C_3N_2–C_2N_2S: IMIDAZO[1,2-*d*][1,2,4]-THIADIAZOLE

Imidazo[1,2-*d*][1,2,4]thiadiazoles (**3.161**) have been synthesized from imidazoles, 1,2,4-thiadiazoles, and vinylene diisothiocyanate, and partially reduced derivatives of the 2,3,5,6-tetrahydro type (**3.162**) are also known.



(3.161)

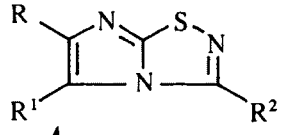


(3.162)
X = O, S
R = Ph, Me

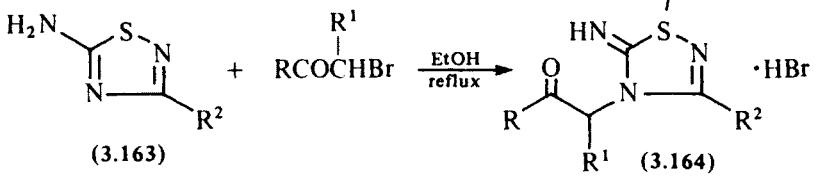
3.15.1. Imidazo[1,2-*d*][1,2,4]thiadiazoles

3.15.1.1. Synthesis from 1,2,4-Thiadiazoles

6-Phenylimidazo[1,2-*d*][1,2,4]thiadiazole (**3.165**, R = Ph, $R^1 = R^2 = H$; mp 130–133°C) has been prepared from 5-amino-1,2,4-thiadiazole (**3.163**, $R^2 = H$) via an isolable thiadiazolium bromide (cf. **3.164**),[111] but transformations of the latter type can be difficult to effect and appear to be sensitive to the substituent combinations (R, R^1, R^2) in the thiadiazolium salt.[112] For example, treatment of 5-amino-1,2,4-thiadiazoles (**3.163**) with phenacyl bromides in ethanol under reflux affords only thiadiazolium salts (cf. **3.164**) for substituent combinations ($R^1 = R^2 = H$, R = aryl; $R^1 = H$, R^2 = Me, R = *p*-$O_2NC_6H_4$), whereas certain other combinations provide access to imidazo[1,2-*d*][1,2,4]thiadiazoles directly, albeit in poor yields (see Table 3.20).[112]



(3.165)



(3.163) (3.164)

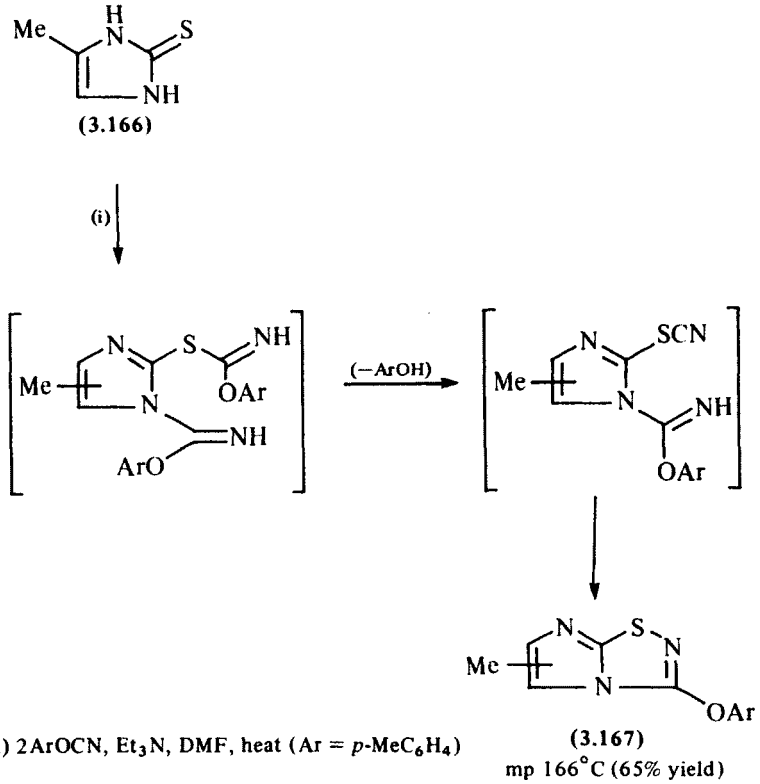
TABLE 3.20. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF IMIDAZO[1,2-*d*][1,2,4]THIADIAZOLES (**3.165**)[112]

Compound **3.165**[a]					
R	R^1	R^2	mp (°C) (Solvent for Recrystallization)	Reaction Time (h)[b]	^{1}H nmr Spectrum[c]
H	H	H	102 (ligroin)	12	7.48 (1H, s, H-6) 7.91 (1H, s, H-5) 8.65 (1H, s, H-3)
Ph	Me	H	142 (ligroin)	18	2.69 (3H, s, Me) 7.32–7.96 (5H, m, Ar–H) 8.38 (1H, s, H-3)
H	H	Me	129 (ligroin)	12	2.65 (3H, s, Me) 7.50 (2H, br, H-5,6)
Ph	H	Me	100 (ligroin)	1	2.65 (3H, s, Me) 7.25–7.65 (3H, m, Ar–H) 7.73 (1H, s, H-5) 7.80–8.50 (2H, m, Ar–H)
p-$O_2NC_6H_4$	H	Me	219 (EtOH)	4	2.74 (3H, s, Me) 7.93 (1H s, H-5) 8.08–8.53 (4H, m, Ar–H)
Ph	Me	Me	254 (EtOH)	18	2.45–2.55 (6H, 2s, Me-3, Me-5) 7.34–8.04 (5H, m, Ar–H)[e]

[a] Yields for the transformation **3.163** → **3.165** are in the range 10–30%.
[b] Reaction conducted in ethanol under reflux unless otherwise stated.
[c] Values quoted are in ppm from tetramethylsilane ($CDCl_3$ solvent).
[d] Reaction solvent is dimethylformamide.
[e] Measured in DMSO-d_6 solvent.

3.15.1.2. Synthesis from Imidazoles

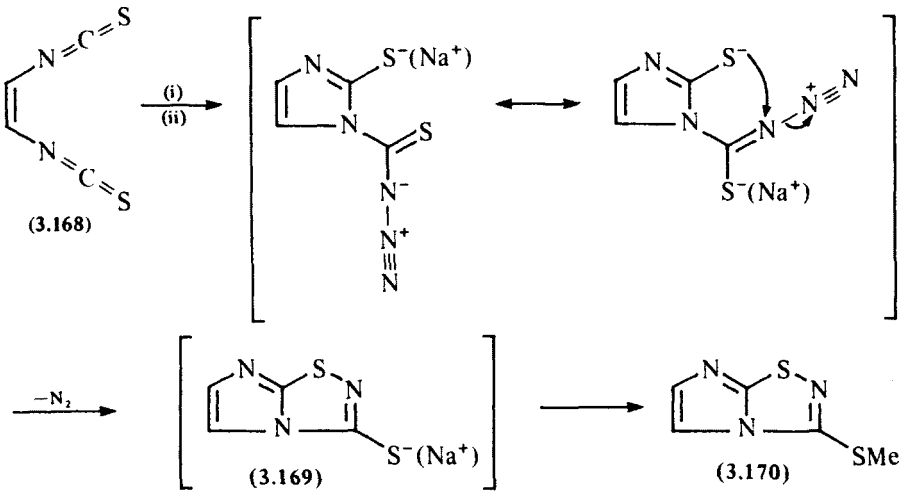
A disubstituted imidazo[1,2-*d*][1,2,4]thiadiazole derivative (**3.167**) has been prepared[113] by treating the imidazolinethione (**3.166**) with *p*-tolylcyanate, but the regiochemical outcome of the process (Scheme 3.13) and the general synthetic value of this type of reaction are unknown.



Scheme 3.13

3.15.1.3. Synthesis from Vinylene Diisothiocyanate

Vinylene diisothiocyanate (**3.168**, prepared[114] from the reaction of imidazole and thiophosgene in basic conditions) reacts with sodium azide in aqueous dimethoxyethane with ring closure and concomitant loss of nitrogen (see Scheme 3.14) to afford the salt (**3.169**) and thence the isolated 3-methylthioimidazo[1,2-*d*][1,2,4]-thiadiazole (**3.170**, 53% yield; ^{1}H nmr (DMSO-d_6) $\delta = 2.8$ (3H, s, Me), 7.4 (1H, d, H-5 or -6), 7.9 (1H, d, H-5 or -6).[115] It may be noted that a series of analogous thiadiazolo[4,5-*a*]benzimidazoles has been synthesized in related reactions of *o*-phenylene isothiocyanate.[116]



(3.168)

(3.169)

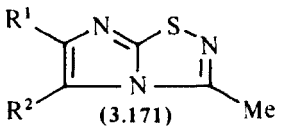
(3.170)

(i) NaN_3, aqueous DME;
(ii) MeI

Scheme 3.14

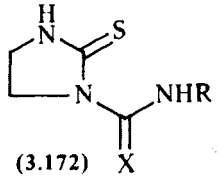
3.15.1.4. Reactions

3-Methylimidazo[1,2-*d*][1,2,4]thiadiazole (**3.171a**) and its derivatives (**3.171b,e**) have been used to evaluate the reactivity of the bicyclic system toward electrophilic attack.[112] Compounds of this type are unreactive in nitrosation (HNO_2) and diazotization (ArN_2^+) reactions, but bromination (Br_2, AcOH) gives 5-bromo derivatives (see **3.171a,b** → **3.171c,d**, respectively), and nitration (conc. H_2SO_4, 86% HNO_3) of the disubstituted derivative (**3.171e**) gives a 5-nitro compound (**3.171f**).[112]



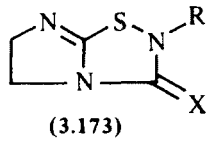
(3.171)

	R^1	R^2	mp (°C) (Ligroin)
a	H	H	–
b	Ph	H	–
c	H	Br	162
d	Ph	Br	147
e	$C_6H_4NO_2$-*p*	H	–
f	$C_6H_4NO_2$-*p*	NO_2	206



(3.172)

