

**Heterocyclic Systems with
BRIDGEHEAD NITROGEN ATOMS**

**In Two Parts
PART TWO**

This is Part Two of the fifteenth volume published in the series
THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Consulting Editor*



Heterocyclic Systems with BRIDGEHEAD NITROGEN ATOMS

Part Two

William L. Mosby
*American Cyanamid Company,
Bound Brook, New Jersey*

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The Chemistry of Heterocyclic Compounds

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

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ARNOLD WEISSBERGER

Preface

The generous assistance of several others has greatly facilitated the completion of this book, and the author gratefully acknowledges their contribution. Initially, this work was begun in collaboration with Dr. L. E. Craig, who, before he was obliged to withdraw from participation, supplied a preliminary literature survey and draft of a manuscript covering approximately fifty ring systems, and contributed to discussions on the organization of the material.

Dr. Leonard T. Capell gave most liberally of his time in checking and correcting the names proposed for approximately 350 ring systems which lacked systematic names. Instruction in the rules of nomenclature and assistance in naming many complex structures were provided by Mrs. Marie Cline.

Many authors, particularly those abroad, kindly supplied reprints of their publications. Drs. J. J. Leavitt and A. P. Paul read critically portions of the manuscript, and the former is responsible for bringing to the author's attention numerous references from the current literature. The author is especially grateful to the American Cyanamid Company for providing freely of excellent library and secretarial facilities.

Bound Brook, New Jersey

WILLIAM L. MOSBY

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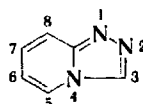
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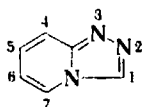
CHAPTER VI

Fused 5/6 Ring Systems with Two Extra Heteroatoms

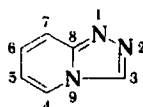
A-476. Pyrido[2,1-*c*]-*s*-triazole. R.I. 712



The names *triazolo[4,3-*a*]pyridine*, *1,2,9-pyridotriazole*, *benztriazole*, *1,2,3a-triazaindene*, *2,3-diazapyrrocoline* and *2,3-diazaindolizine* and the numbering shown in I and II are also encountered.



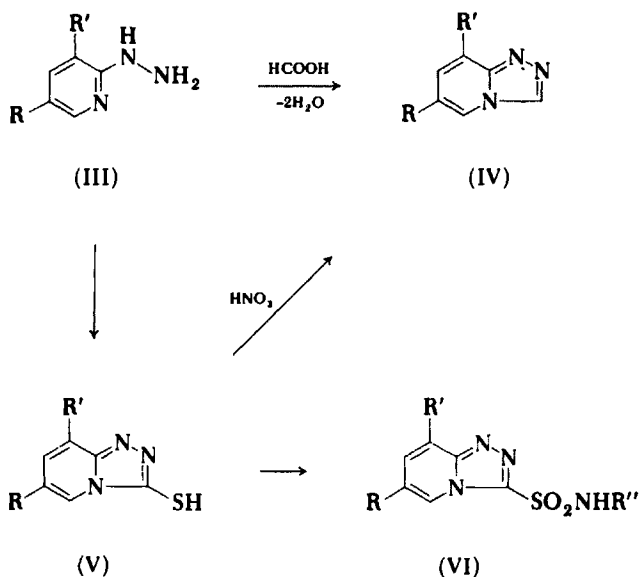
(I)



(II)

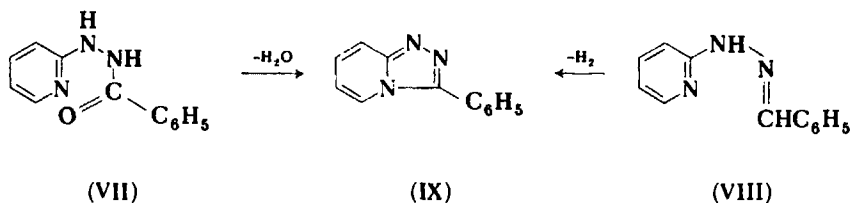
Relatively few compounds with this nucleus have been described. The reaction of 2-pyridylhydrazines (III) with formic acid yields IV ($R = R' = H$, hygroscopic solid,² silver nitrate complex, d. 228°, chloroplatinate, yellow, m. >300°; $R' = H$, $R = COOH$,¹ m. >330°, brucine salt,³ m. 218°, quinine salt,³ m. 135–45°; $R' = Cl$, $R = COOH$,⁴ m. >300°). Derivatives with substituents in the 3-position could doubtless be obtained by substituting other carboxylic acids for formic acid (v.i.).

Treatment of III ($R = R' = H$) with potassium trithiocarbonate,⁵ carbon disulfide or thiophosgene⁶ yielded V ($R = R' = H$, m. 209–10° [205–6°]). Oxidation of V ($R = R' = H$) with nitric acid yielded⁵ IV ($R = R' + H$), while chlorine converted IV

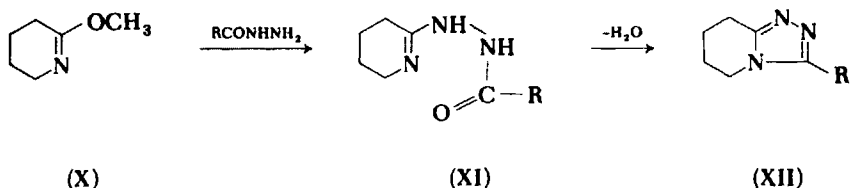


(R = R' = H) into the corresponding sulfonyl chloride (not described), which yielded the amides^{7,8} VI (R = R' = R'' = H, m. 242.0–2.5°; R = R' = H, R'' = C₆H₅, m. 244–5°). The carbonic anhydrase inhibitory power of VI (R = R' = R'' = H) has been studied.⁹

The 3-phenyl homolog (IX, m. 176°; picrate, m. 234°) has been prepared¹⁰ both by dehydration of VII and by oxidation with lead tetraacetate of the hydrazone VIII.



Tetrahydro derivatives of type XII (R = CH₃, m. 86°, b₁₄ 224°; R = OH, m. 131°; R = 4-pyridyl, m. 166°; R = —(CH₂)₄—, m. 185–6° or 184°) were prepared^{11,13} by dehydrating the amidazones (XI) obtained from the condensation of acylhydrazines with the lactim ether X. Several other related systems have been prepared via this type of synthesis (see Sections A-143, A-696 and A-716).

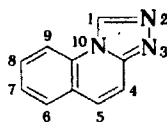


The ultraviolet spectra of IV ($R = R' = H$) and of IX have been compared¹² with those of related polyazaindenes.

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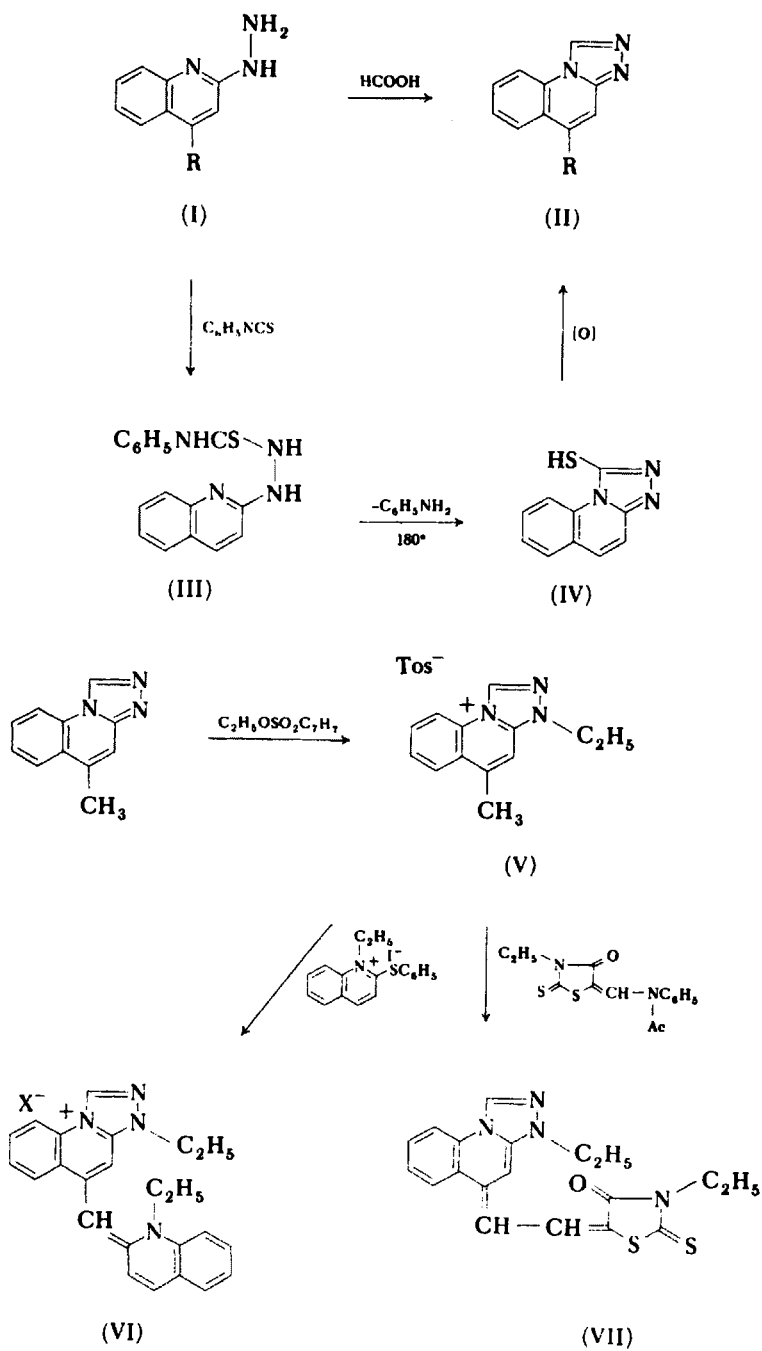
A-477. *s*-Triazolo[4,3-*a*]quinoline. R.I. 1504



This nucleus also has been called *naphthotriazole* and *diaza-2,3-benzo-6,7-pyrrocoline* (or *indolizine*).

Marckwald^{1,2} showed that 2-quinolylylhydrazines (I) could be converted into II by treatment with formic acid. Similarly, I reacted with phenyl isothiocyanate to form III, which lost aniline when heated to 180° and yielded IV. Oxidation of the mercaptan with hot dilute nitric acid produced II.

Brooker converted II ($R = CH_3$) into quaternary salts, (e.g. V), which were condensed with various reagents to yield cyanine³ (e.g. VI) and merocyanine⁴ (e.g. VII) dyes.

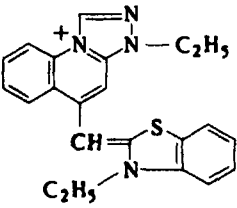
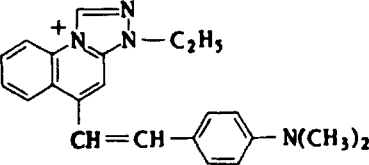
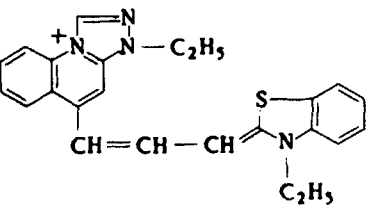
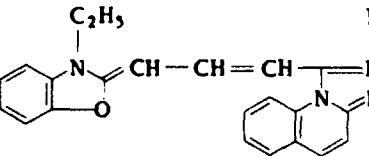
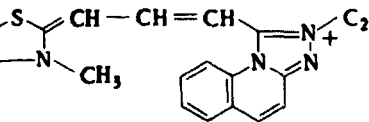
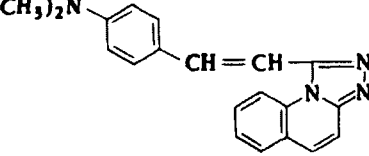
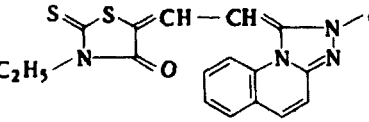


s-Triazolo[4,3-*a*]quinolines

Structure	Properties	Refs.
	m. 175°. Nitrate, m. 202°. Chloroplatinate, m. 323°. Silver nitrate complex, m. 239°.	1
	m. 261°.	1,2
	m. 228-30° d.	4
	m. 155-8°. Ethiodide, m. 192-4° d.	5
	m. ~280°.	2
	m. 229-30°.	6
	Brn., m. 273-4° d.	4
Compound VII	Grn., m. 262-3° d.	4

(continued)

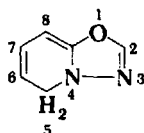
s-Triazolo[4,3-*a*]quinolines (continued)

Structure	Properties	Refs.
	Perchlorate, or., m. 255-7° d.	3
	Iodide, red-brn., m. 278-80° d.	3
Compound VI	Perchlorate, maroon, m. 217-8° d.	3
	Perchlorate, purple, m. 236-8° d.	3
	R = CH ₃ , X = Iodide, deep yel., m. 277-8° d. R = C ₂ H ₅ , X = Iodide, orange, m. 256-7° d.	5 5
	Iodide, brn.-yel., m. 253-4° d.	5
	Iodide, yel., m. 261-2° d.	5
	Red, m. 226-7° d.	5

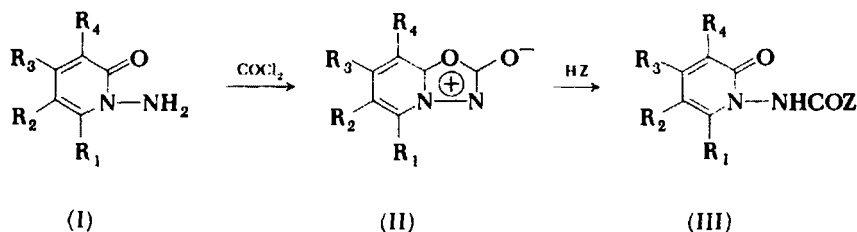
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3. Brooker, U. S. Pat. 2,689,849. Brit. Pat. 736,266.
4. Brooker, U. S. Pat. 2,743,274. Brit. Pat. 782,311.
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7. Kodak S. A., Belg. Pat. 562,142

A-478. 5H-Pyrido[2,1-b][1,3,4]-oxadiazole*



Treatment of 1-amino-2-pyridone and its methyl homologs (I) with phosgene yielded¹ II ($R_1 = R_2 = R_3 = R_4 = H$, m. 225° , $\lambda_{\max}$ 220, 262.5 and 297 $m\mu$ ($\log \epsilon = 4.11, 3.87$ and 3.86); $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$, m. $227.5-8^\circ$, $\lambda_{\max}$ 222, 268, and 290 $m\mu$ ($\log \epsilon = 4.21, 3.95$ and 3.80); $R_2 = CH_3$, $R_1 = R_3 = R_4 = H$, m. $179.5-80^\circ$, $\lambda_{\max}$ 222, 265 and 305 $m\mu$ ($\log \epsilon = 4.15, 3.95$ and 3.85); $R_3 = CH_3$, $R_1 = R_2 = R_4 = H$, m. 169° , $\lambda_{\max}$ 222, 264 and 296 $m\mu$ ($\log \epsilon = 4.11, 3.91$ and 3.87); $R_4 = CH_3$, $R_1 = R_2 = R_3 = H$, m. $177-8^\circ$, $\lambda_{\max}$ 222, 265 and 295 $m\mu$ ($\log \epsilon = 4.19, 3.95$ and 3.82); $R_1 = R_3 = CH_3$, $R_2 = R_4 = H$, m. $187-8^\circ$, $\lambda_{\max}$ 222, 267 and 293* $m\mu$ ($\log \epsilon = 4.07, 3.86$ and 3.82)).

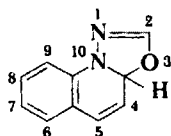


Infrared and ultraviolet spectra seem to support a mesoionic structure such as II. The oxadiazolone ring is opened slowly by the action of alcohols and amines to give products of type III ($Z = OR$ or NHR , etc.). See Sections A-479, A-480 and A-481.

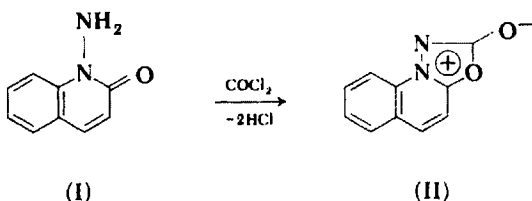
Reference

1. Hoegerle, *Helv. Chim. Acta*, **41**, 548 (1958).

A-479. 3aH-Quino[2,1-b][1,3,4]-oxadiazole*



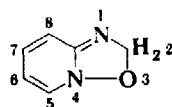
Treatment of a chloroform solution of I with phosgene in the presence of potassium carbonate yielded¹ II [brownish needles, m. 221–3°, $\lambda_{\max}$ 226, 270 and 325 m μ (log ϵ = 4.55, 4.02 and 3.77)]. See Sections A-478 and A-480/1.



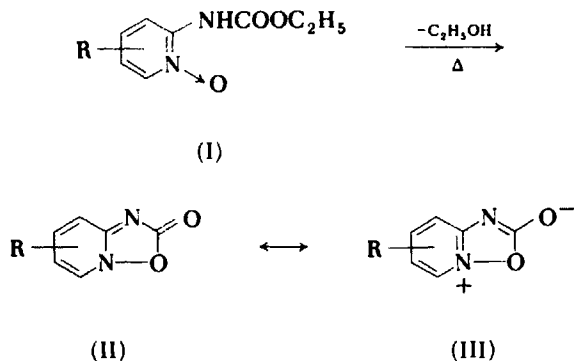
Reference

1. Hoegerle, *Helv. Chim. Acta*, **41**, 548 (1958).

A-480. 2H-[1,2,4]Oxadiazolo[2,3-a]-pyridine*



The name *pyridino(1':2'-2:3)-1-oxa-2:4-diazole* has been used. Katritzky found^{1,2} that urethanes of type I lost ethanol when heated, and gave new products formulated as II, with a substantial contribution to the resonance hybrid by forms such as III. Thus were



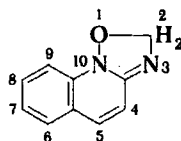
prepared the unsubstituted compound (II, R = H, m. 203–5°, $\lambda_{\max}$ 245 and 310 m μ (ϵ = 17,170 and 4,030), picrolonate, m. 125–6°); the 5-methyl¹ (m. 182.0–3.5°); 6-methyl² (m. 197–8°); 7-methyl¹ (m. 155.5–7.0°, picrate, m. 120–1°) and the 4,6-dimethyl² (m. 167–8°) homologs. Compound II (R = H) was also obtained^{3,4} by treating 2-aminopyridine oxide with phosgene.

Acidic or basic hydrolysis of II yielded¹ the corresponding 2-aminopyridine oxide. Despite the reputed antifungal activity of benzoxazolone, the products of structure II were inactive.²

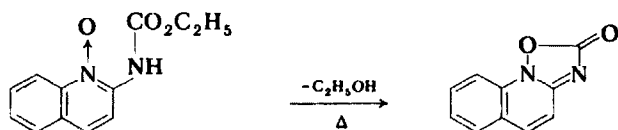
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2. Katritzky, *J. Chem. Soc.*, **1957**, 4385.
3. Boyer, Borgers and Wolford, *J. Am. Chem. Soc.*, **79**, 678 (1957).
4. Hoegerle, *Helv. Chim. Acta*, **41**, 548 (1958).

A-481. 2H-[1,2,4]Oxadiazolo[2,3-*a*]-quinoline*



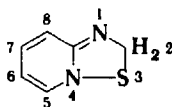
When heated, the urethane I gave¹ II (m. 176–7°), which was named *quinolino-(1':2'-2:3)-1-oxa-2:4-diazol-5-one*. See Section A-480.



Reference

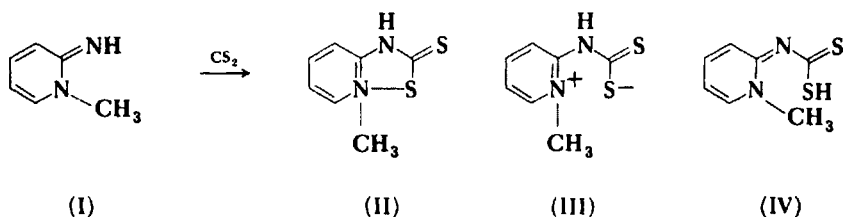
1. Katritzky, *J. Chem. Soc.*, **1957**, 4385.

A-482. 2-Pyrido[1,2-*b*][1,2,4]-thiadiazole. R.I. 692



The reaction¹ of 1-methyl-2-pyridonimine (I) with excess carbon bisulfide was claimed to yield a product (golden yellow, b_3 173°, m.

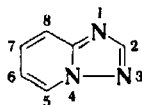
135°), which was given structure II. If this is so, the structure must be written as III or IV, but the reported stability of the compound to distillation and to the action of soda is then surprising.



Reference

1. Topchiev, *Gazz. chim. ital.*, **65**, 317 (1935); *Chem. Abstracts*, **29**, 6599 (1935); *Chem. Zentr.*, **II**, 3240 (1935).

A-483. *s*-Triazolo[1,5-*a*]pyridine*



The name *1,3,3a-triazaindene* has also been used.

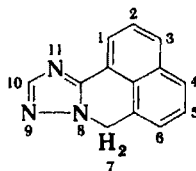
Oxidation of amidines of type I with lead tetraacetate readily yielded¹ II ($R = \text{CH}_3$, m. 49–50°, picrate, m. 177–8°; $R = \text{C}_6\text{H}_5$, m. 141°, picrate, m. 168°; $R = p\text{-tolyl}$, m. 173°).



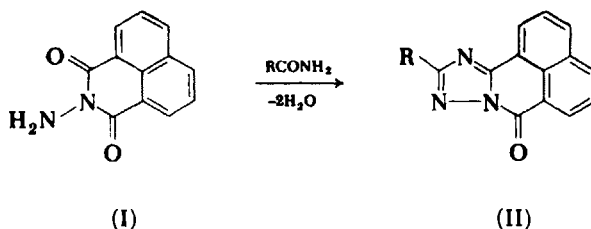
The ultraviolet spectra of II ($R = \text{CH}_3$ and C_6H_5) have been compared² with those of other polyazaindenes.

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2. Bower, *J. Chem. Soc.*, **1957**, 4510.

A-484. 7H-Benzo[de]-s-triazolo[5,1-a]-isoquinoline*

Wilke prepared¹ three examples of structure II by condensing I with various amides. Refluxing I with three equivalents of formamide together with ammonium chloride gave II (R = H, yellow, m. 240°),

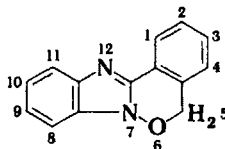


and heating I with benzamide and ammonium chloride at 270° yielded II (R = C₆H₅, orange-yellow, m. 260°), while the methyl homolog (II, R = CH₃, light yellow, m. 208–10°) was best prepared by heating I at 250° with acetamide in a sealed tube. Heating I with phenylacetonitrile and zinc chloride or ammonium chloride gave II (R = C₆H₅CH₂, m. 244°).

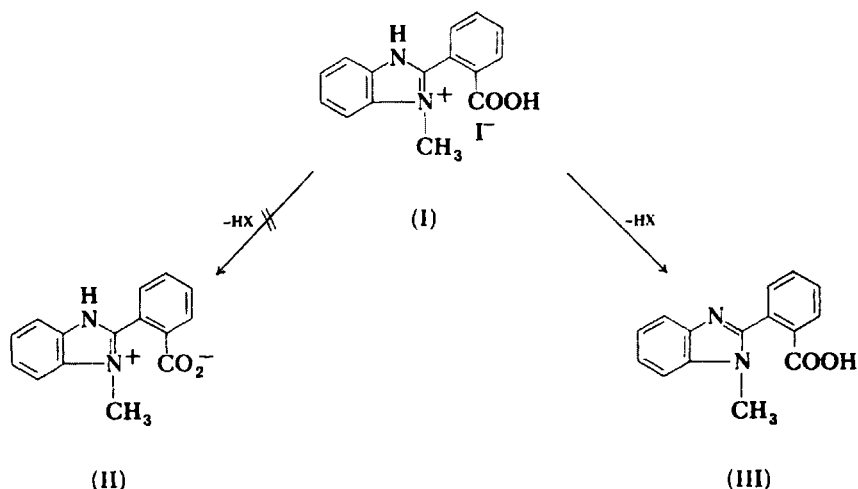
The lactam bond of II is cleaved by fusion with caustic.

Reference

1. Wilke, I.G. *Farbenindustrie, A.G., 44 Wissenschaftlicher Austausch der Gruppe IX*, Leverkusen, May 13, 1942; *PB Report No. 70339*, frames 10986ff.

A-485. 5H-Benzimidazo[1,2-c][2,3]-benzoxazine. R.I. 2379

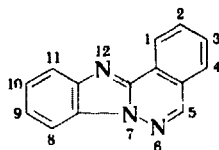
Treatment of I with ammonia or with sodium acetate, was reported¹ to yield II, but structure III seems more reasonable.



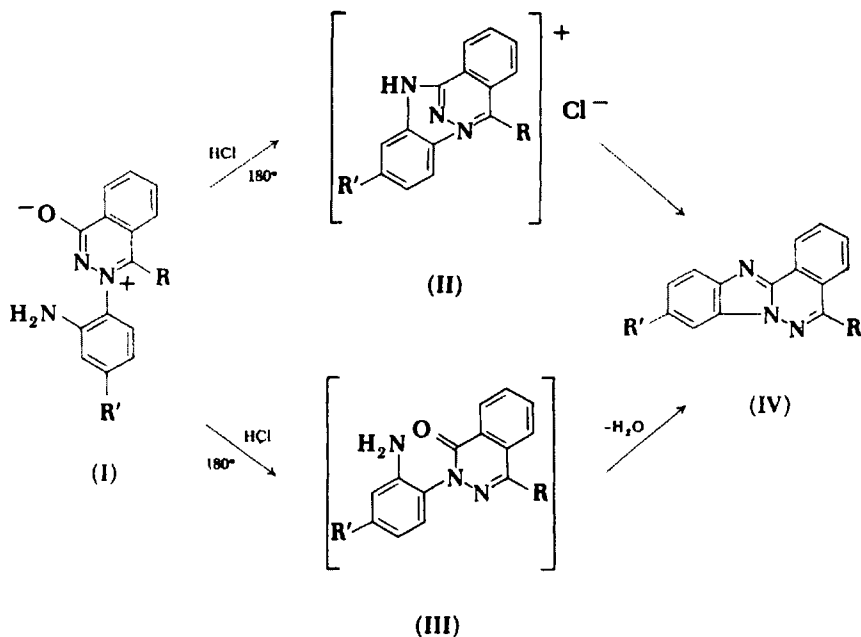
Reference

1. Rupe and Thiess, *Ber.*, **42**, 4287 (1909).

A-486. Benzimidazo[2,1-*a*]phthalazine R.I. 2384



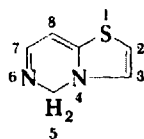
Rowe and his co-workers^{1,2} found that I ($R = H, OH, CH_3$), when heated in a sealed tube at 180° with dilute hydrochloric acid, gave products ($R = R' = H$, m. 178° , $R = H, R' = Cl$, m. 230° ; $R = OH, R' = H$, m. $>430^\circ$, *O*-acetyl derivative, m. $222-3^\circ$; $R = OH, R' = Cl$, m. $>440^\circ$; *O*-acetyl derivative, m. $>440^\circ$; $R = CH_3, R' = H$, m. 163° ; $R = R' = CH_3$, m. 186° ; $R = CH_3, R' = Cl$, m. 193°), to which they assigned structure IV, and which they considered to be formed via the intermediate II. The improbability of structure II was pointed out by Vaughan,³ who suggested that IV was formed instead by rearrangement of I to III followed by dehydration. Of course, in I where $R = OH$, the need for rearrangement to III is obviated, and IV may be formed directly by dehydration.



References

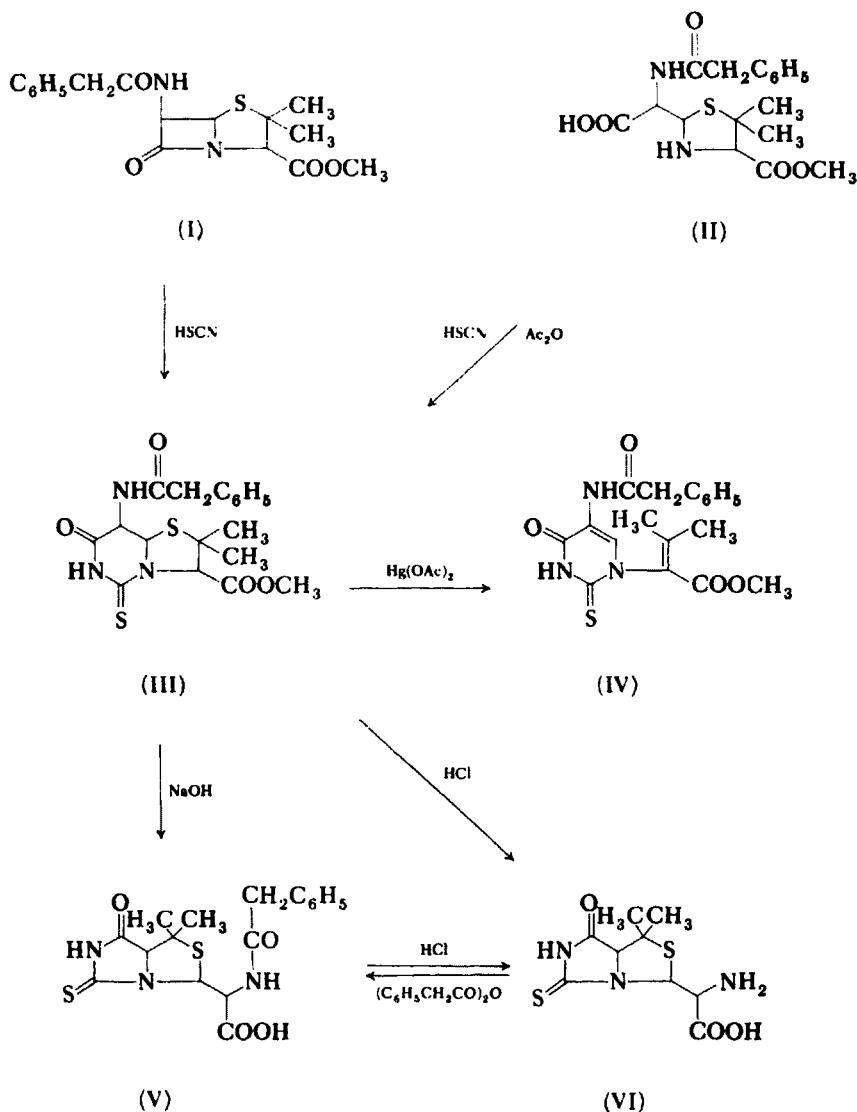
1. Rowe, Adams, Peters and Gillam, *J. Chem. Soc.*, **1937**, 90.
2. Rowe, Lécuyer and Peters, *J. Chem. Soc.*, **1938**, 1079.
3. Vaughan, *Chem. Rev.*, **43**, 447 (1948).

A-487. 5H-Thiazolo[3,2-c]pyrimidine



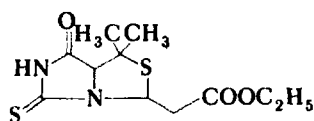
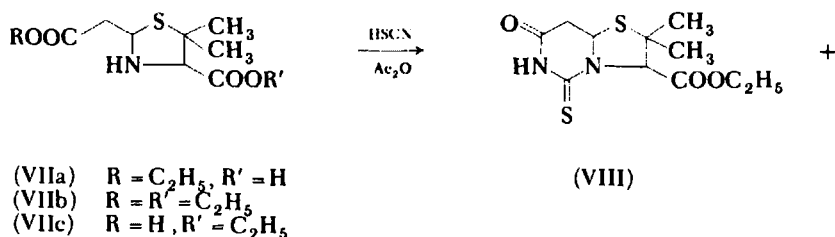
Several representatives of this ring system were obtained in connection with the work on penicillin. Benzylpenicillin methyl ester (I) and β -methyl D- α -benzylpenicilloate (II) each gave,¹ upon treatment with thiocyanic acid in acetic anhydride, the compound III (m. 154–7°). Desulfuration of III with mercuric acetate yielded IV, while with alcoholic caustic, III was saponified and rearranged to V (see Section A-149). Hydrochloric acid caused the same rearrange-

ment together with hydrolysis of the phenylacetyl group, as shown by the interconvertibility of this product (VI) and V.



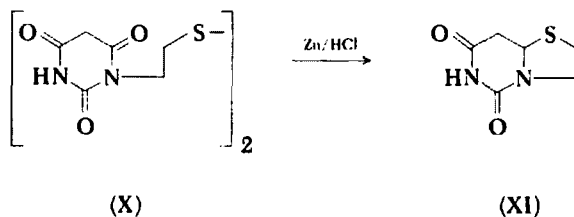
When VIIa or VIIb was treated with thiocyanic acid, a mixture of VIII and IX, with IX predominating, was obtained.¹ With VIIc,

however, substantially pure VIII (m. 155–6°), $\lambda_{\max}$ 233 and 277 m μ ; corresponding acid, m. 250–6°) resulted. Compound VIII could be converted into IX by the action of alcoholic caustic. The reaction of VIIa with phenyl isocyanate yields,² depending upon the conditions, either the *N*-phenyl homolog of VIII (m. 215–7°) or of IX.



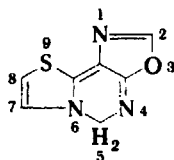
(IX)

A product (m. 300.5–1.0°) obtained³ from the reduction of X may have structure XI, but no evidence exists (beyond the elemental analysis) to support this possibility. See Section A-504.

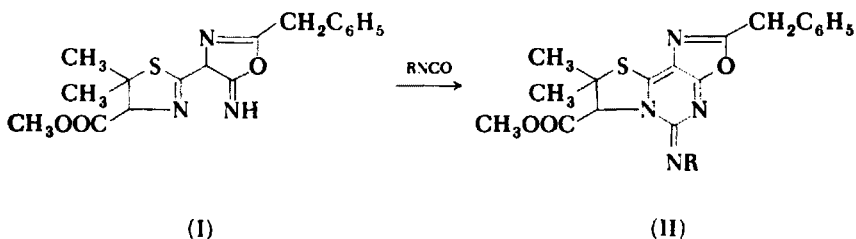


References

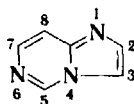
1. duVigneaud and Melville, "The Thiocyanate Derivative of Benzylpenicillin Methyl Ester" in Clarke *et al.*, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 269.
2. Cook and Heilbron, "Thiazolidines" in Clark *et al.*, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 921.
3. Nathan and Bogert, *J. Am. Chem. Soc.*, **63**, 2361 (1941).

A-488. 5H-Oxazolo[4,5-e]thiazolo-[3,2-c]pyrimidine

The reaction of I with methyl and phenyl isocyanates is reported¹ to yield II [R = CH₃, m. 218–9°, λ_{max} 288 and 295 mμ. (E_{1%}^{1cm} 480 and 450); R = C₆H₅, m. 258° d., λ_{max} 291 mμ. (E_{1%}^{1cm} 770) in chloroform].

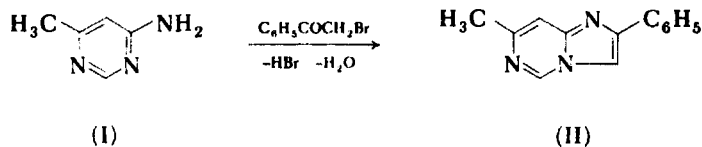
*Reference*

1. Cook and Harris, *J. Chem. Soc.*, **1949**, 3236.

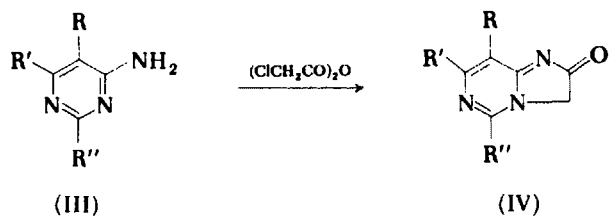
**A-489. Imidazo[1,2-c]pyrimidine.
R.I. 755**

This nucleus has also been called *1,4,6-pyrimidazole*, *imidazo-(1',2'-3,4)pyrimidine*, *imidazo(1',2'-1,6)pyrimidine* and *glyoxalo(1':2'-1:6)pyrimidine*.

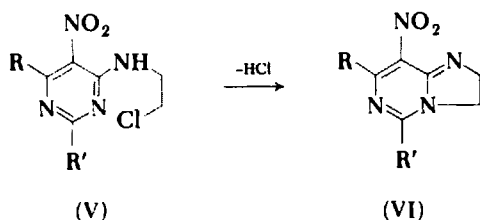
Ochiai and Yanai¹ treated I with phenacyl bromide and obtained II.



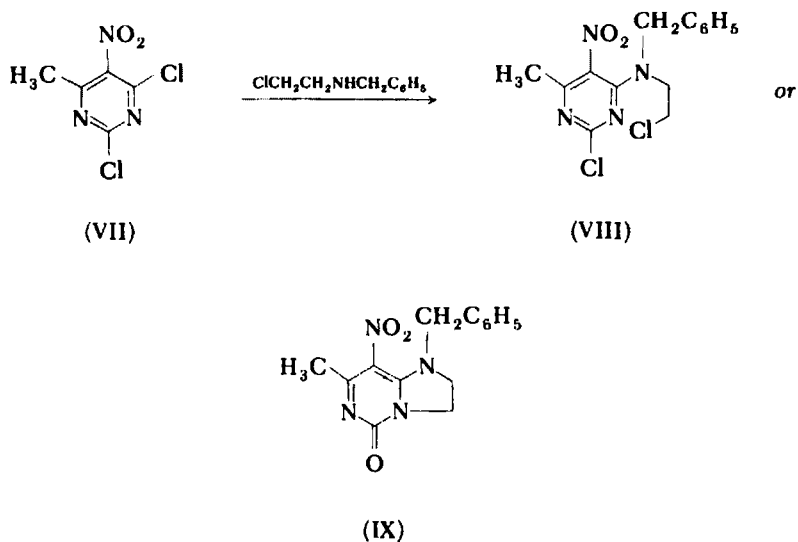
A few 2-oxo derivatives of type IV were obtained² by condensing III with chloroacetic anhydride.



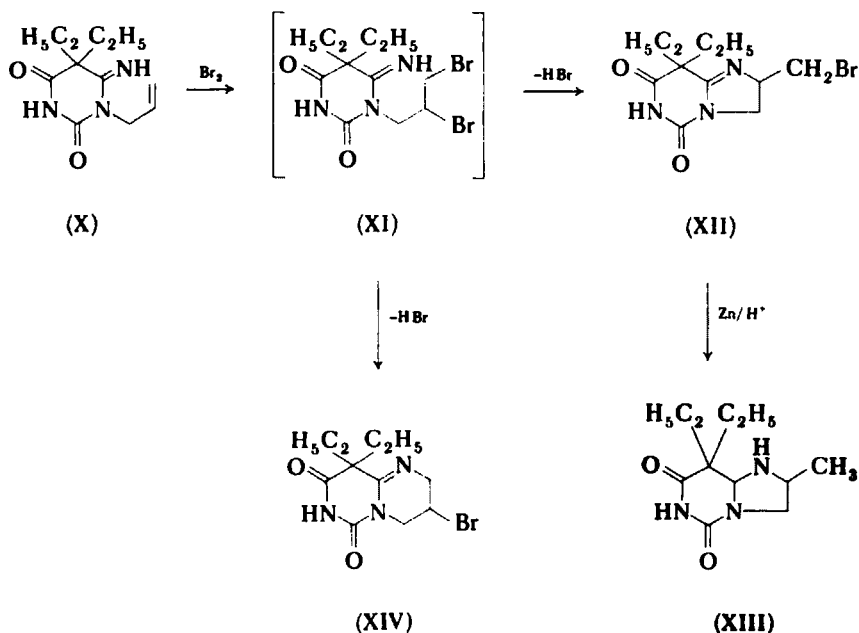
β -Chlorethylaminopyrimidines such as V may be dehydrochlorinated to VI by the action of bases (where R = H, OH or NH₂ and R' = OH, SH or NH₂)^{3,7} or by treatment with hydrogen and Raney nickel in ethanol (where R = H or CH₃, R' = Cl, and whereupon the nitro group of VI is also reduced).⁴ It was shown⁵



that treatment of VII with benzyl-2-chlorethylamine yielded only VIII under anhydrous conditions; but that in the presence of water, some IX was also formed.



Diels⁶ treated X with bromine and isolated (via XI) a product, which he considered to be XII and which could be reduced to XIII. The possibility of forming structure XIV was considered and rejected, probably correctly, but further evidence would seem needed to establish unequivocally the accuracy of structure XII.



Derivatives of Imidazo[1,2-c]pyrimidine

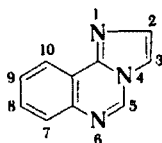
Empirical formula	Substituents or structure	Properties	Refs.
$\text{C}_6\text{H}_6\text{N}_4\text{O}_2\text{S}$	2,3-Dihydro-5-mercapto-8-nitro-	Yel.-red, m. 230–40°. 7	7
$\text{C}_6\text{H}_6\text{N}_4\text{O}_3$	2,3-Dihydro-5-hydroxy-8-nitro-	m. 260–70°. Picrate, m. 210–20°. 7	7
$\text{C}_6\text{H}_7\text{N}_5\text{O}$	2,3-Dihydro-5-hydroxy-	Picrate, m. 228–30°. 7	7
$\text{C}_6\text{H}_7\text{N}_3\text{S}$	2,3-Dihydro-5-mercapto-	m. 310–5°. 7	7
$\text{C}_6\text{H}_7\text{ClN}_4$	8-Amino-5-chloro-2,3-dihydro-	m. 157°. HCl salt, m. > 300°. 4	4
$\text{C}_6\text{H}_7\text{N}_5\text{O}_2$	5-Amino-2,3-dihydro-8-nitro-	Yel., m. 205–20°. 7	7
$\text{C}_6\text{H}_7\text{N}_5\text{O}_2\text{S}$	7-Amino-2,3-dihydro-5-mercapto-8-nitro-	— 7	7

Derivatives of Imidazo[1,2-*c*]pyrimidine (*continued*)

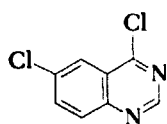
Empirical formula	Substituents or structure	Properties	Refs.
C ₆ H ₇ N ₃ O ₃	5-Amino-2,3-dihydro-7-hydroxy-8-nitro-	m. 330-40°.	7
	7-Amino-2,3-dihydro-5-hydroxy-8-nitro-	Or., m. 320-40°.	7
C ₆ H ₈ N ₄	5-Amino-2,3-dihydro-	Picrate, m. 175-7°.	7
	8-Amino-2,3-dihydro-	m. 140° (hydrate, m. 71°). Picrate, m. 240° d.	4
C ₆ H ₉ N ₅ O	7,8-Diamino-2,3-dihydro-5-hydroxy-	Yel. Picrate, d. 245-8°.	7
C ₆ H ₉ N ₅ S	7,8-Diamino-2,3-dihydro-5-mercapto-	d. 270-292°, m. 330-5°.	7
C ₇ H ₆ ClN ₃ O	5-Chloro-2,3-dihydro-7-methyl-2-oxo-	m. 320°.	2
C ₇ H ₈ N ₄ O ₂ S	2,3-Dihydro-5-mercapto-7-methyl-8-nitro-	m. 270° d.	4
C ₇ H ₈ N ₄ O ₃	2,3-Dihydro-5-hydroxy-7-methyl-8-nitro-	m. 286°.	4
C ₇ H ₉ ClN ₄	8-Amino-5-chloro-2,3-dihydro-7-methyl-	m. 163°. HCl salt, m. > 300°.	4
C ₇ H ₉ N ₅ O ₂	5-Amino-2,3-dihydro-7-methyl-8-nitro-	m. > 300°.	4
C ₇ H ₁₀ N ₄	8-Amino-2,3-dihydro-7-methyl-	m. 108°. HI salt, m. 265°. Picrate, m. 244° d.	4
C ₇ H ₁₀ N ₄ S	8-Amino-2,3-dihydro-5-mercapto-7-methyl-	m. 300° d.	4
C ₈ H ₉ N ₃ O	2,3-Dihydro-5,7-dimethyl-2-oxo-	m. 235-40°.	2
C ₈ H ₉ N ₃ O ₂	2,3-Dihydro-8-hydroxy-5,7-dimethyl-2-oxo-	d. > 350°.	2
C ₈ H ₉ N ₃ O ₂ S	5-Carboxymethylthio-2,3-dihydro-	—	7
C ₁₁ H ₁₆ BrN ₃ O ₂	Compound <i>XII</i>	m. 151-2°. HBr salt, m. ~265° d.	6
C ₁₁ H ₁₇ N ₃ O ₂	Compound <i>XIII</i>	m. 246°.	6
C ₁₃ H ₁₁ N ₃	7-Methyl-2-phenyl-	d. 244°. HCl salt, d. 247-50°. Picrate, d. 212-4°.	1
C ₁₄ H ₁₄ N ₄ O ₃	Compound <i>IX</i>	Yel., m. 171-2°. HCl salt, pale yel., m. 230° d.	5

References

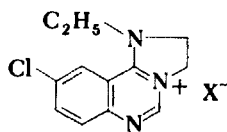
1. Ochiai and Yanai, *J. Pharm. Soc. Japan*, **59**, 18 (in Japanese) or 97 (in German) (1939); *Chem. Abstracts*, **33**, 3791 (1939); *Brit. Chem. Abstracts*, **A11**, 451 (1939).
2. Shabarova and Prokofev, *Doklady Akad. Nauk S.S.S.R.*, **101**, 699 (1955); *Chem. Abstracts*, **50**, 3457 (1956).
3. Pecher, Mathieu and Martin, *Handbook of XIV Intern. Congr. Pure and Appl. Chem.*, Zurich, 1955, p. 252.
4. Ramage and Trappe, *J. Chem. Soc.*, **1952**, 4410.
5. Brook and Ramage, *J. Chem. Soc.*, **1955**, 896.
6. Diels, *Ann.*, **432**, 115 (1923).
7. Martin and Mathieu, *Tetrahedron*, **1**, 75 (1957).

A-490. Imidazo[1,2-c]quinazoline

The reaction of 4,6-dichloroquinazoline (I) with 2-chlorethyl-ethylamine yielded¹ a cyclic product, probably of structure II (X = Cl⁻, m. 281-2°; X = I⁻, m. 261.6-2.2°; X = picrate, m. 154.2-4.7°).



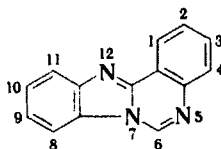
(I)



(II)

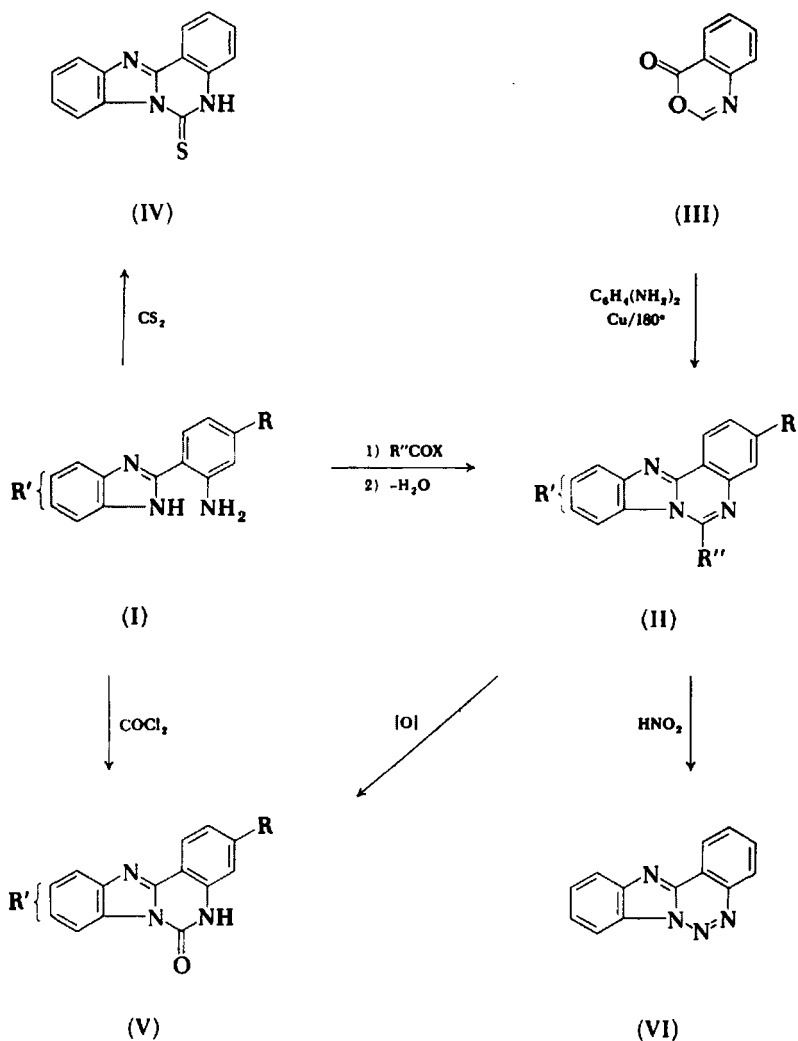
Reference

1. Sherrill, Ortelt, Duckworth and Budenstein, *J. Org. Chem.*, **19**, 699 (1954).

**A-491. Benzimidazo[1,2-c]quinazoline.
R.I. 2383**

This nucleus has also been called *methenyl-(β)-o-aminophenylbenzimidazole* and *quinazoline-3,4-benziminazole*.

A number of compounds of type II were prepared¹ by the acylation and cyclodehydration of I: (II, $R = R' = R'' = H$, m. 211° , HCl salt, m. $225-31^\circ$; $R = R' = H$, $R'' = CH_3$, m. $177-8^\circ$, HCl salt, m. 252° ; $R = R' = H$, $R'' = C_2H_5$, m. 147° ; $R = R' = H$, $R'' = C_6H_5$, m. 239° , HCl salt, m. 235° ; $R = R' = H$, $R'' = C_6H_5CH_2$, m. 196° ; $R' = H$, $R = R'' = CH_3$, m. $187-9^\circ$, chloraurate, m. 225° ; $R' = H$, $R = CH_3$, $R'' = C_6H_5$, m. 240° , chloroplatinate, m. 286° d.; $R = R'' = H$, $R' = CH_3$, m. 237° ; $R = H$,



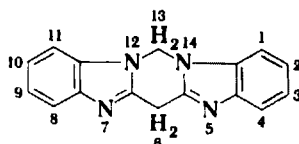
$R' = R'' = \text{CH}_3$, m. 160° ; $R'' = \text{H}$, $R = R' = \text{CH}_3$, m. 212° ; $R = R' = R'' = \text{CH}_3$, a mixture of products, m. 172° , 193° and 218°). Compound II ($R = R' = R'' = \text{H}$) was also prepared² by the condensation of III with *o*-phenylenediamine. Treatment of I ($R = R' = \text{H}$) with carbon disulfide gave¹ IV (m. 291°), and with phosgene or ethyl chlorocarbonate I yielded V ($R = R' = \text{H}$, m. 334° ; $R' = \text{H}$, $R = \text{CH}_3$, m. 343° ; $R = R' = \text{CH}_3$, m. 182°).

Oxidation of II gave¹ V, while reduction or basic hydrolysis converted II into I. Treatment of II ($R = R' = \text{H}$) with nitrous acid produced VI (see Section A-612).

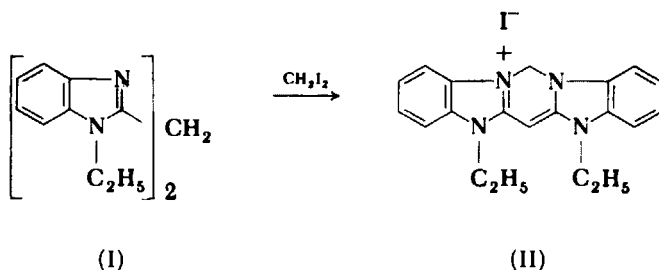
References

1. v. Niementowsky, *Ber.*, **32**, 1456 (1899).
2. Ghosh, *J. Indian Chem. Soc.*, **14**, 411 (1937); *Chem. Abstracts*, **32**, 571 (1938).

A-492. 6*H*,13*H*-Bisbenzimidazo-[1,2-*c*, 2',1'-*f*]pyrimidine



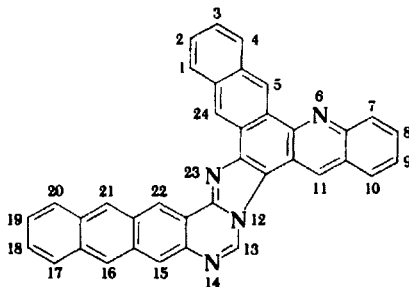
The quaternary salt II (pale yellow, m. $> 320^\circ$, strong blue fluorescence in ethanol solution) was prepared¹ from I and methylene iodide.



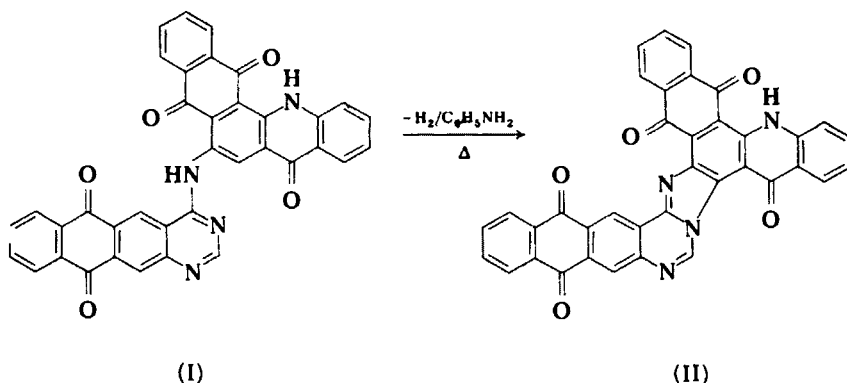
Reference

1. Brooker, U. S. Pat. 2,479,152; Brit. Pat. 618,889.

A-493. Naphtho[2,3-*g*]naphtho-[2',3',4,5]quino[2'',3'',6,7]-benzimidazo[1,2-*c*]quinazoline*



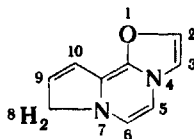
In a rather unusual reaction, I is thought¹ to have been oxidized to II by refluxing it with aniline. While the use of amines as oxidizing agents is not unprecedented, these conditions are singularly mild for such a cyclization.



Reference

1. Baumann and Schwechten, *I.G. Farbenindustrie, A.G., 41 Wissenschaftlicher Austausch der Gruppe IX*, Leverkusen, June 16/7, 1939; *PB Report No. 70340*, frame 12345.

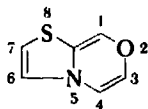
A-494. 8*H*-Oxazolo[3,2-*a*]pyrrolo-[2,1-*c*]pyrazine



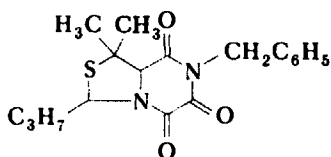
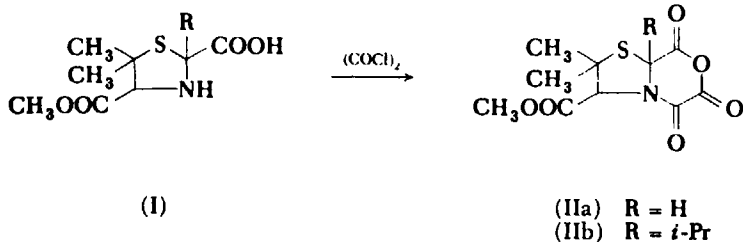
Derivatives of this nucleus are considered^{1,2,3} to be present in the structures of certain of the ergot alkaloids.

References

1. Stoll, Hofmann and Petrzilka, *Helv. Chim. Acta*, **34**, 1544 (1951).
2. Grob and Meier, *Helv. Chim. Acta*, **39**, 776 (1956).
3. Stoll and Schlientz, *Helv. Chim. Acta*, **38**, 585 (1955).

A-495. Thiazolo[2,3-*c*]-*p*-oxazine

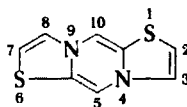
The reaction of I with oxalyl chloride in dioxane gave^{1,2} II ($R = H$, m. 128–30°; $R = i\text{-Pr}$, two stereoisomers: m. 137–8° and 139°, mixed m.p. 120°). The anhydride ring is readily opened by hydroxylic solvents. Treatment² of IIb with benzylamine causes scission of the anhydride ring, involvement of the adjacent carbomethoxy group and loss of the tertiary carboxy group, followed by recyclization to III (see Section A-544).



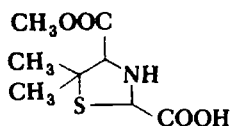
(III)

References

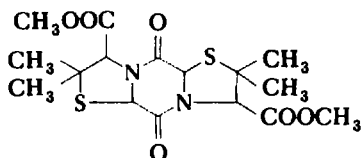
1. Bentley, Cook, Elvidge and Shaw, *J. Chem. Soc.*, **1949**, 2351.
2. Bentley, Cook and Elvidge, *J. Chem. Soc.*, **1949**, 2357.

A-496. Bisthiazolo[3,2-*a*, 3',2'-*d*]-pyrazine

The dehydration of I by treatment in pyridine solution with (a) oxalyl chloride or (b) toluenesulfonyl chloride yields¹ two modifications [m.p. (a) 170° and (b) 195–7°], presumably stereoisomeric, of structure II (see Section A-545).



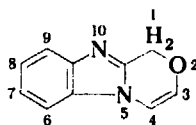
(I)



(II)

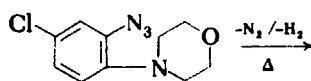
Reference

1. Bentley, Cook, Elvidge and Shaw, *J. Chem. Soc.*, **1949**, 2351.

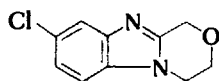
A-497. 1*H*-*p*-Oxazino[4,3-*a*]-benzimidazole

The name *morpholino*(3':4'-1:2)*benziminazole* was applied to 3,4-dihydro derivatives of this nucleus.

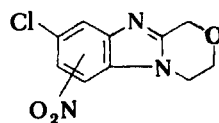
By thermal decomposition of the azide I, Saunders¹ obtained II (m. 200.0–0.5°; hydrochloride, m. 228–30°; methiodide, m. 242–4°d.) in about 50% yield. Nitration of II in sulfuric acid solution yielded a mixture of mononitro compounds, from which the major component (III, m. 219–20°) was isolated by fractional crystalliza-



(I)



(II)



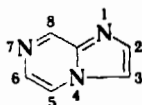
(III)

tion. This nitro derivative (III) was reduced to an amine (m. 262–3°) of unknown orientation.

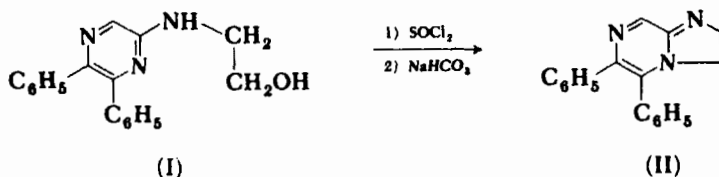
Reference

1. Saunders, *J. Chem. Soc.*, **1955**, 3275.

A-498. Imidazo[1,2-*a*]pyrazine*



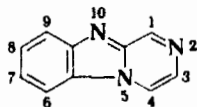
Treatment of I with thionyl chloride and a base yielded¹ II (orange, m. 183.5–4.5°, $\lambda_{\max}$ 297 m μ (log ϵ 4.14), $\lambda_{\min}$ 253 and 350 m μ (log ϵ 3.95 and 3.19); picrate, yellow, m. 182–8° d.).



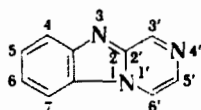
Reference

1. Martin and Tarasiejska, *Bull. soc. chim. Belges*, **66**, 136 (1957); *Chem. Abstracts*, **51**, 10545 (1957).

A-499. Pyrazino[1,2-*a*]benzimidazole*



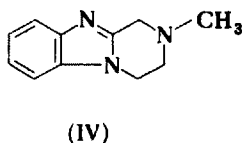
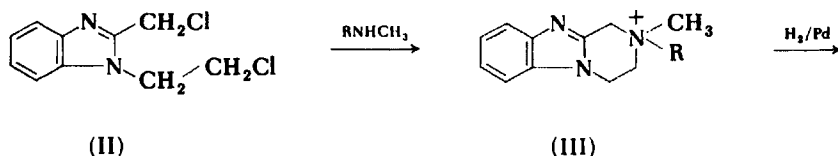
The 1,2,3,4-tetrahydro derivative of this nucleus was named *piperazino*(1',2':1,2)*benzimidazole* and numbered as shown in I.



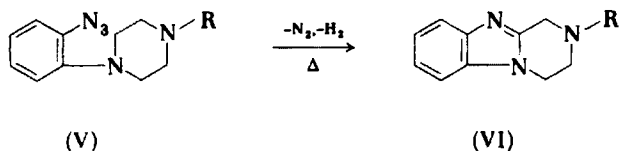
(I)

Two syntheses of this nucleus have been described. The piperazine ring was constructed¹ by the reaction of II with secondary amines

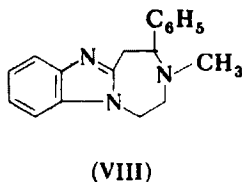
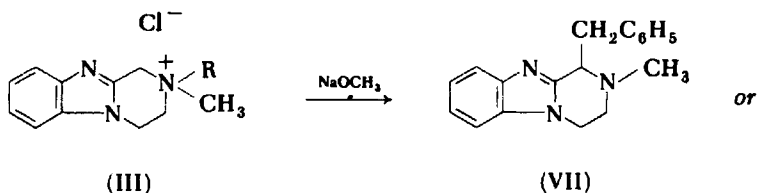
to give, in good yield, III, which (where R = benzyl) could be hydrogenolyzed to IV.

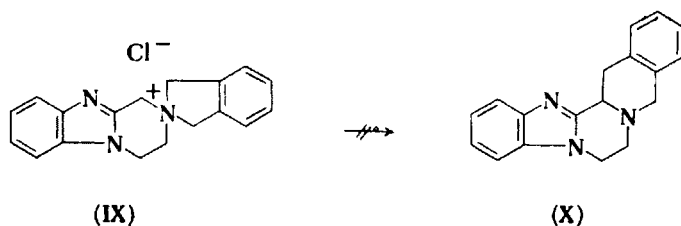


The alternative synthesis constructs^{1,2} the imidazole ring to form VI from the pyrolysis of V. The yields in this reaction are poor, the best being about 24%.



Quaternary salts such as III undergo the Stevens rearrangement, and treatment of III (R = $C_6H_5CH_2$) with sodium methoxide gave, in 54% yield, a crystalline tertiary base, thought to be VII or (less likely) VIII. Attempts to rearrange IX to X gave instead an 88% yield of an unstable crystalline tertiary base of unknown constitution.



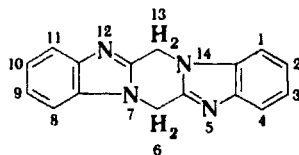


1,2,3,4-Tetrahydropyrazo[a]benzimidazoles

Empirical formula	Substituents	Properties	Refs.
C ₁₀ H ₁₁ N ₃	Unsubstituted	m. 130-1°. Di-HCl salt, m. 237-42° d.	1
C ₁₁ H ₁₂ N ₄ O	2-Carbamyl-	m. 263-6° d.	1
C ₁₁ H ₁₃ N ₃	2-Methyl-	m. 146-7°. Di-HBr salt, m. 243-55° d. 2-Methiodide, m. 212-5° d. 2-Methochloride, m. 233-5°. 2-Benzyl chloride, m. 193-4° d. 2-Benzyl bromide m. 187-9° d.	1
C ₁₂ H ₁₃ N ₃ O	2-Acetyl-	m. 140.0-0.5°.	1
C ₁₃ H ₁₄ ClN ₃ O ₂	2-Carboethoxy-8-chloro-	m. 129-31°.	2
C ₁₃ H ₁₅ N ₃ O ₂	2-Carboethoxy-	m. 126-7°. Picrate, m. 216-8°.	2
C ₁₈ H ₁₈ N ₃ Cl	2-(2'-Spirodihydroisindolinium) chloride	m. 247-50° d.	1
C ₁₈ H ₁₉ N ₃	1-Benzyl-2-methyl-	m. 116-7°.	1

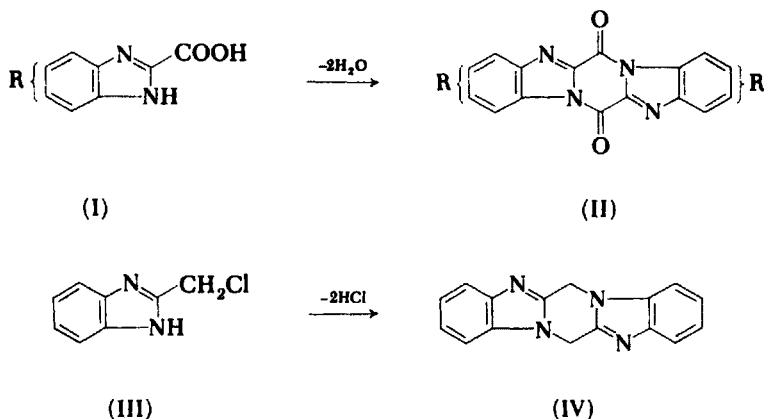
References

- Schmutz and Künzle, *Helv. Chim. Acta*, **39**, 1144 (1956).
- Saunders, *J. Chem. Soc.*, **1955**, 3275.

A-500. 6H,13H-Bisbenzimidazo-[1,2-*a*, 1',2'-d]pyrazine

Efforts to obtain the acid chlorides of 2-benzimidazolecarboxylic acids (I) by treatment with thionyl chloride, produced instead the

dimeric anhydrides II ($R = H^1$, m. $> 300^\circ$; $R = Cl^3$, m. $> 350^\circ$). Similarly 2-chloromethylbenzimidazole (III) yielded² IV (m. $> 300^\circ$).

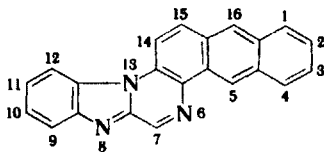


In many respects II behaves as an acid anhydride, giving¹ amides with ammonia or amines, and esters with alcohols.

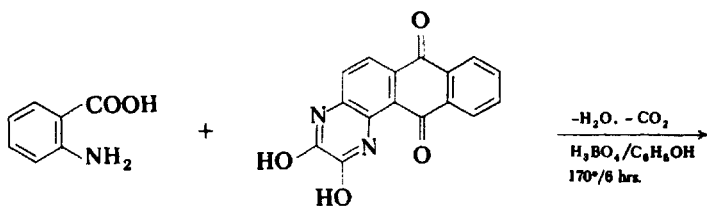
References

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2. Skolnik, Miller and Day, *J. Am. Chem. Soc.*, **65**, 1854 (1943).
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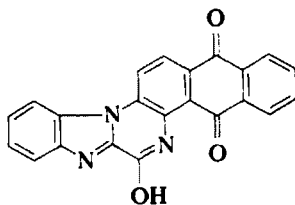
A-501. Benzimidazo[1,2-a]naphtho-[2,3-f]quinoxaline



The condensation of I with anthranilic acid yielded¹ the bright scarlet dye II (m. $\sim 340^\circ$; red vat) rated 7-8 on lightfastness and 2-3 on strength-loss and 2 on shade change during the wash fastness test. A bromo (mono- plus di-) derivative (m. $\sim 320^\circ$) and a dichloro derivative (m. $330-6^\circ$) were golden yellow dyes (reddish vats) with fastness similar to II. Treatment of II with methyl sulfate gave the *O*-methyl ether (m. $> 400^\circ$), also a scarlet dye (red-brown vat).



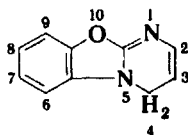
(I)



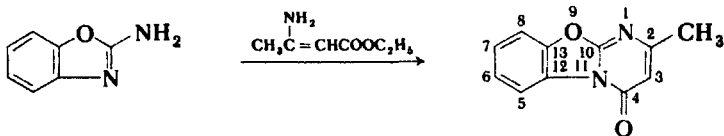
(II)

Reference

1. Oken, U. S. Pat. 2,751,385.

A-502. 4*H*-Pyrimido[2,1-*b*]benzoxazole

By condensing 2-aminobenzoxazole (I) with β -aminocrotonic ester, Antaki and Petrov¹ prepared II (m. 146°), which they named



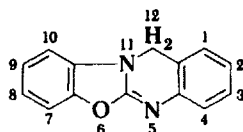
(I)

(II)

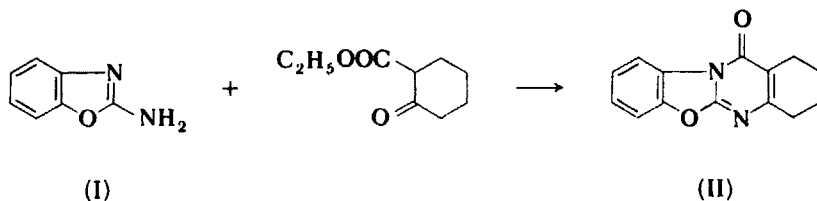
as a derivative of 4,11-dihydro-1,11-diaza-9-oxafluorene, and numbered as shown.

Reference

1. Antaki and Petrov, *J. Chem. Soc.*, **1951**, 551.

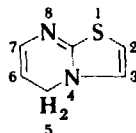
A-503. 12*H*-Quinazo[2,3-*b*]benzoxazole

The reaction of 2-carbethoxycyclohexanone with 2-aminobenzoxazole (I) yielded¹ II (m. 198°), which was named 4,11-dihydro-4-keto-2,3-cyclohexeno-1,11-diaza-9-oxafluorene.

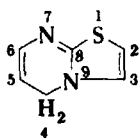


Reference

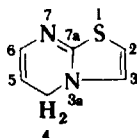
1. Antaki and Petrov, *J. Chem. Soc.*, **1951**, 551.

A-504. 5*H*-Thiazolo[3,2-*a*]pyrimidine

This nucleus has also been called *pyrimido*[2,1-*b*]*thiazole*, 7,9-diazathianaphthene (I), 4:9-dihydro-1-thia-7:9-diazaindene (I), and 3,4a-dihydro-1-thia-3a,7-diazaindene (II).

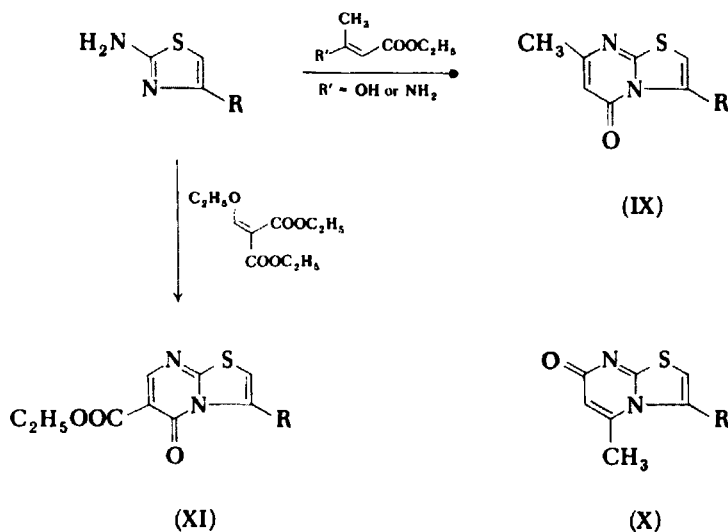


(I)

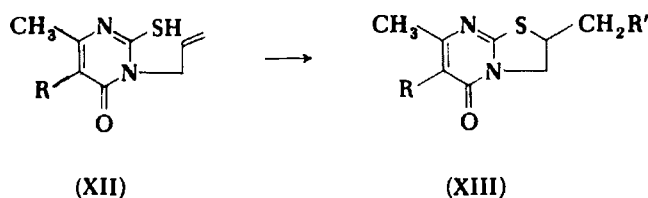


(II)

Antaki and Petrov⁷ investigated the reactions of acetoacetic and β -aminocrotonic esters with various 2-aminoheterocycles. From 2-aminothiazoles they obtained products, which there is good reason to believe (see Section A-780) have structure IX, rather than the alternative X. Ohta^{8,9} prepared the same compound (IX, R = CH₃), but assigned to it structure X, since this product was also formed from the sulfuric acid cyclization of 2-acetoacetylaminopyridine. However, in the case of 2-acetoacetylaminopyridine, such acidic cyclizations were shown (see Section A-780) to proceed with rearrangement, and it seems likely that an analogous rearrangement also occurs here, so that the product actually obtained by both routes is IX (R = CH₃) rather than X (R = CH₃). With ethoxymethyl-enemalonic ester, XI was obtained.⁹

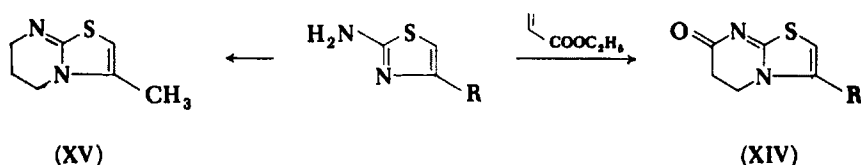


Treatment of XII with aqueous hydrochloric acid, or aqueous potassium iodide-iodine solution or with bromine in acetic acid, was

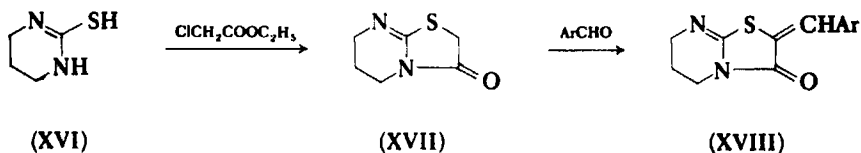


reported^{10, 18} to yield XIII ($R' = H, I$ or Br , respectively; $R = H$ or CH_3).

The only demonstrably authentic 7-oxo derivatives (XIV) of this ring system were prepared by Hurd and Hayo¹¹ by the reaction of 2-aminothiazoles with acrylic or 2-bromopropionic ester. The 6,7-dihydro compound XV was obtained¹² from the aminothiazole and trimethylene bromide.



The 3-oxo derivative XVII was prepared¹⁵ from XVI, and with benzaldehydes it yields benzal derivatives of structure XVIII.



Almost nothing is known about the substitution reactions of this nucleus. Using nitric and sulfuric acids, Antaki and Petrov⁷ obtained a mononitro derivative of IX ($R = H$), presumably the 6-nitro compound.