(i) Br_2, $CHCl_3$, EtOH;
(ii) $NaHCO_3$

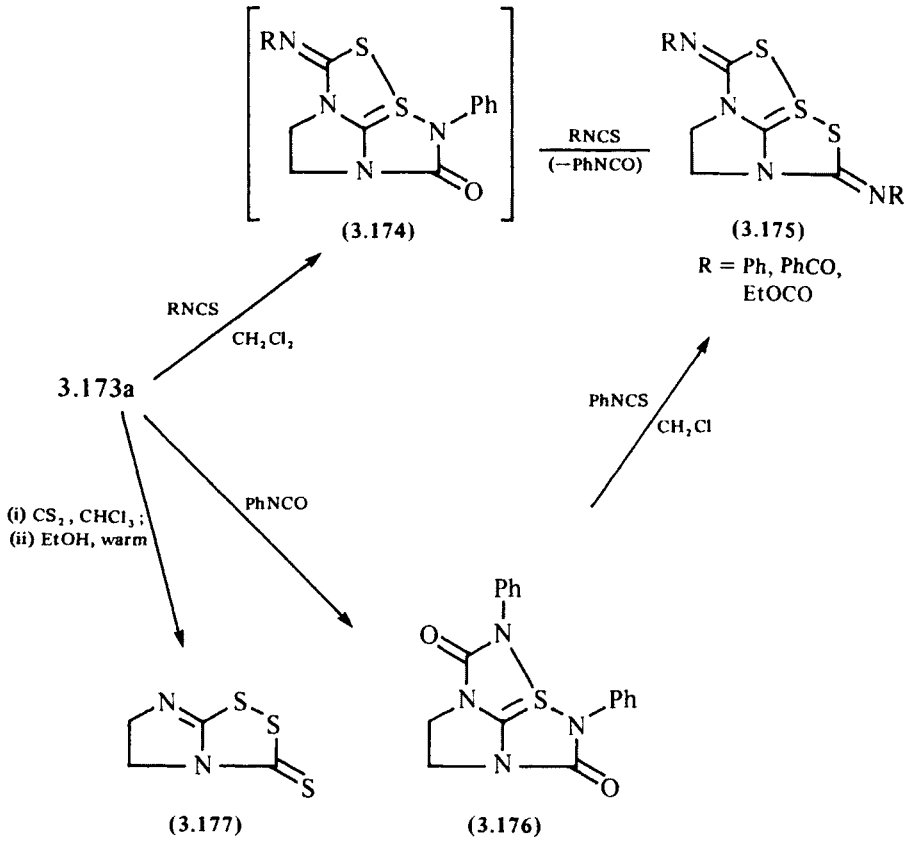


(3.173)

	R	X	mp (°C)	uv, λ_{max}^{MeOH} (nm, ϵ)
a	Ph	O	172–173	255 (9600)
b	Me	S	160–161	240 (10,600)
c	Me	O	181–182	225 (5300), 254 (6800)

3.15.2. 2,3,5,6-Tetrahydroimidazo[1,2-*d*][1,2,4]thiadiazoles

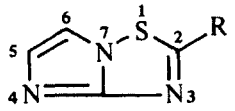
3-Oxo and 3-thiono derivatives in this class (**3.173a–c**) have been prepared by the oxidative cyclization of appropriately substituted imidazolidinones (cf. **3.172**).[117] Compounds of the former type are reactive toward heterocumulenes across the S–C-7*a*–N-7 part of the bicyclic framework, and reactions of this type provide access to novel heterocumulenes (see **3.173a** → **3.175** and **3.173a** → **3.176** in Scheme 3.15).[117] It is interesting to note that the intermediate (**3.174**) cannot be isolated and that the heteropentalene (**3.176**) is relatively labile; the latter reacts rapidly with phenyl isothiocyanate to afford a less strained heteropentalene (**3.175**) containing S–S–S rather than N–S–N in the tricyclic framework. An uncharacterized intermediate addition product is formed when the bicyclic derivative (**3.173a**) is treated with carbon disulfide, and this can be decomposed in hot ethanol to afford 5,6-dihydroimidazo[2,1-*c*][1,2,4]dithiazole-3-thione (**3.177**).[117]



Scheme 3.15

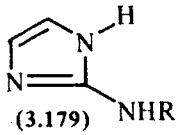
3.16. RING SYSTEM C_3N_2–C_2N_2S: IMIDAZO[1,2-*b*][1,2,4]-THIADIAZOLE

Examples of compounds in the imidazo[1,2-*b*][1,2,4]thiadiazole ring system (**3.178a**) are confined to fungicidal 2-substituted derivatives (e.g., **3.178b,c**), prepared in stepwise fashion from 2-aminoimidazole (e.g., **3.179a** → **3.179b** → **3.179c** → **3.178b**);[118] the last step of oxidative cyclization can be achieved by using sulfuryl chloride or other oxidants such as bromine, hydrogen peroxide, or *m*-chloroperbenzoic acid.[118]



(3.178)

	R
a	H
b	Ph
c	heteroaryl

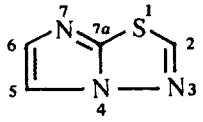


(3.179)

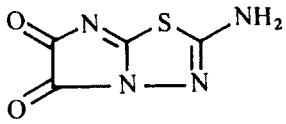
	R
a	H
b	COPh
c	CSPh

3.17. RING SYSTEM C_3N_2–C_2N_2S: IMIDAZO[2,1-*b*][1,3,4]-THIADIAZOLE

In contrast to many of the condensed imidazoles described in this volume, the chemistry of imidazo[2,1-*b*][1,3,4]thiadiazoles is concerned almost entirely with the fully unsaturated ring system (**3.180**), although there is an isolated example of a 5,6-dihydro-5,6-dioxo derivative (**3.181**). The bicyclic system is constructed in both cases (cf. **3.180**, **3.181**) from 1,3,4-thiadiazoles.



(3.180)

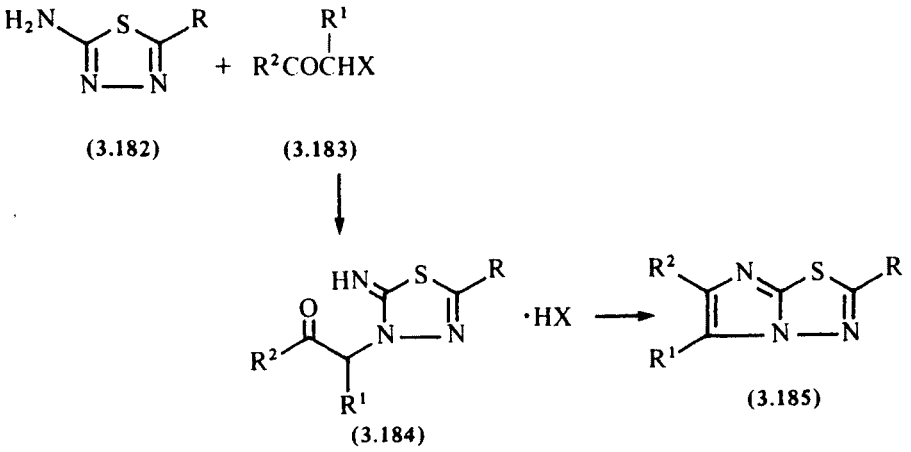


(3.181)

3.17.1. Imidazo[2,1-*b*][1,3,4]thiadiazoles

3.17.1.1. Synthesis from 1,3,4-Thiadiazoles

The procedure outlined in Scheme 3.16 leading to imidazo[2,1-*b*][1,3,4]-thiadiazoles (**3.185**) was devised by S. Ban and co-workers in the 1950s and the physical properties of compounds emerging from their work are collected in Mosby's volume.[132] In this method a 5-amino-1,3,4-thiadiazole derivative (**3.182**)



Scheme 3.16

and an α-haloketone (**3.183**) are heated under reflux in ethanol to give either the hydrohalide salt of an iminothiazoline derivative (**3.184**) or, more often, direct conversion to the bicyclic compound (**3.185**). Intermediates of the former type (**3.184**) can be converted into the bicyclic compounds (**3.185**) by heating them under reflux, usually in water,[120,121,124] but acetic acid[125] and polyphosphoric acid[122] have also been employed (see Table 3.21). The regiochemical outcome of one transformation of the type **3.182** + **3.183** → **3.185** (R = SO_2NH_2, R^1 = H, R^2 = *t*-Bu) has been determined by X-ray crystallography,[130] and the initial mode of alkylation (cf. **3.182** → **3.184**) is thus confirmed.

3.17.1.2. Physiochemical Studies

The ^{1}H nmr spectra of imidazo[2,1-*b*][1,3,4]thiadiazole (**3.186a**) and three of its derivatives (**3.186b–d**) have been analyzed (see Table 3.22).[133] It appears that H-2 is at higher field and that H-5 and H-6 are at lower fields with respect to the parent thiadiazole and imidazole ring systems, respectively; in this sense, the thiadiazole ring behaves qualitatively like the pyridine, pyrimidine, and thiazole rings in the corresponding condensed imidazoles. Measurements in acidic media (D_2O, DCl, and CF_3CO_2H) suggest that the influence of protonation is highest on H-2 followed by H-5 and H-6, but this behavior is not considered[133] to be conclusive for determining the site of protonation. In contrast, ^{1}H nmr experiments with the paramagnetic shift reagent Eu(fod)$_3$ on compound **3.186d** indicate a large shift (24.35 ppm) for the C-6 methyl group and smaller shifts for H-5 (6.07 ppm) and the C-2 methyl group (0.94 ppm). It can thus be concluded that N-7 is the most effective site in providing electrons for coordination to the metal.

The crystal and molecular structures of 5,6-dimethylimidazo[2,1-*b*][1,3,4]-thiadiazole (**3.186c**) and its hydrobromide salt have been determined by X-ray analysis.[133] These data indicate that protonation of **3.186c** occurs at N-7.

TABLE 3.21. SYNTHESIS OF IMIDAZO[2,1-*b*][1,3,4]THIADIAZOLES (**3.185**) FROM 5-AMINO-1,3,4-THIADIAZOLE DERIVATIVES (**3.182**)

Compound **3.185**							
R	R^1	R^2	Synthetic Method[a]	Reaction Conditions	mp (°C) (Solvent for Recrystallization)	Yield (%)	Reference
SCH_2Ph	H	Ph	A	EtOH, reflux	144 (*n*-PrOH)	62	119
SCH_2Ph	H	Me	A	EtOH, reflux	69–70	42	119
SCH_2Ph	H	*p*-BrC_6H_4	A	EtOH, reflux	180 (*n*-PrOH)	95	119
SCH_2Ph	Me	Ph	A	EtOH, reflux	115–116 (EtOH)	80	119
SCH_2Ph	Me	*p*-BrC_6H_4	A	EtOH, reflux	114–115 (EtOH)	50	119
SCH_2Ph	Ph	Ph	A	EtOH, reflux	138 (EtOH)	41	119
SCH_2Ph	CO_2Et	Me	A	EtOH, reflux	98 (EtOH)	33	119
Me	H	(5-Nitro-2-furyl)	B	H_2O, reflux	262–264 (dec.)	83	120
NH_2	H	Me	B	H_2O, heat	215–217	–	121
NH_2	H	Ph	B	H_2O, heat	194–195	–	121
NH_2	H	*p*-MeC_6H_4	B	H_2O, heat	264–265	–	121
NH_2	H	*p*-$MeOC_6H_4$	B	H_2O, heat	197–197.5	–	121
NH_2	H	*p*-ClC_6H_4	B	H_2O, heat	266.5–267	–	121
NH_2	H	*p*-BrC_6H_4	B	H_2O, heat	268–269	–	121
NH_2	H	*p*-$O_2NC_6H_4$	B	H_2O, heat	> 360	–	121
H,Me	H	Aryl	B	Polyphosphoric acid, heat	–	–	122
Me	H	(5-Nitro-2-furyl)	A	Dimethylformamide, heat	180 (dec.) (MeOH)	–	123
H	H	Me	B	H_2O, reflux	50 (petroleum ether)	–	124[b]
H	H	Ph	B	H_2O, reflux	132 (EtOH)	–	124
H	H	*p*-MeC_6H_4	B	H_2O, reflux	148 (ligroin)	–	124
H	H	*p*-$MeOC_6H_4$	B	H_2O, reflux	143 (ligroin)	–	124
H	H	*p*-BrC_6H_4	B	H_2O, reflux	193 (ligroin)	–	124
H	Me	Me	A	EtOH, reflux	94	–	124
Me	H	Me	A	EtOH, reflux	70 (ligroin)	–	124
Me	H	Ph	A	EtOH or DMF, reflux	137 (EtOH)	–	124
Me	H	*p*-MeC_6H_4	A	DMF, reflux	158 (C_6H_6)	–	124

Me	H	*p*-$MeOC_6H_4$	A	DMF, reflux	200 (DMF)	–	124
Me	H	*p*-BrC_6H_4	A	DMF, reflux	210 (C_6H_6)	–	124
Me	H	*p*-$O_2NC_6H_4$	A	DMF, reflux	255 (xylene)	–	124
Me	Me	Me	A	DMF, reflux	98 (ligroin)	–	124
Benzothiazol-2-yl	H	Me	B	AcOH, heat	241–242 (dioxan)	–	125
Benzothiazol-2-yl	H	Ph	B	AcOH, heat	278–280 (DMF)	–	125
Benzothiazol-2-yl	H	*p*-$O_2NC_6H_4$	B	AcOH, heat	360 (DMF)	–	125
Me	H	$CH_2P(O)(OEt)_2$	A	EtOH, reflux	118[c]	45	126
SMe	H	Ph	B	H_2O, reflux	194–195 (*i*-PrOH)	73	127[d]
Me	H	3,4-$ClFC_6H_3$	A	EtOH, reflux	89 (MeOH)	50	128
Me	H	3,4-$MeFC_6H_3$	A	EtOH, reflux	199 (MeOH)	48	128
CF_3	H	2,4-$MeFC_6H_3$	A	EtOH, reflux	123 (MeOH)	45	128
Et	H	3,4-$ClFC_6H_3$	A	EtOH, reflux	84 (MeOH)	58	128
Et	H	3,4-$MeFC_6H_3$	A	EtOH, reflux	210 (MeOH)	53	128
n-Pr	H	3,4-$MeFC_6H_3$	A	EtOH, reflux	83 (MeOH)	58	128
i-Pr	H	4-FC_6H_4	A	EtOH, reflux	102 (MeOH)	56	128
n-C_5H_{11}	H	3,4-$MeFC_6H_3$	A	EtOH, reflux	132 (MeOH)	56	128
n-C_5H_{11}	H	4-FC_6H_4	A	EtOH, reflux	110 (MeOH)	56	128
n-C_5H_{11}	H	3,4-$ClFC_6H_3$	A	EtOH, reflux	74 (MeOH)	52	128
2-furyl	H	Ph	A	DMF, heat	–	–	129
SO_2NH_2	H	H	A	EtOH, reflux	207–210 (dec.) (EtOH)	26	130[e]
t-Bu	H	*t*-Bu	A	EtOH, reflux	98–99 (petroleum ether)	53	131

[a]Procedures: (A) direct method, **3.182** + **3.183** → **3.185**; (B) indirect method, **3.182** + **3.183** → **3.184** → **3.185**; conditions quoted refer to transformation of **3.184** → **3.185**.

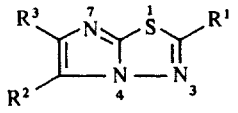
[b]For syntheses listed under ref. 124, yields are in the range 30–70%; highest yields are achieved with 2-amino-5-methylthiadiazole and mild reaction conditions.

[c]Forms a picrate, mp 200°C.

[d]Twenty-eight related 2-alkythio-6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles are described in this paper.

[e]Fifteen related 6-substituted imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides are described in this paper.

TABLE 3.22. ^{1}H NMR SPECTRAL DATA FOR IMIDAZO[2,1-*b*][1,3,4]THIADIAZOLES (3.186)[133]



(3.186)

	R^1	R^2	R^3
a.	H	H	H
b.	H	H	Me
c.	H	Me	Me
d.	Me	H	Me

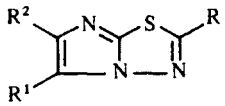
		Chemical Shifts (δ) and Coupling Constants (Hz)[a]				
Compound	Solvent[b]	δ_2	δ_5	δ_6	$J_{5,6}$	$J_{2,6}$
3.186a	A	8.56	7.82	7.38	1.42	0.97
3.186b	A	8.47	7.54	2.36	0.92	
3.186c	A	8.44	2.43	2.31	0.67	
3.186d	A	2.66	7.41	2.33	0.93	
3.186a	B	9.22	8.20	7.80	2.45	1.24
		(0.66)	(0.38)	(0.42)		
3.186b	B	9.15	7.91	2.60	1.12	
		(0.68)	(0.37)	(0.24)		
3.186b	C	9.16	7.88	2.45	1.09	
		(0.69)	(0.34)	(0.09)		
3.186b	C[c]	9.39	8.10	2.57	1.17	
		(0.92)	(0.56)	(0.21)		
3.186c	B	9.11	2.63	2.52	0.73	
		(0.67)	(0.20)	(0.21)		
3.186d	B	2.91	7.80	2.56	1.06	
		(0.25)	(0.39)	(0.23)		

[a]Solutions are 0.5 *M* in all solvents. Values in parentheses are differences between measurements for trifluoroacetic acid or acidified aqueous solution and those for deuteriochloroform.
[b]Solvents: (A) $CDCl_3$; (B) CF_3CO_2H; (C) 0.25 *M* DCl in D_2O.
[c]Chemical shifts measured relative to the methyl peak of internal *t*-butyl alcohol and translated to the tetramethylsilane scale by employing $\delta_{Me} = 1.31$.

3.17.1.3. Reactions with Electrophiles

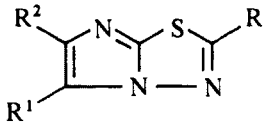
Reactions of this type can lead to products of ring substitution or to the modification of side-chain substituents. Bromination and nitration reactions of the former type can be effected by bromine in acetic acid,[124,131] and concentrated nitric and sulfuric acids,[124,131] respectively (see Table 3.23). For both reagents, substitution occurs in the bicyclic system exclusively at the 5-position, but concomitant nitration of the aryl ring occurs for 6-phenylimidazo[2,1-*b*][1,3,4] thiadiazoles.[124]

TABLE 3.23. PRODUCTS (3.187) FROM ELECTROPHILIC SUBSTITUTION REACTIONS OF IMIDAZO[2,1-*b*][1,3,4]THIADIAZOLES



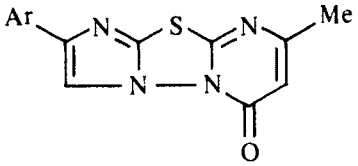
(3.187)

Starting Material (3.187)			Product (3.187)						
R	R^1	R^2	R	R^1	R^2	Reaction Conditions	mp (°C) (Solvent for Recrystallization)	Yield (%)	Reference
H	H	Ph	H	Br	Ph	Br_2, AcOH, room temp.	130 (ligroin)	–	124
Me	H	Ph	Me	Br	Ph	Br_2, AcOH, room temp.	137 (ligroin)	–	124
Me	H	*p*-BrC_6H_4	Me	Br	*p*-BrC_6H_4	Br_2, AcOH, room temp.	198 (ligroin)	–	124
t-Bu	H	*t*-Bu	*t*-Bu	Br	*t*-Bu	Br_2, AcOH, NaAc, room temp.	81 (MeCN)	80	131
H	H	Ph	H	NO_2	*p*-$O_2NC_6H_4$	Concentrated H_2SO_4, 86% HNO_3	273 (xylene)	–	124
Me	H	Ph	Me	NO_2	*p*-$O_2NC_6H_4$	Concentrated H_2SO_4, 86% HNO_3	228 (xylene)	–	124
t-Bu	H	*t*-Bu	*t*-Bu	NO_2	*t*-Bu	Concentrated H_2SO_4, conc. HNO_3	132–135 (*i*-PrOH)	86	131



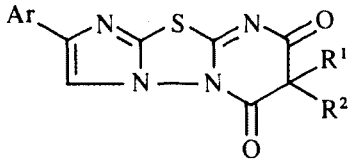
(3.188)

	R	R^1	R^2
a	N=CHAr	H, Me	Me, Et
b	$NHCOCH_2COMe$	H	Me, aryl



(3.189)

Ar = aryl



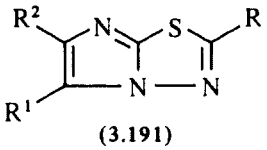
(3.190)

Ar = aryl; R^1, R^2 = H, Et

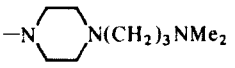
Electrophilic reactions at the 2-amino side chain of imidazo[2,1-*b*]thiadiazoles include their transformation (with ArCHO) into arylidene derivatives (**3.188a**)[134] and (with $MeCOCH_2CO_2t$-Bu or ketene dimer) into the 2-acetoacetylamino derivatives (**3.188b**).[135] Compounds of the latter type (**3.188**, R^1 = H, R^2 = aryl) can be converted (polyphosphoric acid, 80°C) into condensed pyrimidones (**3.189**)[136] in a process which must involve cleavage of the acetoacetyl moiety, acylation at N-3, and cyclization. Condensed pyrimidine derivatives (**3.190**) have also been synthesized by the reaction of 2-aminoimidazo[2,1-*b*] [1,3,4] thiadiazoles (cf. **3.188**, R = NH_2) with diethylsuccinate derivatives in polyphosphoric acid.[137]

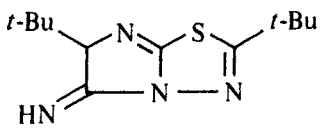
3.17.1.4. Miscellaneous Reactions Including Ring Cleavage

Conversion of the 5-bromo derivative (**3.191a**) into the 5-cyano compound (**3.191b**) can be achieved by using cuprous cyanide under forcing conditions (DMF, 150–160°C, 6 h).[131] Reduction of the 5-nitro derivative (**3.191c**) with aluminum amalgam gives a product existing in the 5-imino tautomeric form (**3.192**) rather than in the fully unsaturated 5-amino form.[131] In contrast, reduction of the nitro compound (**3.191c**) with sodium dithionite in sodium bicarbonate or ammonium hydroxide affords products (**3.193a** or **b** respectively) resulting from fission of the imidazole ring.[131] Prolonged treatment of the *S*-benzyl derivatives (**3.191d**) with hot hydrazine hydrate causes cleavage of the thiadiazole ring to give 1-amino-2-mercaptoimidazoles (**3.194**).[119]



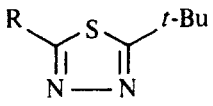
(3.191)

	R	R^1	R^2
a	*t*-Bu	Br	*t*-Bu
b	*t*-Bu	CN	*t*-Bu
c	*t*-Bu	NO_2	*t*-Bu
d	SCH_2Ph	H, Me, Ph	aryl
e	H, Me	SCN	Me, aryl
f	e.g. alkyl, aryl	$C(R^1)=C(R^2)COR^3$ R^1 = e.g., alkyl R^2 = e.g., CN, NO_2 R^3 = NH_2	e.g., alkyl, aryl
g		H	Ph
h	alkyl, CF_3	H	fluoroaryl
i	H, Me	$CH=CHZ^+$ (X^-) (Z = quaternized heterocycle)	*p*-$O_2NC_6H_4$
j	H	N_2Z^+ (X^-) (Z = quaternized heterocycle)	Ph



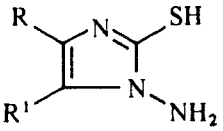
(3.192)

mp 199–202°C



(3.193)

	R
a	NHCO-*t*-Bu
b	$N=C(NH_2)$*t*-Bu



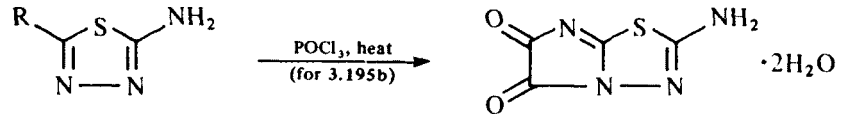
(3.194)

R = aryl
R^1 = H, Me, Ph

3.17.1.5. Commercial Applications

A variety of imidazo[2,1-*b*][1,3,4]thiadiazoles have proved to be interesting from a commercial viewpoint. The thiocyanates (**3.191e**) are active as bactericides and viricides,[138] and the unsaturated ketones (**3.191f**) have been synthesized for use as diuretics, antihypertensives, and uricosurics.[139] The piperazines (**3.191g**) are effective against trypanosomes,[140] and slight fungicidal activity against *Fusarium roseum* is exhibited by the 6-fluoroaryl derivatives (**3.191h**).[128]

The imidazo[2,1-*b*][1,3,4]thiadiazole framework has been incorporated into cyanine (**3.191i**) and azo dyestuffs (**3.191j**) to provide materials of value in color photography[141] and for the dyeing of polyacryl nitrile fibers,[142] respectively.