The alleged antineuritic activity of IX ($R = H$) has been disclaimed,¹³ and the acid corresponding to the ester XI ($R = H$) was found¹⁴ valueless against the spirochetes of relapsing fever. Photographic sensitizing agents derived from IX have been discussed¹⁶ and patented.¹⁷

Derivatives of 5*H*-Thiazolo[3,2-*a*]pyrimidine

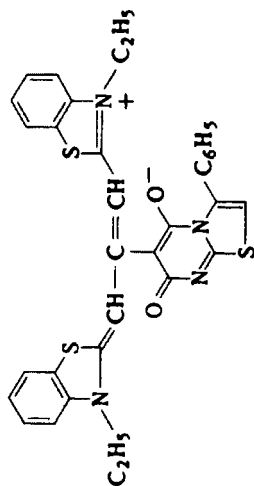
Empirical formula	Substituents or structure	Properties	Refs.
C ₆ H ₆ N ₂ OS	6,7-Dihydro-7-oxo-	m. 197°. HCl salt, m. 280° d. λ _{max} 256 and 301 mμ (log ε 3.82 and 4.14).	11
C ₆ H ₆ N ₂ O ₂ S	2,3,6,7-Tetrahydro-5,7-dioxo-	m. 244.5-5.5°.	1
C ₆ H ₈ N ₂ OS	2,3,6,7-Tetrahydro-3-oxo-	HCl salt, m. 260°. Picrate, m. 195°.	15
C ₇ H ₅ N ₃ O ₃ S	7-Methyl-(6?)-nitro-5-oxo-	m. 165°.	7
C ₇ H ₆ N ₂ OS	3-Methyl-5-oxo-	m. 129-30°.	9
	7-Methyl-5-oxo-	m. 130°. Methiodide, m. 304° d. Nitrate, m. 148° d.	7
C ₇ H ₈ N ₂ OS	6,7-Dihydro-3-methyl-7-oxo-	HBr salt, m. 308° d. λ _{max} 266 and 306 mμ (log ε 3.72 and 4.16).	11
C ₇ H ₈ N ₂ O ₂ S	2,3,6,7-Tetrahydro-6-methyl-5,7-dioxo-	m. 272-6°.	1
C ₇ H ₁₀ N ₂ S	6,7-Dihydro-3-methyl-	Oil. HBr salt, m. 335.5-7°.	12
C ₈ H ₆ N ₂ O ₃ S	6-Carboxy-3-methyl-5-oxo-	m. 255°. Ethyl ester, m. 191°.	9
C ₈ H ₈ N ₂ OS	3,7-Dimethyl-5-oxo-	m. 137° (136°).	7-9
C ₈ H ₈ Br ₂ N ₂ OS	2-Bromo-2-bromomethyl-2,3-dihydro-7-methyl-5-oxo-	m. 146°.	18
C ₈ H ₉ BrN ₂ OS	2-Bromo-2,3-dihydro-2,7-dimethyl-5-oxo-	m. 126-8°.	18
	2-Bromomethyl-2,3-dihydro-7-methyl-5-oxo-	m. 130°.	18
C ₈ H ₉ IN ₂ OS	2,3-Dihydro-2-iodomethyl-7-methyl-5-oxo-	m. 126°.	10
C ₈ H ₁₀ N ₂ OS	2,3-Dihydro-2,7-dimethyl-5-oxo-	m. 56°.	10,18
C ₈ H ₁₀ N ₂ O ₂ S	6-Ethyl-2,3,6,7-tetrahydro-5,7-dioxo-	m. 224.4-4.7°.	1
C ₉ H ₁₀ Br ₂ N ₂ OS	2-Bromo-2-bromomethyl-2,3-dihydro-6,7-dimethyl-5-oxo-	m. 122°.	18

(continued)

Derivatives of 5*H*-Thiazolo[3,2-*a*]pyrimidine (*continued*)

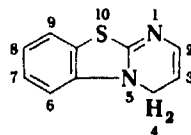
Empirical formula	Substituents or structure	Properties	Refs.
C ₉ H ₁₁ BrN ₂ OS	2-Bromomethyl-2,3-dihydro-6,7-dimethyl-5-oxo-	m. 106°.	18
C ₉ H ₁₂ N ₂ O ₂ S	2,3,6,7-Tetrahydro-6- <i>i</i> -propyl-5,7-dioxo-	m. 262.3-2.8°.	1
C ₁₀ H ₁₄ N ₂ O ₂ S	6,6-Diethyl-2,3,6,7-tetrahydro-5,7-dioxo-	m. 138.2-8.7°.	1
C ₁₁ H ₁₄ N ₂ O ₃ S	2,3,6,7-Tetrahydro-2,2-dimethyl-3,5,7-trioxo-6- <i>n</i> -propyl-	m. 213-4°.	2
C ₁₁ H ₁₆ N ₂ O ₂ S	6- <i>n</i> -Butyl-6-ethyl-2,3,6,7-tetrahydro-5,7-dioxo-	m. 92.6-3.1°.	1
C ₁₂ H ₁₀ N ₂ OS	5,6-Dihydro-7-oxo-3-phenyl-	HBr salt, m. 281° d.	11
C ₁₂ H ₁₀ N ₂ O ₂ S	2,3,6,7-Tetrahydro-5,7-dioxo-6-phenyl-	m. 247.2-7.7°.	1
C ₁₂ H ₁₆ N ₂ O ₃ S	6- <i>n</i> -Butyl-2,3,6,7-tetrahydro-2,2-dimethyl-3,5,7-trioxo-	m. 210-1°.	11
C ₁₂ H ₁₈ N ₂ O ₂ S	6- <i>n</i> -Butyl-6-ethyl-2,3,6,7-tetrahydro-5,7-dioxo-	m. 89.7-90.3°.	1
C ₁₃ H ₁₂ N ₂ OS	2-Benzylidene-2,3,6,7-tetrahydro-3-oxo-	m. 135°. HCl salt, m. 223-5°. Methiodide m. 272-5°.	15

$C_{13}H_{12}N_2O_2S$	6-Benzyl-2,3,6,7-tetrahydro-5,7-dioxo-	m. 241.9-2.3°.	1
$C_{13}H_{18}N_2O_3S$	6- <i>n</i> -Amyl-2,3,6,7-tetrahydro-2,2-dimethyl-3,5,7-trioxo-	m. 155-6°.	2
$C_{14}H_{14}N_2O_2S$	6-Ethyl-2,3,6,7-tetrahydro-5,7-dioxo-6-phenyl-	m. 120.3-1.3°.	1
$C_{15}H_{16}N_2O_2S$	2-Anisylidene-2,3,6,7-tetrahydro-3-oxo-6-Benzyl-6-ethyl-2,3,6,7-tetrahydro-5,7-dioxo-	m. 132-3°. Methiodide, m. 235-7° d. m. 136.0-6.4°.	15 1



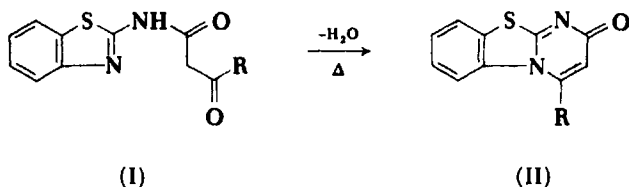
References

1. Masters and Bogert, *J. Am. Chem. Soc.*, **64**, 2709 (1942).
2. Heald and Walker, *J. Chem. Soc.*, **1950**, 1127.
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4. Anish, U. S. Pats. 2,423,218; 2,464,780 and 2,482,532; Brit. Pats. 638,504 and 637,648; Can. Pat. 469,722.
5. Kendall and Duffin, U. S. Pat. 2,527,265; Brit. Pat. 634,591; *Chem. Abstracts*, **44**, 9287 (1950).
6. Kendall and Duffin, U. S. Pat. 2,527,266; Brit. Pat. 634,592; *Chem. Abstracts*, **44**, 9287 (1950).
7. Antaki and Petrov, *J. Chem. Soc.*, **1951**, 551.
8. Ohta, *J. Pharm. Soc. Japan*, **71**, 1428 (1951); *Chem. Abstracts*, **46**, 8099 (1952).
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11. Hurd and Hayao, *J. Am. Chem. Soc.*, **77**, 117 (1955).
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13. Schultz, *Z. physiol. Chem.*, **272**, 29 (1941); *Chem. Abstracts*, **37**, 4432 (1943).
14. Thompson, Walker and Dunn, *J. Am. Pharm. Assoc.*, **42**, 647 (1953); *Chem. Abstracts*, **48**, 1581 (1954).
15. Van Allen, *J. Org. Chem.*, **21**, 24 (1956).
16. Birr, *Z. wiss. Phot.*, **47**, 2 (1952).
17. Brooker and White, U. S. Pat. 2,739,964.
18. Giambrore, *Boll. sci. fac. chim. ind. Bologna*, **11**, 86 (1953); *Chem. Abstracts*, **49**, 4662 (1955).

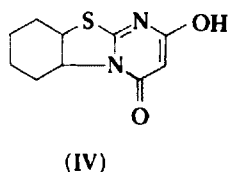
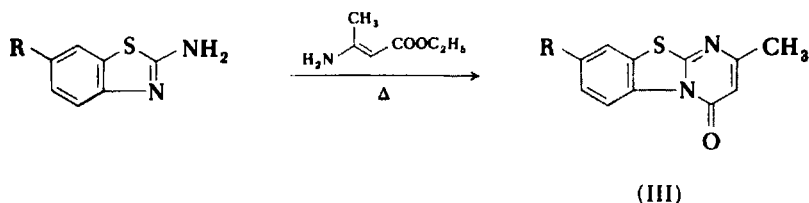
A-505. 4*H*-Pyrimido[2,1-*b*]benzothiazole

This nucleus has also been called 4,11-dihydro-1,11-diaza-9-thiafluorene.

Schrader¹ indicated that acylacetamides such as I could be dehydrated to II, but no details were reported.



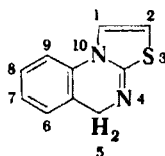
By heating 2-aminobenzothiazoles with β -aminocrotonic ester, Antaki and Petrov² prepared a group of compounds of structure III ($R = H$, m. 199°; $R = NHAc$, m. 290°; $R = Cl$, m. 220°; $R = C_2H_5O$, m. 198°; $R = COOC_2H_5$, m. 202–5°). It seems possible that the compounds Schrader considered to be II are, in fact, 4-oxo derivatives of type III. The use of IV in the preparation of mero-cyanine dyes has been patented³ but no details were given.



References

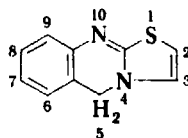
1. Schrader, Ger. Pat. 603,623; *Frdl.*, **21**, 317 (1937).
2. Antaki and Petrov, *J. Chem. Soc.*, **1951**, 551.
3. Anish, U. S. Pats. 2,482,532, 2,423,218 and 2,464,780; Brit. Pats. 637,648 and 638,504; Can. Pat. 469,722.
4. Birr, *Z. wiss. Phot.*, **47**, 2 (1952).

A-506. 5*H*-Thiazolo[3,2-*a*]quinazoline



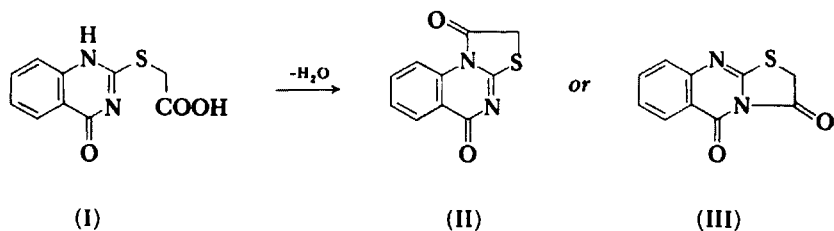
and

A-507. 5*H*-Thiazolo[2,3-*b*]quinazoline

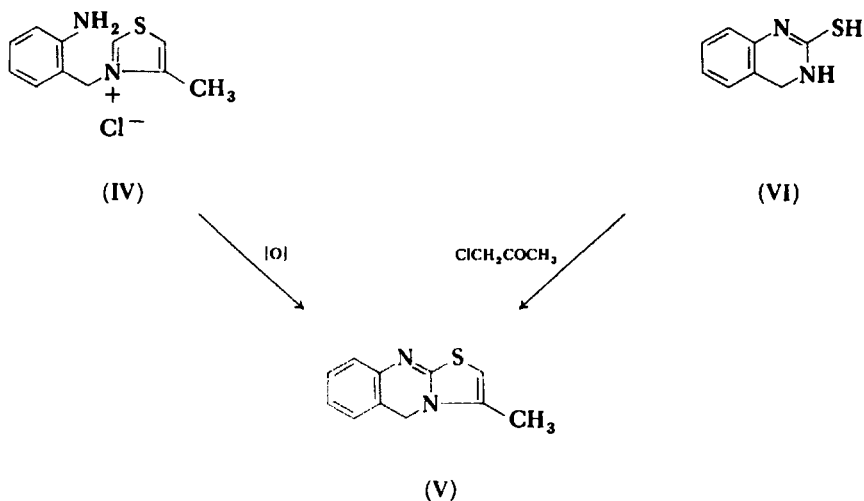


The first examples of these nuclei were prepared by Kendall and Duffin,^{1,2} who treated I with acetic anhydride and pyridine and

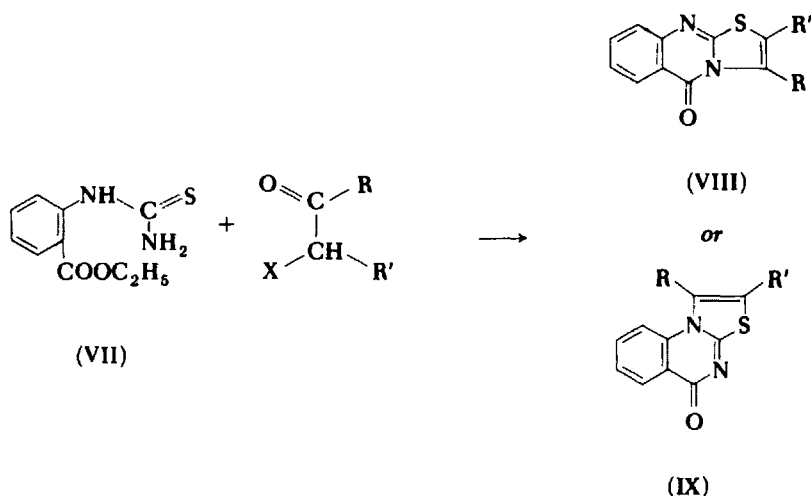
obtained a product, which could be either II or III. No precise information was given regarding this product, but it was condensed (at the cite of the methylene group) with pseudoindolium and benzothiazolium salts to yield² sensitizing dyes.



Sykes³ was unable to prepare V by the oxidation of IV with alkaline ferricyanide solutions (analogous to the preparation of thiochrome [see Section A-508] from thiamine), but the use of iodine in alkaline solution did oxidize IV to V. The structure of V was confirmed by its alternative synthesis from VI. The name *quinazolino-(2':3'-2:3)thiazole* was given to the nucleus of V.



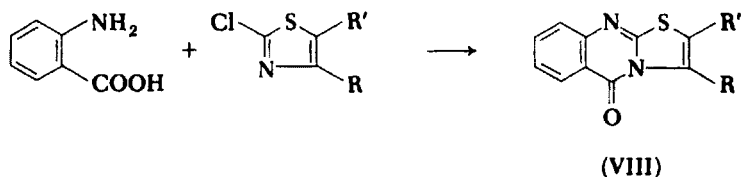
The most extensive work on these ring systems has come from Narang and his co-workers.^{4-15, 18} They found⁴⁻⁷ that 2-carbethoxyphenylthiourea (VII) condensed with α -haloketones to yield products, which were thought to have structure VIII rather than IX.



These were named,⁶ respectively, *10:11-thiopegan* and *9:10-thiopegan*. The condensation of α,β -dihalides with VII yielded^{4,5,7} the 2,3-dihydro derivatives of, presumably, VIII. The preference for structure VIII over IX was based⁷ upon an observation by Traumann¹⁴ that phenylthiourea reacted with chloracetone to yield exclusively 2-anilino-4-methylthiazole. By this reaction a number of compounds thought to be of type VIII were prepared in yields averaging about 70%. A variation of the reaction involved the condensation of α -thiocyanoketones with anthranilic esters.¹² It was not found possible,⁸ however, to obtain VIII (or IX) by cyclization of the thioalkylcarbonyl compounds prepared by condensing 2-mercaptoquinazol-4(3*H*)-one with phenacyl bromide, chloroacetic ester or bromomalonic ester. Possible mechanisms for, and intermediates in the formation of VIII and IX have been considered.⁹

In certain cases of the above reactions, two isomeric products were obtained,⁷ and the second was considered to have structure IX. The reason for the obtention of two products in only certain cases is not clear. In view of the yields reported, it is possible that the second isomer is formed but often discarded during the isolation process.

The condensation of 2-chlorothiazoles with anthranilic acid, a synthesis designed to give only the linear product (VIII), was next studied.¹⁰⁻¹⁴ The products so obtained were isomeric and not identi-



cal with the products of the first reactions (v.s.). Since the products prepared from the 2-chlorothiazoles were presumed to be linear (VIII), it was suggested¹⁰⁻¹² that the earlier products were the angular (IX) isomers. The condensation of 2-chlorobenzoic acid with 2-aminothiazoline was reported¹⁸ unsuccessful.

The condensation of anthranilic acid with allyl mustard oil yields a product thought to be 3-allyl-2-mercaptoquinazolinone¹⁶ or 2,3-dihydro-2-methylthiazolo[2,3-b]quinazolin-5-one.¹⁷ Recent work¹⁵ supports the accuracy of the first alternative.

Several compounds of types VIII and IX exhibit antimalarial activity.^{15,21}

5H-Thiazolo[3,2-a]quinazolines

Empirical formula	Substituents	Properties	Refs.
C ₁₁ H ₇ ClN ₂ OS	7-Chloro-1-methyl-5-oxo-	m. 315°.	12
C ₁₁ H ₈ N ₂ OS	1-Methyl-5-oxo-	m. 302°.	5
C ₁₂ H ₉ ClN ₂ OS	7-Chloro-1,2-dimethyl-5-oxo-	m. 227-8°.	12
C ₁₂ H ₁₀ N ₂ OS	1,2-Dimethyl-5-oxo-	m. 281°.	5
	1,7-Dimethyl-5-oxo-	m. 307-8°.	7,11
	1-Ethyl-5-oxo-	m. 282°.	5
C ₁₃ H ₁₂ N ₂ OS	1,2,7-Trimethyl-5-oxo-	m. 280°.	7
C ₁₄ H ₁₂ N ₂ O ₃ S	2-Carbethoxy-1-methyl-5-oxo-	m. 194°.	5
C ₁₆ H ₈ BrClN ₂ OS	1-(4-Bromophenyl)-7-chloro-5-oxo-	m. 352°.	12
C ₁₆ H ₈ Cl ₂ N ₂ OS	1-(4-Chlorophenyl)-7-chloro-5-oxo-	m. 340°.	12
C ₁₆ H ₉ BrN ₂ OS	1-(4-Bromophenyl)-5-oxo-	m. 263°.	12
C ₁₆ H ₉ ClN ₂ OS	7-Chloro-5-oxo-1-phenyl-	m. 320°.	12
	1-(4-Chlorophenyl)-5-oxo-	m. 268°.	5
C ₁₆ H ₉ N ₃ O ₃ S	1-(3-Nitrophenyl)-5-oxo-	m. 309°.	5
C ₁₆ H ₁₀ N ₂ OS	5-Oxo-1-phenyl-	m. 54°.	5
		(correct?).	

H-Thiazolo[3,2- α]quinazolines (*continued*)

Empirical formula	Substituents	Properties	Refs.
$C_{16}H_{10}N_2O_3S$	1-(2,4-Dihydroxyphenyl)-5-oxo-	m. 315°.	12
$C_{17}H_{11}ClN_2OS$	7-Chloro-5-oxo-1- <i>p</i> -tolyl-	m. 315°.	12
	1-(4-Chlorophenyl)-7-methyl-5-oxo-	m. 326°.	7
$C_{17}H_{11}ClN_2O_2S$	1-(4-Anisyl)-7-chloro-5-oxo-	m. 310°.	12
$C_{17}H_{12}N_2OS$	7-Methyl-5-oxo-1-phenyl-	m. 264°.	7
	1-(4-Anisyl)-5-oxo-	m. 222°.	5
$C_{18}H_{14}N_2OS$	7-Methyl-5-oxo-1- <i>p</i> -tolyl-	m. 254°.	7
$C_{18}H_{14}N_2O_2S$	1-(4-Anisyl)-7-methyl-5-oxo-	m. 244°.	7
$C_{22}H_{14}N_2OS$	5-Oxo-1,2-diphenyl-	m. 176-7°.	12

H-Thiazolo[2,3-*b*]quinazolines

Empirical formula	Substituents	Properties	Refs.
$C_{10}H_8N_2OS$	2,3-Dihydro-5-oxo-	m. 240°. HBr salt, m. 297°.	5
$C_{11}H_7BrN_2OS$	2-Bromomethyl-5-oxo-	m. 210°.	15
$C_{11}H_7ClN_2OS$	7-Chloro-3-methyl-5-oxo-	m. 160°.	10
$C_{11}H_8N_2OS$	2-Methyl-5-oxo-	m. 181°.	15
	3-Methyl-5-oxo-	m. 179°.	10
	2,3-Dihydro-2-methylene-5-oxo-	m. 202°.	15
$C_{11}H_8Br_2N_2OS$	2-Bromo-2-bromomethyl-2,3-dihydro-5-oxo-	m. 298° d.	15
$C_{11}H_9BrN_2OS$	2-Bromomethyl-2,3-dihydro-5-oxo-	m. 118°. HBr salt, m. 307° d.	15
$C_{11}H_{10}N_2OS$	2,3-Dihydro-2-methyl-5-oxo-	m. 110°. HCl salt, m. 246°.	15
	2,3-Dihydro-7-methyl-5-oxo-	m. 270°. HBr salt, m. 305°.	15
$C_{11}H_{10}N_2S$	3-Methyl-	m. 174° d. HCl salt, m. 282°.	3
$C_{12}H_9BrN_2OS$	2-Bromomethyl-7-methyl-2-oxo-	m. 250°.	19
$C_{12}H_9ClN_2OS$	7-Chloro-2,3-dimethyl-5-oxo-	m. 155°.	13

(continued)

5H-Thiazolo[2,3-*b*]quinazolines (*continued*)

Empirical formula	Substituents	Properties	Refs.
C ₁₂ H ₁₀ N ₂ OS	2,3-Dimethyl-5-oxo-	m. 172°.	10
	2,7-Dimethyl-5-oxo-	m. 180-1° (168°?)	11, 19
	3,9-Dimethyl-5-oxo-	m. 174-5°.	14
	2,3-Dihydro-7-methyl-2-methylene-5-oxo-	m. 150°. HBr salt, 323-4°.	19
C ₁₂ H ₁₀ Br ₂ N ₂ OS	2-Bromo-2-bromomethyl-2,3-dihydro-7-methyl-5-oxo-	m. 320-1°.	19
C ₁₂ H ₁₀ N ₂ O ₂ S	7-Methoxy-3-methyl-5-oxo-	m. 152°.	20
C ₁₂ H ₁₁ BrN ₂ OS	2-Bromomethyl-2,3-dihydro-7-methyl-5-oxo-	m. 129°. HBr salt, m. 322-3° d.	19
C ₁₂ H ₁₂ N ₂ OS	2,3-Dihydro-2,7-dimethyl-5-oxo-	m. 117-8°. HCl salt, m. 250°.	19
C ₁₂ H ₁₃ N ₂ OS	2,3,9-Trimethyl-5-oxo-	m. 175-6°.	14
C ₁₂ H ₁₃ N ₂ O ₂ S	7-Methoxy-2,3-dimethyl-5-oxo-	m. 160°.	20
	3-Ethyl-7-methoxy-5-oxo-	m. 143°.	20
C ₁₄ H ₁₁ ClN ₂ O ₃ S	2-Carbethoxy-7-chloro-3-methyl-5-oxo-	m. 168-9°.	13
C ₁₄ H ₁₂ N ₂ O ₃ S	2-Carbethoxy-3-methyl-5-oxo-	m. 132°.	10
C ₁₅ H ₁₄ N ₂ OS	2-Carbethoxy-3,9-dimethyl-5-oxo-	m. 173°.	14
C ₁₅ H ₁₄ N ₂ O ₄ S	2-Carbethoxy-7-methoxy-3-methyl-5-oxo-	m. 185°.	20
C ₁₅ H ₁₇ N ₃ OS	2-Diethylaminomethyl-5-oxo-	m. 145°. HCl salt, m. 250°.	19
C ₁₆ H ₈ BrClN ₂ OS	3-(4-Bromophenyl)-7-chloro-5-oxo-	m. 255°.	13
C ₁₆ H ₈ Cl ₂ N ₂ OS	3-(4-Chlorophenyl)-7-chloro-5-oxo-	m. 240°.	13
C ₁₆ H ₉ BrN ₂ OS	2-(4-Bromophenyl)-5-oxo-	m. 239-40°.	11
C ₁₆ H ₉ ClN ₂ OS	7-Chloro-3-phenyl-5-oxo-	m. 180°.	13
	2-(4-Chlorophenyl)-5-oxo-	m. 235-6°.	11
C ₁₆ H ₁₀ N ₂ OS	5-Oxo-2-phenyl-	m. 214-5°.	11
C ₁₆ H ₁₂ N ₂ OS	2,3-Dihydro-2-(or 3)-phenyl-5-oxo-	m. 235°. HBr salt, m. 300°.	5

H-Thiazolo[2,3-*b*]quinazolines (*continued*)

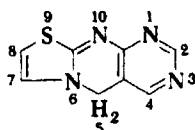
Empirical formula	Substituents	Properties	Refs.
$\text{C}_{16}\text{H}_{15}\text{N}_3\text{OS}$	2-(1-Piperidinomethyl)-5-oxo-	m. 165°. HCl salt, m. 315° d.	19
$\text{C}_{17}\text{H}_{11}\text{BrN}_2\text{OS}$	2-(4-Bromophenyl)-7-methyl-5-oxo-	m. 228-9°.	11
$\text{C}_{17}\text{H}_{11}\text{ClN}_2\text{OS}$	7-Chloro-5-oxo-3- <i>p</i> -tolyl-2-(4-Chlorophenyl)-7-methyl-5-oxo-	m. 211-2°. m. 219°.	13 11
	3-(4-Chlorophenyl)-9-methyl-5-oxo-	m. 220-1°.	14
$\text{C}_{17}\text{H}_{11}\text{BrN}_2\text{O}_2\text{S}$	3-(4-Bromophenyl)-7-methoxy-5-oxo-	m. 228°.	20
$\text{C}_{17}\text{H}_{11}\text{ClN}_2\text{O}_2\text{S}$	3-(4-Anisyl)-7-chloro-5-oxo-	m. 180°.	13
$\text{C}_{17}\text{H}_{12}\text{N}_2\text{OS}$	5-Oxo-2- <i>p</i> -tolyl-7-Methyl-5-oxo-2-phenyl-	m. 195-6°. m. 197-8°.	11 11
$\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$	7-Methoxy-3-phenyl-5-oxo-	m. 206°.	20
$\text{C}_{17}\text{H}_{17}\text{N}_3\text{OS}$	7-Methyl-2-(1-piperidinomethyl)-5-oxo-	m. 147°.	19
$\text{C}_{18}\text{H}_{14}\text{N}_2\text{OS}$	7-Methyl-5-oxo-2- <i>p</i> -tolyl-9-Methyl-5-oxo-3- <i>p</i> -tolyl-	m. 194-5°. m. 161°.	11 14
$\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$	2-(4-Anisyl)-7-methyl-5-oxo-7-Methoxy-5-oxo-3- <i>p</i> -tolyl-	m. 165°. m. 186°.	11 20
$\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$	3-(4-Anisyl)-7-methoxy-5-oxo-	m. 225°.	20

References

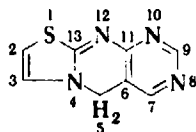
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2. Kendall and Duffin, U. S. Pat. 2,527,266; Brit. Pat. 634,952; *Chem. Abstracts*, **44**, 9287 (1950).
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A-508. Thiachromine. R.I. 1532



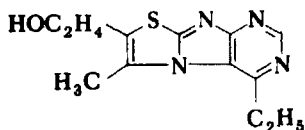
The name *thiochrome* has been given to the compound 2,7-dimethyl-8-(2-hydroxyethyl)-thiachromine, a fluorescent substance obtained from the alkaline oxidation of vitamin B₁. The alternative numbering (I) has been used. Because of its fluorescence and its bio-



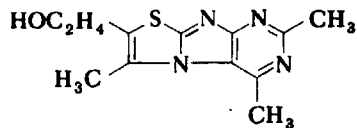
(I)

chemical interest, thiochrome has been the subject of numerous investigations, and, in the selected bibliography for this section, only references to synthetic studies have been included.

Before the correct structure (VI) for thiochrome was postulated by Todd and Bergel,¹ structures II and III had been considered.

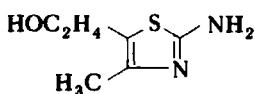


(II)



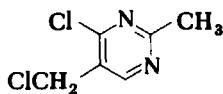
(III)

However, the product [VI, light yellow, m. 229–30°d. (225–6°); ICl salt, m. 235–6°; HI salt, d. 240°; *O*-acetyl derivative, m. 117° or 100° as the hydrate)] obtained^{2,3} from IV and V was identical with thiochrome formed by the oxidation of vitamin B₁ (VII), and the correct structure was thereby demonstrated.

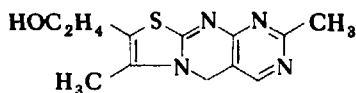


(IV)

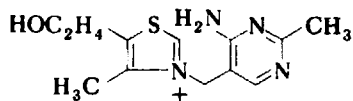
+



(V)



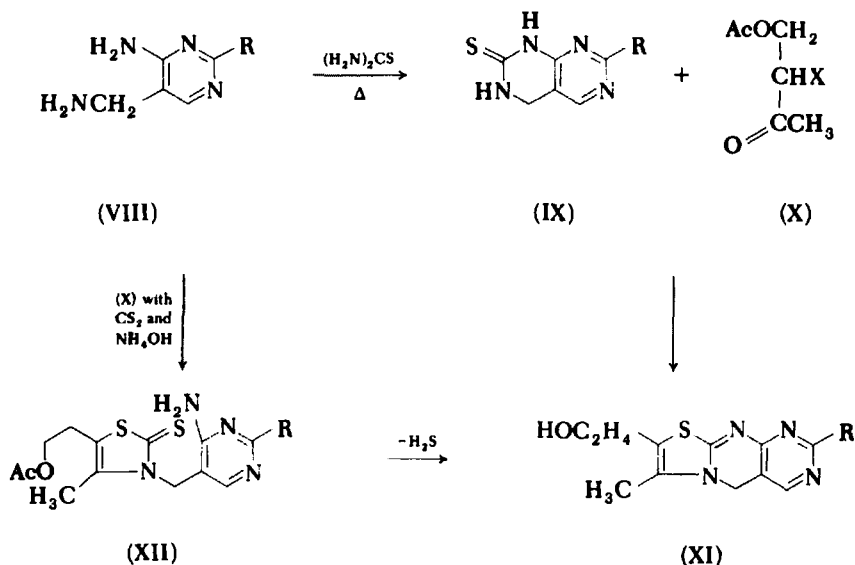
(VI)



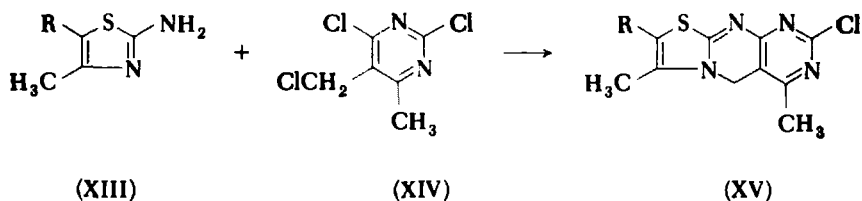
(VII)

A second, slightly different, general synthesis for this nucleus was also found by Bergel and Todd,⁴ who converted VIII (R = CH₃),

by reaction with thiourea, into IX and condensed this with X ($X = Cl$) to obtain XI ($R = CH_3$, identical with VI). In a variation of this synthesis Matsukawa and Morita⁵ obtained XI ($R = CH_3$) by reacting X ($X = SCN$) directly with VIII ($R = CH_3$). When VIII and X together were allowed to react with carbon bisulfide and ammonia, the intermediate aminothione XII was formed,⁶ which could be converted into XI by treatment with mercuric chloride⁶ or alkylating agents (e.g., C_2H_5I , $(CH_3)_2SO_4$, etc.).^{7, 15}



By these methods several thiochrome analogs of structure XI have been prepared: XI, $R = C_2H_5$, m. 192° , *O*-acetyl derivative, m. 52° ; $R = C_6H_5CH_2$, m. 198° ; $R = CH_2OH$, m. $212-5^\circ$. Similarly, by the reaction of XIII with XIV, was obtained XV ($R = H$, yellow, m. $291-2^\circ\text{d.}$; $R = HOC_2H_4$, yellow, m. $260-1^\circ\text{d.}$).

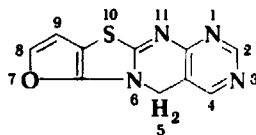


The mechanism of the oxidation of VII and its derivatives¹² to /I has been studied by Sykes and Todd^{8,9} and by Nesbitt and Sykes.¹² See Section A-509.

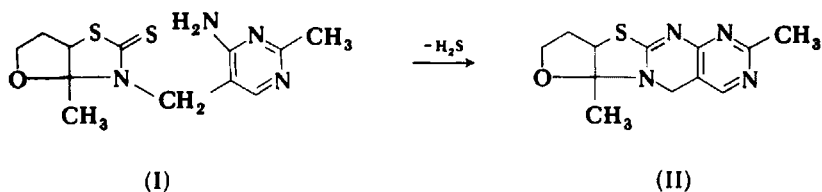
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A-509. 5*H*-Furo[2,3-*h*]thiachromine



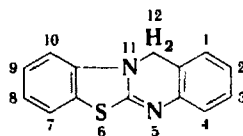
The desulfuration of I by oxidation with hydrogen peroxide, or by treatment with mercuric chloride yielded II (m. 150°d.; HCl salt, m. 194°d.; 2HCl salt, m. 230°d.).^{1,2} When II was heated with 10% aqueous hydrochloric acid, thiochrome was produced through fission of the furan ring. (See Section A-508).



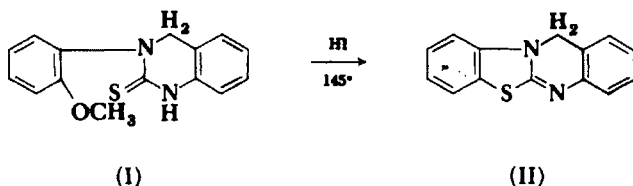
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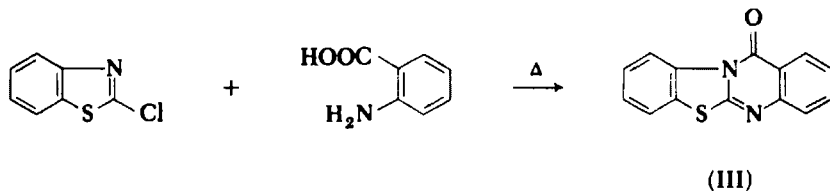
A-510. 12*H*-Benzo[*d*]quinazo[2,3-*b*]-thiazole. R.I. 2368



Busch and Birk¹ heated I in a sealed tube and isolated a product to which they assigned structure II. A more convenient synthesis



of this nucleus was found by Bose and Pathak,² who condensed 2-chlorobenzothiazoles with anthranilic acid and obtained III. Treat-



ment of III with nitric and sulfuric acids introduced two nitro groups into unspecified positions.

Derivatives of 12*H*-Benzo[*d*]quinazo[2,3-*b*]thiazole

Empirical formula	Substituents	Properties	Refs.
${}_{14}\text{H}_6\text{N}_4\text{O}_3\text{S}$	α,α -Dinitro-12-oxo-	Yel., m. 279°.	2
${}_{14}\text{H}_8\text{N}_2\text{OS}$	12-Oxo-	m. 193° (189°).	1,3
${}_{14}\text{H}_{10}\text{N}_2\text{S}$	Unsubstituted	m. 160–1°. Chloroplatinate, 1 or., m. > 280°.	1
${}_{15}\text{H}_8\text{N}_4\text{O}_3\text{S}$	8-Methyl- α,α -dinitro-12-oxo-	Yel., m. 280°.	2
${}_{15}\text{H}_9\text{N}_3\text{O}_3\text{S}$	8-Methyl- α -nitro-12-oxo-	Yel., m. 304°.	2
${}_{15}\text{H}_{10}\text{N}_2\text{OS}$	8-Methyl-12-oxo-	m. 226°.	2
	9-Methyl-12-oxo-	m. 180°.	2
${}_{15}\text{H}_{10}\text{N}_2\text{O}_3\text{S}_2$	3-Methylsulfonyl-12-oxo-	m. 256°.	4

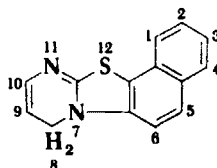
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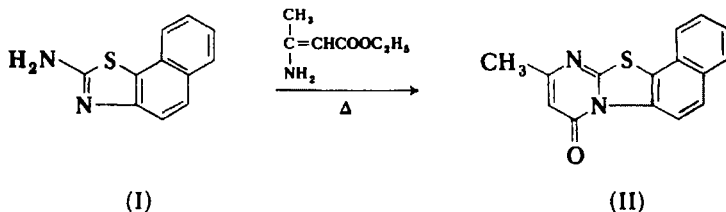
Bose and Pathak, *J. Indian Chem. Soc.*, **11**, 463 (1934); *Chem. Zentr.*, **II**, 3255 (1934); *Chem. Abstracts*, **29**, 165 (1935).

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Katz, Karger, Schroeder and Cohen, *J. Org. Chem.*, **18**, 1380 (1953).

-511. 8*H*-Naphtho[2,1-*d*]pyrimido-[2,1-*b*]thiazole

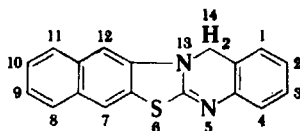
The condensation of I with ethyl β -aminocrotonate was found¹ to yield II (m. 207°), which was named 4,11-dihydro-4-keto-2-methyl-8-benzo-1:11-diaza-9-thiafluorene.



Reference

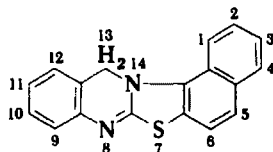
Antaki and Petrov, *J. Chem. Soc.*, **1951**, 551.

**A-512. 14H-Naphtho[2,3-d]quinazo-
[2,3-b]thiazole. R.I. 3032**

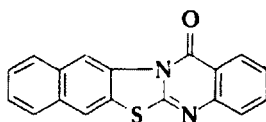


and

**A-513. 13H-Naphtho[1',2',4,5]thiazolo-
[2,3-b]quinazoline***

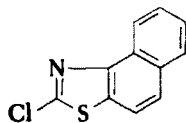


From a material which they called "1-chloro- α -naphthothiazole (m.p. 75°)," Bose and Pathak¹ prepared, by condensation with anthranilic acid, a product (m. 261°) to which they assigned structure I, but which they named α -naphthothiazoloneyl quinazoline. The

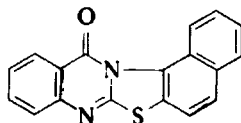
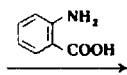


(I)

inconsistency here is apparent, but a further difficulty arises in trying to identify the 2-chloronaphthothiazole employed initially. None melting at 75° has been reported, the closest being II, which melts at 80°, and which, upon condensation with anthranilic acid, would lead to III. It therefore seems probable that Bose and Pathak's prod-



(II)

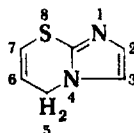


(III)

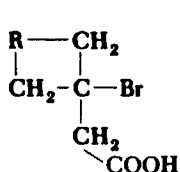
uct is III instead of I, and there are, consequently, no examples of the first ring system. The erroneous linear formula, however, has found its way into the *Ring Index* as well as all of the abstract journals.

Reference

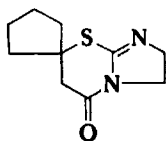
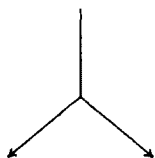
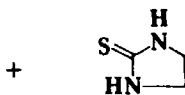
1. Bose and Pathak, *J. Indian Chem. Soc.*, **11**, 463 (1934); *Chem. Abstracts*, **29**, 165 (1935); *Chem. Zentr.*, **II**, 3255 (1934); *British Chem. Abstracts*, **A**, 1116 (1934).

A-514. 5*H*-Imidazo[2,1-*b*]-*m*-thiazine*

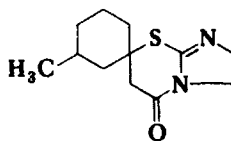
Two products, II (m. 90–1°) and III (m. 80–2°) were obtained¹ from the condensation of ethylenethiourea with halocycloalkaneacetic acids of type I ($R = \text{CH}_2\text{CH}_2-$ and $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)-$, respectively).



(I)



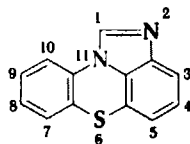
(II)



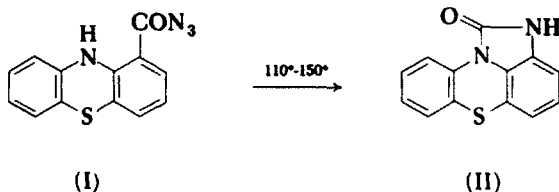
(III)

Reference

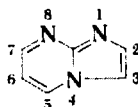
1. Wheeler, Seyler and Van Campen, U. S. Pat. 2,772,268.

A-515. Imidazo[4,5,1-kl]phenothiazine

Thermal rearrangement of the azide I is reported¹ to yield II (m. 289–90°).

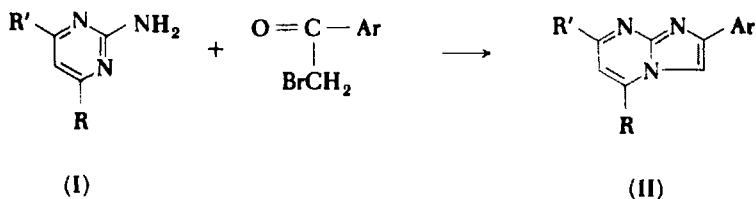
*Reference*

1. Savitskaya and Shchukina, *Zhur. Obshch. Khim.*, **24**, 152 (1954); *Chem. Abstracts*, **49**, 3202 (1955).

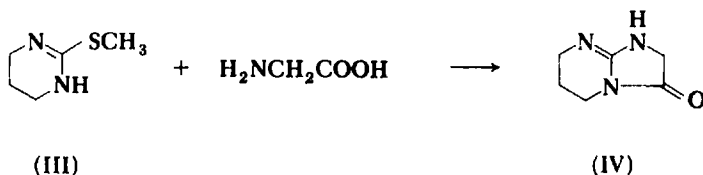
**A-516. Imidazo[1,2-a]pyrimidine.
R.I. 756**

The names *1,4,8-pyrimidazole*, *aza-8-pyrimidazole*, *pyrimidino-2,3:2',-3'-imidazole* and *3,4-diazaindolizine* are also encountered.

The reaction of 2-aminopyrimidines (I) with phenacyl halides has been utilized^{1,2,3,15} to prepare a number of products of type II. When I with R = H or CH₃ and R' = OH or H was used, the products were assigned structure II (R = H or CH₃, R' = OH or H) rather than the alternative structure (II, R = OH or H, R' = H or CH₃).

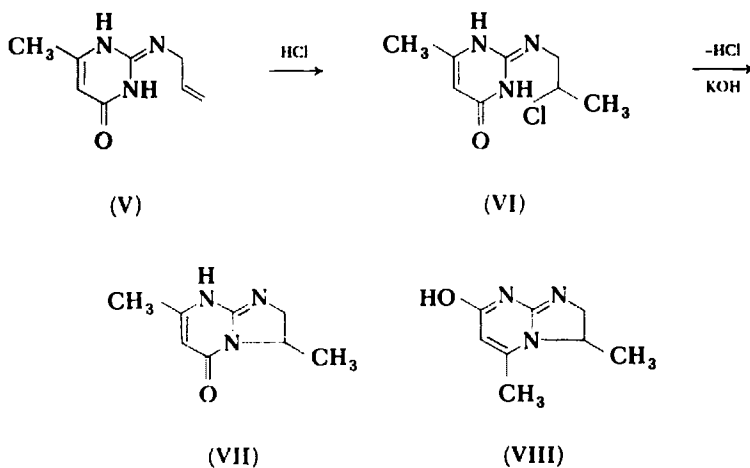


Condensation of III with glycine yielded⁴ IV, isolable as the picrate, but which underwent scission of the lactam linkage upon at-



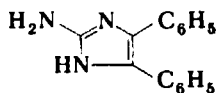
tempted recrystallization. This instability is reminiscent of that manifested by imidazo[1,2-*a*]pyrid-3(2*H*)-one (see Section A-271).

Majima condensed⁵ allylguanidine with acetoacetic ester and obtained V, which added hydrogen chloride to give VI. Dehydrochlorination of VI with alcoholic potash yielded the so-called *γ-Körper*, which was assigned structure VII. However, structure VIII would seem to be an alternative possibility. The only authentic 7-mono-

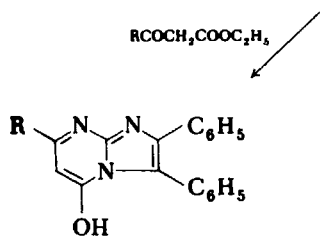


hydroxy derivative appears to be X, obtained⁶ by reacting IX with ethoxymethylenemalonate. 5-Monohydroxy derivatives (XI) have been obtained^{7,8} similarly by condensing 2-aminoimidazoles (such as IX) with β -ketoesters.

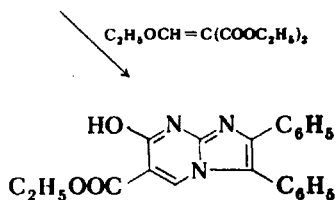
Prokof'ev and his co-workers found⁹⁻¹¹ that guanidine acids such as XII may be converted directly into XIV, or may first be cyclized to the 2-amino-4-imidazolinone (XIII) and this condensed



(IX)

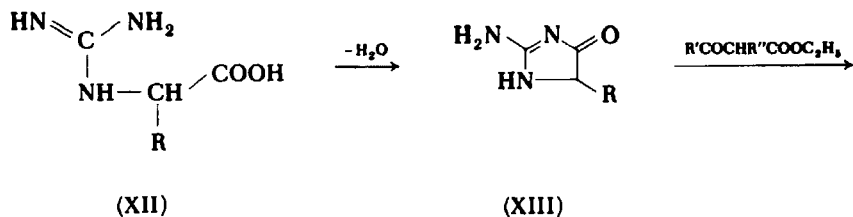


(XI)



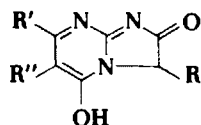
(X)

with a β -ketoester to yield XIV. The use of malonic esters leads to XIV in which $R' = OH$. Dehydrohalogenation of XV was reported⁹



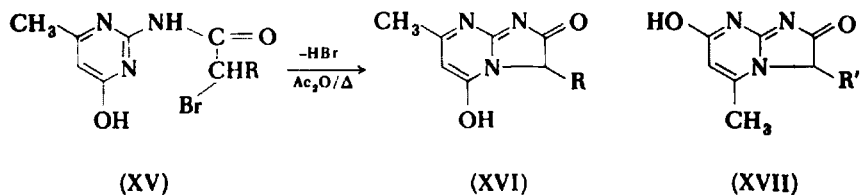
(XII)

(XIII)



(XIV)

to yield XVI when $R = C_2H_5$, but a mixture¹² of XVI and XVII when $R = CH_3$.

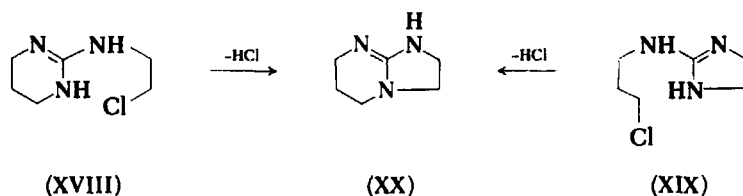


(XV)

(XVI)

(XVII)

The same hexahydro compound (XX) was obtained¹⁸ by the dehydrochlorination of either XVIII or IX, and treatment of XX with nitric acid yielded the 1-nitro derivative.



Some of these products may find an application in photography,^{7,13} and others have been examined¹⁴ for tuberculostatic activity. A number of derivatives of this nucleus have been claimed¹⁷ as optical bleaches for use in the whitening of various textile fibers. The ultraviolet absorption spectra of several hydroimidazo[1,2-*a*]-pyrimidinones have been reported.²⁰

Imidazo[1,2-*a*]pyrimidines

Empirical formula	Substituents	Properties	Refs.
C ₆ H ₅ N ₃ O ₃	2,5,7-Trihydroxy-	d. when heated.	10
C ₆ H ₉ N ₃ O	1,2,3,5,6,7-Hexahydro-3-oxo-	Unstable. Picrate, m. 155.0–5.4°.	4
C ₆ H ₁₁ N ₃	1,2,3,5,6,7-Hexahydro-	b _{0.1} 103–5°; m. 64–5°. Picrate, m. 238°.	18
C ₆ H ₁₀ N ₄ O ₂	1,2,3,5,6,7-Hexahydro-1-nitro-	Nitrate, m. 100–1°. Picrate, m. 144.0–4.5°.	18
C ₇ H ₇ N ₃ O ₂	2,5-Dihydroxy-7-methyl-	m. 310°.	9
C ₇ H ₇ N ₃ O ₃	2,5,7-Trihydroxy-3-methyl-	m. 225°.	11
C ₇ H ₉ N ₃ O	2,3-Dihydro-5-hydroxy-7-methyl-	m. 228–30° (> 275°?).	7,8
C ₈ H ₉ N ₃ O ₂	2,5-Dihydroxy-3,7-dimethyl-	m. 283° (282°) d. K ⁺ salt, m. 360°. Ag ⁺ salt, d. 290°.	9,11,12, 16
	2,5-Dihydroxy-6,7-dimethyl-	m. 289–90° d.	10
	2,7-Dihydroxy-3,5-dimethyl-	m. 221–3°.	12
	2,3,7,8-Tetrahydro-5,8-dimethyl-2,7-dioxo-	m. 261–2°.	12

(continued)

Imidazo[1,2-*a*]pyrimidines (*continued*)

Empirical formula	Substituents	Properties	Refs.
$C_8H_9N_3O_3$	6-Ethyl-2,5,7-trihydroxy-	m. 292-3° d.	10
$C_8H_{11}N_3O$	2,3-Dihydro-5-hydroxy-3,7-dimethyl-	m. 184-5°. Picrate, m. 200-1°.	5
$C_9H_{11}N_3O_2$	3-Ethyl-2,5-dihydroxy-7-methyl-	m. 213°.	9
	6-Ethyl-2,5-dihydroxy-7-methyl-	m. 261-2° d.	10
	2,3,7,8-Tetrahydro-3,5,8-trimethyl-2,7-dioxo-	m. 187-9°.	12
$C_9H_{11}N_3O_3$	6-Ethyl-2,5,7-trihydroxy-3-methyl-	d. 290-1°.	11
$C_{10}H_{13}N_3O_2$	6-Ethyl-2,5-dihydroxy-3,7-dimethyl-	m. 263°. K^+ salt, d. 243°.	11,16
	3-Ethyl-2,3,7,8-tetrahydro-5,8-dimethyl-2,7-dioxo-	m. 158-60°.	12
$C_{10}H_{13}N_3O_3$	6-Butyl-2,5,7-trihydroxy-	m. 278° d.	10
$C_{11}H_{15}N_3O_2$	6-Butyl-2,5-dihydroxy-7-methyl-	m. 252°.	11
$C_{11}H_{15}N_3O_2$	6-Ethyl-5-hydroxy-1,3,7-trimethyl-2(1 <i>H</i>)-oxo-	m. 160°.	16
$C_{11}H_{15}N_3O_3$	6-Butyl-2,5,7-trihydroxy-3-methyl-	m. 228°.	11
$C_{12}H_7Cl_2N_3$	2-(3,4-Dichlorophenyl)-	m. 286°.	15
$C_{12}H_8BrN_3$	2-(4-Bromophenyl)-	m. 279°.	15
$C_{12}H_8ClN_3$	2-(4-Chlorophenyl)-	m. 274°.	15
$C_{12}H_8FN_3$	2-(4-Fluorophenyl)-	m. 238°.	15
$C_{12}H_8N_4O_2$	2-(4-Nitrophenyl)-	m. > 370°.	2,3
$C_{12}N_9N_3$	2-Phenyl-	m. 202°.	15
$C_{12}H_{10}N_4$	2-(4-Aminophenyl)-	m. 264°. Picrate, d. 223°.	2,3
$C_{12}H_{11}N_3O$	2,3-Dihydro-5-hydroxy-7-phenyl-	m. 262-3°.	8
$C_{12}H_{17}N_3O_2$	6-Butyl-2,5-dihydroxy-3,3,7-dimethyl-	m. 229°.	11
$C_{13}H_{10}BrN_3O$	2-(3-Bromo-4-anisyl)-	m. 232°.	15
	2-(3-Bromo-2-hydroxy-4-tolyl)-	m. 264°.	15
$C_{13}H_{10}N_4O_2$	5-Methyl-2-(4-nitrophenyl)-	d. 317°.	2,3

Imidazo[1,2-a]pyrimidines (*continued*)

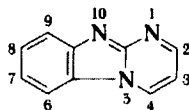
Empirical formula	Substituents	Properties	Refs.
C ₁₃ H ₁₀ N ₄ O ₃	7-Hydroxy-5-methyl-2-(4-nitrophenyl)-	m. > 370°.	2,3
C ₁₃ H ₁₁ N ₃	5-Methyl-2-phenyl-	m. 223-4°. HBr salt, d. 260-1°. Picrate, d. 239.0-40.5°. HCl salt, d. 240-3°.	1
C ₁₃ H ₁₁ N ₃ O ₃	2,5,7-Trihydroxy-3-methyl-6-phenyl-	d. 315°.	11
C ₁₃ H ₁₂ N ₄	2-(4-Aminophenyl)-5-methyl-	m. 298°. Picrate, d. 235-6°.	2,3
C ₁₃ H ₁₂ N ₄ O	2-(4-Aminophenyl)-7-hydroxy-5-methyl-	m. > 300°. Picrate, d. 253-4°.	2,3
C ₁₄ H ₈ N ₄ O ₅	2,5,7-Trihydroxy-6-phthalimido-	d. when heated.	10
C ₁₄ H ₁₁ N ₄ O	2-(4-Acetaminophenyl)-	m. 302°.	2,3
C ₁₄ H ₁₃ N ₃	2-(3,4-Dimethylphenyl)-	m. 181°.	15
C ₁₅ H ₁₄ N ₄ O	2-(4-Acetaminophenyl)-5-methyl-	m. 300°.	2,3
C ₁₅ H ₁₄ N ₄ O ₂	2-(4-Acetaminophenyl)-7-hydroxy-5-methyl-	m. > 370°.	2,3
C ₁₆ H ₁₀ FN ₂	2-(4-Fluoro-1-naphthyl)-	m. 158°.	19
C ₁₉ H ₁₃ N ₃ O	5-Hydroxy-7-methyl-2,3-diphenyl-	m. 309°.	8
C ₂₁ H ₁₇ N ₃ O ₃	6-Carbethoxy-7-hydroxy-2,3-diphenyl-	m. 304-5°.	6

References

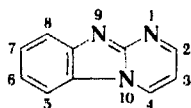
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10. Prokof'ev and Shvachkin, *Zhur. Obshchei Khim.*, **24**, 1046 (1954); *Chem. Abstracts*, **49**, 9661 (1955).
11. Prokof'ev and Shvachkin, *Zhur. Obshchei Khim.*, **25**, 975 (1955); *Chem. Abstracts*, **50**, 3458 (1956).
12. Antonovich and Prokof'ev, *Vestnik Moskov. Univ.*, 10, No. 3; *Ser. Fiz.-Mat. i Estesven. Nauk*, No. 2, 57 (1955); *Chem. Abstracts*, **49**, 10972 (1955).
13. Birr, *Z. wiss. Phot.*, **47**, 2 (1952).
14. Matsukawa and Ban, *J. Pharm. Soc. Japan*, **72**, 884 (1952); *Chem. Abstracts*, **47**, 6410 (1953).
15. Buu-Hoi and Xuong, *Compt. rend.*, **243**, 2090 (1956).
16. Shvachkin and Prokof'ev, *Zhur. Obshchei Khim.*, **26**, 3416 (1956); *Chem. Abstracts*, **51**, 9628 (1957).
17. Craig, U. S. Pat. 2,785,133.
18. McKay and Kreling, *Can. J. Chem.*, **35**, 1438 (1957).
19. Buu-Hoi, Xuong and Yen, *J. Org. Chem.*, **23**, 539 (1958).
20. Prokof'ev, Antonovich and Shvachkin, *Vestnik Moskov. Univ., Ser. Mat. Mekh., Astron., Fiz., Khim.*, **12**, No. 3, 199 (1957); *Chem. Abstracts*, **52**, 9145 (1958).

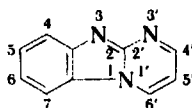
A-517. Pyrimido[1,2-*a*]benzimidazole.
R.I. 1565



The names *1,9,11-triazafluorene*, *benzimidpyrimidine* (I) and *pyrimidino-1',2':1,2-benzimidazole* (II) also have been used.

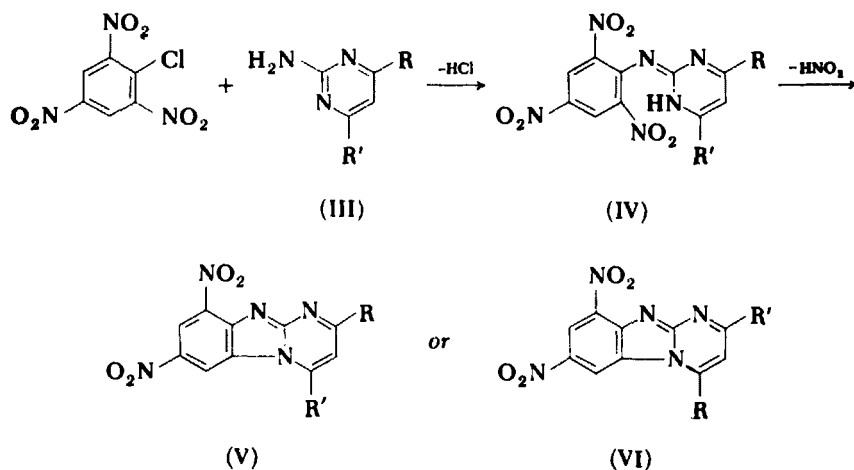


(I)

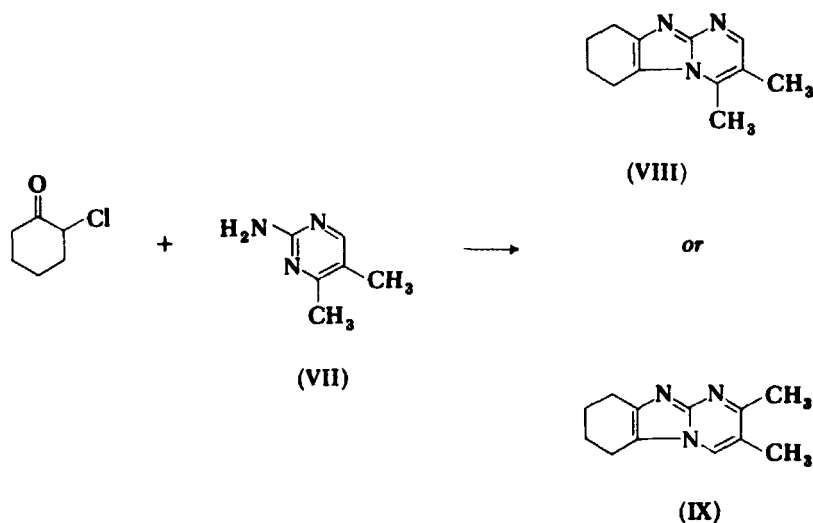


(II)

In a reaction analogous to Morgan and Stewart's synthesis of pyrido[1,2-*a*]benzimidazoles (see Section A-274), 2-aminopyrimidines (III) have been condensed with picryl chloride to yield pyrimido[1,2-*a*]benzimidazoles. The reaction proceeds via IV, and might, therefore, yield either V or VI. The former structure was assigned by Ochiai and Yani¹ (who, however, admitted the alternative possibility), while the latter was used without comment by Berg and Petrov.² Efforts² to replace picryl chloride by 2,4-dinitrobromobenzene in the condensation with III (R = H, R' = CH₃) were unsuccessful.

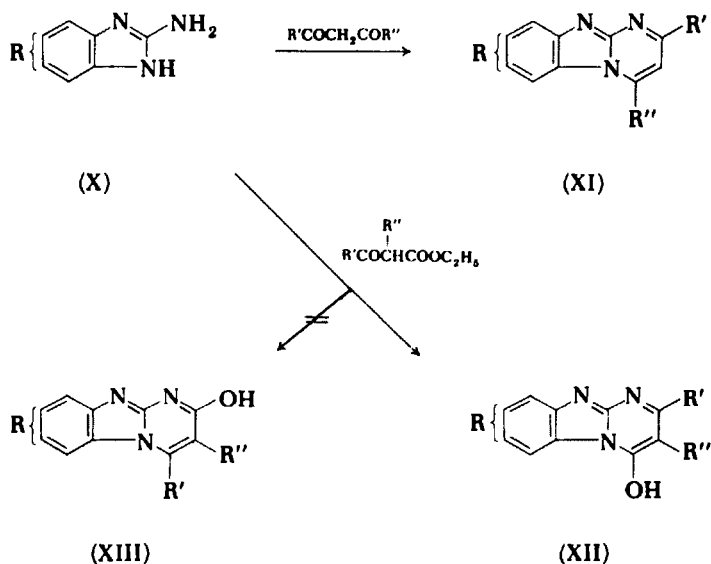


Reitmann³ condensed VII with 2-chlorocyclohexanone and obtained a product assigned structure VIII, but again, IX would seem to be an alternative possibility.



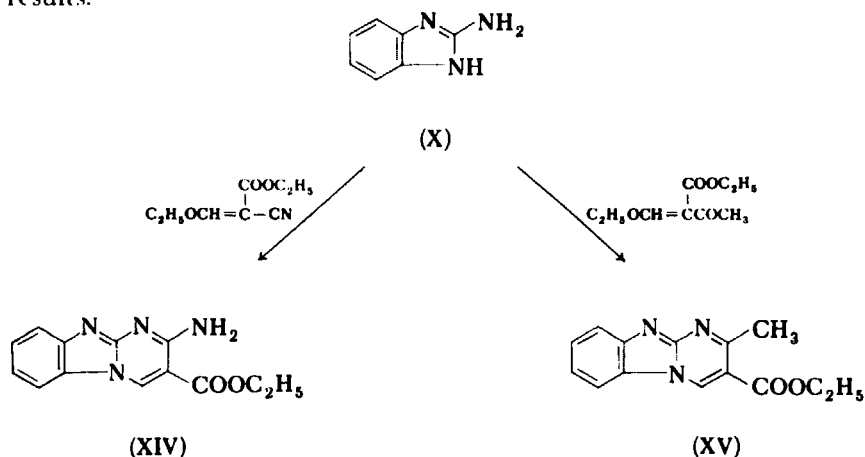
A convenient synthesis of this nucleus was found^{4,5} in the condensation of 2-aminobenzimidazoles (X) with β -diketones. Here again, however, the precise structure of several of the products has not been demonstrated conclusively. For example, the product derived from X ($R = H$) and benzoylacetone was assigned⁵ struc-

ture XI ($R = H$, $R' = CH_3$ and $R'' = C_6H_5$), while that from X ($R = H$) and acetoacetaldehyde or 4,4-dimethoxy-2-butanone¹⁶ was written as XI ($R = R'' = H$, $R' = CH_3$). No reference was made to the possible alternative structures. Similarly, products derived from X ($R = NO_2$, OCH_3 or OC_2H_5) were arbitrarily considered⁵ to be 8-substituted derivatives of XI ($R = NO_2$, OCH_3 or OC_2H_5 , $R' = R'' = CH_3$), although the 7-position must also be considered.



The formation of XI from X is very similar to the older preparation of XII from X by its reaction with β -ketoesters. Although two possible products (XII and XIII) might be formed, structure XII was preferred⁶ initially, and there seems no reason to doubt its correctness.⁷ Numerous compounds of structure XII have thus been prepared.⁶⁻¹¹ Bromination of XII ($R = R'' = H$, $R' = CH_3$) yields⁶ the 3,3-dibromo derivative. In the reaction with X, β -ketonitriles^{8,9} or β -iminonitriles⁷ may be substituted for the β -ketoester, with the result that 4-amino instead of 4-hydroxy derivatives of type XII are produced. The reaction of X ($R = H$) with diethylmalonyl chloride yields¹² 3,3-diethyl-1,2,3,4-tetrahydropyrimido-[1,2-a]benzimidazole-2,4-dione, and the condensation of X with azoacetoacetic esters is claimed¹³ to yield yellow dyes of type XII, where $R'' =$ an azoarylsulfonic acid group.

The reaction of X with various β -ethoxymethylene esters and nitriles¹⁴ produces pyrimido[1,2-*a*]benzimidazoles substituted in the 2 and 3 positions. For example, with ethoxymethylene malonic ester, the 2-hydroxy-3-carbethoxy compound is formed, and with ethoxymethylenemalononitrile, the 2-amino-3-cyano-derivative results. With α -acetyl- β -ethoxyacrylic ester, XV rather than the 3-acetyl-2-hydroxy compound is produced,¹⁴ while with α -cyano- β -ethoxyacrylic ester, XIV rather than the 3-cyano-2-hydroxy derivative results.



Some of these products have been examined^{15, 16, 17} as photographic fog-inhibitors.

Pyrimido[1,2-*a*]benzimidazoles

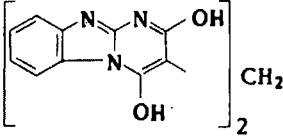
Empirical formula	Substituents	Properties	Refs.
$\text{C}_{10}\text{H}_5\text{N}_5\text{O}_4$	7,9-Dinitro-	m. 196° d.	1
$\text{C}_{10}\text{H}_7\text{N}_3\text{O}_2$	2,4-Dihydroxy-	Yel., m. $> 340^\circ$ ($> 280^\circ$).	5,9
$\text{C}_{10}\text{H}_8\text{N}_4\text{O}$	4-Amino-2-hydroxy-	m. $211-2^\circ$.	8
$\text{C}_{10}\text{H}_9\text{N}_5$	7,9-Diamino-	Grn., m. $> 300^\circ$.	2
$\text{C}_{11}\text{H}_7\text{Br}_2\text{N}_3\text{O}$	3,3-Dibromo-3,4-dihydro-2-methyl-4-oxo-	m. $> 300^\circ$.	6
$\text{C}_{11}\text{H}_7\text{N}_5$	2-Amino-3-cyano-	m. $> 350^\circ$.	14

(continued)

Pyrimido[1,2-*a*] benzimidazoles (*continued*)

Empirical formula	Substituents	Properties	Refs.
C ₁₁ H ₇ N ₃ O ₄	4-(2-?)-Methyl-7,9-dinitro-	m. > 300°.	1
C ₁₁ H ₈ ClN ₃ O	7- or 8-Chloro-4-hydroxy-2-methyl-	m. 312-6°.	9
C ₁₁ H ₈ N ₆ O ₄	2-Amino-4-methyl-7,9-dinitro-	m. > 330°. Acetyl deriv., m. 323-5° d.	1
C ₁₁ H ₉ N ₃	2-Methyl-	Yel., m. 229° (233°).	5,16
C ₁₁ H ₉ N ₃ O	4-Hydroxy-2-methyl-	m. 294° d. (280°; > 280°; 292°; 293-4°; 306-8°).	5-11,15
C ₁₁ H ₁₀ N ₄	4-Amino-2-methyl-	m. > 300°.	7
C ₁₁ H ₁₁ N ₅	7,9-Diamino-2-methyl-	Yel., m. > 300°.	2
C ₁₁ H ₁₂ N ₆	4,7,9-Triamino-2-methyl-	Yel., m. > 300°.	2
C ₁₂ H ₈ N ₄ O	3-Cyano-4-hydroxy-2-methyl-	m. 293-5°.	9
C ₁₂ H ₁₀ N ₄ O ₂	2,4-Dimethyl-8 (or 7)-nitro-	Yel. d. without m. > 260°.	5
C ₁₂ H ₁₁ N ₃	2,4-Dimethyl-	m. 231-2°. Complex with 2 moles of 2-aminobenzimidazole, m. 242-3°.	5
C ₁₂ H ₁₁ N ₃ O	4-Hydroxy-2,3-dimethyl-	m. > 330°.	9
C ₁₂ H ₁₁ N ₃ O ₂	3-Ethyl-2,4-dihydroxy-	m. 284-5°.	9
C ₁₂ H ₁₂ N ₄	4-Amino-2,3-dimethyl-	m. > 300°. HCl salt, m. 325-30°.	8,9
C ₁₂ H ₁₅ N ₃	6,7,8,9-Tetrahydro-2,3- (or 3,4)-dimethyl-	m. 186°.	3
C ₁₃ H ₁₀ ClN ₃ O ₃	3-Carbethoxy-7 or 8-chloro-2-hydroxy-	m. > 350°.	14
C ₁₃ H ₁₁ N ₃ O ₃	3-Carbethoxy-2-hydroxy-	m. 270-1°.	14
C ₁₃ H ₁₁ N ₃ O ₄	3-Carbethoxy-2,4-dihydroxy-	m. > 330°.	8,9
C ₁₃ H ₁₂ N ₄ O ₂	2-Amino-3-carbethoxy-	m. 248-50°.	14
C ₁₃ H ₁₃ N ₃ O	3-Ethyl-4-hydroxy-2-methyl-7 (or 8)-Methoxy-2,4-dimethyl-	m. 284° d. (285°).	7,11,15
C ₁₄ H ₉ N ₃ O ₂	2-(2-Furyl)-4-hydroxy-	m. 197°.	5
C ₁₄ H ₁₃ N ₃ O ₂	3-Carbethoxy-2-methyl-	m. 318-20°.	8,9
C ₁₄ H ₁₃ N ₃ O ₃	2-Carbethoxymethyl-4-hydroxy-	m. 210-2°.	14
C ₁₄ H ₁₄ N ₃ O ₂	3,3-Diethyl-1,2,3,4-tetrahydro-2,4-dioxo-	m. 202-4°.	9
C ₁₄ H ₁₄ N ₃ O ₂	3,3-Diethyl-1,2,3,4-tetrahydro-2,4-dioxo-	m. 243°.	12
C ₁₄ H ₁₅ N ₃ O	7 (or 8)-Ethoxy-2,4-dimethyl-4-Hydroxy-2-methyl-3- <i>i</i> -propyl-	Pale yel., m. 204°.	5
		m. 294°.	7

Pyrimido[1,2-*a*]benzimidazoles (*continued*)

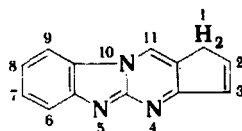
Empirical formula	Substituents	Properties	Refs.
C ₁₅ H ₁₇ N ₃ O ₃	3-Ethoxy-2-ethoxymethyl-4-hydroxy-	m. 223–5°.	9
C ₁₆ H ₁₁ N ₃ O	4-Hydroxy-2-phenyl- 4-Hydroxy-3-phenyl-	m. 315–7° (309–11°). m. 295–8°.	9,10 9
C ₁₆ H ₁₂ N ₄	4-Amino-2-phenyl-	m. > 330° (> 300°).	7,9
C ₁₇ H ₁₃ N ₃	2-Methyl-4-phenyl-	Yel., m. 173°. Complex with 2 moles of 2-aminobenzimidazole, m. 243°.	5
C ₂₁ H ₁₄ N ₆ O ₄		m. > 300°.	9
C ₂₁ H ₁₅ N ₃ O ₂	3-Benzoylmethyl-4-hydroxy-2-methyl-	m. 286–8°.	9

References

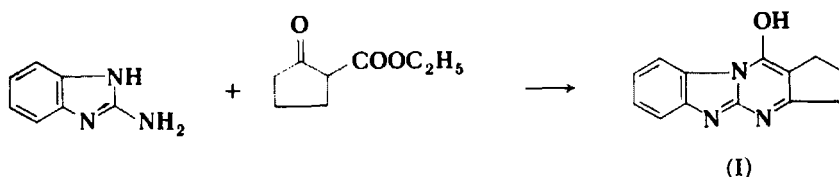
- Ochiai and Yanai, *J. Pharm. Soc. Japan*, **60**, 493 (in Japanese) or 192 (in German) (1940); *Brit. Chem. Abstracts*, **AII**, 337 (1941); *Chem. Abstracts*, **35**, 743 (1941).
- Berg and Petrov, *J. Chem. Soc.*, **1952**, 784.
- Reitmann, Ger. Pat. 547,985; *Frdl.*, **18**, 2782 (1933). U. S. Pat. 2,057,978. Brit. Pat. 360,027.
- Delfs, *Überblick über die Entwicklung der Zwischenprodukten-Chemie in der I.G. in den letzten 10 Jahren*; *PB Report No.* 5213, frames 314–5.
- Henecka, Ger. Pat. 641,598; *Frdl.*, **23**, 270 (1940).
- Crippa and Perroncito, *Gazz. chim. ital.*, **65**, 1067 (1935).
- Antaki and Petrov, *J. Chem. Soc.*, **1951**, 551.
- DeCat, VanDormael and DeSmet, Ger. Pat. 813,088.
- DeCat, and Van Dormael, *Bull. soc. chim. Belges*, **59**, 573 (1950).
- Ridi and Checchi, *Ann. chim. (Rome)*, **44**, 28 (1954); *Chem. Abstracts*, **49**, 4658 (1953).
- Murobushi, Kuwabara, Baba and Aoki, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **58**, 440 (1955); *Chem. Abstracts*, **49**, 14544 (1955).
- Crippa and Perroncito, *Gazz. chim. ital.*, **65**, 38 (1935).
- Heimbach, U. S. Pat. 2,432,419. Ger. Pat. 882,883.
- DeCat and VanDormael, *Bull. soc. chim. Belges*, **60**, 69 (1951).

15. Kuwabara and Aoki, *Konishiroku Rev.*, **6**, 1 (1955); *Chem. Abstracts*, **49**, 11473 (1955).
16. Burness, U. S. Pat. 2,837,521.
17. Kikuchi and Akiba, *J. Soc. Sci. Phot. (Japan)*, **18**, 20 (1955); *Chem. Abstracts*, **50**, 2331 (1956).

A-518. 1*H*-Cyclopenta[4,5]pyrimido-[1,2-*a*]benzimidazole



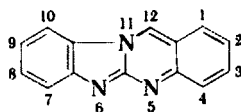
The condensation of 2-aminobenzimidazole with 2-carbethoxycyclopentanone is reported^{1,2,3} to yield I (m. 310-2°,¹ 297-8°² or 304°³), which was named³ *4,11-dihydro-2,3-cyclopenteno-1:9:11-triazafluorene*.



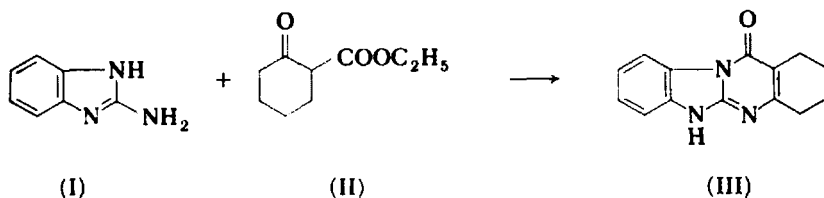
References

1. De Cat and Van Dormael, *Bull. soc. chim. Belges*, **59**, 573 (1950); *Chem. Abstracts*, **45**, 10247 (1951).
2. De Cat, Van Dormael and De Smet, Ger. Pat. 813,088.
3. Antaki and Petrov, *J. Chem. Soc.*, **1951**, 551.

A-519. Benzimidazo[2,1-*b*]quinazoline



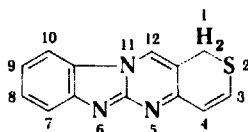
Antaki and Petrov prepared¹ III (m. 296°; methiodide, d. $\approx 228^\circ$) as shown from I and II, and called it *4,11-dihydro-4-keto-2,3-cyclohexeno-1:9:11-triazafluorene*.



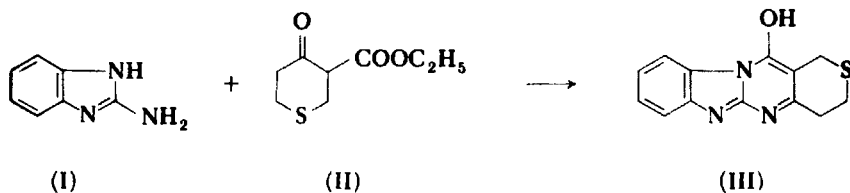
Reference

1. Antaki and Petrov, *J. Chem. Soc.*, **1951**, 551.

A-520. 1*H*-Thiapyrano[4',3',4,5]-pyrimido[1,2-*a*]benzimidazole



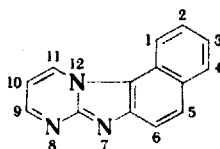
The condensation of I with II is reported¹ to yield III (m. > 300°).



Reference

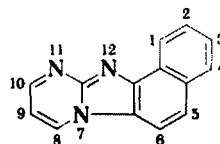
1. De Cat and Van Dormael, *Bull. soc. chim. Belges*, **59**, 573 (1950); *Chem. Abstracts*, **45**, 10247 (1951).

A-521. Naphtho[2,1-*d*]pyrimido[1,2-*a*]imidazole



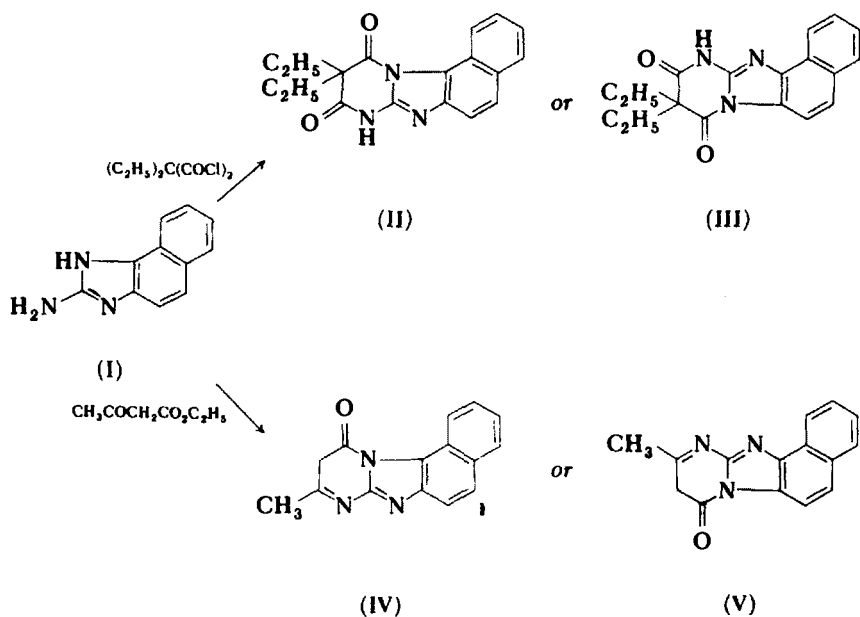
and

A-522. Naphtho[1,2-*d*]pyrimido[1,2-*a*]imidazole*

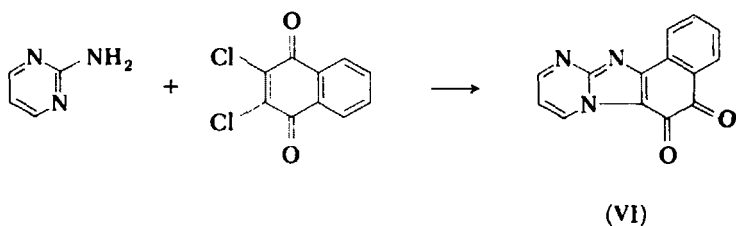


The reaction of I with diethylmalonyl chloride, and with acetoacetic ester yielded two products (m. 204° and 315°, respectively), which, provisionally, were assigned¹ structures II and IV, although III and V remain possibilities. An orange-red azo dye, supposedly derived from IV, has been patented.²

Condensation of 2-aminopyrimidine with 2,3-dichloro-1,4-naphthoquinone yielded³ a yellow quinone (m. 343.5--5.1°) shown, by

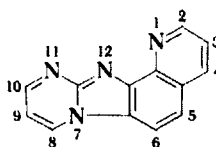


its conversion into a phenazine derivative, to be an *ortho*-quinone, and for which, by analogy with related systems (see Section A-283), structure VI was proposed.