(3.195) (3.196)

R
a, NH_2
b, $NHCOCO_2H$

mp > 360°C (60% yield)

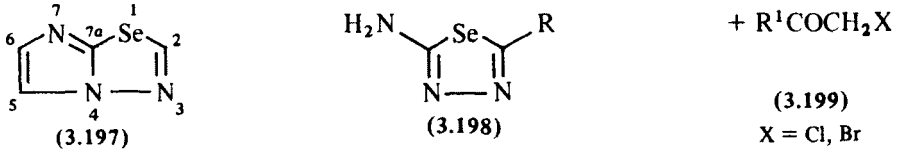
Scheme 3.17

3.17.2. 5,6-Dihydroimidazo[2,1-*b*][1,3,4]thiadiazoles

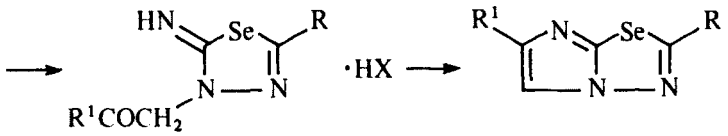
The 5,6-dihydro-5,6-dioxo derivative (**3.196**) has been synthesized from 2,5-diamino-1,3,4-thiadiazole (**3.195a**) via an isolated oxalylamino intermediate (**3.195b**) (see Scheme 3.17).[143] The bicyclic product (**3.196**) can also be prepared by treating 2,5-diamino-1,3,4-thiadiazole (**3.195a**) with oxalyl chloride in benzene under reflux, but the yield is only moderate (30%).[143]

3.18. RING SYSTEM C_3N_2–C_2N_2Se: IMIDAZO[2,1-*b*][1,3,4]-SELENADIAZOLE

There is a small number of characterized compounds in the imidazo[2,1-*b*]-[1,3,4]selenadiazole ring system (**3.197**), but there are no known examples of partially or fully reduced derivatives in this group. Compounds of the former type (cf. **3.201** and Table 3.24)[144,145] have been prepared following a procedure analogous to that outlined in the previous section for isosteric imidazo[2,1-*b*][1,3,4]-thiadiazoles (cf. Scheme 3.16). In this method, readily available 5-aminoselenadiazoles (**3.198**, prepared from selenosemicarbazide and the appropriate carboxylic acid) are treated with α-haloketones (**3.199**) in ethanol under reflux to give either the bicyclic derivatives (**3.201**) directly[145] or to afford isolable intermediate iminoselenadiazoline hydrohalide salts (**3.200**);[144] the latter are transformed into the bicyclic compounds (cf. **3.201**) by heating them under reflux in water.[144] The chemical reactivity of compounds in this group has not been investigated.



(3.197) (3.198) (3.199)



(3.200) (3.201)

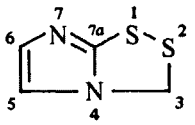
TABLE 3.24. PHYSICAL PROPERTIES OF IMIDAZO[2,1-*b*][1,3,4]SELENADIAZOLES (**3.201**)

Compound **3.201**						
R	R^1	Method of Preparation[a]	mp (°C) (Solvent for Recrystallization)	Yield (%)	uv Spectrum λ_{max}^{EtOH} (log ϵ)	Reference
H	Ph	A	157–158 (EtOH)	42	257 (3.17)	144
Me	Ph	A	151–152 (EtOH)	48	257 (3.33)	144
Et	Ph	A	105–106 (EtOH)	53	257 (3.02)	144
CF_3	Ph	A	145–146 (EtOH)	60	257 (3.19)	144
Ph	Ph	B	196–197 (BuOH)	87	–	145
Ph	p-$O_2NC_6H_4$	B	287–288 (DMF)	98	–	145

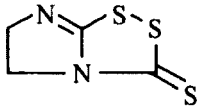
[a]Synthetic methods: (A) **3.198** + **3.199**, EtOH, reflux → **3.200**; then **3.200**, H_2O, reflux → **3.201**; (B) **3.198** + **3.199**, EtOH, reflux → **3.201**.

3.19. RING SYSTEM C_3N_2–C_2NS_2: 3*H*-IMIDAZO[2,1-*c*][1,2,4]-DITHIAZOLE

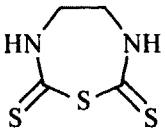
There are no known compounds in the parent 3*H*-imidazo[2,1-*c*][1,2,4]-dithiazole ring system (**3.202**), and this section is concerned entirely with the chemistry of 5,6-dihydro-3*H*-imidazo[2,1-*c*][1,2,4]dithiazole-3-thione (**3.203**). The latter is a yellow, antifungal compound, mp 125–126°C, isolated as a product of the air oxidation[146] of the fungicide Nabam [disodium ethylenebis(dithiocarbamate), $NaS_2CNH(CH)_2NHCS_2Na$].[146] It was earlier formulated[147] as the enethiol tautomer of ethylenethiuram monosulfide (hexahydro-1,3,6-thiadiazepin-2,7-dithione, **3.204**) but this structure was later revised to **3.203** on the basis of spectroscopic analysis (see Section 3.19.1).[148–150]



(3.202)



(3.203)

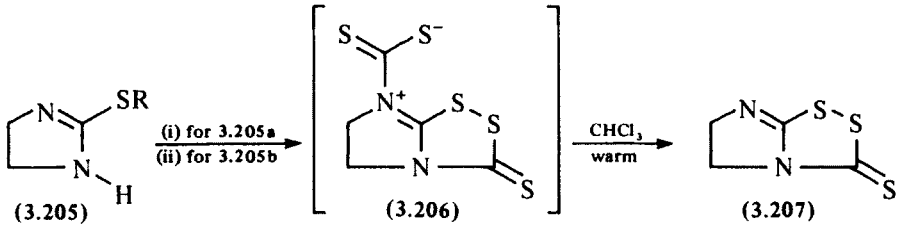


(3.204)

3.19.1. 5,6-Dihydro-3*H*-imidazo[2,1-*c*][1,2,4]dithiazole-3-thione

3.19.1.1. Synthesis

The oxidative transformation of Nabam described in the preceding paragraph has been elaborated to a series of substituted disodium ethylenebisdithiocarbamates using ammonium persulfate as an oxidant;[151] the ensuing bicyclic products (cf. **3.203**) have been evaluated for use as fungicides, bactericides, and pesticides.[151] A more recent synthesis that should have general applicability is outlined in Scheme 3.18.[152] Annulation of suitably *S*-substituted derivatives of 2-mercaptoimidazoline (**3.205a,b**) is achieved by using carbon disulfide to give a red carbon disulfide adduct (**3.206**) of the desired bicyclic derivative (**3.207**); the former adduct (**3.206**) readily loses carbon disulfide on work-up in warm chloroform.



(3.205) (3.206) (3.207)

	R		
a	SCH_2Ph	(i) $NaHCO_3$, CS_2, room temperature; (ii) CS_2, reflux	mp 125°C ($CHCl_3$–EtOAc)
b	CH_2COPh		

Scheme 3.18

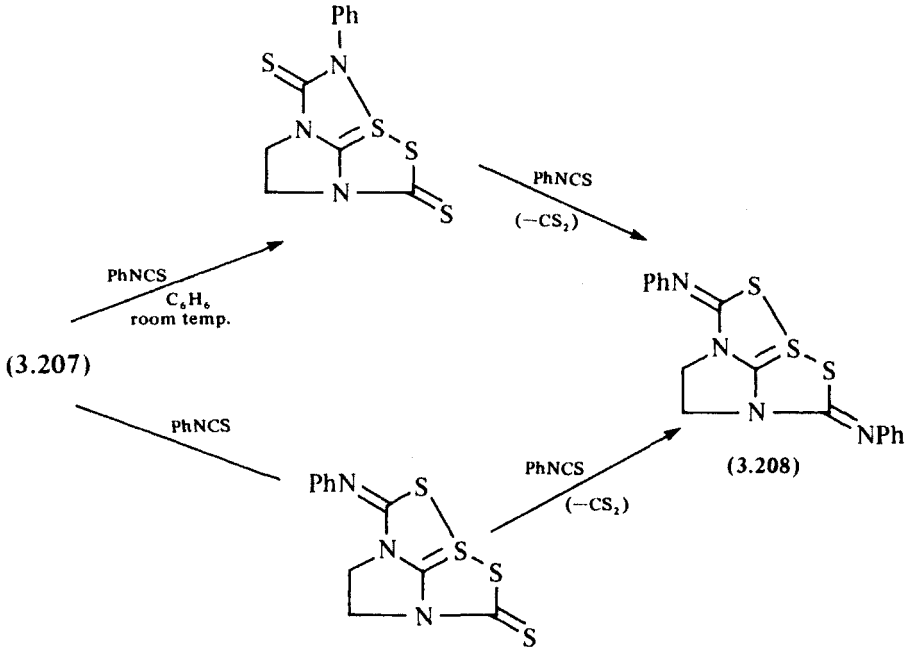
3.19.1.2. Spectroscopic and Analytical Studies

The ^1H[148] and ^{13}C[150] nmr spectra [$CDCl_3$ solvent, shifts (ppm) from TMS] of the bicyclic derivative (**3.207**) are as follows: $\delta = 3.93$ (2H,t), 4.52 (2H,t); and $\delta = 184$ (*C*=S), 163 (*C*=N), 64 (CH_2), and 48 (CH_2). The uv spectum of **3.207** shows $\lambda_{max}^{EtOH} = 227.5$ nm (ϵ, 8800) and 280 (19,600).[147]

A suitable thin-layer chromatographic eluant for **3.207** is acetonitrile:water (9:1) with development by either potassium hydroxide in aqueous methanol (blue) or 2-(*p*-iodophenyl)-3-(*p*-nitrophenyl)-5-phenyl-2*H*-tetrazolium chloride (pink).[153] The bicyclic derivative (**3.207**) labeled by ^{14}C has been used to monitor its disappearance from the kidneys of rats.[154]