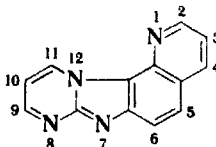


References

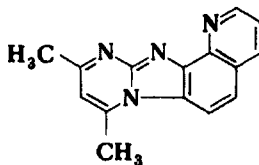
1. Crippa and Maffei, *Gazz. chim., ital.*, **71**, 418 (1941).
2. Heimbach, U. S. Pat. 2,432,419. Ger. Pat. 882,883.
3. Mosby and Boyle, *J. Org. Chem.*, **24**, 374 (1959).

A-523. Pyrimido[2',1',2,3]imidazo-[4,5-*h*]quinoline*

or

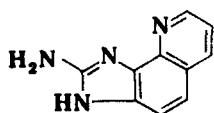
A-524. Pyrimido[1',2',1,2]imidazo-[4,5-*h*]quinoline*

From the reaction of I with acetylacetone Henecka obtained¹ a product (d. 245–50°), to which he assigned structure II, but for which, in the absence of further evidence, structure III must also be considered. The hindrance inherent in structure III would seem to make it less likely than II.

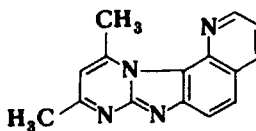


(II)

or



(I)

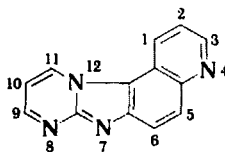


(III)

Reference

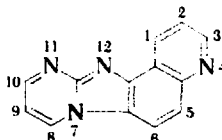
1. Henecka, Ger. Pat. 641,598; *Frdl.*, **23**, 270 (1940).

**A-525. Pyrimido[2',1',2,3]imidazo-
[4,5-f]quinoline***

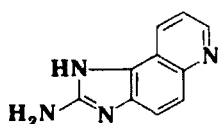


or

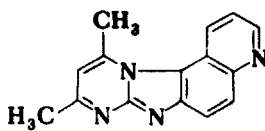
**A-526. Pyrimido[1',2',1,2]imidazo-
[4,5-f]quinoline***



The condensation of I with acetylacetone yielded¹ a product (m. 285–6°), which was assigned structure II, but no evidence was offered to exclude the alternative possibility, III.

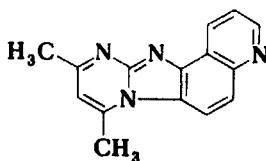


(I)



(II)

or

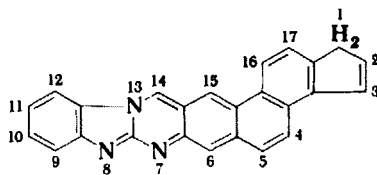


(III)

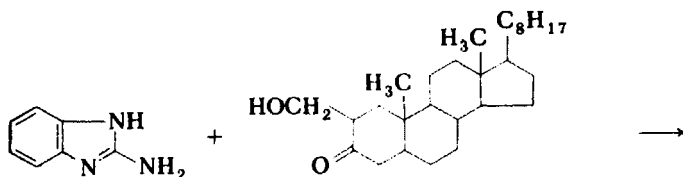
Reference

1. Henecka, Ger. Pat. 641,598; *Frdl.*, **23**, 270 (1940).

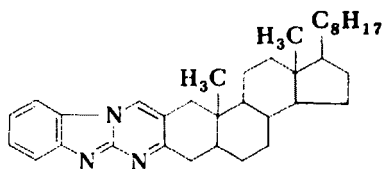
A-527. 1*H*-Benzimidazo[2,1-*b*]cyclopentano[5,6]naphtho[1,2-*g*]-quinazoline*



The reaction of I with 2-aminobenzimidazole yielded ¹ II [yellow, m. 295°; $[\alpha]_D^{24} = +78.1^\circ$ (c, 0.467)], which was called 1':9':-11'-triazafluoreno(3':2'-2:3)cholestane.



(I)

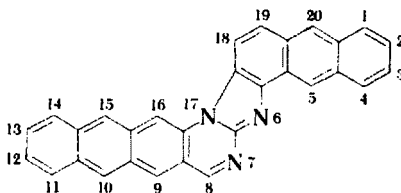


(II)

Reference

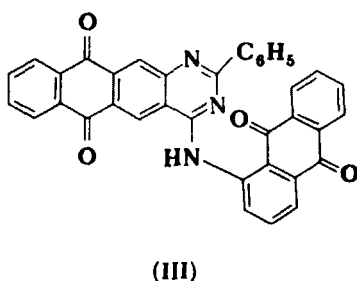
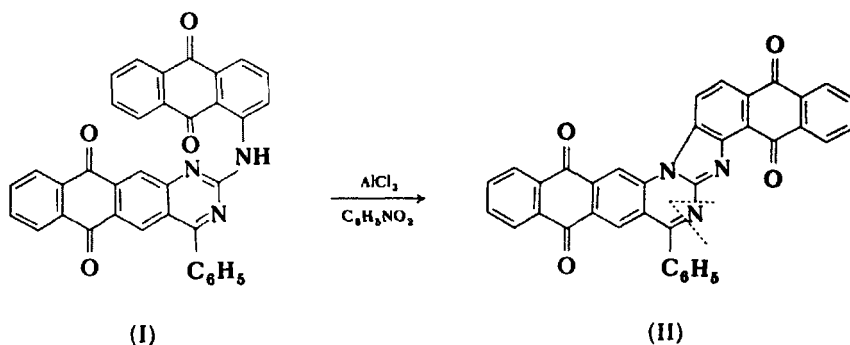
1. Antaki and Petrow, *J. Chem. Soc.*, **1951**, 901.

A-528. Anthra[1',2',4,5]imidazo-[1,2-*a*]naphtho[2,3-*g*]-quinazoline*



Treatment ¹ of I with aluminum chloride in nitrobenzene gave a yellow dye thought to have structure II. The dye is sensitive to

alkali-pyridine solutions however, possibly because of ring scission (dotted lines in II).

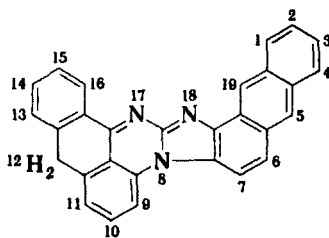


Compound III was unchanged by treatment with aluminum chloride in nitrobenzene.

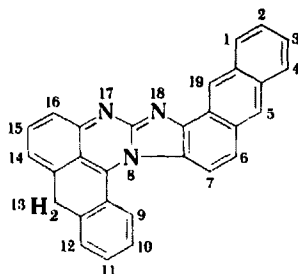
Reference

1. Baumann and Schwechten, *I.G. Farbenindustrie, A.G., 37 Wissenschaftlicher Austausch der Gruppe IX*, Ludwigshafen, March 18/9, 1937; *PB Report No.* 70339, frames 11707-11715.

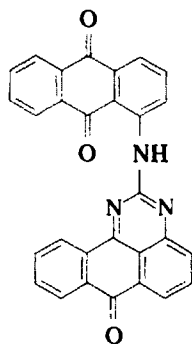
A-529. 12H-Anthra[1',2',4,5]imidazo-[1,2-a]benzo[e]perimidine*



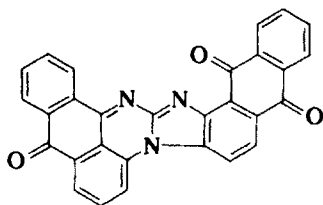
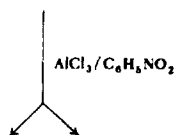
or

A-530. 13H-Anthra[1'2',4,5]imidazo-[1,2-a]benzo[j]perimidine*

Treatment of I with aluminum chloride in nitrobenzene yielded ¹ a yellow dye thought to be II or III. The dye has several disadvantages (e.g., an insoluble and very stable leuco derivative), and is of no commercial value.

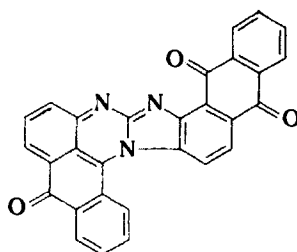


(I)



(II)

or

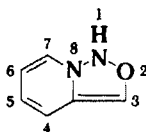


(III)

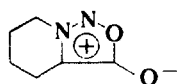
Reference

1. Baumann and Schwechten, *I.G. Farbenindustrie, A.G., 37 Wissenschaftlicher Austausch der Gruppe IX*, Ludwigshafen, March 18/9, 1937; *PB Report No.* 70339, frames 11707-11715.

A-531. 1*H*-[1,2,3]Oxadiazolo[3,4-*a*]-pyridine*



The only reported¹ representative of this nucleus is the sydnone I (m. 104.5°), but no details beyond its melting point were recorded. See Sections A-532/3.

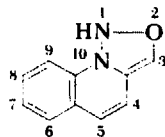


(I)

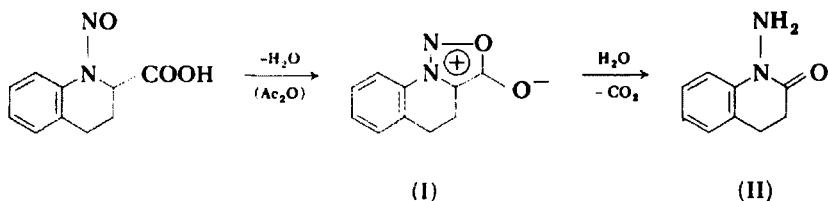
Reference

1. Hammick and Voaden, *Chem. and Ind.*, **1956**, 739.

A-532. 1*H*-[1,2,3]Oxadiazolo[3,4-*a*]-quinoline



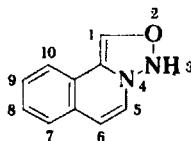
The sydnone of structure I (m. 146.5-7.0°) was prepared^{1,2} as shown. Hydrolysis by hot dilute acid yielded II. The proper representation of the sydnone structures, including that of I, has been discussed.^{3,4}



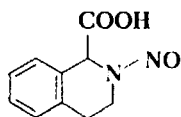
References

1. Hammick, Roe and Voaden, *Chem. and Ind.*, **1954**, 251.
2. Kruger, *Chem. and Ind.*, **1954**, 465.
3. Katritzky, *Chem. and Ind.*, **1955**, 521.
4. Baker and Ollis, *Quart. Rev.*, **11**, 15 (1957).

A-533. 3H-[1,2,3]Oxadiazolo[4,3-a]-isoquinoline



From the dehydration of I, the sydnone II (m. 166°) has been obtained.¹ The proper structural representation of the sydnones has been discussed.^{2,3}



(I)

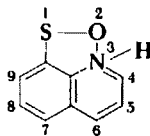


(II)

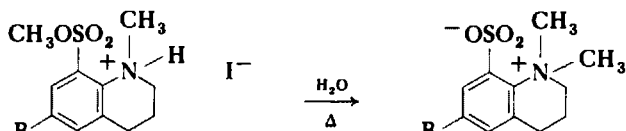
References

1. Kruger, *Chem. and Ind.*, **1954**, 465.
2. Katritzky, *Chem. and Ind.*, **1955**, 521.
3. Baker and Ollis, *Quart. Rev.*, **11**, 15 (1957).

A-534. 3H-[1,2,5]Oxathiazolo[ij]-quinoline. R.I. 1477



Only sulfobetaines¹ of structure I (R = H or Br) represent this nucleus.

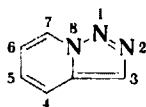


(I)

Reference

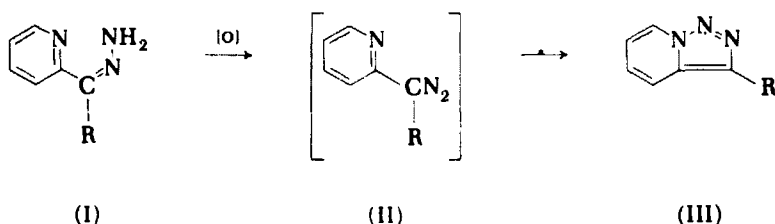
1. Claus and Günther, *J. prakt. Chem.*, **55**, 94 (1897).

A-535. Pyrido[1,2-*c*]-*v*-triazole

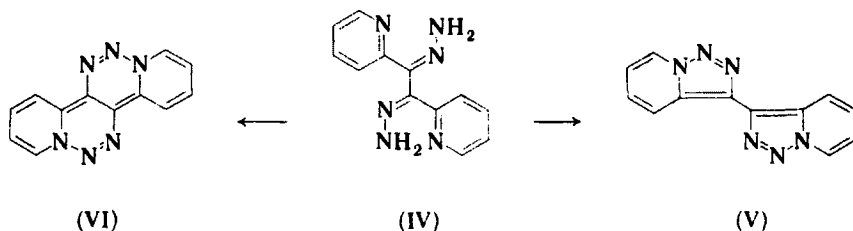


The name *1,2,7a-triazaindene* has been used.

Oxidation of I with silver oxide¹ or with alkaline ferricyanide⁴ yielded III ($R = H$, $b_{0.09}$ 78° , m. $39-40^\circ$ ($34-5^\circ$), methiodide, m. 176° , $AgNO_3$ complex, m. 136° ; $R = CH_3$, m. $84-5^\circ$; $AgNO_3$ complex, m. 195° ; $R = C_6H_5$, m. $113-5^\circ$). The formation of III proceeded¹ via the labile intermediate II, although neither II nor III was formed from the diazotization of 2-aminomethylpyridine. Similar

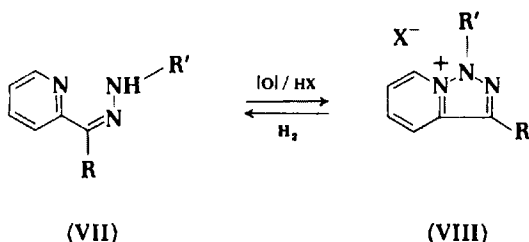


treatment of the dihydrazone of α -pyridil (IV) yielded a product (m. $272-4^\circ$ d.) assigned¹ structure V on the basis of the infrared spectrum, although structure VI could not be excluded. It would seem that the ultraviolet spectrum of the product would readily distinguish between structures V and VI.



Quaternary salts of structure VIII (where $X = Br^-$ and $R = H$, $R' = C_6H_5$, d. $163-4^\circ$; $R = H$, $R' = p-CH_3C_6H_4$, d. $158-9^\circ$; $R = H$, $R' = p-CH_3OC_6H_4$, d. $146-7^\circ$; $R = Br$, $R' = p-ClC_6H_4$, d.

183°; R = 2-pyridyl, R' = C₆H₅, d. 230–2°; where X = Cl⁻ and R = CH₃, R' = C₆H₅, d. 183–4°; R = R' = C₆H₅, d. 201.5°) have been prepared^{2,3} by the oxidation of VIII with *N*-bromosuccinimide in ethyl acetate, or with lead tetraacetate. Reduction of VIII readily reforms VII.

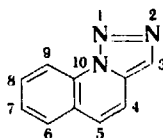


The ultraviolet spectrum of III (R = H) has been compared⁵ with those of other polyazaindenes. When heated with phenol or with carboxylic acids, III yields⁶ phenyl ethers, or the carboxylic acid esters of 2-pyridylmethanol.

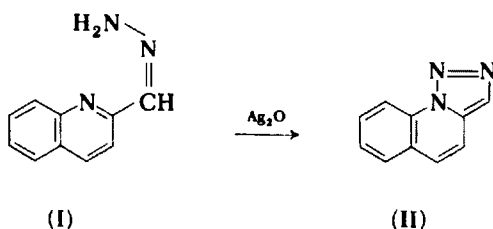
References

1. Boyer, Borgers and Wolford, *J. Am. Chem. Soc.*, **79**, 678 (1957).
2. Kuhn and Münzing, *Chem. Ber.*, **85**, 29 (1952).
3. Kuhn and Münzing, *Chem. Ber.*, **86**, 858 (1953).
4. Bower and Ramage, *J. Chem. Soc.*, **1957**, 4506.
5. Bower, *J. Chem. Soc.*, **1957**, 4510.
6. Boyer and Wolford, *J. Am. Chem. Soc.*, **80**, 2741 (1958).

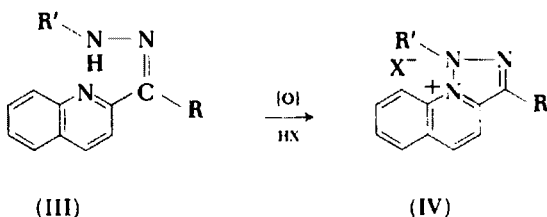
A-536. *ν*-Triazolo[1,5-*a*]quinoline



Oxidation of I with silver oxide yielded¹ II (m. 81°).



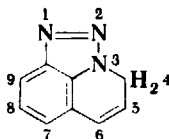
Kuhn and Münzing^{2,3} obtained compounds of structure IV ($X = R = Br$, $R' = C_6H_5$, d. 154–5°; $X = R = Br$, $R' = p\text{-CH}_3C_6H_4$, d. 149°; $X = Cl$, $R = CH_3$, $R' = C_6H_5$, d. 178–9°) by oxidizing III with lead tetraacetate or with *N*-bromosuccinimide.



References

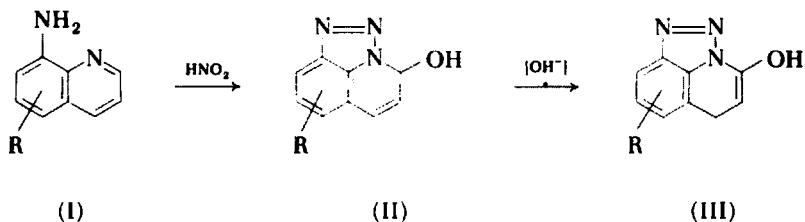
1. Boyer, Borgers and Wolford, *J. Am. Chem. Soc.*, **79**, 678 (1957).
2. Kuhn and Münzing, *Chem. Ber.*, **85**, 29 (1952).
3. Kuhn and Münzing, *Chem. Ber.*, **86**, 858 (1953).

A-537. 4*H*-Triazolo[4,5,1-*ij*]quinoline. R.I. 1505



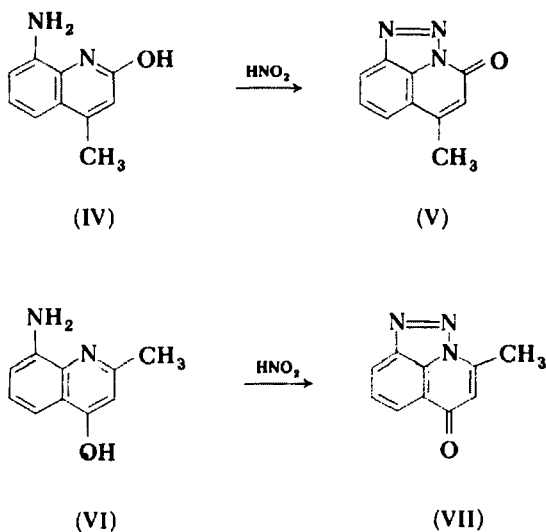
This system has also been named *1,8-azo-1,2-dihydroquinoline* and *quinoline-1,8-diazoimide*.

Ach and von Hofe treated 8-aminoquinolines (I) with nitrous acid and obtained¹ products which they considered to be of type II ($R = H$, pale red, m. 153°; $R = 8\text{-Cl}$, m. 170°, acetyl derivative, m. 190°; $R = 8\text{-CH}_3O$, m. 201° d.; $R = 8\text{-C}_2H_5O$, m. 182° d.). These products, when heated with aqueous bases (2*N* sodium hydroxide, barium hydroxide, magnesium oxide or even trimethylamine), yielded² isomeric materials thought to be III ($R = H$, d.



202°; R = 7-Cl, d. 214°; R = 8-Cl, d. 221°, acetyl derivative, m. 203°; R = 8-CH₃O, d. 233-4°; R = 8-C₂H₅O, d. 198°). The keto form corresponding to the enol structure III would seem to be a more probable structure for these products.

The isomeric compounds IV³ and VI⁴ have similarly been converted into V (m. 236.0-7.5°d.) and VII (m. >400°). Compound

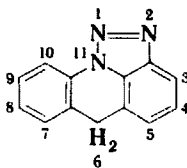


V could be recrystallized from ethanol without decomposition, but when charcoal was added to the ethanol solution, the odor of acetaldehyde became evident and 2-hydroxylepidine was recovered. Because of a misconception regarding the structure of IV, compound V was at first⁵ thought to be 5-hydroxy-3-pyrido[4,3,2-*de*]cinnoline.

References

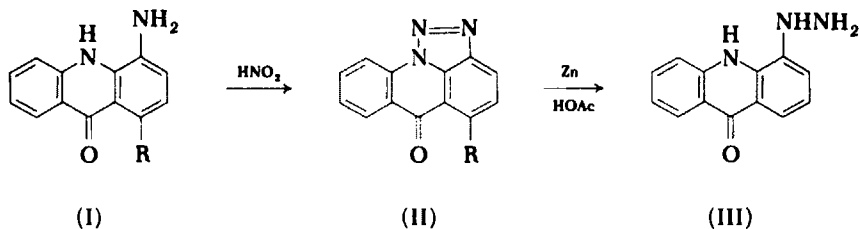
1. Ach and von Hofe, Ger. Pat. 576,119; *Frdl.*, **20**, 716 (1935). U. S. Pat. 2,065,879.
2. Ach and von Hofe, Ger. Pat. 613,627; *Frdl.*, **22**, 495 (1939).
3. Krahler and Burger, *J. Am. Chem. Soc.*, **64**, 2417 (1942).
4. Halcrow and Kermack, *J. Chem. Soc.*, **1945**, 415.
5. Krahler and Burger, *J. Am. Chem. Soc.*, **63**, 2367 (1941).

A-538. 6*H*-Triazolo[*de*]acridine.
R.I. 2348

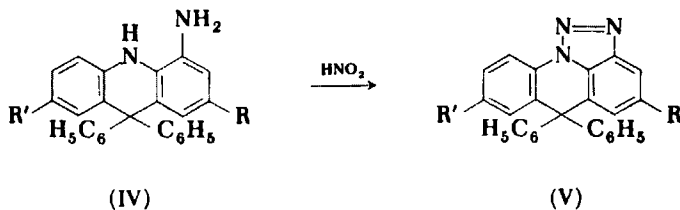


The names *isotriazoloacridine* and *acridinediazole* are also encountered.

The reaction of 4-aminoacridones (I) with nitrous acid yields II ($R = H$, brown, m. $266^{\circ}d.$,¹ or pale red, m. $258-9^{\circ}$,² $R-Cl$, pink,



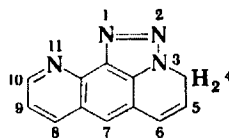
m. $218^{\circ}d.$). A group of *aminonitrocarbazines* (IV) is thought³ similarly to yield products of type V ($R = NO_2$, $R' = H$, m. 216° ; $R = H$, $R' = NO_2$, no sharp m.p.; $R = R' = NO_2$, m. $294^{\circ}d.$).



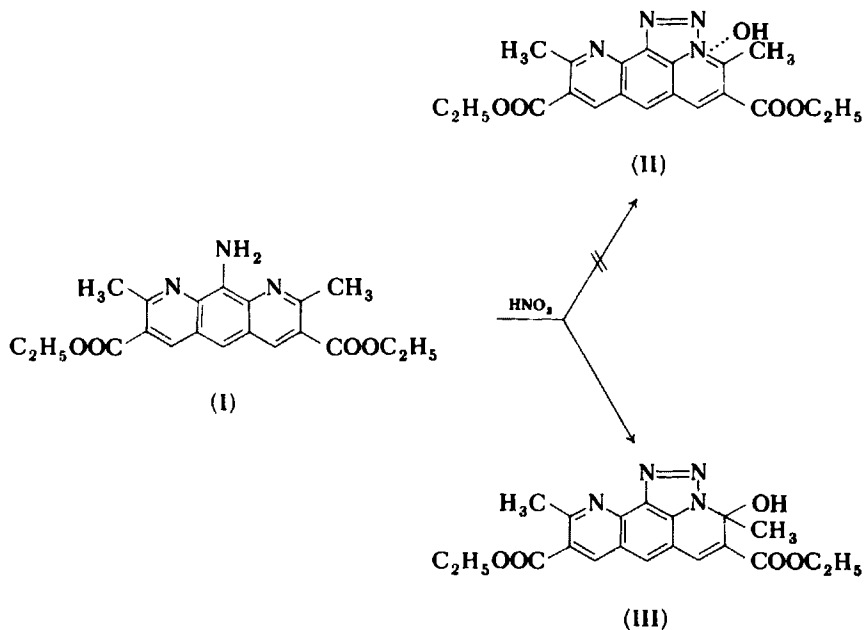
Reduction of II ($R = H$) with zinc and acetic acid causes scission of the triazole ring and yields the hydrazine III.

References

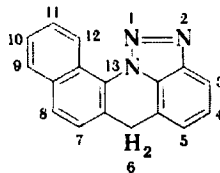
1. Clemo, Perkin and Robinson, *J. Chem. Soc.*, **125**, 1751 (1924).
2. Lehmstedt and Schrader, *Ber.*, **70**, 1526 (1937).
3. Kehrman and Rohr, *Helv. Chim. Acta*, **10**, 596 (1927).

A-539. 4*H*-Pyrido[3,2-*g*]triazolo-[4,5,1-*ij*]quinoline

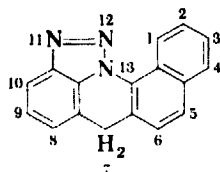
Ruggli and Fry¹ treated I with nitrous acid and obtained a yellowish crystalline product (m. 195°), to which they assigned structure II, but for which structure III now seems more acceptable.

*Reference*

1. Ruggli and Fry, *Helv. Chim. Acta*, **22**, 1403 (1939).

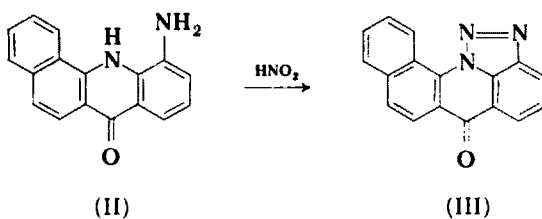
A-540. 6*H*-Benzo[*c*]triazolo-*[fg]*acridine

The name *triazolo[fg]benz[c]acridine* and the numbering shown in I have also been used.



(I)

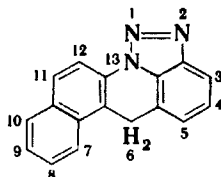
The treatment¹ of II with nitrous acid yielded III (light yellow, m. 212–3°d.).



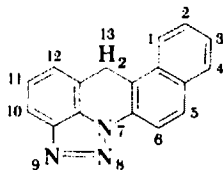
Reference

1. Bachman and Cowen, *J. Org. Chem.*, **13**, 89 (1948).

A-541. 6H-Benzo[*a*]triazolo[*fg*]acridine

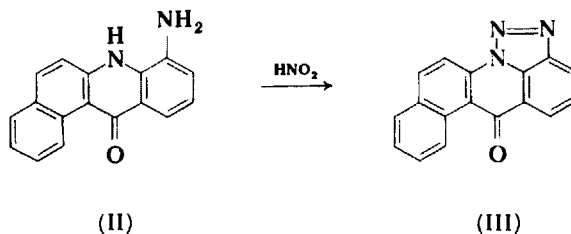


The name *triazolo[fg]benz[a]acridine* (numbered as shown in I) has also been used.



(I)

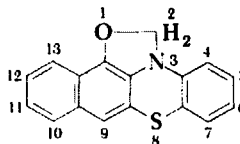
The sole example of this nucleus (III, light yellow, m. 226–8°) was obtained as shown from II.



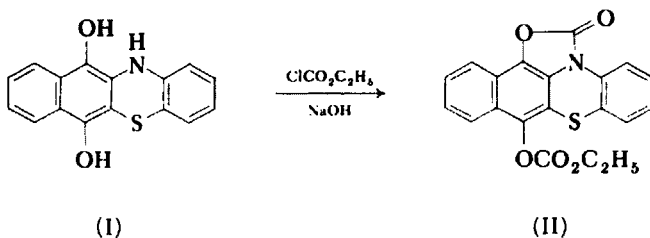
Reference

1. Bachman and Cowen, *J. Org. Chem.*, **13**, 89 (1948).

A-542. 2*H*-Benz[*b*]oxazolo[3,4,5-*mn*]phenothiazine*



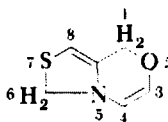
Treatment of I with ethyl chlorocarbonate yielded¹ II (greenish-yellow, m. 203°d.). Efforts to hydrolyze the ester group in II gave only I.



Reference

1. Fries and Kerkow, *Ann.*, **427**, 281 (1922).

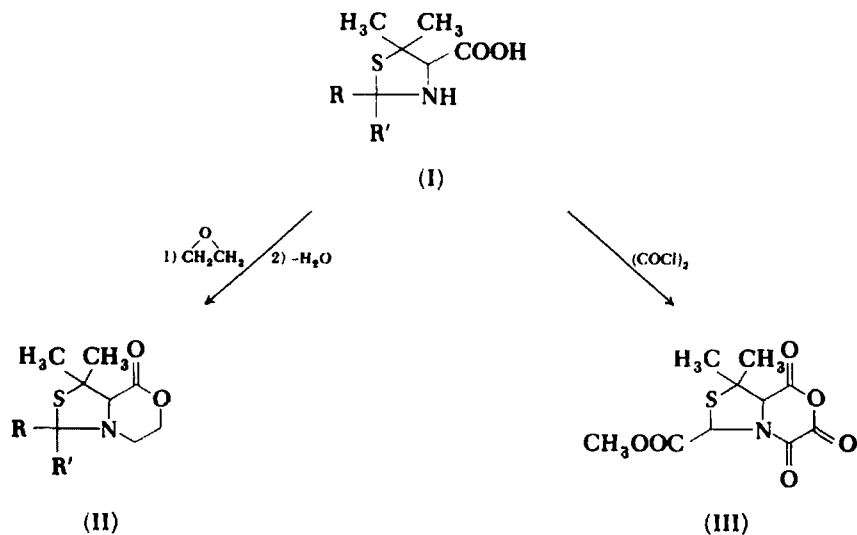
A-543. 1*H*,6*H*-Thiazolo[4,3-*c*]-*p*-oxazine



The reaction of various substituted 5,5-dimethylthiazolidine-4-carboxylic acids (I, R = R' = CH₃) with ethylene oxide, and dehydration of the resulting *N*-hydroxyethyl intermediates, yielded^{1,2}

lactones of structure II ($R = R' = \text{CH}_3$, m. 102° ; $R = \text{H}$, $R' = \text{C}_6\text{H}_5$, m. $104-5^\circ$; $R = \text{H}$, $R' = \text{CH}(\text{COOC}_2\text{H}_5)\text{NHCOC}_6\text{H}_{11}$, m. $132-3^\circ$; $R = \text{H}$, $R' = \text{CH}_2\text{NHCOCH}_2\text{C}_6\text{H}_5$, m. 166° ; $R = \text{H}$, $R' = \text{CH}(\text{COZ})\text{NHCOC}_6\text{H}_5$; when $Z = \text{OH}$, m. 175° ; $Z = \text{ONH}_3\text{CH}_2\text{C}_6\text{H}_5$, m. $255-7^\circ$; $Z = \text{OC}_2\text{H}_5$, m. $153-4^\circ$; $Z = \text{NHCH}_2\text{C}_6\text{H}_5$, m. $200-2^\circ$).

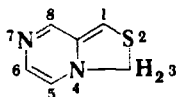
Oxalyl chloride reacts with I ($R = \text{H}$, $R' = \text{COOC}_2\text{H}_5$) to yield³ III (m. $173-5^\circ$).



References

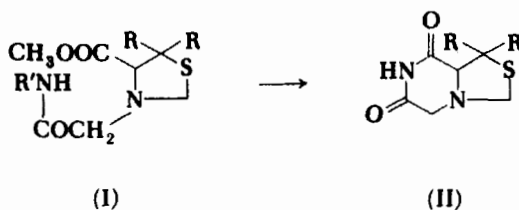
1. Cook and Heilbron, "Thiazolidines" in Clark *et al.*, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 921.
2. Heilbron and Cook, Brit. Pat. 595,958; *Chem. Abstracts*, **42**, 3781 (1948).
3. Bentley, Cook, Elvidge and Shaw, *J. Chem. Soc.*, **1949**, 2351.

A-544. 3H-Thiazolo[3,4-a]pyrazine

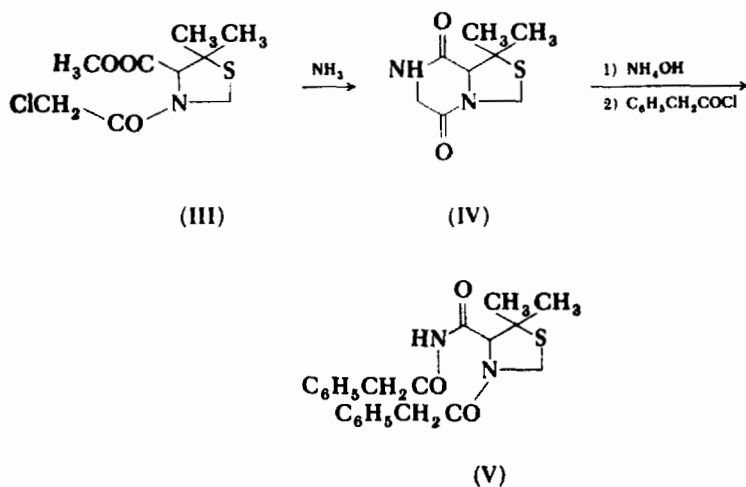


Treatment of the *d*- or *l*- isomer of I ($R = \text{CH}_3$, $R' = \text{Ac}$) with caustic yielded¹ the *d*- or *l*- isomer of II ($R = \text{CH}_3$, each m. $176-$

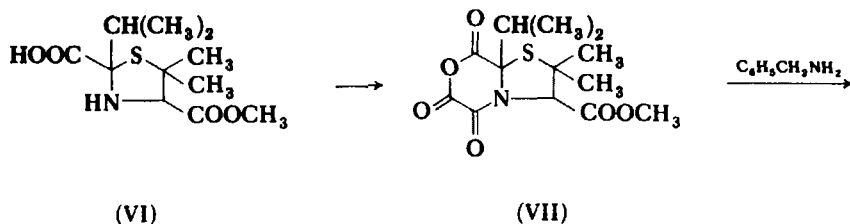
8°), together with a little racemized material (m. 198–201°d.). However, merely heating the hydrochloride of I (when $R = R' = H$) in ethanol produced² II ($R = H$, m. 190–2°).



Süs prepared³ IV (m. 167°; *N*-phenylacetyl derivative, m. 143°) by permitting III to react with ammonia. Further treatment⁴ of IV with ammonium hydroxide at 100°, followed by reaction with phenylacetyl chloride, produced V.



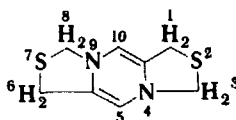
The reaction of VI with oxalyl chloride yielded⁵ VII (see Section A-495), which upon being heated with benzylamine, underwent decarboxylation and rearrangement to VIII (m. 189°).



References

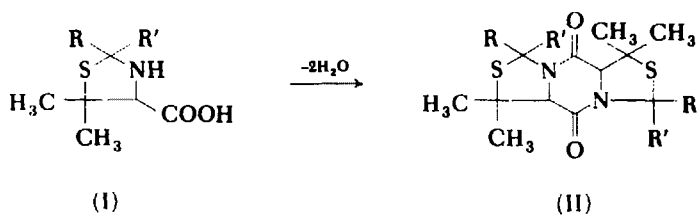
1. Werner, Wettstein and Miescher, *Helv. Chim. Acta*, **30**, 432 (1947).
2. Neher, Wettstein and Miescher, *Helv. Chim. Acta*, **29**, 1815 (1946).
3. Süss, *Ann.*, **561**, 31 (1948).
4. Süss, *Ann.*, **564**, 54 (1949).
5. Bentley, Cook and Elvidge, *J. Chem. Soc.*, **1949**, 2357.

A-545. 1*H*,3*H*,6*H*,8*H*-Bisthiazolo- [3,4-*a*,3',4'-*d*]pyrazine

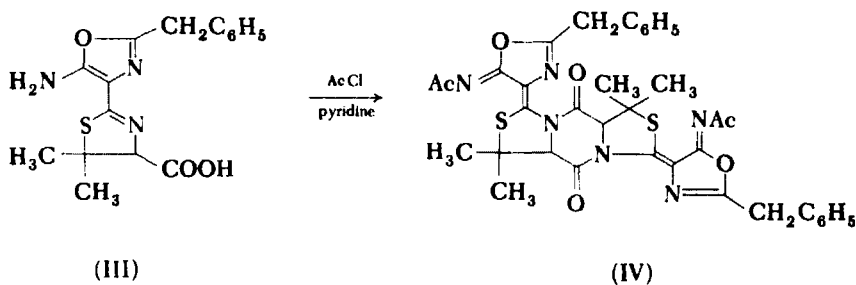


The *Chemical Abstracts* name lacks the 1*H*,3*H*,6*H*,8*H*-prefix.