3.19.1.3. Reactions

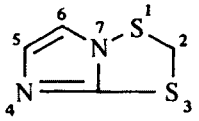
The condensed dithiazole (**3.207**) can be reduced electrochemically[150] or microbiologically[155] to afford 2-mercaptoimidazoline, and the latter is also obtained from chemical reduction by glutathione, L-cysteine hydrochloride, or D-ascorbic acid in phosphate buffer.[155] It reacts with dimethyl sulfate in benzene under reflux to form a yellow methosulfate, mp 118–120°C, and with phenyl isothiocyanate at room temperature to afford the heteropentalene (**3.208**) probably by one of the two routes indicated in Scheme 3.19.[152]



Scheme 3.19

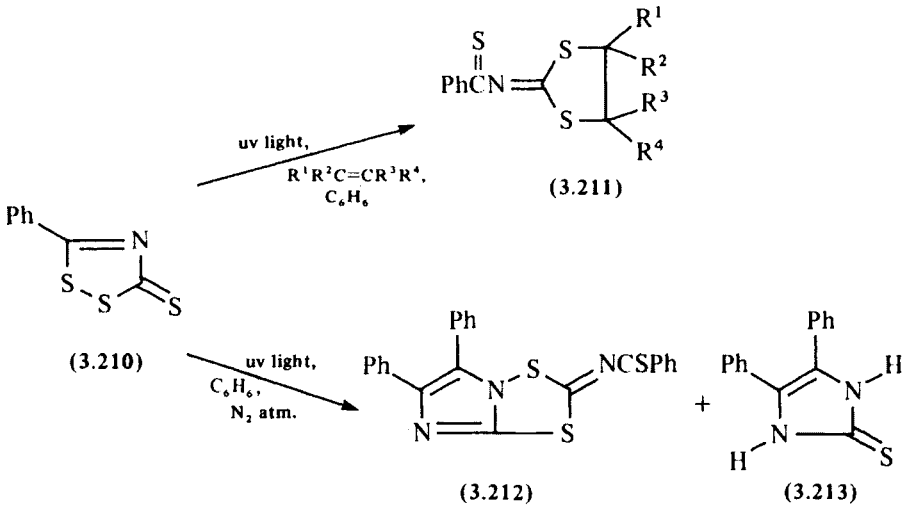
3.20. RING SYSTEM C_3N_2–C_2NS_2: IMIDAZO[1,2-*b*] [1,4,2]-DITHIAZOLE

A single compound in the imidazo[1,2-*b*] [1,4,2] dithiazole ring system (**3.209**) exists. The uv photolysis of 5-phenyl-1,2,4-dithiazole-3-thione (**3.210**) in the presence of olefines affords a series of 1,3-dithiolans (**3.211**, R^1–R^4 = e.g., CH_3) but in contrast, in the absence of olefins, gives the condensed imidazole (**3.212**)



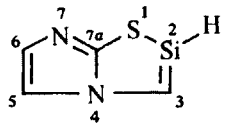
(3.209)

and the imidazolthione (**3.213**).[156] The mechanism of formation of the purple, crystalline bicyclic derivative is not clear, but the imidazolthione (**3.213**) probably arises from an exothermic thermal decomposition of **3.212** during chromatographic purification. The absorption spectrum of **3.212** [$\lambda_{max}^{CH_2Cl_2}$ = 263 nm (ϵ, 54,100), 319 (22,000), 369 (13,000), and 510 (4370)] is very similar to model compounds containing the PhC(S)N=C(S–)S framework, but nmr spectral evidence that might lend support to structure **3.212** is not provided.



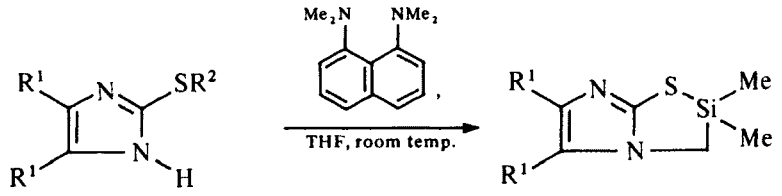
3.21. RING SYSTEM C_3N_2–C_2NSSi: IMIDAZO[1,2-*d*] [1,4,2]-THIAZASILOLE

The intriguing imidazo[1,2-*d*] [1,4,2] thiazasilole ring system is constructed in a formal sense by replacing a CH fragment of the imidazo[2,1-*b*] thiazole system by SiH and is represented in the *Ring Index* in the fully unsaturated form (**3.214**).



(3.214)

There are two examples of compounds of the 2,3-dihydro type (**3.216a,b**) prepared in stepwise fashion from 2-mercaptoimidazoles (**3.215a**) via the dehydrohalogenation of bromomethyldimethylsilylated intermediates (**3.215b**).[157] The choice of a strong non-nucleophilic base [1,8-bis(dimethylamino)naphthalene] for the cyclization step is important, since nucleophiles such as hydroxide or methoxide ion cleave the sulfur–silicon bond of the *S*-silyl derivatives (**3.215b**). The chemical reactivity of the bicyclic compounds (**3.216a,b**) has not been studied.



(3.215) (3.216)

	R
a	H
b	$Si(Me)_2CH_2Br$

	R^1	mp (°C)	Yield (%)
a	H	128–133	80–85
b	Ph	150 (dec.)	80–90

REFERENCES

1. H. R. Kwasnik, J. E. Oliver, and R. T. Brown, *J. Heterocycl. Chem.*, **9**, 1429 (1972).
2. J. P. Ferris and F. R. Antonucci, *J. Am. Chem. Soc.*, **96**, 2010 (1974).
3. G. Rio and B. Serkiz, *J. Chem. Soc., Chem. Commun.*, **1975**, 849.
4. T. Tishimura and K. Kitajima, *J. Org. Chem.*, **44**, 818 (1979).
5. J. Nematollahi and R. Ketcham, *J. Org. Chem.*, **28**, 2378 (1963).
6. F. B. Slezak, H. Bluestone, T. A. Magee, and J. H. Wotiz, *J. Org. Chem.*, **27**, 2181 (1962).
7. S. Gautam, R. Ketcham, and J. Nematollahi, *Synth. Comm.*, **9**, 863 (1979).
8. A. R. Butler and E. Leitch, *J. Chem. Soc., Perkin Trans. II*, **1980**, 103.
9. A. R. Butler, I. Hussain, and E. Leitch, *J. Chem. Soc., Perkin Trans. II*, **1980**, 106.
10. A. R. Butler and I. Hussain, *J. Chem. Soc., Perkin Trans. II*, **1981**, 310.
11. Badische Anilin und Soda Fabrik, British Patent 717,287 (1954); *Chem. Abstr.*, **49**, 15976d.
12. T. Shimizu, S. Furuhashi, and K. Tanaka, Japanese Patent 75 101,379 (1975); *Chem. Abstr.*, **84**, 59464s.

13. V. A. Eros'ko, L. V. Epishina, O. V. Lebedev, M. V. Povstyanoi, L. I. Khmel'nitski, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1980**, 1595; *Chem. Abstr.*, **93**, 204547p, Engl. transl. in *Bull. Acad. Sci. USSR. Div. Chem. Sci.*, **1980**, 1138.
14. J. C. Speck, U.S. Patent 2,885,305 (1959); *Chem. Abstr.*, **54**, 574e; see also A. J. Stokes, U.S. Patent 2,777,856 (1957); *Chem. Abstr.*, **51**, 9705b.
15. M. Lempert-Sréter, V. Solt, and K. Lempert, *Magy. Kem. Folyoirat*, **69**, 237 (1963); *Chem. Abstr.*, **59**, 10022b.
16. K. Lempert and M. Lempert-Sréter, *Chem. Ber.*, **94**, 796 (1961).
17. M. Furukawa, K. Matsuoka, T. Yoshida, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull. Japan*, **22**, 1 (1974).
18. H. Greenberg, T. Van Es, and O. G. Backeberg, *J. Org. Chem.*, **31**, 3951 (1966).
19. V. L. Hines, C. R. Hubbard, A. D. Mighell, and A. J. Fatiadi, *Acta Crystallogr., Sect. B*, **B34**, 3102 (1978).
20. L. I. Suvorova, V. A. Eres'ko, L. V. Epishina, O. V. Lebedev, L. I. Khmel'nitskii, S. S. Novikov, M. V. Povstyanoi, V. D. Krylov, and G. V. Korotkova, *Izv. Akad. Nauk SSSR. Ser. Khim.*, **1979**, 1306; *Chem. Abstr.*, **91**, 140829f; Engl. transl. in *Bull. Acad. Sci. USSR. Div. Chem. Sci.*, **1979**, 1222; see also USSR Patent 366,709 (1978); *Chem. Abstr.*, **89**, 24381p, British Patent 1,404,611 (1975); *Chem. Abstr.*, **83**, 193327g; British Patent 1,404,612 (1975); *Chem. Abstr.*, **83**, 193328h; French Patent 2,160,382 (1973); *Chem. Abstr.*, **79**, 137212w; German Patent 2,236,732 (1973); *Chem. Abstr.*, **79**, 42581b.
21. L. I. Suvorova, L. V. Epishina, O. V. Lebedev, L. I. Khmel'nitskii, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1979**, 2282; *Chem. Abstr.*, **92**, 94365x; Engl. transl. in *Bull. Acad. Sci. USSR. Div. Chem. Sci.*, **1979**, 2104.
22. D. Kühling, *Justus Liebigs Ann. Chem.*, **1973**, 263; see also idem, German Patent 1,966,944 (1975); *Chem. Abstr.*, **83**, 179061j; Henkel und Cie G.m.b.h., French Patent 2,012,790 (1970); *Chem. Abstr.*, **74**, 13152d.
23. D. Kühling, German Patent 1,966,502 (1973); *Chem. Abstr.*, **78**, 97655p.
24. H. G. Goodman, U.S. Patent 2,697,714 (1954); *Chem. Abstr.*, **49**, 14035i.
25. T. M. Chempolil, U.S. Patent 3,767,669 (1973); *Chem. Abstr.*, **80**, 82983m.
26. A. Makower and H. Raubach, GDR Patent 108,085 (1974), *Chem. Abstr.*, **82**, 156313h.
27. (a) V. Haug, GDR Patent 99,788 (1973); *Chem. Abstr.*, **80**, 95949e; (b) P. Politzsch, GDR Patent 123,467 (1976); *Chem. Abstr.*, **87**, 135329f.
28. K. Sugimoto, Y. Shimizu, and M. Mitomi, Japanese Patent 74 95,992 (1974); *Chem. Abstr.*, **82**, 156298g.
29. J. P. Kehren, Sprengst: *Grundlagen Technol. Anwend Int. Jahrestag. Inst. Chem. Treib. Explovist, Fraunhofer-Ges*, **1976**, 47; *Chem. Abstr.*, **89**, 113423w; see also J. Bouleau, J. M. L. Emeury, and J. P. Kehren, German Patent 2,462,330 (1976); *Chem. Abstr.*, **86**, 75499d; German Patent 2,435,651 (1975); *Chem. Abstr.*, **83**, 30483r.
30. J. M. Emeury and H. H. Girardon, European Patent Application, 6,782 (1980); *Chem. Abstr.*, **93**, 71778r; idem, U.S. Patent 4,211,874 (1980).
31. D. Savostianoff, French Patent 2,291,203 (1976); *Chem. Abstr.*, **86**, 121377n.
32. W. A. Freeman, M. L. Mock, and N. Y. Shih, *J. Am. Chem. Soc.*, **103**, 7367 (1981).
33. C. Hase and D. Kühling, *Justus Liebigs Ann. Chem.*, **1975**, 95.
34. L. I. Suvorova, L. V. Epishina, O. V. Lebedev, L. I. Khmel'nitskii, and S. S. Novikov, *Izv. Akad. Nauk SSSR*, **1979**, 2286; *Chem. Abstr.*, **92**, 94366y: Engl. transl. in *Bull. Acad. Sci. USSR. Div. Chem. Sci.*, **1979**, 2108.
35. S. F. Nelsen and P. J. Hintz, *J. Am. Chem. Soc.*, **94**, 7114 (1972).
36. D. M. Smith, in Benzimidazoles and Congeneric Tricyclic Compounds (P. N. Preston,

Ed.), Wiley, New York, 1981, Part I, p. 332.