The compounds of this nucleus were all prepared in connection with the studies upon penicillin. Treatment of various thiazolidine-carboxylic acid derivatives (I) in pyridine solution with acid chlorides (e.g., tosyl chloride, acetyl chloride, benzoyl chloride, etc.) results in the dehydration of I to diketopiperazine derivatives (II, R = R' = CH₃, m. 210–2°;¹ R = H, R' = COOCH₃, m. 186–7° with clearing from ~190–205°;² R = H, R' = CH₂NHCOC₅H₁₁, m. 185–6°;^{3, 4, 6} R = H, R' = CH₂NHCOCH₂C₆H₅, m. 234–5°;^{3, 6} R = H, R' = CH(COOCH₃)NHCOC₂H₅, m. 176–7°, [α]_D = +263°³).



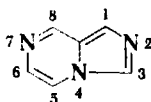
A slight modification of this basic reaction was shown⁵ in the synthesis of IV (m. 179°) from III.



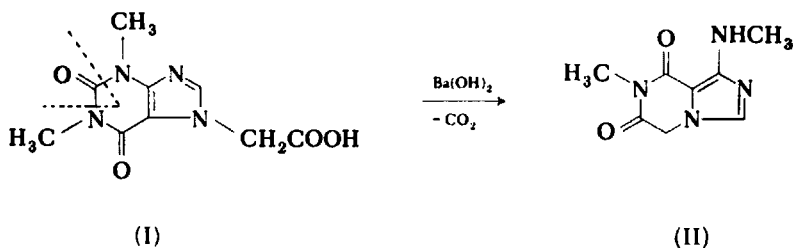
References

1. Cook and Heilbron, "Thiazolidines" in Clarke *et al.*, *The Chemistry of Penicillin*, Princeton University Press, Princeton, New Jersey, 1949, p. 921.
2. Bentley, Cook, Elvidge and Shaw, *J. Chem. Soc.*, **1949**, 2351.
3. Mozingo and Folkers, "The Penilloic and Penicilloic Acids, *etc.*" in Clarke *et al.*, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 541.
4. Heilbron, Cook and Elvidge, Brit. Pat. 600,245; *Chem. Abstracts*, **42**, 8215 (1948).
5. Cook and Harris, *J. Chem. Soc.*, **1949**, 3236.
6. Cook, "Pennilic Acids and Penillamines" in Clarke *et al.*, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 105.

A-546. Imidazo[1,5-*a*]pyrazine*



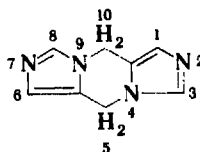
Heating theophylline-7-acetic acid (I) with barium hydroxide leads¹ to ring scission and recyclization to II (m. 208°).



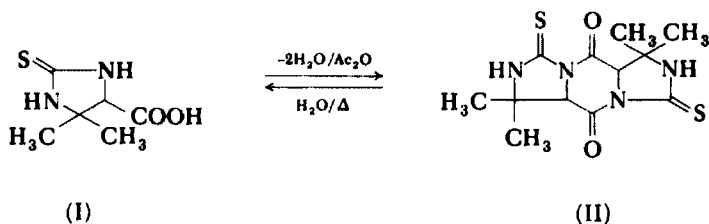
Reference

1. Crippa and Crippa, *Il Farmaco (Pavia) Ed. Sci.*, **10**, 616 (1955); *Chem. Abstracts*, **50**, 1840 (1956).

A-547. 5*H*,10*H*-Diimidazo- [1,5-*a*, 1',5'-*d*]pyrazine*



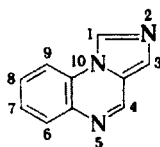
When I was heated with acetic anhydride, a neutral product (m. 340°d.) thought to be II was obtained.¹ When heated with 48% hydrobromic acid it was hydrolyzed to I.



Reference

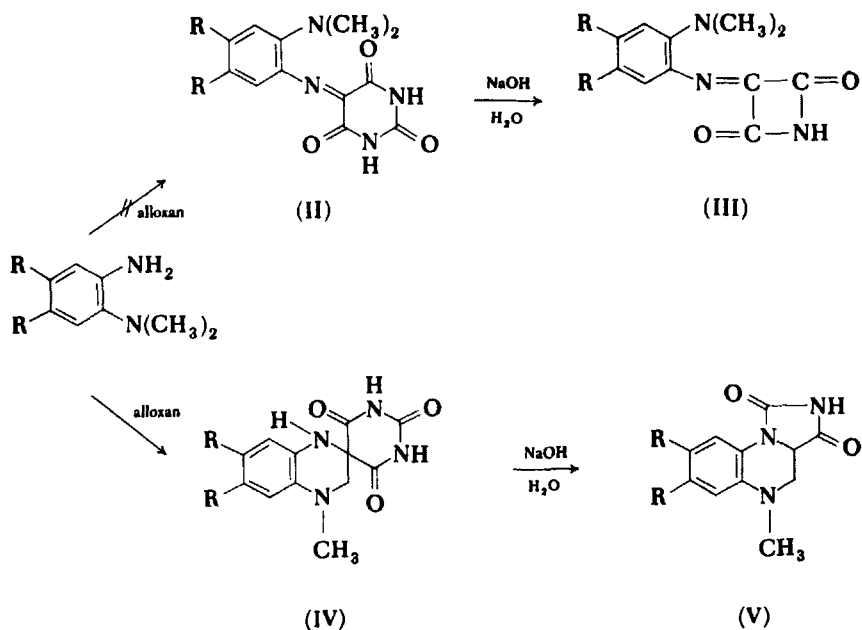
1. Doyle, Holland and Nayler, *J. Chem. Soc.*, **1955**, 2265.

A-548. Imidazo[1,5-*a*]quinoxaline

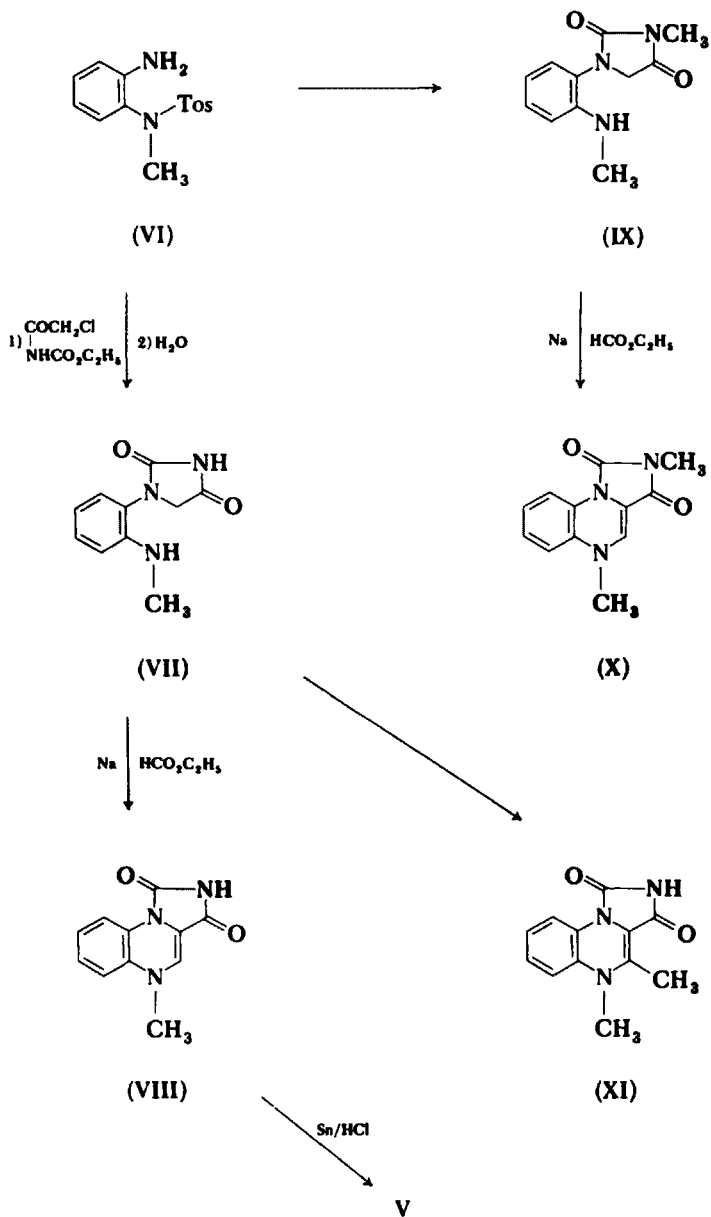


This nucleus has also been called *glyoxalino*(1':5'-1:2)quinoxaline.

Rudy and Cramer¹⁻⁴ condensed I with alloxan and obtained a product, which they considered to be II. When this product was boiled with 30% caustic, it was degraded to a second material, to which they assigned structure III. These reactions were reinvestigated by King and Clark-Lewis, who showed⁵ that Rudy and Cramer's products were actually IV and V ($R = H$, m. 240°; $R = CH_3$, m. 250°). Treatment^{1,5} of V with diazomethane yielded the 2-methyl homolog [m. 156-7° (154°), $\lambda_{\max}$ in ethanol, 218, 260 and 307 $m\mu$ ($\epsilon = 26,500, 8,600$ and $4,700$); picrate, brown, m. 133°].



The identity of V was demonstrated⁵ by its alternative synthesis from chloroacetylurethane and VI, as shown, via VIII (yellow, m. 270°). Similarly, the methyl homolog X [orange-yellow, m. 260° (256°); $\lambda_{\max}$ in ethanol, 218, 255-6, 266, 281.5, 343 and 437 $m\mu$ ($\epsilon = 15,650, 15,230, 12,700, 12,500, 5,470$, and $6,390$)] and dimethyl homolog (XI, yellow, m. 190-1°) were prepared.⁵ Compound X was reduced with tin and hydrochloric acid to the 2-methyl homolog of V, which in turn could be reoxidized⁶ to X by the action of oxygen upon its solution in hot acetic acid.

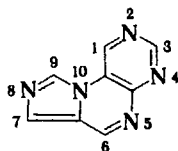


References

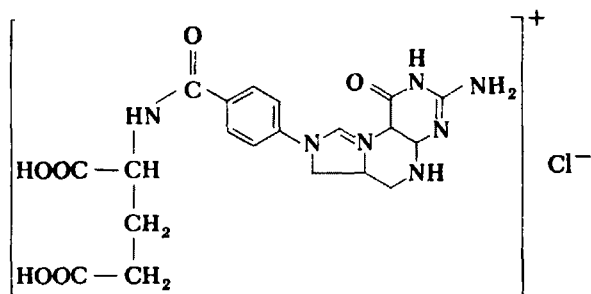
1. Rudy and Cramer, *Ber.*, **71**, 1234 (1938).
2. Rudy and Cramer, *Ber.*, **72**, 227 (1939).

3. Rudy and Cramer, *Ber.*, **72**, 728 (1939).
4. Rudy and Cramer, *Österr. Chem. Ztg.*, **42**, 329 (1939); *Chem. Abstracts*, **34**, 1628 (1940).
5. King and Clark-Lewis, *J. Chem. Soc.*, **1951**, 3080.
6. King and Clark-Lewis, *J. Chem. Soc.*, **1953**, 172.

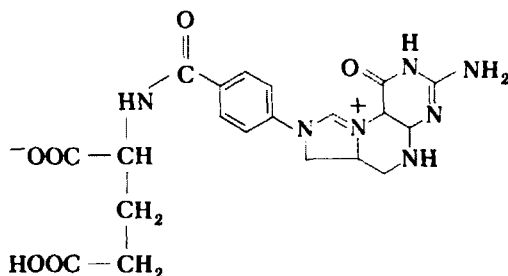
**A-549. Imidazo[1,5-*a*]pyrimido-
[4,5-*c*]pyrazine**



The compounds *isoleucovorin* and *anhydroleucovorin-A* (I and II), derived from the growth factor *leucovorin*, are thought¹ to contain this nucleus, as is an intermediate^{2,3} in the enzymatic formylation of tetrahydrofolic acid.



(I)

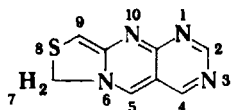


(II)

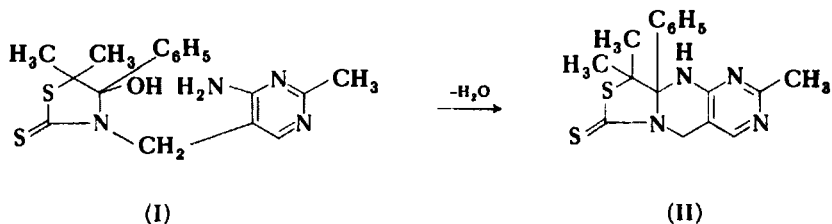
References

1. Cosulich, Roth, Smith, Hultquist and Parker, *J. Am. Chem. Soc.*, **73**, 5006 (1951) and **74**, 3252 (1952).
2. Rabinowitz and Pricer, *J. Am. Chem. Soc.*, **78**, 5702 (1956).
3. Greenberg and Jaenicke in Wolstenholme and O'Connor, Editors, *Ciba Foundation Symposium on the Chemistry and Biology of Purines*, Little, Brown & Co., Boston, 1957, p. 204.

A-550. 7H-Pyrimido[4,5-d]thiazolo-[3,4-a]pyrimidine



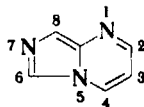
Treatment of I with hydrogen chloride in ethanol or acetic acid yielded¹ II (m. 265° d.).



Reference

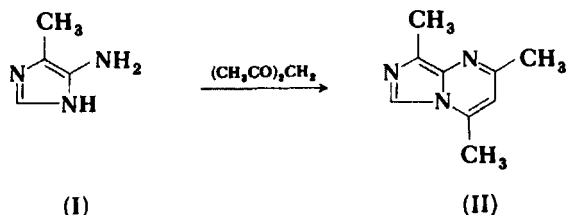
1. Hirano, *J. Pharm. Soc. Japan*, **75**, 252 (1955).

A-551. Imidazo[1,5-a]pyrimidine
R.I. 757M



This nucleus has also been called *imidazolo-1',5':1,2-pyrimidine* and *glyoxalino-1:5-1':2'-pyrimidine*.

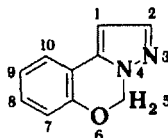
The condensation of I with acetylacetone yielded¹ II (hydrate, m. 80.5–82°; picrate, d. 201°) evidently the only example of this ring system.



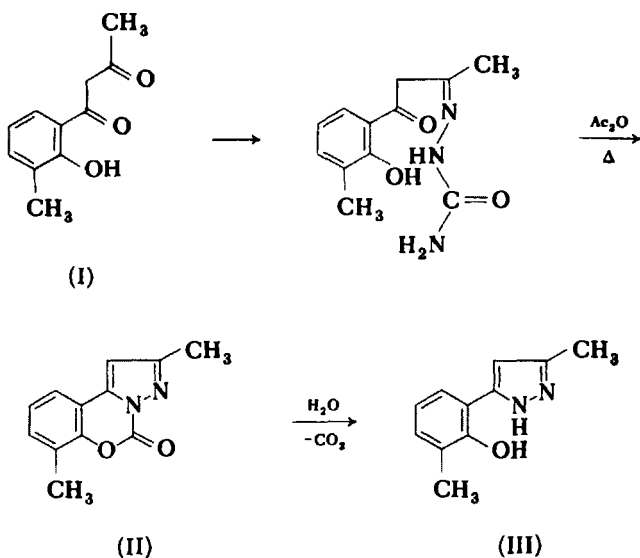
Reference

1. Ochiai and Sibata, *J. Pharm. Soc. Japan*, **59**, 185 (in Japanese) and 256 (in German) (1939); *Chem. Abstracts*, **33**, 4989 (1939); *British Chem. Abstracts*, **A11**, 234 (1940).

A-552. 5H-Pyrazolo[c][1,3]benzoxazine.
R.I. 1560



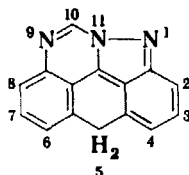
From the reaction of the semicarbazone of I with acetic anhydride, Wittig and Blumenthal¹ isolated II (m. 200–1°), which was decarboxylated by caustic to III.



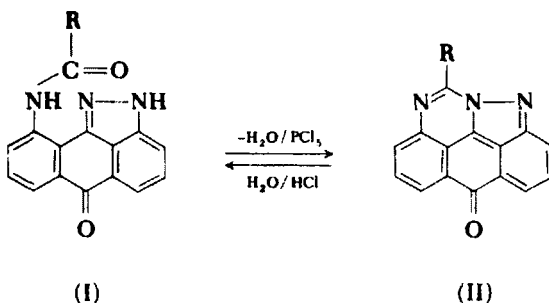
Reference

1. Wittig and Blumenthal, *Ber.*, **60**, 1085 (1927).

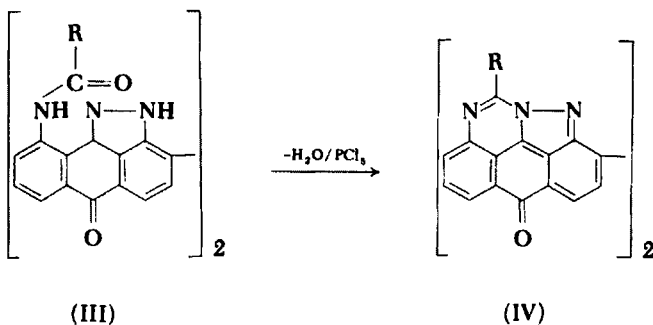
A-553. 5H-Indazolo[2,3,4-cde]-perimidine*



Bauman and Schwechten¹ prepared dyes of type II by the dehydration of I. Where $R = C_6H_5$ (yellow-brown needles, m. 295°), II is reconverted into I by treatment with acetic and hydrochloric acids. Compound II ($R = C_6H_5$) was difficult to vat, and showed little affinity for cotton, and the dyes of type II where R is a *m*-phenylene or 2-anthraquinonyl group showed little improvement; where R is a 1-nitro-2-anthraquinonyl group, a red-brown dye of somewhat improved affinity resulted. Introduction of a benzamido group at the 4-position of II ($R = C_6H_5$) gave an eosin-red dye (m. 312°) showing a green fluorescence in pyridine or nitrobenzene solution, but still with poor affinity.



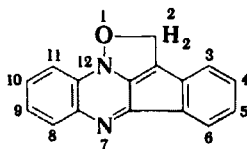
A group of reddish-blue to violet dyes of type IV, having low color value and giving very difficultly-soluble leuco salts, were obtained from III ($R = C_6H_5$, $p\text{-CH}_3OC_6H_4$, and $2,5\text{-C}_6H_3Cl_2$). The violet dye IV ($R = C_6H_5$) was rated 4 on soda-boil and chlorine-fastness, 4-5 on light-fastness and 1 on waterspotting. Chlorination of IV ($R = C_6H_5$) gave a very insoluble, weak blue dye.



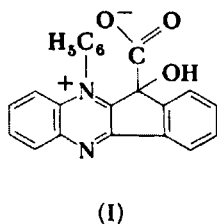
Reference

1. Baumann and Schwechten, *I.G. Farbenindustrie, A.G., 34 Wissenschaftlicher Austausch der Gruppe IX*, Leverkusen, October 25/6, 1935; *PB Report No. 70339*, frames 11319/24; *PB Report No. 25632*, frames 471 and 544.

A-554. 2*H*-Indeno[2',1',3,4]isoxazolo-[2,3'-*ab*]quinoxaline.*
R.I. 2931



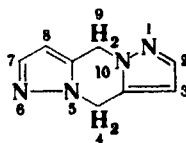
The nearest approach to this ring system is *isorosindonic acid* (I).^{1,2}



References

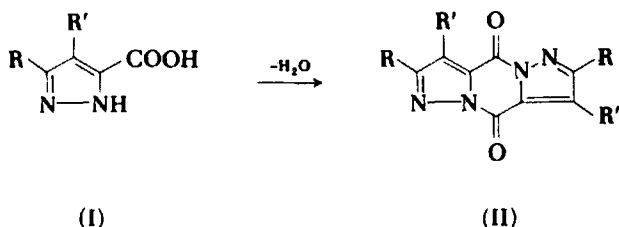
1. Fischer, *Ber.*, **36**, 3622 (1903).
2. Fischer and Hepp, *Ann.*, **262**, 237 (1891).

A-555. 4*H*,9*H*-Dipyrazolo[1,5-*a*,1',5'-*d*]-pyrazine. R.I. 1352



The *Ring Index* name omitted the 4*H*, 9*H*- prefix.

Rojahn and Kühling treated¹ acids of type I ($R = CH_3$, $R' = H$ and $R = H$, $R' = CH_3$) with thionyl chloride, and isolated chlorine-free products, which they thought were simple anhydrides of I. However, v. Auwers and Cauer showed² the products to have structure II. Thionyl chloride often may be replaced in this reaction by aryl sulfonyl chlorides, acyl chlorides or acyl anhydrides. Products of type II are high-melting and frequently decompose near



their melting points, a fact which may account for some of the large discrepancies in the melting points reported for the same products by different workers.

Compounds of Type II

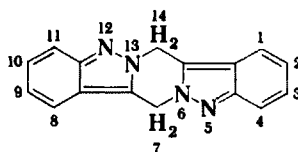
R	R'	Properties	Refs.
H	H	Lt. yel., m. 325° d.	2,8
CH ₃	Br	—	7
CH ₃	NO ₂	Yel., d. ~ 340° with partial m.	6
CH ₃	H	Yel., m. > 320° (m. ~ 346°; d. > 270°).	1,5,6
H	CH ₃	Lt. yel., m. > 320°.	1
CH ₃	CH ₃	Lt. brn., m. 285–6°.	2
H	C ₆ H ₅	Yel.-grn.	2
C ₆ H ₅	C ₆ H ₅	m. 346° (257° ?).	2,3,4

References

1. Rojahn and Kühling, *Arch. Pharm.*, **264**, 337 (1926); *Chem. Zentr.*, **II**, 413 (1926).
2. v. Auwers and Cauer, *Ber.*, **61**, 2402 (1928).

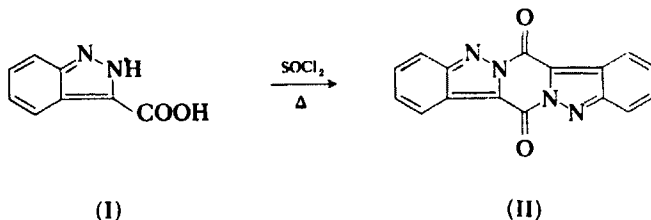
3. Borsche and Hahn, *Ann.*, **537**, 219 (1939).
4. Van Alphen, *Rec. Trav. chim.*, **62**, 485 (1943).
5. Dewar and King, *J. Chem. Soc.*, **1945**, 114.
6. Musante, *Gazz. chim. ital.*, **75**, 121 (1945); *Chem. Abstracts*, **41**, 4144 (1947).
7. Musante, *Gazz. chim. ital.*, **78**, 178 (1948); *Chem. Abstracts*, **42**, 7761 (1948).
8. Musante and Pino, *Gazz. chim. ital.*, **77**, 199 (1947); *Chem. Abstracts*, **42**, 913 (1948).

**A-556. 7H,14H-Diindazolo-
[2,3-*a*, 2',3'-*d*]pyrazine.
R.I. 2938.**



The *Ring Index* name omits the 7H,14H prefix.

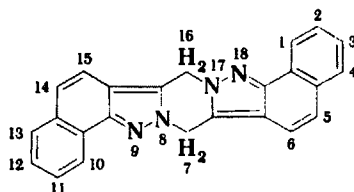
Attempts to prepare the acid chloride of I yielded^{1,2} II (orange, m. > 350°). The 1,2,3,4,8,9,10,11-octahydro homolog of II (m. 298°) was obtained³ similarly. The lactam bond is cleaved by the action of aqueous dimethylamine, giving² the dimethylamide of I.



References

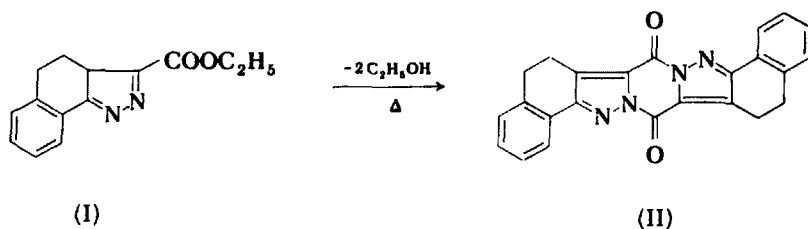
1. v. Auwers and Cauer, *Ber.*, **61**, 2402 (1928).
2. Smith and Kirchner, *J. Org. Chem.*, **23**, 621 (1958).
3. v. Auwers and Wolter, *Ber.*, **63**, 479 (1930).

**A-557. 7H,16H-Bisnaphtho[1,2]pyr-
azolo[2,3-*a*, 2',3'-*d*]pyrazine.
R.I. 3692**



The *Ring Index* name omitted the 7H,16H prefix.

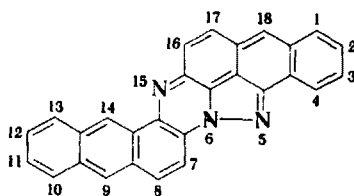
Heating I with benzoyl chloride yielded¹ a yellow product of structure II.



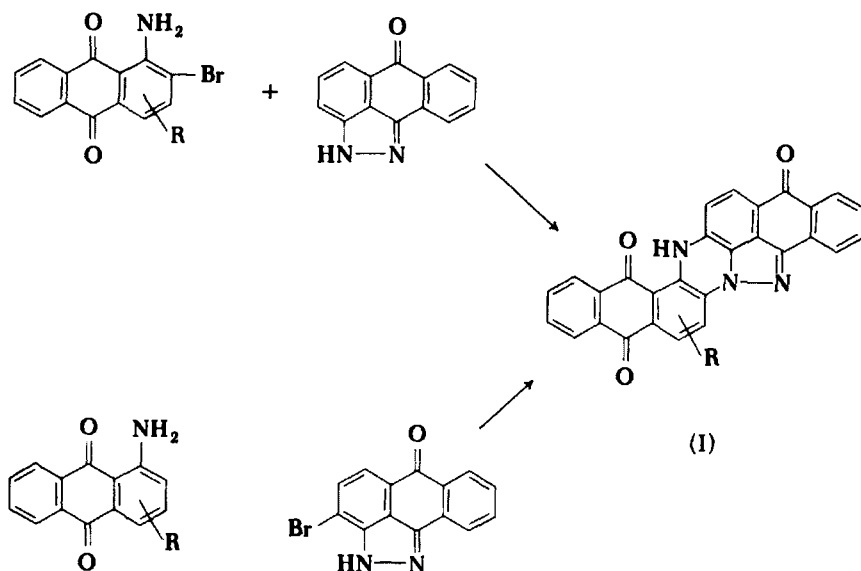
Reference

1. v. Auwers and Enbergs, *J. prakt. Chem.*, **134**, 97 (1932).

A-558. Naphtho[1,2,3-*cd*]naphtho-[2',3',5,6]quinoxalo[3,2,1-*hi*]-indazole. R.I. 3868



Nawiasky and Kraus prepared¹⁻⁴ vat dyes of structure I by the two routes shown. When R = H, I is a blue violet dye (violet vat,

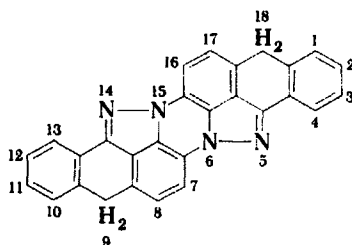


blue sulfuric acid solution); where $R = 8\text{-OH}$, the dye is a deep blue-green shade (blue vat), which changes to grey on chlorination; the dyes where $R = 8\text{-NH}_2$ and $10\text{-NHCOC}_6\text{H}_5$ are, respectively, blue (blue vat) and violet (violet-blue vat, green-blue sulfuric acid solution). Chlorination or bromination of I ($R = \text{H}$) yielded blue dyes with red-violet vats.

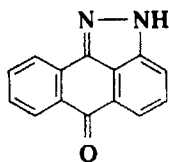
References

1. Nawiasky and Kraus, Ger. Pat. 493,813; *Frdl.*, **16**, 1367 (1931); Fr. Pat. 676,757; Brit. Pat. 321,585.
2. Nawiasky and Kraus, Ger. Pat. 498,067; *Frdl.*, **17**, 1279 (1932).
3. Nawiasky and Kraus, Ger. Pat. 499,353; *Frdl.*, **17**, 1279 (1932).
4. Nawiasky and Kraus, U. S. Pat. 1,838,232.

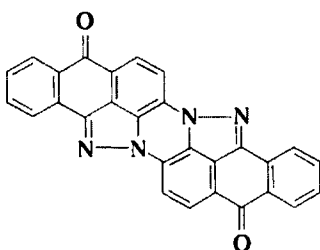
**A-559. 9H,18H-Dipyrzolo-
[5,4,3,2-fgh, 5',4',3',2'-uvw]-
anthrazine.**



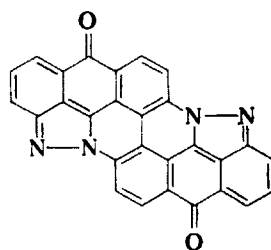
When 1,9-pyrazolanthrone (I) is heated with alcoholic potassium hydroxide, a yellow dye (blue vat) variously called *pyrazolanthrone yellow* or *dipyrzolanthrone*, is obtained.¹ Numerous subsequent patents were issued on this and related dyes. Structure II was originally proposed¹ for pyrazolanthrone yellow, but this was modified to III by Mayer and Heil.² The parent nucleus of III was named *dipyrzolo-[def,qrs]flavanthrene* (*R.I.* 3955). It seems to have been overlooked³



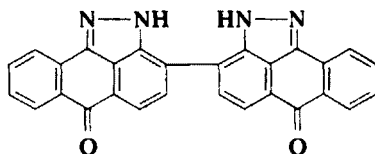
(I)



(II)



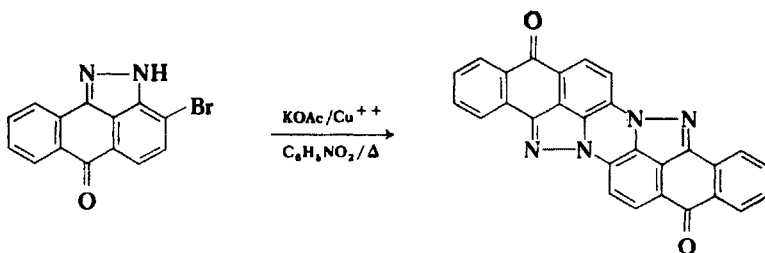
(III)



(IV)

that Lüttringhaus, Nawiasky and Krause⁴ demonstrated (before 1926) that pyrazolanthrone yellow had structure IV, the structure subsequently favored⁵ by Mayer and Heil. Thus no examples of the ring system III are now known.

There is postulated, however, a single example of structure II. Berliner, Stein and Trautner⁶ subjected V to self-condensation under



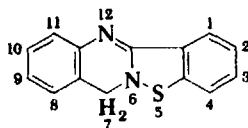
(V)

(II)

Ullmann conditions, and obtained a halogen-free product (red-brown needles; sulfuric acid solution blue), which dyed a clear strong red from a blue-green vat, and was thought to be II.

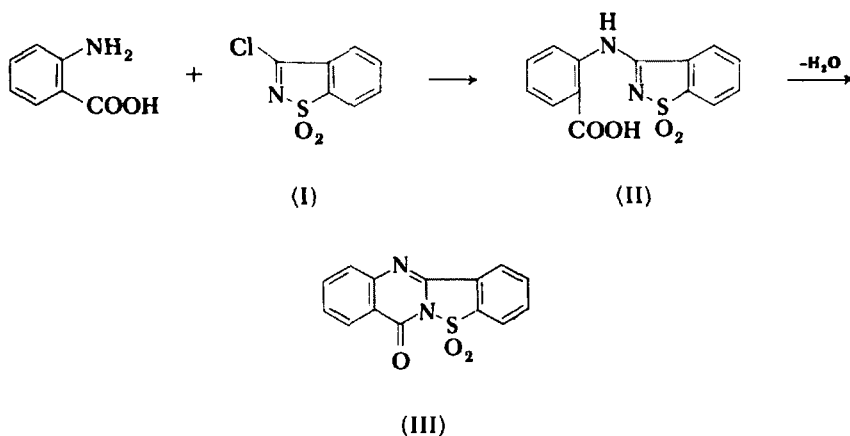
References

1. Chemische Fabrik Griesheim-Elektron, Ger. Pat. 255,641; *Frdl.*, **11**, 583 (1915).
2. Mayer and Heil, *Ber.*, **55**, 2155 (1922).
3. Bradley and Geddes, *J. Chem. Soc.*, **1952**, 1630, 1636.
4. Lüttringhaus, Nawiasky and Krause, Ger. Pat. 457,182; *Frdl.*, **16**, 1371 (1931); U. S. Pat. 1,817,995.
5. Mayer and Heil, *Chem. Ztg.*, **53**, 56 (1929).
6. Berliner, Stein and Trautner, Ger. Pat. 454,425; *Frdl.*, **16**, 1330 (1931); U. S. Pat. 1,695,631.

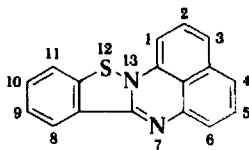
A-560. 7*H*-[1,2]Benzisothiazolo-[3,2-*b*]quinazoline*

The name *benzo[d]quinazo[3:2-*b*]thiazole* has also been used.

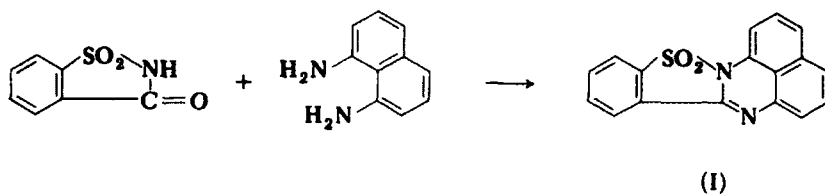
The reaction of ψ -saccharin chloride (I) with anthranilic acid (or its salts, esters or amide) yielded¹ II, which could be dehydrated by the action of acetic anhydride to III (m. 276°).

*Reference*

1. Stephen and Stephen, *J. Chem. Soc.*, **1957**, 490.

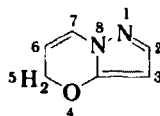
A-561. [1,2]Benzisothiazolo[2,3-*a*]-perimidine*

A product (orange-yellow, d. 270°), possibly of structure I, was obtained¹ by heating saccharin with 1,8-naphthylenediamine. It dissolves in sulfuric acid with a brown color, and in hot aqueous caustic solution with a green color.

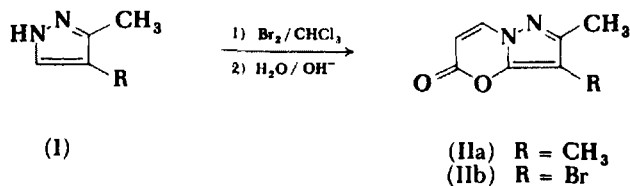


Reference

1. Bayer & Co., Ger. Pat. 202,354; *Frdl.*, **9**, 187 (1911). Fr. Pat. 388,955. Brit. Pat. 7575.

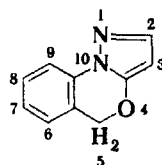
A-562. 5*H*-Pyrazolo[3,2-*b*][1,3]oxazine*

Amongst the products obtained by treating methylpyrazoles of type I with bromine in chloroform followed by alkali, were isolated¹ IIa (R = CH₃, yellow, m. 212°d.) and IIb (R = Br, orange-yellow, d. >61°). See Section A-563. The formation of II results from hydrolytic scission of one molecule of I, followed by condensation with a second molecule of I.

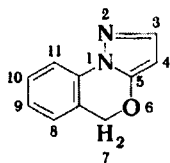


Reference

1. Hüttel, Wagner and Sickenberger, *Ann.*, **607**, 109 (1957).

A-563. 5*H*-Pyrazolo[*a*][3,1]benzoxazine.
R.I. 1559

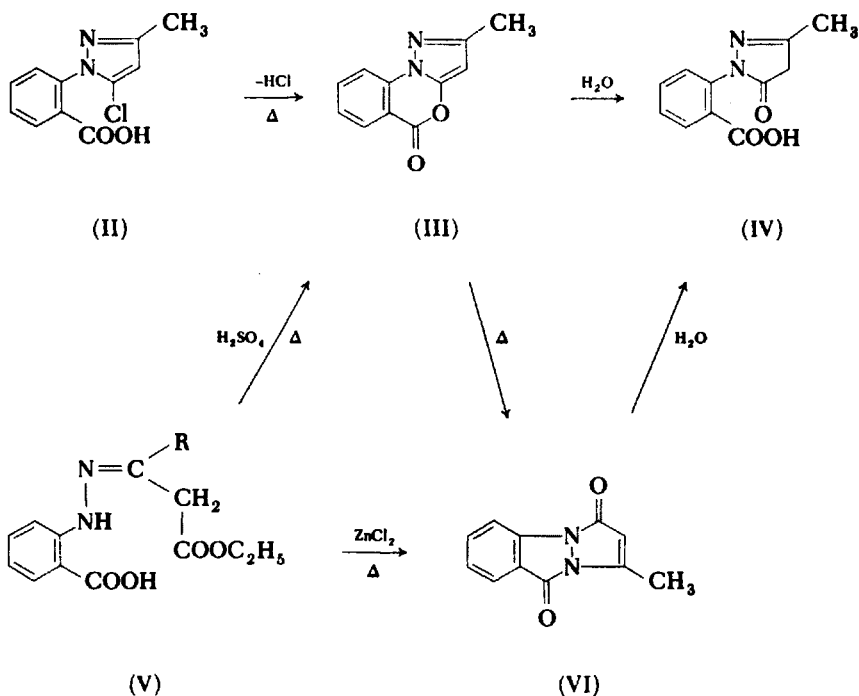
This nucleus has also been called *benzometoxazinepyrazole* and *pyrazoisocumarazone*, and numbered as shown in I.



(I)

Michaelis found¹ that thermal dehydrochlorination of II yielded a product to which he assigned structure III. Further investigation² disclosed that this product, together with two other isomeric materials, could be obtained by the cyclization of V ($R = \text{CH}_3$) under various conditions. These products he termed α -, β - and γ -pyrazoisocumarazones, and proposed structures III and VI to account for two (unspecified which) of the isomers. All three isomers were hydrolyzed to IV. Michaelis also studied the cyclization of V ($R = \text{H}$ and C_6H_5) but obtained only a single isomer in these cases.

Veibel³⁻⁵ reinvestigated these products and showed that γ -pyrazoisocumarazone is a 2:1 eutectic of the β - and α -isomers. From



dipole moment and titration studies, structure III seemed favored for the β -isomer. However, recently, examination⁷ of the infrared spectra of the α - and β -isomers provided good evidence for assigning structure III to the β -isomer and structure VI to the α -isomer. By careful work, Veibel⁴ was able to obtain two isomeric products from the cyclization of V ($R = C_6H_5$) and two others from the ethyl homolog. It seems probable that the lower melting member of these isomeric pairs in each case is of type III and the higher melting product of type VI. The products of type VI are discussed separately (see Section A-176).

Treatment² of III or its phenyl homolog with iodine, bromine or phosphorus pentachloride introduces halogen at the 3-position, while upon treatment with ammonia or primary amines, the ring oxygen is replaced by nitrogen to give² pyrazolo[2,3-*a*]quinazolones (see Section A-567). The phenyl analog of III condenses with phenol, dimethylaniline, etc., in the presence of aluminum chloride, to give products,² the structures of which need further study.

Attempts⁶ to obtain the 2-amino or 2-hydroxy derivatives of this nucleus by condensing 2-carboxyphenylhydrazine with iminomalonic or malonic esters, were unsuccessful.

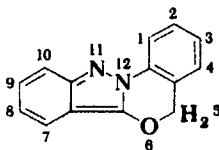
Derivatives of 5*H*-Pyrazolo[*a*][3,1]benzoxazin-5-one

Substituents	Properties	Refs.
Unsubstituted	m. 116°. b ₇₆₀ 308°.	2
3-Bromo-	m. 199°.	2
2-Methyl-	m. 135°.	1-4,7
2-Methyl-3-bromo-	m. 152-3° (151°).	2,3
2-Methyl-3-iodo-	m. 132°.	2
3-Carboxy-2-methyl-	m. 224° (mixture?).	2
3-Ethyl-2-methyl-	m. 107-8°.	4
2-Phenyl-	m. 144-5° (199° or 201-2°?).	2,4

References

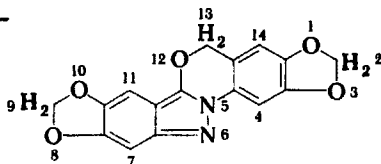
1. Michaelis and Eisenschmidt, *Ber.*, **37**, 2228 (1904).
2. Michaelis, Zeisel, Krug and Leo, *Ann.*, **373**, 129 (1910).
3. Veibel and Arnfeld, *Acta Chem. Scand.*, **2**, 914 (1948).
4. Veibel and Arnfeld, *Acta Chem. Scand.*, **2**, 921 (1948).
5. Veibel, Refn and Friediger, *Acta Chem. Scand.*, **2**, 927 (1948).
6. Jennen, *Ind. chim. belg.*, **16**, 472 (1951); *Chem. Abstracts*, **46**, 6387 (1952).
7. Mosby, *Chem. and Ind.*, **1956**, 1524.

A-564. 5H-Indazolo[3,2-*a*][3,1]-benzoxazine. R.I. 2380

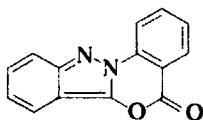


and

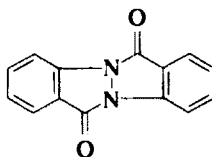
A-565. 13H-1,3-Dioxolo[*g*][1,3]dioxolo-[5,6]indazolo[2,3-*a*][3,1]-benzoxazine. R.I. 3454



A number of references are to be found to compounds thought to contain these nuclei, but a recent study¹ of the infrared spectrum of the simplest of these products disclosed that it probably has structure II rather than I. Accordingly, these compounds are discussed in Section A-177.



(I)

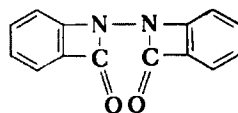


(II)

Heller² found that the gentle dehydration of III with acetic anhydride yielded a product (m. 180–1°), which he called *bisanthranil*, and to which he assigned structure IV. However, the infrared spectrum of bisanthranil is incompatible with a β -lactam structure, and it is thought¹ that the product has structure I. Heller² also found that bisanthranil is converted by heat into an isomeric material (m. 295°), which he thought to be I, but for which structure II is more likely.¹



(III)

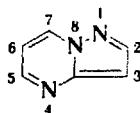


(IV)

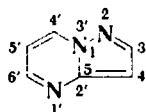
References

1. Mosby, *Chem. and Ind.*, **1957**, 17.
2. Heller, *Ber.*, **49**, 523 (1916).

A-566. Pyrazolo[2,3-*a*]pyrimidine.
R.I. 757

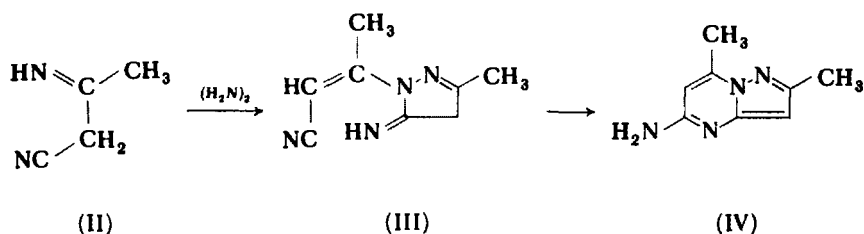


This ring system has also been called *pyrimidopyrazole*, *1,4,7a-triazaindene* and *1,5:2',3'-pyrazopyrimidine*, numbered as shown in I.



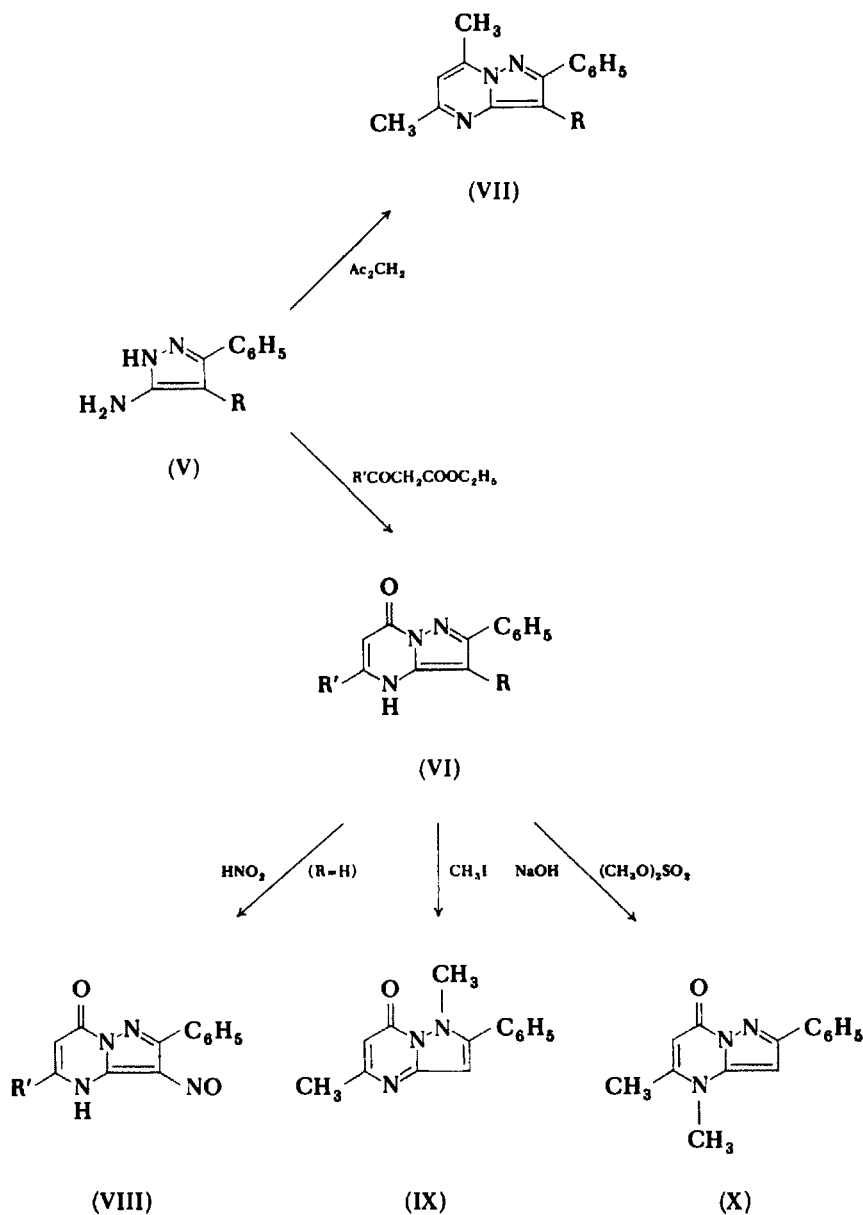
(I)

The reaction of II with hydrazine¹ yields two products, which were assigned² structures III and IV (m. 200–1°; acetyl deriv., m. 106°; phenyl urea, m. 137°). Compound IV is evidently formed by the further cyclization of III.

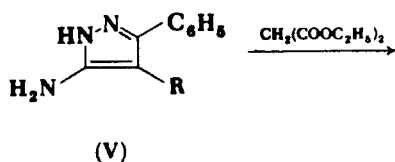
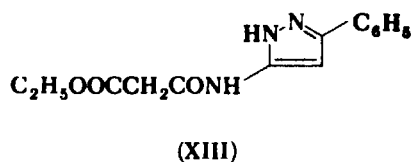
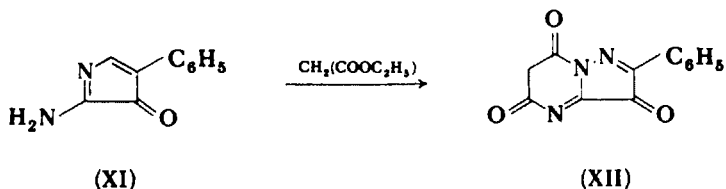


Checchi, Papini and Ridi^{3,4} treated V with acetoacetic and benzoylactic esters and isolated products of type VI⁵ (R = H, R' = CH₃, m. > 320°; R = R' = CH₃, m. 308–10°; R = H, R' = C₆H₅, m. 330–2°). Condensation of V with acetylacetone yielded⁴ VII (R = H, m. 170–2°; R = CH₃, m. 129–32°; R = NO, grn., d. 230°). Nitrosation of VI (R = H) yielded VIII (R' = CH₃ m. 265–7°). Methylation of VI (R = H, R' = CH₃) with methyl iodide in methanol at 120° yielded³ IX (m. 168–70°), while with dimethyl sulfate and caustic, a different methyl compound (X, m. 242–3°) was

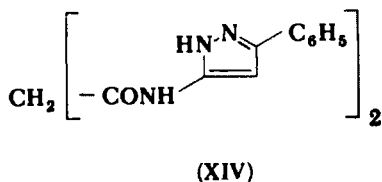
formed. The reaction of 3-amino-4-cyano-5-(2-hydroxyethoxy)pyrazole with acetoacetic ester yielded¹¹ 3-cyano-7-hydroxy-2-(2-hydroxyethoxy)-5-methylpyrazolo[2,3-*a*]pyrimidine (m. > 300°).



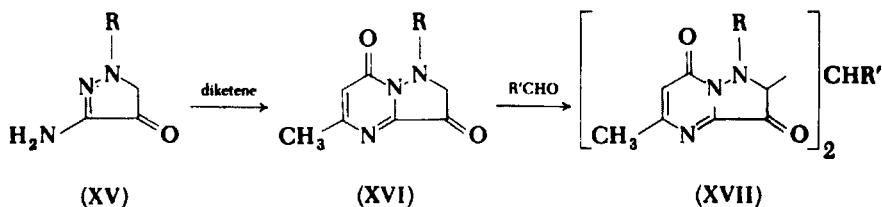
The reaction of malonic ester with XI was claimed to yield XII, which was used⁶ in the preparation of photographic sensitizing agents. However, more recently, products of types XIII and XIV were reported⁴ formed from V (R = H) in this reaction.



and

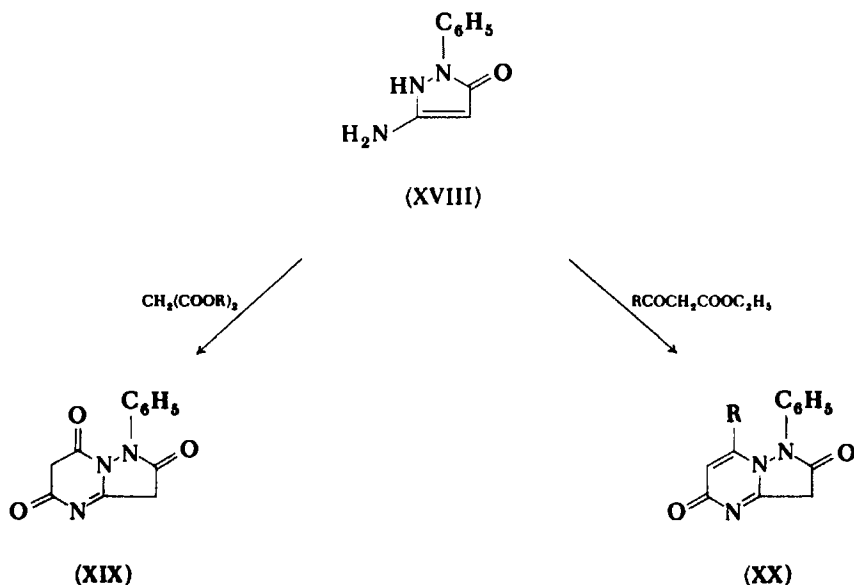


The condensation of XV with diketene was reported⁷ to yield products of type XVI (no properties reported), which were patented as photographic sensitizing agents. Diazonium salts coupled⁸ into the 2-position of XVI, and oxidation of XVI (R = C₆H₅) with hy-

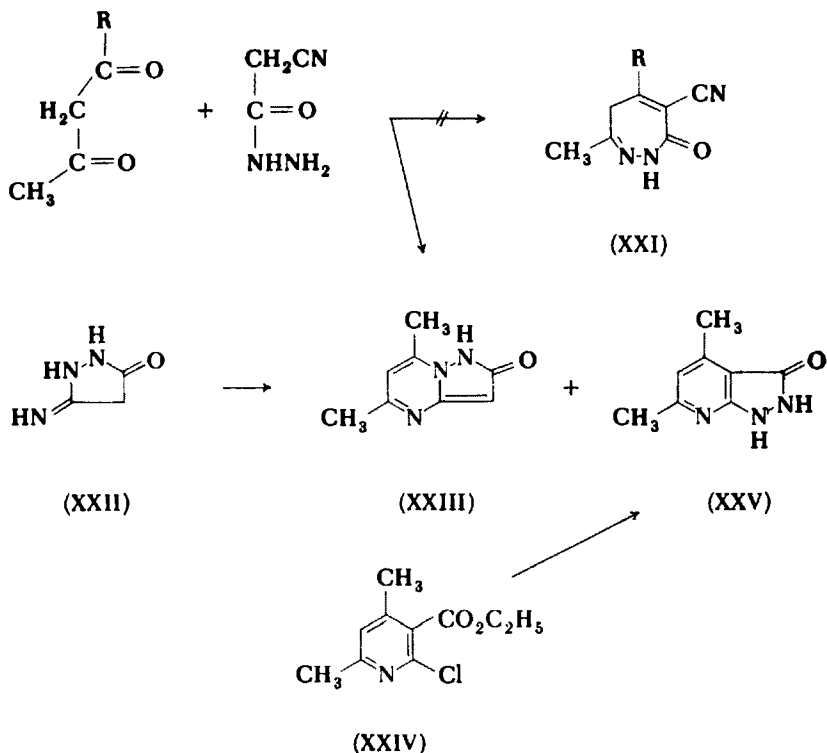


drazine formed a 2,2'-dimeric derivative.⁹ Aldehydes condensed with XVI in the 2-position to give XVII, but no details regarding the products were reported.⁹

The reaction of XVIII with malonic or acylacetic esters yields,¹⁰ respectively, XIX or XX ($R = CH_3$, no details; $R = m-CH_3OC_6H_4$, m. 254-5°; $R = o-CH_3OC_6H_4$, m. 210-2°). These products were claimed as photographic fog-inhibitors.



The reaction of cyanacethydrazide with acylacetones yields products ($R = CH_3$, yellow, m. 237-8° [233-4°¹³ or 215-7°¹²], nitroso deriv., orange, m. 183-4°d.; $R = C_6H_5$, light yellow, m. 257-8°, nitroso deriv., red, m. 216-7°d.) thought¹⁴ to have structure XXI. However, the same product ($R = CH_3$) was recently obtained¹³ from the reaction of XXII with acetylacetone, and it was shown to have structure XXIII. Accompanying XXIII in this synthesis, was another product, shown by its preparation from XXIV to have structure XXV. Compound XXIII had previously been prepared,¹² but was erroneously assigned structure XXV.



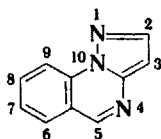
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6. Anish, U. S. Pat. 2,423,218.
7. Bavley, U. S. Pats. 2,481,466 and 2,403,329; Brit. Pat. 599,719.
8. Kellog, U. S. Pat. 2,569,418.
9. Kellog, U. S. Pat. 2,593,890.
10. Allen and Beilfuss, U. S. Pat. 2,735,769.
11. Little, Middleton, Coffman, Engelhardt and Sausen, *J. Am. Chem. Soc.*, **80**, 2832 (1958).
12. Papini, Checchi and Ridi, *Gazz. chim. ital.*, **84**, 769 (1954); *Chem. Abstracts*, **50**, 966 (1956).

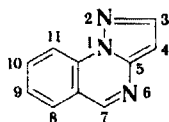
13. Schmidt, Meier and Druey, *Angew. Chem.*, **70**, 344 (1958).

14. Ried and Köcher, *Angew. Chem.*, **70**, 164 (1958).

A-567. Pyrazolo[*a*]quinazoline.
R.I. 1567

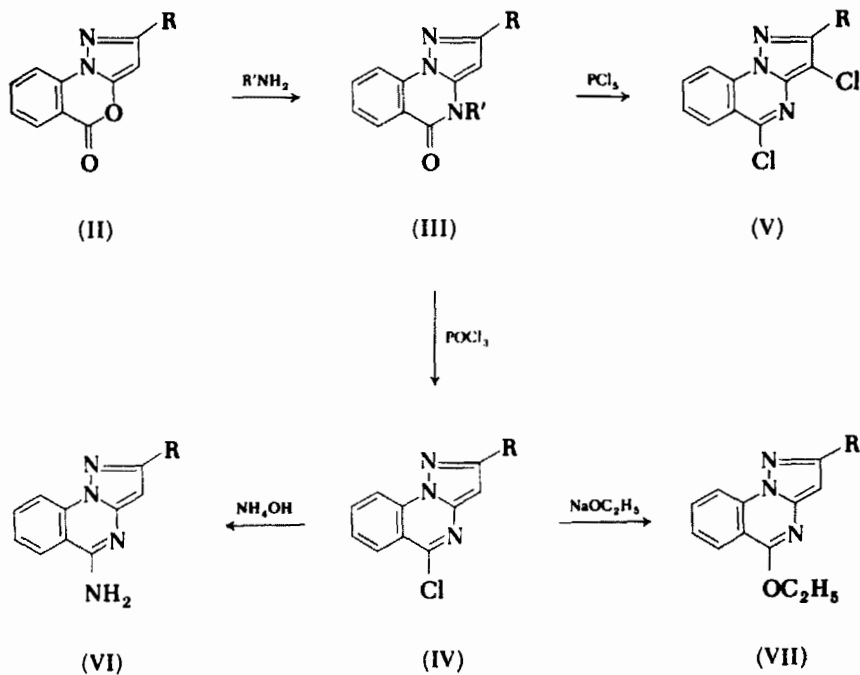


The name *pyrazoquinazoline* and numbering shown in I have been used.



(I)

Treatment of II (see Section A-563) with ammonia or amines is reported¹ to yield III ($R = R' = H$, m. 265° ; $R = CH_3$, $R' = H$, m. $275-6^\circ$; $R = R' = CH_3$, m. $133-4^\circ$; $R = CH_3$, $R' = C_6H_5$, m. 156° ; $R = CH_3$, $R' = C_6H_5NH-$, m. 195° ; $R = CH_3$, $R' = NH_2$, m. 294° ; $R = CH_3$, $R' = N=CHC_6H_5$, m. 174° ; $R = CH_3$, $R' = -N=C(C_6H_5)_2$, m. 257° ; $R = CH_3$, $R' = -NHCONH_2$, m. 265° ; $R = C_6H_5$, $R' = H$, m. 315° ; $R = C_6H_5$, $R' = C_2H_5$, m. 171° ; $R = R' = C_6H_5$, m. 211° ; $R = C_6H_5$, $R' = C_6H_5NH-$, m. 248° ; $R = C_6H_5$, $R' = NH_2$, m. 232° ; $R = C_6H_5$, $R' = -N=CHC_6H_5$, m. 185° ; $R = C_6H_5$, $R' = NHCONH_2$, m. 325° ; $R = C_6H_5$, $R' = OH$, m. 247°). Calcium hypochlorite converts III (where $R' = H$) into the corresponding *N*-chloro derivative (III, $R = CH_3$, $R' = Cl$, m. $230^\circ d.$; $R = C_6H_5$, $R' = Cl$, m. $243-8^\circ d.$). Compound III, where $R' = H$ again, reacts with phosphorus oxychloride to yield IV ($R = H$, m. 130° ; $R = CH_3$, m. 139° ; $R = C_6H_5$, m. 145°), while with phosphorus pentachloride, a second chlorine is simultaneously introduced, giving V ($R = CH_3$, m. $174-5^\circ$; $R = C_6H_5$, m. 160°). Treatment of IV with ammonia yields VI ($R = C_6H_5$, m. 215° , alcoholic solutions show a blue fluorescence), while VII ($R = CH_3$, m. 125° ; $R = C_6H_5$, m. 136°) results from the reaction of IV with sodium ethoxide.

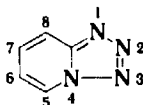
*Reference*

1. Michaelis, Zeisel, Krug and Leo, *Ann.*, **373**, 129 (1910).

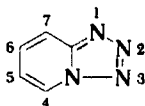
CHAPTER VII

Fused 5/6 Ring Systems with Three Extra Heteroatoms

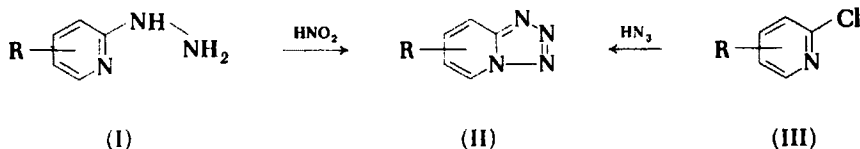
A-568. Pyridotetrazole. R.I. 672



The names *1,2,3-triazaindolizine*, *1,2,3,9-benzisotetrazole* (or simply *benztetrazole*) and the numbering shown in I are also encountered (e.g., in *Chemical Abstracts* first decennial index).

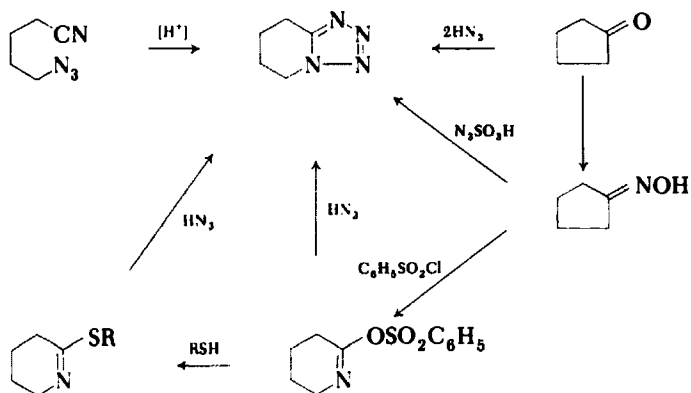


The most commonly used synthesis of the pyridotetrazoles (II) consists in treating 2-pyridylhydrazines (I) with nitrous acid.¹⁻⁸ A variety of substituted pyridotetrazoles have thus been prepared in good yield. An alternative synthesis involves treating 2-halopyridines (III) with hydrazoic acid (not sodium azide, however, which gives only 2-azidopyridines),⁹⁻¹¹ and again, good yields are obtained.

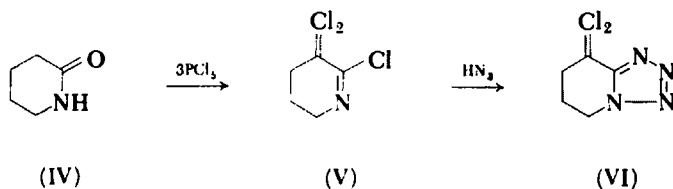


Catalytic reduction of II leads¹² to dihydro, and finally to 5,6,7,8-tetrahydropyridotetrazoles, although these compounds are usually obtained in other ways. For example, they are formed by

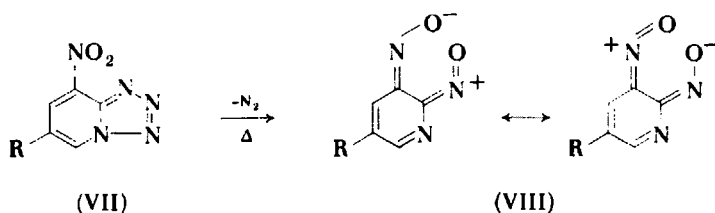
treating δ -azidovaleronitriles with chlorosulfonic acid,¹³ or from the reaction of cyclopentanones¹⁴ or cyclopentanone oximes, or 2-arylsulfonyloxy-3,4,5,6-tetrahydropyridines¹⁵ or 2-alkylthio-3,4,5,6-tetrahydropyridines¹⁶ with hydrazoic acid. Azidosulfonic acid may replace hydrazoic acid in the reaction with cyclopentanone oximes.¹⁷ Most of these syntheses have also been used in the preparation of metrazole (see Section A-703).



Treatment of piperidone (IV) with three moles of phosphorus pentachloride produces the trichloro compound V, which yields VI upon reaction with hydrazoic acid.¹⁸ In one case,¹⁹ a substituted piperidone itself was converted into a tetrahydropyridotetrazole by hydrazoic acid.



Little or nothing is known regarding the reactivity of the pyridotetrazoles. Most of them decompose on melting, and it has been shown^{10,11} that VII may be pyrolyzed to VIII, in nearly quantitative yield. Pyridotetrazoles lacking the 8-nitro group gave unidentified (polymeric ?) products¹⁰ when pyrolyzed.



The pharmacology of several pyridotetrazoles has been studied.^{20,21} The ultraviolet spectrum of II (R = H) has been compared²² with those of other polyazaindenes.

Derivatives of Pyridotetrazole

Empirical formula	Substituents	Properties	Refs.
C ₅ H ₂ BrN ₅ O ₂	8-Bromo-6-nitro-	Pale rose, m. 125°.	7
C ₅ H ₃ N ₅ O ₂	6-Nitro-	m. 142-3° (138-40° d.).	7,10
	8-Nitro-	m. 167-8° d.	10
C ₅ H ₄ N ₄	Unsubstituted	m. 159° (156-8°; 155-6°).	2,8,9,10
C ₅ H ₆ N ₄	α,α -Dihydro-	m. 96-8°.	12
C ₅ H ₆ Cl ₂ N ₄	8,8-Dichloro-5,6,7,8-tetrahydro-	m. 85-6°.	18
C ₅ H ₈ N ₄	5,6,7,8-Tetrahydro-	b ₆ 168-70°; m. 138° ? (m. 115°).	12-14, 16,17
C ₆ H ₃ ClN ₄ O ₂	6-Carboxy-8-chloro-	m. 195-6°. Ethyl ester, m. 95-6°. Diethylamide, m. 113-5°.	3,4
C ₆ H ₃ N ₅ O ₄	6-Carboxy-8-nitro-	m. 189.5-90.0° d. Methyl ester, m. 117° d.	11
C ₆ H ₄ N ₄ O ₂	6-Carboxy-	m. > 330°. Acid azide, m. 103-4°. Various alkaloid salts reported.	1,5
C ₆ H ₄ N ₄ O ₄	6-Carboxy-5,7-dihydroxy-	Solid. Methyl ester, m. 198° d. Also made amide, nitrile, etc.; no m.p. given.	6,21

(continued)

Derivatives of Pyridotetrazole (*continued*)

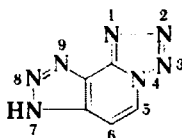
Empirical formula	Substituents	Properties	Refs.
C ₆ H ₆ N ₄	5-Methyl-	m. 152-3°.	12
C ₆ H ₁₀ N ₄	5,6,7,8-Tetrahydro-5-methyl-	m. 92-4°.	12
C ₇ H ₈ N ₄	5,7-Dimethyl-	m. 128-9°.	12
C ₇ H ₁₀ N ₄ O ₂	5-Carboxymethyl-5,6,7,8-tetrahydro-	m. 187-9°. Ethyl ester, m. 76-7°.	19
C ₇ H ₁₂ N ₄	5,6,7,8-Tetrahydro-5,7-dimethyl-	m. 95-7° (95-6°).	12,13
C ₈ H ₁₂ N ₄ O ₂	8(or 5?)-Carbethoxy-5,6,7,8-tetrahydro-	b _{0.5} 172; m. 41°. (Note: this compound, originally shown as the 5-isomer, is probably the 8-isomer.)	13
C ₁₀ H ₁₆ N ₄	5,6,7,8-Tetrahydro-5(or 8)-methyl-6,7-methylene-6(or 7)-isopropyl-	m. 93-5°. From β-thujone oxime.	15
	5,7(or 6,8)-Ethano-5,6,7,8-tetrahydro-5,6,6(or 7,7,8)-trimethyl-	m. 242-3°. "Camphor-tetrazole."	15

References

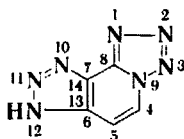
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2. Fargher and Furness, *J. Chem. Soc.*, **107**, 688 (1915).
3. Graf, *J. prakt. Chem.*, **138**, 244 (1933).
4. Graf, *J. prakt. Chem.*, **138**, 259 (1933).
5. Kenner and Statham, *Ber.*, **69**, 187 (1936).
6. Schroeter and Fink, *Ber.*, **71**, 671 (1938).
7. Bremer, *Ann.*, **539**, 276 (1939).
8. Mangini and Colonna, *Boll. sci. facoltà chim. ind. Bologna*, **2**, 197 (1941); *Chem. Abstracts*, **41**, 1224 (1947).
9. v. Braun and Rudolph, *Ber.*, **74**, 264 (1941).
10. Boyer, McCane, McCarville and Tweedie, *J. Am. Chem. Soc.*, **75**, 5298 (1953).
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12. Wolf (Kereszty and Wolf), U. S. Pat. 2,008,536. Ger. Pat. 613,123; *Frdl.*, **22**, 621 (1939). Fr. Pat. 786,884. Austr. Pat. 144,041.
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14. Schmidt (Knoll & Co.), Ger. Pat. 455,585; *Frdl.*, **16**, 2862 (1931).

15. Schmidt, U. S. Pat. 2,029,799. Ger. Pat. 606,615; *Frdl.*, **21**, 675 (1937).
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17. Kereszty and Wolf, Hung. Pat. 134,391; *Chem. Abstracts*, **43**, 2239 (1949).
18. Knoll, A. G., Ger. Pat. 576,327; *Frdl.*, **20**, 762 (1935). Brit. Pat. 350,782. Swiss Pat. 149,836. Austr. Pat. 133,506.
19. Birkofer and Hartwig, *Chem. Ber.*, **89**, 1608 (1956).
20. Issekutz, Leinzinger and Novak, *Arch. exptl. Path. Pharmacol.*, **177**, 397 (1935); *Chem. Abstracts*, **29**, 3783 (1935).
21. Barwanietz, *Arch. wiss. prakt. Tierheilk.*, **71**, 297 (1937); *Chem. Abstracts*, **31**, 7522 (1937).
22. Bower, *J. Chem. Soc.*, **1957**, 4510.

**A-569. 7H-Tetrazolo[1,5-*a*]triazolo-
[c]pyrimidine. R.I. 1310H**

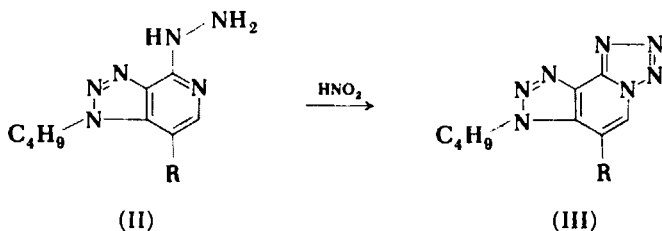


This nucleus has also been called *6,7-benzotetrazolo-13,14-triazole*, and numbered as shown in I.



(I)

Treatment of II with nitrous acid produced¹ III (R = H, m. 157–8°; R = Br, m. 114°).



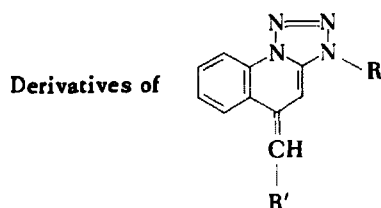
Reference

1. Bremer, *Ann.*, **539**, 276 (1939).

picted in the resonance form having an uncharged tetrazolo[*a*]quinoline nucleus.

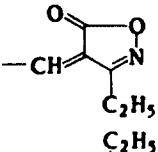
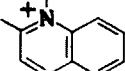
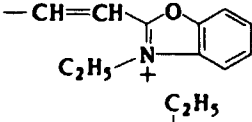
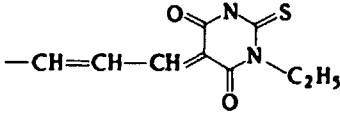
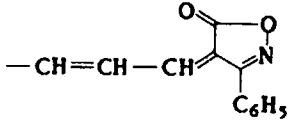
The 4,5-dihydro derivative (m. 101.5–2°) was obtained⁶ by means of the Schmidt reaction upon indanone, and its ultraviolet spectrum was compared with those of related products.

Compounds of structure II have been claimed⁷ as photographic fog inhibitors.



R	R'	Properties	Refs.
CH ₃		Grn., m. 207–8° d.	5
C ₂ H ₅		Grn., m. 238–9° d.	5
C ₂ H ₅		Grn., m. 231–3° d.	5
CH ₃		<i>p</i> -Toluenesulfonate, or., m. 255–6° d.	4
C ₂ H ₅		Iodide, or., m. 245–7° d.	4
C ₂ H ₅		Iodide, maroon, m. 259– 61° d.	4
C ₂ H ₅		Brn., m. 252–3° d.	5

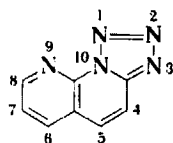
(continued)

R	R'	Properties	Refs.
C ₂ H ₅		Grn., m. 267-8°.	5
C ₂ H ₅		Iodide, or.-brn., m. 244-6° d.	4
C ₂ H ₅		Iodide, bl.-grn., m. 234-6° d.	4
C ₂ H ₅		Dk. purple, m. 201-2° d.	5
C ₂ H ₅		Dk. bl., m. 239-40° d.	5

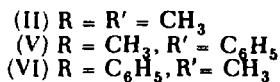
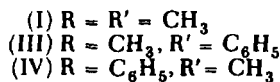
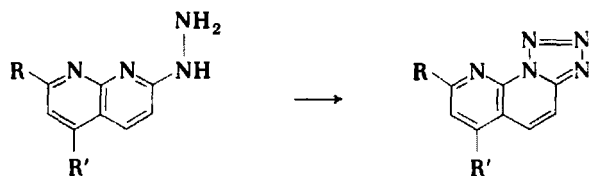
References

1. Marckwald and Meyer, *Ber.*, **33**, 1885 (1900).
2. Marckwald and Chain, *Ber.*, **33**, 1895 (1900).
3. v. Braun and Rudolph, *Ber.*, **74**, 264 (1941).
4. Brooker, U. S. Pat. 2,689,849. Brit. Pat. 736,266.
5. Brooker, U. S. Pat. 2,743,274. Brit. Pat. 782,311.
6. Huisgen and Ugi, *Ann.*, **610**, 57 (1957).
7. Kodak, S. A., Belg. Pat. 562,142.

A-571. Tetrazolo[*a*][1,8]-naphthyridine



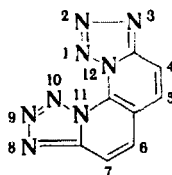
The reaction of I with nitrous acid is reported¹ to yield II (m. 240°d.). A homolog of I, thought to be either III or IV, similarly yielded V or VI (m. 260-1°d.).



Reference

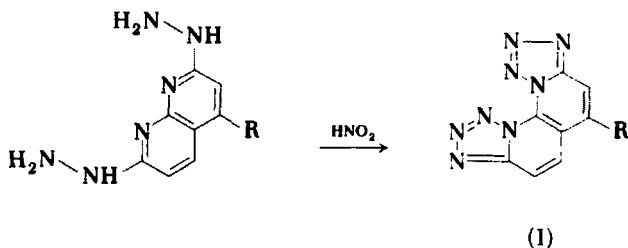
1. Mangini and Colonna, *Gazz. chim. ital.*, **73**, 323, 330 (1943); *Chem. Abstracts*, **41**, 1225 (1947).

A-572. Ditetrazolo[*a,h*]naphthyridine. R.I. 2247



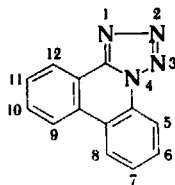
This ring system has also been named *1,2,7,8-di[tetrazolo-1',5']-[1,8-naphthyridine]*.

Two derivatives (I, R = CH₃, m. ~190°d.; R = C₆H₅, m. 203°) of this nucleus have been described,^{1,2} both prepared, as shown, from naphthyridine derivatives.

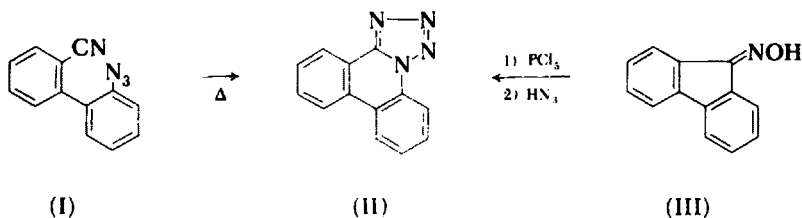


References

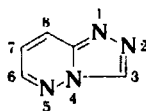
1. Seide, *Ber.*, **59**, 2465 (1926).
2. Mangini and Colonna, *Boll. sci. fac. chim. ind. Bologna*, **1941**, 85; *Chem. Zentr.*, **I**, 2131 (1942); *Chem. Abstracts*, **37**, 3096 (1943).

A-573. Tetrazolo[*l*]phenanthridine*

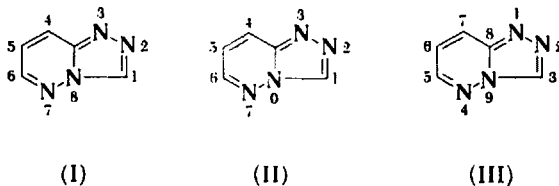
Thermal isomerization of I yielded II (m. 221.5–3.5°), the structure of which was demonstrated¹ by its alternative synthesis from III.