37. J. P. A. M. Kehren and R. A. Ousset, German Patent 2,804,914 (1978); *Chem. Abstr.*, **90**, 25628g.
38. Nobel-Bozel, French Patent 2,050,956 (1971); *Chem. Abstr.*, **76**, 101574q.
39. Henkel und Cie G.m.b.h., Netherlands Patent Application 76 04,692 (1976); *Chem. Abstr.*, **87**, 41104b.
40. G. L. Spandini, I. D. Tolliday, and A. C. McRitchie, German Patent 2,744,642 (1978); *Chem. Abstr.*, **88**, 193201q.
41. R. Puchta, K. Schwadtke, H. Harder, and R. Weber, German Patent 2,744,457 (1979); *Chem. Abstr.*, **91**, 22833e.
42. D. Kühling, H. Bellinger, and P. Krings, German Patent 2,025,831 (1971); *Chem. Abstr.*, **76**, 85814k.
43. D. Kühling, H. Bellinger, and K. Disch, German Patent 2,030,189 (1971); *Chem. Abstr.*, **76**, 115227r.
44. K. Tachibana, S. Watanabe, M. Sato, and S. Daibo, Japanese Patent 71 26,502 (1971); *Chem. Abstr.*, **76**, 14540g.
45. R. J. Horvath and C. G. Parsons, German Patent 2,042,585 (1971); *Chem. Abstr.*, **76**, 37447w.
46. D. Mihaita, F. I. Runcan, A. Boeru, S. Mihaita, and A. A. Pasat, Romanian Patent 64,800 (1977); *Chem. Abstr.*, **92**, 95127h.
47. M. D. McIntosh, British Patent 1,116,179 (1966); *Chem. Abstr.*, **69**, 36765s.
48. O. C. Elmer, U.S. Patent 4,009,134 (1977); *Chem. Abstr.*, **87**, 54343d.
49. G. G. Parekh, *Org. Coat. Plast. Chem.*, **39**, 407 (1978); *Chem. Abstr.*, **93**, 187,813c; idem, *J. Coat. Technol.*, **51**, 101 (1979); *Chem. Abstr.*, **92**, 78186j; idem, German Patent 2,854,440 (1979); *Chem. Abstr.*, **91**, 93124k.
50. (a) F. E. Kempter, E. Gulbins, A. Haag, and R. Kroker, German Patent 2,606,831 (1977); *Chem. Abstr.*, **87**, 153541y; (b) G. G. Parekh, German Patent 2,704,344 (1977); *Chem. Abstr.*, **87**, 119465s; (c) T. Dimenc, H. Petersen, G. Faulhaber, and H. Fuetterer, German Patent 2,628,271 (1978); *Chem. Abstr.*, **88**, 122626w.
51. E. Meuller and J. Pedain, German Patent 2,005,693 (1971); *Chem. Abstr.*, **76**, 34864u.
52. A. Makower, H. Raubach, and D. Joel, GDR Patent 108,760 (1973); *Chem. Abstr.*, **83**, 60410g.
53. M. Minugawa, Y. Nakahara, and M. Nonoyama, Japanese Patent 75 106,881 (1975); *Chem. Abstr.*, **84**, 45277w.
54. (a) I. V. Zaikonnikova, I. E. Zimakova, V. S. Chudnovskii, N. A. Avdonina, V. A. Babichev, S. S. Novikov, L. I. Khmel'nitskii, O. V. Lebedev, and L. V. Epishina, USSR Patent 644,482; *Chem. Abstr.*, **90**, 145962h; (b) Yu. B. Vol'Kenshtein, V. M. Pavlova, N. V. Serov, A. S. Berlyand, and A. Z. Knizhnik, *Khim-Farm. Zh.*, **12**, 142 (1978); *Chem. Abstr.*, **89**, 220969a; (c) G. P. Vdovina, V. A. Safin, G. I. Oleshko, V. M. Pavlova, and A. Z. Knizhnik, Deposited Document, 1979, VINITI 253–279; *Chem. Abstr.*, **92**, 220735h; (d) E. V. Kompantseva and O. V. Lebedev, *Farmatsiya*, **29**, 28 (1980); *Chem. Abstr.*, **94**, 90452s.
55. H. Fischer, C. Hase, and M. Budnowski, German Patent 3,003,356 (1980); *Chem. Abstr.*, **95**, 187252k.
56. H. Scheuermann and A. Woerner, German Patent 1,061,324 (1959); *Chem. Abstr.*, **55**, 10471h.
57. H. Petersen and H. Bille, German Patent 2,027,203 (1971); *Chem. Abstr.*, **76**, 114770a.
58. T. Simenc and H. Petersen, German Patent 2,901,823 (1980); *Chem. Abstr.*, **93**, 241123t.

59. H. G. Weiland, *Book Pap. National Technical Conference, AATCC* 1974, 376–379; *Chem. Abstr.*, **82**, 59653m.

60. Durand and Huguenin AG, French Patent 1,348,381 (1964); *Chem. Abstr.*, **61**, 10815d.

61. (a) T. A. Addiscott and V. H. Thomas, *Chem. Ind.* (London), **1979**, 29; (b) L. Verstraeten and J. Livens, *Agricultura* (Heverlee, Belgium), **27**, 427 (1979); *Chem. Abstr.*, **92**, 197005j.

62. (a) M. A. K. Markwell and F. C. Fox, *Biochemistry*, **17**, 4807 (1978); (b) L. C. Knight, A. Z. Budzynski, and S. A. Olexa, *Thromb. Haemostatis*, **46**, 593 (1981); *Chem. Abstr.*, **96**, 31135j; (c) W. G. Wood, C. Wachter, and P. C. Scriba, *J. Clin. Chem. Clin. Biochem.*, **19**, 1051 (1981); *Chem. Abstr.*, **96**, 30975w; (d) K. H. Sullivan and R. P. Williams, *Anal. Biochem.*, **120**, 254 (1982); *Chem. Abstr.*, **96**, 177364e.

63. R. W. McClard, *Anal. Biochem.*, **112**, 278 (1981); *Chem. Abstr.*, **95**, 20588n.

64. C. N. M. Bakker, F. M. Kaspersen, A. Van Langevelde, and E. K. J. Pauwels, *Int. J. Appl. Radiat. Isot.*, **31**, 513 (1980); *Chem. Abstr.*, **94**, 84051u.

65. A. Dornow and E. Hinz, *Chem. Ber.*, **91**, 1834 (1958).

66. I. I. Grandberg and G. V. Klyuchko, *Zh. Obshch. Khim.*, **32**, 1898 (1962); *Chem. Abstr.*, **58**, 4537h.

67. M. Lange, R. Quell, H. Lettau, and H. Schubert, *Z. Chem.*, **17**, 94 (1977); *Chem. Abstr.*, **87**, 53160e.

68. V. Sudarsanam, K. Nagarajan, K. Rama Rao, and S. J. Shenoy, *Tetrahedron Lett.*, **21**, 4757 (1980).

69. F. S. Babichev, L. Al. Yusofi, and V. N. Bubsnovskaya, *Ukr. Khim. Zh.*, **44**, 725 (1978); *Chem. Abstr.*, **89**, 163506w; Engl. transl. in *Ukr. J. Chem.*, **44**, 57 (1978).

70. L. Al. Yusofi, V. N. Bubsnovskaya, and F. S. Babichev, *Ukr. Khim. Zh.*, **39**, 1289 (1973); *Chem. Abstr.*, **80**, 70754z; Engl. transl. in *Ukr. J. Chem.*, **39**, 88 (1973).

71. P. J. Taylor, F. L. Rose, G. J. Stacey, and T. W. Thompson, *J. Chem. Soc., Chem. Commun.*, **1970**, 1524.

72. S. Nicholson, S. G. Stacey, and P. J. Taylor, *J. Chem. Soc., Perkin Trans. II*, **1972**, 4.

73. R. Faure, E. J. Vincent, R. M. Claremunt, J. M. Fabrega, and J. Elguero, *Tetrahedron*, **32**, 341 (1976).

74. F. L. Scott, J. K. O'Halloran, J. O'Driscoll, and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. I*, **1972**, 2224.

75. A. Hetzheim, H. Pusch, and H. Beyer, *Chem. Ber.*, **103**, 3533 (1970).

76. J. A. Bogie and T. Norris, *Res. Discl.*, **162**, 73 (1977); *Chem. Abstr.*, **88**, 38940m.

77. A. Kreutzberger and B. Meyer, *Chem. Ber.*, **105**, 1810 (1972).

78. A. Sitte, R. Wessel, and H. Paul, *Monatsh. Chem.*, **106**, 1291 (1975).

79. L. Almiranti, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli A. Gamba, A. Olivi, and W. Murmann, *J. Med. Chem.*, **9**, 29 (1966).

80. H. Meyer, H. Horstmann, E. Möller, and B. Garthoff, German Patent DE 3,020,421 (1981); *Chem. Abstr.*, **96**, 85561p; see Also European Patent Application., EP 41,215 (1981).

81. T. P. Kofman, N. Yu Medvedeva, T. L. Uspenskaya, and M. S. Pevsner, *Khim. Geterotsikl. Soedin*, **1977**, 1271; *Chem. Abstr.*, **88**, 22771w; Engl. transl. in *Chem. Heterocycl. Compd.*, **1977**, 1026.

82. A. Kreutzberger and B. Meyer, *Chem. Ber.*, **105**, 3974 (1972).

83. W. J. Middleton and D. Metzger, *J. Org. Chem.*, **35**, 3985 (1970).

84. (a) D. W. Wiley, W. O. Webster, and E. P. Blanchard, *J. Org. Chem.*, **41**, 1889 (1976); (b) W. O. Webster, U.S. Patent 3,093,653 (1963); *Chem. Abstr.*, **59**, 11507e.

85. (a) K. Meguro and Y. Kuwada, *Heterocycles*, **2**, 335 (1974); (b) idem, Japanese Patent 75 129,586 (1975); *Chem. Abstr.*, **85**, 5643b.

86. K-H. Weber and H. Daniel, *Justus Liebigs Ann. Chem.*, **1979**, 328.

87. H. Behringer and R. Ramert, *Justus Liebigs Ann. Chem.*, **1975**, 1272.

88. H. W. Heine, A. B. Smith, and J. D. Bower, *J. Org. Chem.*, **33**, 1097 (1968).

89. G. I. Shchukin and L. B. Volodarskii, *Izv. Akad. Nauk SSSR Ser. Khim.*, **1979**, 223; *Chem. Abstr.*, **90**, 137741v; Engl. transl. in *Bull. Acad. Sci. USSR Div. Chem. Sci.*, **1979**, 208.

90. I. A. Grigorev, G. I. Shchukin, A. G. Druganov, and L. B. Volodarsky, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk.*, **1979**, 80; *Chem. Abstr.*, **91**, 5159x.

91. V. A. Chuiguk and A. G. Maidannik, *Khim. Geterotsiki. Soedin*, **1980**, 1695; *Chem. Abstr.*, **94**, 175032e.

92. N. I. Viswanathan and V. Balakrishnan, *J. Chem. Soc., Perkin Trans I*, **1979**, 2361.

93. Y. Goto, N. Honjo, and M. Yamakazi, *Chem. Pharm. Bull.* (Japan), **18**, 2000 (1970).

94. Y. Goto and N. Honjo, *Chem. Pharm. Bull.* (Japan), **26**, 3798 (1978).

95. K. H. Schulz, W. Hartmann, and H. G. Heine, German Patent 2,713,431 (1978); *Chem. Abstr.*, **90**, P54937n; see also idem, U.S. Patent 4,294,973.

96. (a) F. Foti, G. Grassi, F. Risitano, and F. Coruso, *J. Chem. Res.* (S), **1983**, 230; (b) idem, *J. Chem. Res.* (S), **1983**, 172; *J. Chem. Res.* (M), **1983**, 1680.

97. K. H. Magosch, German Patent 2,155,753 (1973); *Chem. Abstr.*, **79**, 42516j.

98. A. Hetzheim and H. Beyer, *Chem. Ber.*, **103**, 272 (1970).

99. G. Westphal and P. Henklein, *Z. Chem.*, **9**, 25 (1969).

100. H. Meyer, H. Horstmann, E. Möller, and B. Garthoff, European Patent Application, EP 41,215 (1981); *Chem. Abstr.*, **96**, 122803s, idem, German Patent DE 3,020,421 (1980); *Chem. Abstr.*, **96**, 85561p.

101. T. R. Vakula and V. R. Srinivasan, *Indian J. Chem.*, **9**, 901 (1971); *Chem. Abstr.*, **75**, 151733r.

102. G. Westphal and P. Henklein, *Z. Chem.*, **9**, 425 (1969); *Chem. Abstr.*, **72**, 43579z.

103. H. Naarmann and H. Pohlemann, *Macromol. Chem.* (Suppl. 1), **1975**, 71; *Chem. Abstr.*, **83**, 131962b.

104. B. A. J. Clark, T. J. Evans, and R. G. Simmonds, *J. Chem. Soc., Perkin Trans. I*, **1975**, 1803.

105. B. Dash and S. K. Mahaptra, *Curr. Sci.*, **39**, 559 (1970); *Chem. Abstr.*, **75**, 20292y.

106. Z. I. Moshalenko and G. P. Shumelyak, *Khim. Geterotsikl. Soedin*, **81**, 120531t.

107. R. Ketcham and E. Schaumann, *J. Org. Chem.*, **45**, 3748 (1980).

108. A. Takamizawa, K. Hirai, S. Matsumoto, S. Sakai, and Y. Nakagawa, *Chem. Pharm. Bull.* (Japan), **17**, 910 (1969).

109. A. Takamizawa and S. Matsumoto, Japanese Patent 70 31,945 (1970); *Chem. Abstr.*, **74**, 53795x.

110. A. Takamizawa and S. Matsumoto, *Chem. Pharm. Bull.* (Japan), **21**, 1300 (1973).

111. J. Goerdeler and W. Roth, *Chem. Ber.*, **96**, 534 (1963).

112. L. Pentimalli, G. Milani, and F. Biavati, *Gazz. Chem. Ital.*, **107**, 1 (1977); *Chem. Abstr.*, **87**, 102239y.

113. D. Martin, A. Wenzel, and R. SSacaioglu, *J. Prakt. Chem.*, **320**, 677 (1978); *Chem. Abstr.*, **89**, 215309f.

114. R. Hull and T. P. Seden, *Synth. Comm.*, **10**, 489 (1980).

115. R. Hull and T. P. Seden, *J. Chem. Soc., Perkin Trans. I*, **1980**, 2717.

116. D. Griffiths, R. Hull, and T. P. Seden, *J. Chem. Soc., Perking Trans. I*, **1980**, 2608.

117. R. J. S. Beer, H. Singh, D. Wright, and L. K. Hansen, *Tetrahedron*, **37**, 2485 (1981).

118. C. C. Beard, U.S. Patent 3,901,903 (1975); *Chem. Abstr.*, **84**, 17364d.

119. T. Pyl, F. Waschk, and H. Beyer, *Liebigs Ann. der Chemie*, **663**, 113 (1963).

120. N. Saldabols, S. Hillers, L. N. Alekseeva, and B. Brizga, *Khim. Farm. Zh.*, **1**, 27 (1967); *Chem. Abstr.*, **68**, 2856m.

121. A. Sitte, P. Heinz, and H. Günter, *Z. Chem.*, **7**, 341 (1967); *Chem. Abstr.*, **67**, 108608b.

122. S. Kano, *Yakugaku Zasshi*, **92** 935 (1972); *Chem. Abstr.*, **77**, 126492v.

123. V. P. Arya, F. Fernandes, and V. Sudarsanam, *Indian. J. Chem.*, **10**, 598 (1972); *Chem. Abstr.*, **78**, 4212d.

124. L. Pentimalli, G. Milani, and F. Biavati, *Gazz. Chim. Ital.*, **105**, 777 (1975).

125. F. Russo and M. Santagati, *Farmaco Ed. Sci.*, **31**, 41 (1976); *Chem. Abstr.*, **84**, 90090r.

126. M. Baboulene and G. Sturz, *Phosphorus Sulfur*, **5**, 87 (1978); *Chem. Abstr.*, **90**, 168672c.

127. M. A. Eldawy, S. A. Shams El-Dine, and K. M. El-Brembaly, *Pharmazie*, **34**, 144 (1979); *Chem. Abstr.*, **91**, 56918b.

128. C. K. Joshi, V. N. Pathak, and P. Panwar, *Indian. J. Chem.*, **56**, 716 (1979); *Chem. Abstr.*, **92**, 35789r.

129. H. Horstmann, K. Meng, F. Senter, and E. Moeller, German Patent 2,832,686 (1979); *Chem. Abstr.*, **92**, 215440d.

130. I. T. Barnish, P. E. Cross, R. P. Dickinson, B. Gadsby, M. J. Parry, M. J. Randall, and I. W. Sinclair, *J. Med. Chem.*, **23**, 117 (1980).

131. T. L. Hough, *J. Heterocycl. Chem.*, **20**, 1003 (1983).

132. W. L. Mosby, *Heterocyclic Compounds with Bridgehead Nitrogen*, Interscience, New York, 1961, Part. 1, pp. 201–202.

133. M. L. Schenetti, F. Taddei, L. Greci, L. Marchetti, G. Milani, G. Andretti, D. Giovanni, G. Bocelli, and P. Sgarabotto, *J. Chem. Soc., Perkin Trans. II*, **1980**, 421.

134. H. Paul, A. Sitte, and R. Wessel, *Monatsh. Chem.*, **108**, 665 (1977); *Chem. Abstr.*, **87**, 201420g.

135. H. Paul and A. Sitte, *Z. Chem.*, **17**, 176 (1977); *Chem. Abstr.*, **87**, 167947x.

136. H. Paul, A. Sitte, and R. Wessel, *Arch. Pharm.* (Weinheim), **314**, 359 (1981); *Chem. Abstr.*, **95**, 80873m.

137. H. Paul and R. Wessel, *Arch. Pharm.* (Weinheim), **315**, 12 (1982); *Chem. Abstr.*, **96**, 122699n.

138. S. Kano and T. Noguchi, Japanese Patent 71 26,514 (1971); *Chem. Abstr.*, **75**, 140865j.

139. H. Meyer, H. Horstmann, E. Moeller, and B. Garthoff, European Patent Application EP 41,215 (1981); *Chem. Abstr.*, **96**, 122803s, idem, German Patent DE 3,020,421 (1981).

140. A. S. Tomcufcik and P. F. Fabio, Belgian Patent 637,271 (1964); *Chem. Abstr.*, **62**, 11830f.

141. J. W. Carpenter, J. D. Mee, and D. W. Heseltine, U.S. Patent 3,615,639 (1971); *Chem. Abstr.*, **77**, 103346m; idem U.S. Patent 3,809,691 (1974); *Chem. Abstr.*, **81**, 51156k; idem, French Patent 2,006,142; *Chem. Abstr.*, **74**, 8370u; idem, German Patent 1,804,465 (1969); *Chem. Abstr.*, **74**, 100620y.

142. J. F. Dawson and E. Teale, British Patent 1,401,968 (1975); *Chem. Abstr.*, **84**, 19161j.

143. H. Paul and G. Huschert, *Z. Chem.*, **21**, 185 (1981); *Chem. Abstr.*, **95**, 132764y.

144. I. Lalezari and A. Shafiee, *J. Heterocycl. Chem.*, **8**, 835 (1971).

145. E. Bulka and D. Ehlers, *J. Prakt. Chem.*, **315**, 510 (1973); *Chem. Abstr.*, **79**, 53232q.

146. (a) R. A. Ludwig and G. D. Thorn, *Plant Disease Rep.*, **37**, 127 (1953); (b) idem, *Can. J. Chem.*, **32**, 872 (1954); (c) idem, *J. Appl. Chem.*, **1962**, 90.

147. G. D. Thorn, *Can. J. Chem.*, **38**, 2349 (1960).

148. C. W. Pluijgers, J. W. Vonk, and G. D. Thorn, *Tetrahedron Lett.*, **1971**, 1317.

149. W. R. Benson, R. D. Ross, J. T. Chen, R. P. Barron, and D. Mastbrook, *J. Assoc. Off. Anal. Chem.*, **55**, 44 (1972); *Chem. Abstr.*, **76**, 113136m.

150. M. Alvarez, R. W. Creekmore, and R. T. Rasen, *Tetrahedron Lett.*, **1973**, 939.

151. T. G. Stowe, U.S. Patent 3,557,134 (1971); *Chem. Abstr.*, **74**, 100063u.

152. R. J. S. Beer, N. H. Holmes, and A. Naylor, *J. Chem. Soc., Perkin I*, **1979**, 2909.

153. N. M. Roscher and J. H. Onley, *J. Chromatogr.*, **140**, 109 (1979); *Chem. Abstr.*, **87**, 193285z.

154. F. Iverson, W. H. Newsome, and S. L. Hierlihy, *Bull. Environ. Contam. Toxicol.*, **18**, 541 (1977); *Chem. Abstr.*, **88**, 70121f.

155. J. W. Vonk and A. K. Sijpesteijn, *J. Environ. Sci. Health, Part B*, **11**, 33 (1976); *Chem. Abstr.*, **84**, 160304q.

156. R. Okazaki, F. Ishii, K. Okawa, K. Ozawa, and N. Inamoto, *J. Chem. Soc., Perkin Trans. I*, **1975**, 270.

157. H. Alper and M. S. Wolin, *J. Org. Chem.*, **40**, 437 (1975).

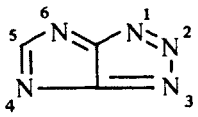
Chemistry of Heterocyclic Compounds, Volume 46
P. N. Preston

CHAPTER 4

Condensed Imidazoles of Type 5-5 with Three Additional Heteroatoms

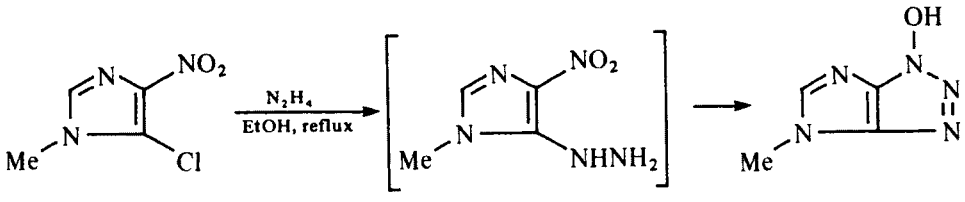
4.1. RING SYSTEM C_3N_2–C_2N_3: IMIDAZO[4,5-*d*][1,2,3]-TRIAZOLE

There are no examples of derivatives in the fully aromatic imidazo[4,5-*d*][1,2,3]-triazole ring system (**4.1**) during the literature period covered. A compound



(4.1)

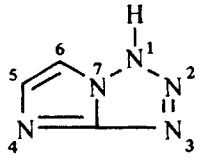
thought to be 1,4-dihydro-1-hydroxy-4-methylimidazo[4,5-*d*][1,2,3]triazole (**4.4**) has been prepared from the nitroimidazole derivative (**4.2**) and hydrazine (see **4.2** → **4.3** → **4.4**).[1] The product (**4.4**) does not melt below 400°C and surprisingly is bright purple in color and does not exhibit an O–H stretching frequency in the ir spectrum. It is assumed[1] that the bicyclic compound (**4.4**) exists as a hydrogen-bonded dimer (through *N*-2), but further spectroscopic data are required before structure (**4.4**) can be accepted.



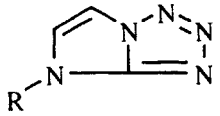
(4.2) (4.3) (4.4)

4.2. RING SYSTEM C_3N_2–CN_4: IMIDAZO[1,2-*d*]TETRAZOLE

In principle, compounds in the imidazo[1,2-*d*]tetrazole ring system can belong to either the 1*H*- (**4.5**), 3*H*-, or 4*H*- (**4.6**) categories. Most of the literature on this ring system describes physicochemical studies of the tetrazolo–azido equilibrium depicted in **4.6** ⇌ **4.7**.[2]

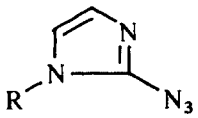


(4.5)



(4.6)

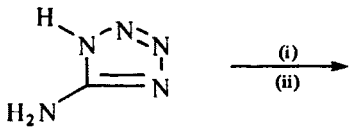
	R
a	H
b	Ac



(4.7)

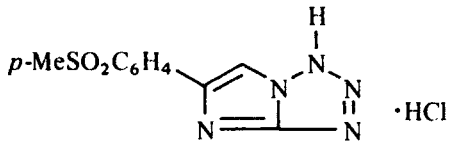
	R
a	H
b	Ac

The cyclizative condensation of 5-amino-1*H*-tetrazole (**4.8**) with ω-bromo-*p*-methylsulfonylacetophenone is reported[3] to give the 1*H*-imidazo[1,2-*d*]tetrazole (**4.9**), but no evidence is presented for establishment of an azido–tetrazolo equilibrium (cf. **4.6** ⇌ **4.7**) in this case.



(4.8)

(i) *p*-$MeSO_2C_6H_4COCH_2Br$, 95% EtOH, 60°C;
(ii) Recrystallize from 10% HCl



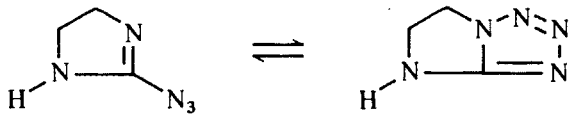
(4.9)

mp 235–238°C;
60% yield

The existence of such an equilibrium was recognized for 2-azidoimidazoline (cf. **4.10** ⇌ **4.11**) from ir and uv spectral measurements.[4] Thus the tetrazole form (**4.11**) is dominant in the solid state, whereas the imidazoline form (**4.10**) exists in ethanol solution. In constrast to this behavior, 2-azidoimidazole (**4.7a**) exists in the azido form (ν_{max} = 2200–2130 cm^{-1}) in the solid state and also in solution in chloroform or dimethylsulfoxide.[5] It has been subsequently established that the position of this equilibrium is determined by the nature of the 1-substituent of the imidazole ring. For example, 1-acetyl-2-azidoimidazole (**4.7b**) is present as a 3:2 equilibrium mixture with the tetrazole form (**4.6b**) in dimethyl sulfoxide;[5] the proportion of imidazo[1,2-*d*]tetrazole (cf. **4.6**) in the equilibrium mixture increases with increasing steric bulk of the 1-acyl substituent[6] and also with the increasing electron-withdrawing mesomeric influence of the 1-substituent.[7] The ir spectrum

TABLE 4.1. PHYSICAL AND SPECTROSCOPIC PROPERTIES OF IMIDAZO[1,2-*c*][1,2,3,5]THIATRIAZOLE-2-*S*(IV) DERIVATIVES (**4.15a, b**) AND THEIR SELENIUM ANALOGS (**4.15c, d**)[10]

Compound	Color	mp (°C) (Solvent for Recrystallization)	Yield (%)	^{1}H nmr Spectrum δ (ppm) from TMS ($CDCl_3$ Solvent)	uv Spectrum λ_{max}^{MeOH} (nm) (log ε)
4.15a	Orange	145–146 (dec.) (C_6H_6–petroleum ether)	68	7.4 (m)	428 (3.87), 278 (4.17), 220 (4.33)
4.15b	Yellow	169–170 (dec.) (C_6H_6–petroleum ether)	40	8.27 (s, 1H, H-6), 7.65 (m, Ar–H)	401 (4.02), 315 (4.05), 223 (4.16), 212 (4.16)
4.15c	Maroon	206–206.5 (EtOH)	69	7.2–7.9 (m)	472 (3.82), 337 (4.03), 279 (3.97), 233 (4.13).
4.15d	Orange	165–166 (dec.) ($CHCl_3$)	5	8.22 (s, 1H, H-6), 8.05 (m, 2H), 7.37 (m, 3H)	442 (3.91), 345 (4.03), 263 (3.44), 229 (4.09).

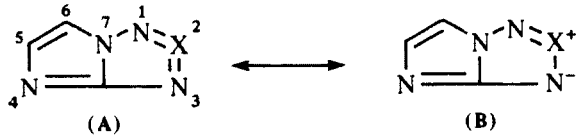


(4.10) (4.11)

of a solution of 2-azidoimidazole (**4.7a**) in ethanolic sodium ethoxide does not exhibit a band that could be assigned to the azido group, and it has been concluded that the anion of **4.7** exists entirely in the tetrazolo form.[5] Existence of the anion in the tetrazolo form is also predicted from molecular orbital calculations.[8,9] From MNDO semiempirical SCF calculations, the bicyclic anion derived from **4.6a** is predicted to be 70.7 kJ/mol more stable than the neutral bicyclic molecule; the shift of the equilibrium to the tetrazole form in the case of the anion is attributed mainly to delocalization of the negative charge on the tetrazole part of the bicyclic system.[9]

4.3. RING SYSTEMS $C_3N_2-CN_3S$ AND $C_3N_2-CN_3Se$: IMIDAZO[1,2-*c*][1,2,3,5]THIATRIAZOLE-2-*S*(IV) AND IMIDAZO[1,2-*c*][1,2,3,5]SELENATRIAZOLE-2-*Se*(IV)

The title condensed imidazoles (**4.12** and **4.13**) are of interest because of their potential chemical reactivity as 1,3-dipoles (see, e.g., **4.12A** ↔ **4.12B**). They have been prepared by annulation reactions of 1,2-diamino-4-phenylimidazoles (see **4.14** → **4.15** and Table 4.1),[10] but a restriction on the synthetic method is caused by the inaccessibility of 1,2-diamino-4-phenyl-5-alkylimidazoles that would provide 6-alkyl analogs of the bicyclic products (viz., **4.15**, R = alkyl). It is believed[10] that the condensed thiatriazoles (**4.15a,b**) are formed in a stepwise fashion through thionitroso oxides and cyclic *S*-oxides.

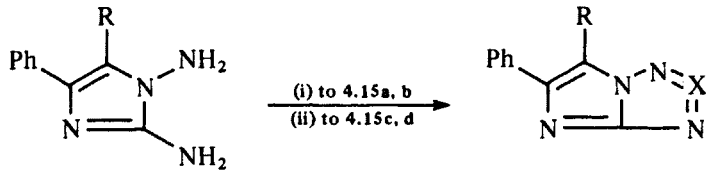


(A) (B)

(**4.12**, X = S)
(**4.13**, X = Se)

The ^1H nmr spectra of the two pairs of compounds (**4.15a,b** and **4.15c,d**) are very similar with *H*-6 appearing for **4.15b** and **d** near $\delta = 8.25$. A notable feature in the electronic absorption spectra is the bathochromic shift observed in the long-wavelength band in passing from sulfur to selenium (see Table 4.1).

Disappointingly, the condensed thiatriazoles (**4.15a,b**) and selenatriazoles (**4.15c,d**) fail to react with electron-deficient 1,3-dipolarophiles under a wide variety of reaction conditions.



(4.14) (4.15)

(i) $SOCl_2$, pyridine, 125°C (to **4.15a**) or room temperature (to **4.15b**);
(ii) SeO_2, EtOH, heat (to **4.15c**) or room temperature (to **4.15d**)

	R	X
a	Ph	S
b	H	S
c	Ph	Se
d	H	Se

REFERENCES

1. A. Kreutzberger, *J. Org. Chem.*, **27**, 886 (1962).
2. M. Tisler, *Synthesis*, **1975**, 123.
3. L. Almiranti, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Gamba, A. Olivi, and W. Murmann, *J. Med. Chem.*, **9**, 29 (1966).
4. J. H. Boyer and E. J. Miller, *J. Am. Chem. Soc.*, **81**, 4671 (1959).
5. E. Alcalde and R. M. Claramunt, *Tetrahedron Lett.*, **1975**, 1523.
6. M. Rull and J. Vilarrasa, *Tetrahedron Lett.*, **1976**, 4175; R. Granados, M. Rull, and J. Vilarrasa, *J. Heterocycl. Chem.*, **13**, 281 (1976).
7. M. Rull and J. Vilarrasa, *J. Heterocycl. Chem.*, **14**, 33 (1977).
8. R. M. Claramunt, J. Elguero, A. Fruchier, and M. J. Nye, *Afinidad*, **34**, 545 (1977); *Chem. Abstr.*, **90**, 203258w.
9. S. Olivella and J. Vilarrasa, *J. Heterocycl. Chem.*, **16**, 685 (1979).
10. K. T. Potts, R. D. Cody, and R. J. Dennis, *J. Org. Chem.*, **46**, 4065 (1981).

Chemistry of Heterocyclic Compounds, Volume 46
P. N. Preston

Author Index

Chemistry of Heterocyclic Compounds, Volume 46
P. N. Preston

Subject Index