*Reference*

1. Smith, Clegg and Hall, *J. Org. Chem.*, **23**, 524 (1958).

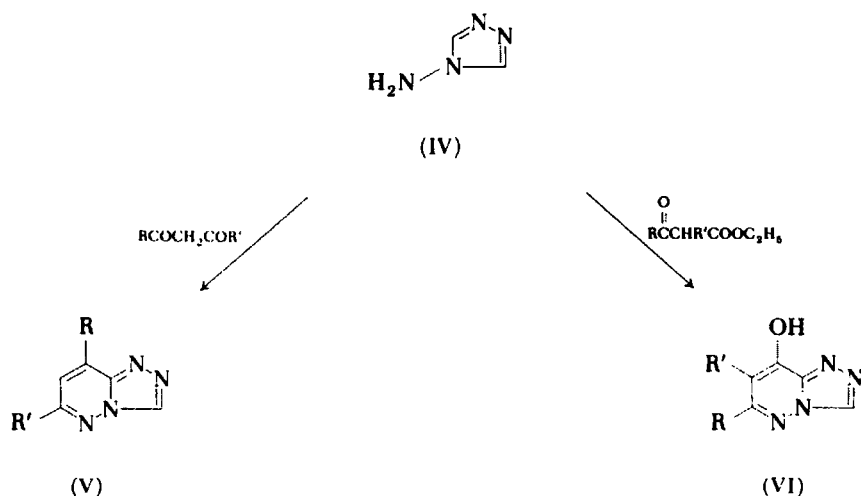
A-574. *s*-Triazolo[4,3-*b*]pyridazine.*
R.I. 706

The *Ring Index* name is *s-triazolo[b]pyridazine*, but use of the above name would seem necessary to insure adequate specificity. The names 2,3,7-triazaindolizine (numbered as shown in I), 1,2,3a,4-tetrazaindene, and 2,3-triazo-7,0-pyridazine (II) have been used, and the numbering shown in III was suggested by Richter.

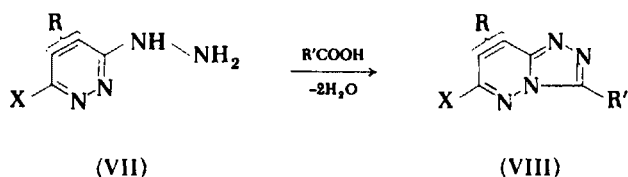


Two general methods have been used for the preparation of derivatives of this ring system. Bülow treated 4-amino-*s*-triazole (IV)

with 1,3-diketones¹ and obtained V, while with β -ketoesters, products were obtained, which he considered^{2,3} to have structure VI. These 8-hydroxy derivatives (VI) give² a ferric chloride (enol) test, and may be converted³ readily into the corresponding chloro compounds. A slight variation in this synthesis was introduced by Heimbach, who claimed⁴ as photographic antihalation agents a group of azo derivatives of VI, which he prepared by coupling various diazonium salts with acetoacetic ester and condensing the resulting azo esters with IV.



The second general synthesis, recently described by Takahayashi,⁵ utilizes pyridazine derivatives such as VII, and constructs the triazole ring, giving VIII. This synthesis has the additional interest that it provides a route to the 6-hydroxy derivatives, isomeric with VI. Where the R group of VII is other than hydrogen, it is not known which of the two positions it occupies, and consequently it may be in either the 7- or 8-position of VII. It would be interesting to



compare the properties of isomeric compounds of structures VI and VIII, and incidently to confirm Bülow's assignment of structure VI to his products, but the requisite isomers have not been described.

The chlorine atom of VIII ($R = R' = H$, $X = Cl$) is readily replaced by H, OH, SH, NH_2 , $NHNH_2$, etc., and this method has been used to prepare the prototype of the ring system.

Compounds of structure V are very stable and may be distilled without decomposition; they form insoluble complexes with salts of heavy metals, and Bülow refers¹ to their high toxicity.

Products of type VI have been studied⁹⁻¹¹ as photographic fog-inhibitors.

Derivatives of *s*-Triazolo[4,3-*b*]pyridazine

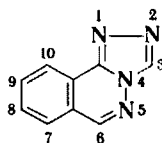
Empirical formula	Substituents	Properties	Refs.
$C_5H_3ClN_4$	6-Chloro-	m. 203.5°.	5
$C_5H_4N_4$	Unsubstituted	m. 134°. HCl salt, m. 230°.	8
$C_5H_4N_4O$	6-Hydroxy-	m. 291° d.	8
$C_5H_4N_4S$	6-Mercapto-	m. 236° d. (190-3° d?).	5,8
$C_5H_5N_5$	6-Amino-	m. 272.5°.	8
$C_5H_6N_6$	6-Hydrazino-	m. 221°. <i>N</i> -Formyl deriv., m. 252°.	8
$C_6H_5ClN_4$	6-Chloro-3-methyl-	m. 103.5°.	5
	6-Chloro-7 (or 8)-methyl-	m. 107°.	5
	8-Chloro-6-methyl-	Yel., m. 185°.	3
$C_6H_5IN_4$	8-Iodo-6-methyl-	m. 211-2°.	3
$C_6H_6N_4$	6-Methyl-	m. 168-9° (167-8°, 158-9°). Picrate, m. 162-3°.	3,10-12
$C_6H_6N_4O$	8-Hydroxy-6-methyl-	m. > 295° (250-7°). Benzoate ester, m. 157-8°.	2,3,5-7
	6-Methoxy-	m. 178°.	5
$C_6H_6N_4S$	8-Mercapto-6-methyl-	m. > 280°.	3
$C_7H_7ClN_4$	6-Chloro-2,7 (or 2,8)-dimethyl-	m. 135°.	5
$C_7H_8N_4$	6,8-Dimethyl-	m. 122-3°. Mononitrate, m. 180-1°.	1
$C_7H_8N_4O$	8-Hydroxy-6,7-dimethyl-	m. 252°.	2
	6-Methoxy-2-methyl-	m. 166°.	5
	6-Methoxy-7 (or 8)-methyl-	m. 120.5°.	5
$C_8H_{10}N_4$	6,7,8-Trimethyl-	m. 129°.	1

Derivatives of *s*-Triazolo[4,3-*b*]pyridazine (continued)

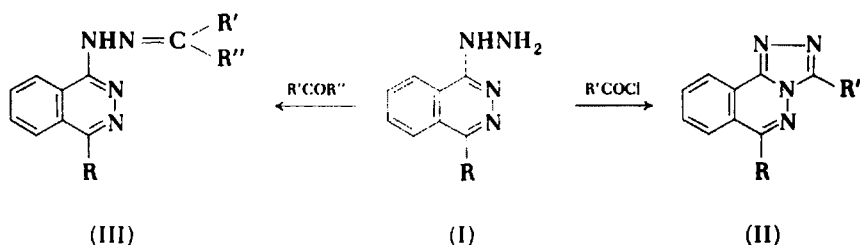
Empirical formula	Substituents	Properties	Refs.
$C_8H_{10}N_4O$	8-Ethoxy-6-methyl-	m. 170–1°.	3
	8-Hydroxy-7-ethyl-6-methyl-	m. 229°.	6,9,11
$C_{11}H_8N_4O$	8-Hydroxy-6-phenyl-	m. 282°. Complex with IV, 2 m. 243–4°.	2
$C_{12}H_{11}N_4$	6 (or 8)-Methyl-8 (or 6)-phenyl-	m. 152–3°. $HgCl_2$ complex; 1 m. 181°.	1

References

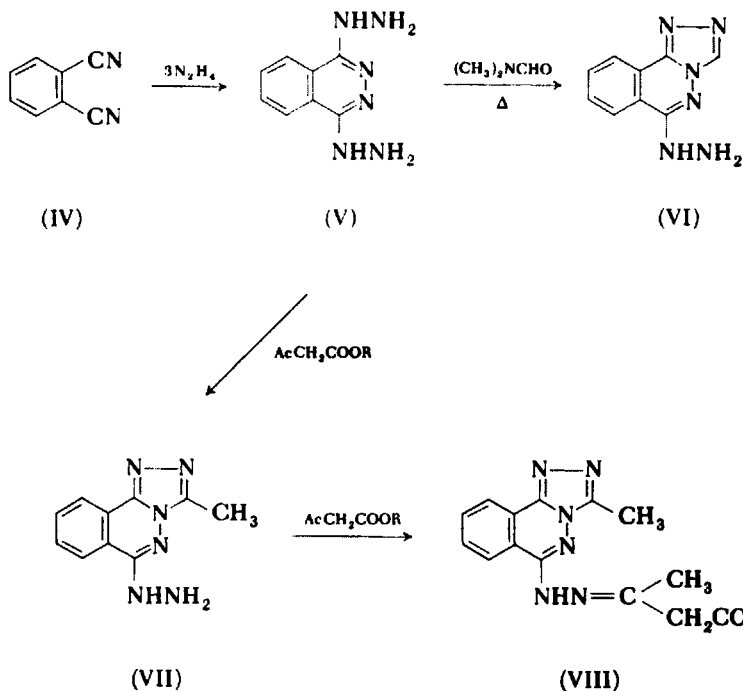
1. Bülow, *Ber.*, **42**, 2208 (1909).
2. Bülow, *Ber.*, **42**, 2594 (1909).
3. Bülow and Haas, *Ber.*, **43**, 1975 (1910).
4. Heimbach, U. S. Pat. 2,390,707.
5. Takahayashi, *J. Pharm. Soc. Japan*, **75**, 1242 (1955); *Chem. Abstracts*, **50**, 8655 (1956).
6. Murobushi, Kuwabara, Baba and Aoki, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **58**, 440 (1955); *Chem. Abstracts*, **49**, 14544 (1955).
7. Birr, *Z. wiss. Phot.*, **47**, 2 (1952).
8. Takahayshi, *J. Pharm. Soc. Japan*, **76**, 765 (1956); *Chem. Abstracts*, **51**, 1192 (1957).
9. Kuwabara and Aoki, *Komishiroku Rev.*, **6**, 1 (1955); *Chem. Abstracts*, **49**, 11473 (1955).
10. Burness, U. S. Pat. 2,837,521.
11. Kikuchi and Akiba, *J. Soc. Sci. Phot. (Japan)*, **18**, 20 (1955); *Chem. Abstracts*, **50**, 2331 (1956).
12. Allen *et al.*, *J. Org. Chem.*, **24**, 796 (1959).

A-575. *s*-Triazolo[3,4-*a*]phthalazine

A group of derivatives of this nucleus (II) was recently prepared^{1,2} by the condensation of acids, esters or acid halides with 1-hydrazinophthalazines (I). The condensation of acetoacetic ester with I also gave II by cleavage of acetic ester from the intermediate hydrazone III. No cyclized products were formed from the hydrazones (III) of acetophenone or acetone, where cleavage of either



methane or benzene would be necessitated.¹ The hydrazone of cyclopentanone [III, $R = H$, $R' + R'' = (CH_2)_4$] rearranged when heated to 250° to give an unidentified product ($C_{13}H_{14}N_4$), containing an acidic NH group.¹ The reaction of I ($R = H$) with pyruvic acid did not give II, but the intermediate of type III ($R = H$, $R' = CH_3$, $R'' = COOH$) cyclized¹ to a 6/6 ring system (see Section A-867). With potassium cyanate, I ($R = H$) gave phthalazinyldiazine, and with allyl isothiocyanate I ($R = CH_3$) gave III ($R = CH_3$, $R' = SH$, $R'' = NHCH_2CH = CH_2$), which upon recrystallization from acetic acid yielded two products of type

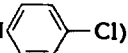


II ($R = CH_3$, $R' = SH$ and $R = CH_3$, $R' = NHCH_2CH = CH_2$).

A very convenient synthesis of dihydrazinophthalazines (V, or I where $R = NHNH_2$) consists in treating³ phthalonitrile with three moles of hydrazine. If the reaction is carried out in the presence of a formylating agent such as dimethylformamide, VI can be obtained directly. The reaction of V with one mole of acetoacetic ester yields⁴ VII, while with two moles, VIII is formed. Products such as VIII show no inclination to cyclize a second time to form bistriazolophthalazines (see Sections A-642, A-645/6 and A-649).

The interest in these compounds derives chiefly from their activity as hypotensive agents.^{1,3,5}

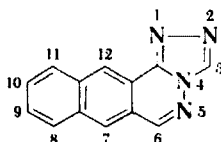
Derivatives of *s*-Triazol[3,4-*a*]phthalazine

Empirical formula	Substituents	Properties	Refs.
$C_9H_5ClN_4$	3-Chloro-	m. 205°.	1
$C_9H_6N_4$	Unsubstituted	m. 190-1°.	1,2
$C_9H_6N_4O$	3-Hydroxy-	m. 275-7°.	1
$C_9H_8N_6$	6-Hydrazino-	d. ~295°.	3
$C_{10}H_6Cl_2N_4$	3-Dichloromethyl-	m. 213-5°.	1
$C_{10}H_7ClN_4$	3-Chloromethyl-	m. 188-9°.	1
$C_{10}H_8N_4$	3-Methyl-	m. 171-2°.	1,2
$C_{10}H_8N_4S$	3-Mercapto-6-methyl-	m. ~300°.	1
$C_{10}H_{10}N_6$	6-Hydrazino-3-methyl-	m. 305-7° d.	4
$C_{13}H_{13}N_5$	3-Allylamino-6-methyl-	m. 139-40°.	1
$C_{13}H_{14}N_4$	3- <i>n</i> -Butyl-	m. 101-2°.	1
	3- <i>i</i> -Butyl-	m. 91-2°.	1
$C_{14}H_7Cl_2N_5$	3-(2,6-Dichloro-4-pyridyl)-	m. 292-5°.	6
$C_{15}H_{10}N_4$	3-Phenyl-	m. 208-9°.	1
$C_{15}H_{16}N_6O_2$	6-($\text{---NHN}=\overset{\text{CH}_3}{\text{CCOOCH}_3}$)	m. 198° d.	4
$C_{15}H_{18}N_4$	3- <i>n</i> -Hexyl-	m. 71-3°.	1
$C_{16}H_{12}N_4$	6-Methyl-3-phenyl-	m. 212° (210°).	1,2
$C_{16}H_{12}ClN_5$	6-($\text{---NHN}=\text{CH}$  Cl)		3
$C_{16}H_{13}H_5$	6-($\text{---NHN}=\text{CHC}_6\text{H}_5$)	m. 280-1°.	4
$C_{16}H_{18}N_6O_2$	6-($\text{---NHN}=\overset{\text{CH}_3}{\text{CCOOC}_2\text{H}_5}$)	m. 207-8°.	4
$C_{18}H_{17}N_5O_2$	3-(2,6-Diethoxy-4-pyridyl)-	Yel., m. 207-11°.	6

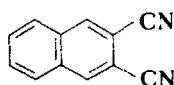
References

1. Druey and Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).
2. Hartmann and Druey, U. S. Pat. 2,484,029.
3. Kunze, Ger. Pat. Appl'n. C 8884-IVb/12p.
4. Zerweck and Kunze, Ger. Pat. Appl'n. C 7864-IVb/12p.
5. Walker, Wilson, Atkins, Garrett and Richardson, *J. Pharmacol. Exptl. Therap.*, **101**, 368 (1951); *Chem. Abstracts*, **45**, 6294 (1951).
6. Roche Products Ltd., Brit. Pat. 711,756; *Chem. Abstracts*, **49**, 11724 (1955).

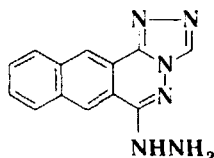
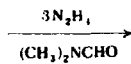
A-576. Benzo[*g*]-*s*-triazolo[3,4-*a*]-phthalazine



Compound II (d. 315–20°; *p*-chlorobenzalhydrazone, m. 295°) was prepared¹ by the condensation of I with three moles of hydrazine in dimethylformamide solution. See Section A-575 and A-577/8.



(I)

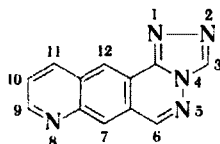


(II)

Reference

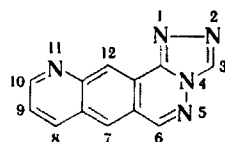
1. Kunze, Ger. Pat. Appl'n. C8884 IVb/12p.

A-577. Pyrido[2,3-*g*]-*s*-triazolo[3,4-*a*]-phthalazine*



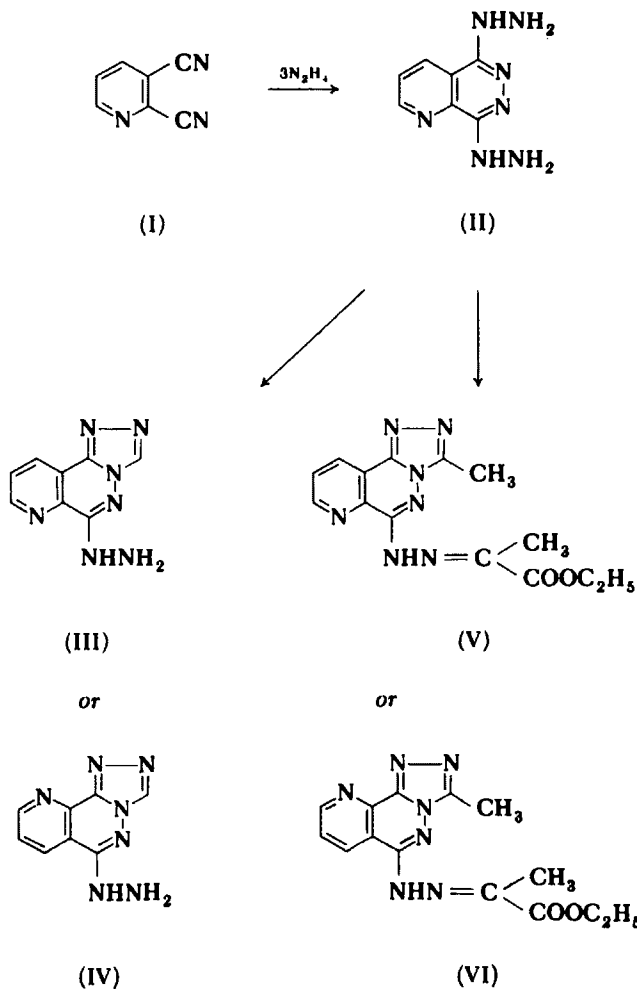
or

A-578. Pyrido[3,2-*g*]-*s*-triazolo[3,4-*a*]-phthalazine*



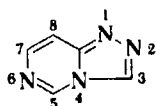
The reaction of I with three moles of hydrazine yields II, which upon reaction with formylating agents (formic acid, dimethylform-

amide, etc.), gives¹ a product (m. 240–2°d.) having either structure III or IV. Similarly, treatment of II with two moles of acetoacetic ester gives² a substance (m. 185–6°) thought to be either V or VI. See Sections A-575/6.

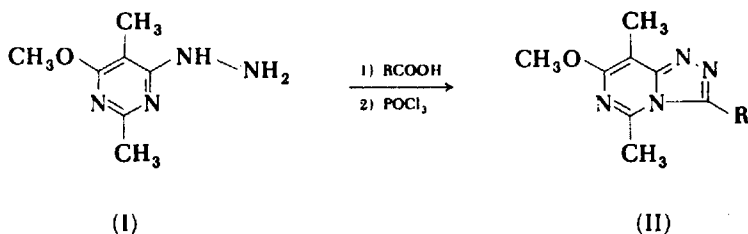


References

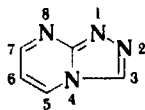
1. Kunze, Ger. Pat. Appl'n. C8884 IVb/12p.
2. Zerweck and Kunze, Ger. Pat. Appl'n. C7864 IVb/12p.

A-579. *s*-Triazolo[4,3-*c*]pyrimidine

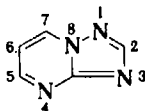
Condensation of the hydrazine I with various carboxylic acids, and dehydration with phosphorus oxychloride of the intermediate acylhydrazines, yielded¹ the triazolopyrimidines II (R = H, m. 182°; R = CH₃, m. 238°; R = C₂H₅, m. 202°; R = C₃H₇, m. 140°; R = (CH₃)₂CHCH₂, m. 126°; R = C₆H₅, m. 142–3°). Compound II (R = CH₃) was also obtained by refluxing I in acetic anhydride with a drop of sulfuric acid. Similarly, 7-methyl-3-phenyl-*s*-triazolo[4,3-*c*]pyrimidine (m. 187°) was prepared² from 4-hydrazino-6-methylpyrimidine.

*References*

1. Shiho, Tagami, Takahayashi and Honda, *J. Pharm. Soc. Japan*, **76**, 804 (1956); *Chem. Abstracts*, **51**, 1196 (1957).
2. Bower and Doyle, *J. Chem. Soc.*, **1957**, 727.

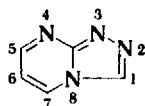
A-580. *s*-Triazolo[4,3-*a*]pyrimidine*

and

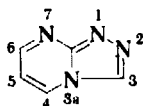
**A-581. *s*-Triazolo[2,3-*a*]pyrimidine.
R.I. 707**

The first ring system has also been called 2,3,4-triazaindolizine (I), 1,2,8-triazaindolizine and 1,2,3a,7-tetrazaindene (II), while the names pyrimidotriazole, 1,3,4-triazaindolizine (III), 1,3-triaza-7,0'-pyrimi-

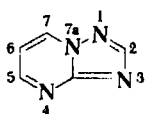
dine (IV) and 1,3,3a,7-tetrazaindene (V) have been applied to the latter nucleus.



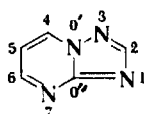
(I)



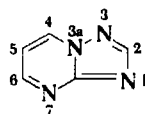
(II)



(III)



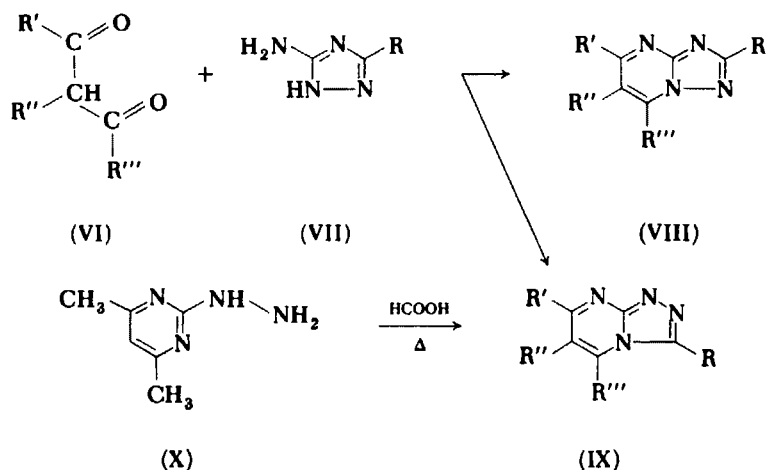
(IV)



(V)

The literature concerning these ring systems is in a state of considerable confusion. At least two, and often four isomeric structures usually are possible for the derivatives of these nuclei, and until very recently, evidence permitting a choice between any of them was unavailable. Most of the references are to patents, which contain little or no structural evidence, while the continued arbitrary employment of unaccepted systems of nomenclature approaches obscurantism.

Bülow and Haas prepared¹ the first examples of these ring systems by condensing 3-amino-1,2,4-triazole (VII, R = H) with various 1,3-dicarbonyl compounds (VI). With symmetrically constituted diketones such as acetylacetone (VI, R'' = H, R' = R''' = CH₃), products of either type VIII or IX (R = R'' = H, R' = R''' = CH₃) might be expected. Bülow and Haas assigned structure VIII to their products, and Allen *et al.*³³ demonstrated the formation of VIII (R = R'' = R''' = H, R' = CH₃), *not* IX, from the reaction of VII (R = H) with 1-methoxybuten-3-one. However, Bower and Doyle claim²⁵ to have obtained the same product from (1) the reaction of VII (R = H) with acetylacetone and (2) the condensation of X with boiling formic acid, and because of the latter synthesis, they assign structure IX (R = R'' = H, R' = R''' = CH₃) to the substance. While under acidic conditions, the rearrangement (*v.i.*) of certain compounds of type IX, in which R''' = OH, to isomers of type VIII has been demonstrated,³¹ no evidence is available con-



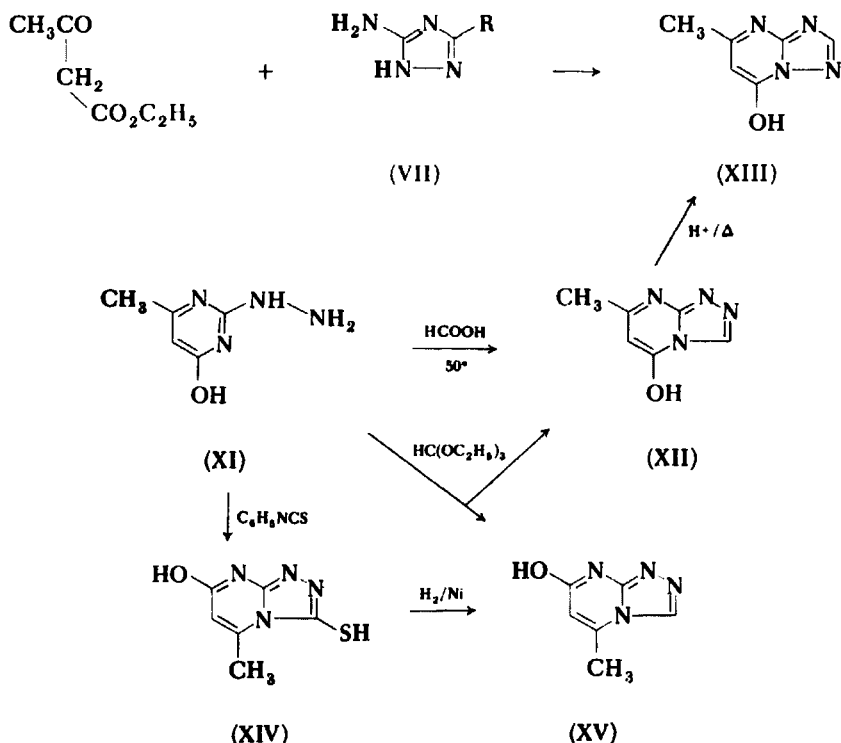
cerning the rearrangement of alkyl or aryl homologs of IX (R''' = alkyl or aryl), and it cannot be certain that the reaction of X with formic acid was unaccompanied by rearrangement. Condensation of X with ethyl orthoformate, however, should give an unequivocal answer to this question.

The reactions of VII with *asymmetric* 1,3-dicarbonyl compounds superimpose the problem of position isomerism upon the previously discussed question of nuclear isomerism. Thus, when Bülow and Haas condensed benzoylacetone (VI, $R' = \text{CH}_3$, $R'' = \text{H}$, $R''' = \text{C}_6\text{H}_5$) with VII ($R = \text{H}$), they formulated¹ the product as a 7-phenyl homolog (VIII, $R = R'' = \text{H}$, $R' = \text{C}_6\text{H}_5$, $R''' = \text{CH}_3$), but in an analogous reaction with VII ($R = \text{CH}_3$) the product was assigned² the 5-phenyl structure (VIII, $R = R' = \text{CH}_3$, $R'' = \text{H}$, $R''' = \text{C}_6\text{H}_5$). No comment was made upon the discrepancy. It seems probable that such reactions often yield mixtures of the two position isomers, one of which may be discarded during the isolation process. The reaction of VII ($R = \text{H}$) with 1,1-dimethoxy-2-methylbutan-3-one was reported³³ to yield *both* the 5,6- and 6,7-dimethyl derivatives of type VIII.

The reaction of 3-aminotriazoles (VII) with β -ketoesters leads to products for which four structures are possible (two each of types VIII and IX, in which either R' or $R''' = \text{OH}$). These products usually have been formulated^{1,2,4-19} as VIII or IX with $R''' = \text{OH}$. Bülow and Haas¹ arbitrarily assigned structure VIII ($R =$

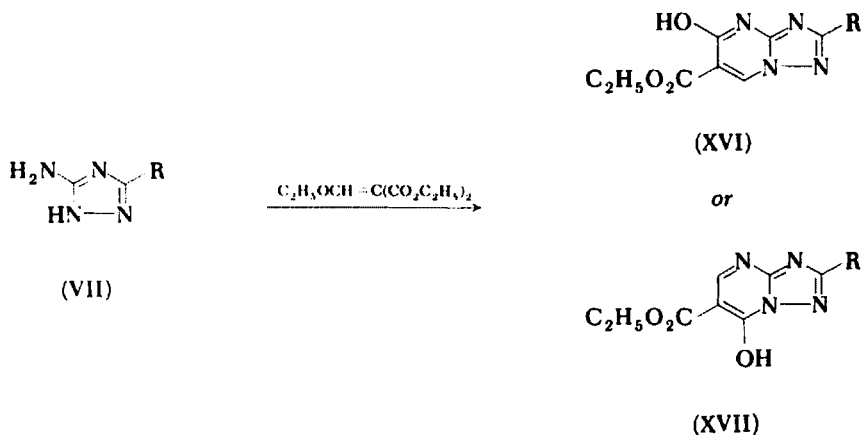
$R'' = \text{H}$, $R' = \text{CH}_3$, $R''' = \text{OH}$) to the substance obtained by treating VII ($R = \text{H}$) with acetoacetic ester, and after considerable dispute,^{17,18,29} this hypothesis has been vindicated.^{30,31}

In an attempt to demonstrate the structure of this product, Birr and Walter¹⁸ treated XI with formic acid and as the product was identical with that prepared from VII ($R = \text{H}$) and acetoacetic ester, they assumed it had structure XII. However, Allen *et al.*³¹ showed that the nature of the product obtained thus from XI depends upon the conditions of the reaction. Under mild conditions of acidity and temperature, XII is, indeed, produced. But, in the presence of mineral acid, or with boiling formic acid, XII is isomerized rapidly to XIII, and this explains the cause of Birr and Walter's confusion. To complicate the matter further, it was shown³¹ that the reaction of XI with phenyl isothiocyanate gave XIV, which could be desulfurized by Raney nickel to produce XV. Finally, condensation of XI with ethyl orthoformate yielded a mixture of XII

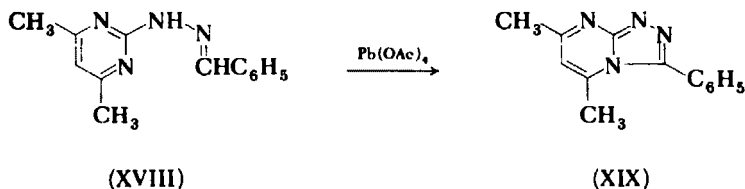


and XV. Thus one is able to prepare three of the four isomers possible in these reactions. It is interesting that, while VII ($R = H$) reacted¹⁸ with β -chlorocrotonic ester to yield XIII, the reaction of 3-bromo-*s*-triazole with β -aminocrotonic ester was unsuccessful.¹⁸

Heimbach,⁴ and deCat and Van Dormael³ treated 3-amino-*s*-triazoles with ethoxymethylenemalonic and related esters, and obtained a group of products, which they thought were of type XVI. The ester group could be removed by alkaline hydrolysis, giving hydroxy compounds which Birr¹⁷ claimed were "chemically different from, and much more weakly acidic" than the isomeric substances obtained via Bülow's synthesis. However, without reference to this earlier work, Allen *et al.*^{31,34} assert that, because of their ultraviolet spectra, these products have structure XVII. While this opinion may be accurate, the data presented³¹ constitute less than a convincing proof in the absence of authentic examples of type XVI for comparison, and it is difficult to reconcile with Birr's statement above.

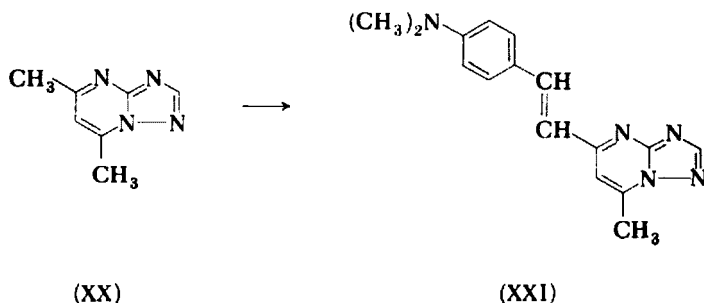


An apparently unequivocal synthesis of the *s*-triazolo[4,3-*a*]-pyrimidine nucleus was described by Bower and Doyle,²⁵ who oxidized XVIII with lead tetraacetate and obtained XIX, which was quite different from the isomeric substance obtained by condensing VII ($R = C_6H_5$) with acetylacetone. Several other derivatives of type XIX were obtained by this technique.



The reaction of guanazole (VII, $R = \text{NH}_2$) with acetoacetic or benzoylacetic esters yields^{5,21} high-melting products, which were assigned²¹ a 5/5 bicyclic structure (see Section A-181), but it seems probable⁵ that structure VIII ($R = \text{NH}_2$, $R'' = \text{H}$, $R''' = \text{OH}$, $R' = \text{CH}_3$ or C_6H_5) is correct.

Condensation of the dimethyl compound XX (or its [4,3-*a*]isomer) with *p*-dimethylaminobenzaldehyde is said¹⁷ to yield XXI (or its [4,3-*a*] isomer), and quaternization of XX with methyl iodide is pictured^{9,17} as placing the methyl group in the 4-position. Num-



erous cyanine dyes containing these nuclei have been patented,^{9,10} Nitrosation occurs⁸ in the 6-position of VIII ($R = R'' = \text{H}$, $R' = \text{NH}_2$ or OH , $R''' = \text{OH}$). The 6-position of XIII again is the site of diazonium coupling,^{13,14} chlorination³¹ or hydroxylation by the action of persulfate³¹ or permanganate.¹⁷ Numerous ill-described derivatives of these nuclei are mentioned^{4, 7-17, 22} in connection with applications as photographic anti-fogging agents, anti-halation dyes, toners, sensitizers, etc., and most of these are not included in the tables. There has been considerable discussion^{20, 24, 26, 27, 29} and study of the photographic applications of derivatives of these nuclei.

s-Triazolo[4,3-*a*]pyrimidines

Empirical formula	Substituents	Properties	Refs.
C ₆ H ₆ N ₄ O	5-Hydroxy-7-methyl-	m. 252-4°; λ _{max} 210, 246 and 294 mμ (ε 17,700, 4,800 and 6,800).	30,31
	7-Hydroxy-5-methyl-	m. 296-8°; λ _{max} 210 and 248 mμ (ε 22,700 and 7,000).	30,31
C ₆ H ₆ N ₄ OS	7-Hydroxy-3-mercapto-5-methyl-	m. 280° (273°) d.	25,31
C ₇ H ₈ N ₄ O	5-Hydroxy-3,7-dimethyl-	m. 310-1°; λ _{max} 209, 248 and 298 mμ (ε 17,000, 4,600 and 9,200).	30,32
	7-Hydroxy-3,5-dimethyl-	m. 309-10°; λ _{max} 210 and 248 mμ (ε 23,000 and 6,600).	30,32
C ₇ H ₈ N ₄ S	3-Mercapto-5,7-dimethyl-	m. 241° d.	25
C ₈ H ₈ N ₄ O ₃ S	3-Carboxymethylthio-7-hydroxy-5-methyl-	m. 239-41° (251°) d.	25,28
C ₈ H ₁₀ N ₄ O ₂	5-Hydroxy-3-(2-hydroxyethyl)-7-methyl-	m. 237-40°.	32
C ₉ H ₁₀ N ₄ O ₂ S	3-Carboxymethylthio-5,7-dimethyl-	m. 183°.	25
C ₁₂ H ₉ BrN ₄ O	3-(4-Bromophenyl)-5-hydroxy-7-methyl-	m. >340°.	25
C ₁₂ H ₉ N ₅ O ₃	5-Hydroxy-7-methyl-3-(3-nitrophenyl)-	m. >340°.	25
C ₁₂ H ₁₀ N ₄ O	5-Hydroxy-7-methyl-3-phenyl-	m. >340°.	25
C ₁₃ H ₁₁ BrN ₄	3-(4-Bromophenyl)-5,7-dimethyl-	m. 286° d.	25
C ₁₃ H ₁₂ N ₂	5,7-Dimethyl-3-phenyl-	m. 260°.	25

s-Triazolo[2,3-*a*]pyrimidines

Empirical formula	Substituents	Properties	Refs.
C ₅ H ₄ N ₄	Unsubstituted	m. 140-2°.	33
C ₅ H ₄ N ₄ O	5-Hydroxy-	m. 287-8° (204-5° as the EtOH solvate).	29,32
	7(?) -Hydroxy-	—	4,17

s-Triazolo[2,3-*a*]pyrimidines (*continued*)

Empirical formula	Substituents	Properties	Refs.
C ₅ H ₄ N ₄ O ₂	5,7-Dihydroxy-	m. 278°.	8,11,19, 20
C ₅ H ₅ N ₅ O ₂	2-Amino-5,7-dihydroxy-	m. > 285°.	5
C ₅ H ₆ N ₆ O	2,7-Diamino-5-hydroxy-	m. 300°.	5
C ₆ H ₄ ClN ₄	5-Chloro-7-methyl-	m. 151-2°; λ _{max} 222 and 272 mμ (ε 23,500 and 5,000).	19,30, 31
C ₆ H ₅ ClN ₄ O	6-Chloro-5-hydroxy-7-methyl-	m. > 350°, d. > 300; λ _{max} 262 and 298 mμ (ε 7,200 and 10,800).	31
C ₆ N ₃ N ₇	5-Azido-7-methyl-	m. 120° d.	31
C ₆ H ₆ N ₄	7-Methyl	m. 185° (182-3°); λ _{max} 234 and 271 mμ (ε 1,500 and 4,000). Ethio-dide, m. 262°.	19,28, 30,31, 33
C ₆ H ₆ N ₄ O	5-Hydroxy-6-methyl-	m. > 300; λ _{max} 224 and 280 mμ (ε 4,800 and 9,000).	30,32
	5-Hydroxy-7-methyl-	m. 277-8° (273°, 261°); λ _{max} 256 and 278 mμ (ε 6,400 and 10,800). <i>O</i> -Ethyl ether, m. 149°.	1,18,19, 23,24, 26,29, 30,31
C ₆ H ₆ N ₄ S	5-Mercapto-7-methyl-	m. 310° d; λ _{max} 235 and 336 mμ (ε 9,000 and 20,800).	30,31
C ₆ H ₆ N ₄ OS	5-Hydroxy-2-mercapto-7-methyl-	m. > 290°.	6
C ₆ H ₆ N ₄ O ₂	5,6-Dihydroxy-7-methyl-	m. > 330°, d. > 300°.	31
C ₆ H ₆ N ₄ O ₂ S	5,7-Dihydroxy-2-methylthio-	m. 244°.	6
C ₆ H ₇ N ₅	2-Amino-7-methyl-	m. 210-1.5°.	28,33
	5-Amino-7-methyl-	m. 244°; λ _{max} 288 mμ (ε 13,500).	30,31

(continued)

s-Triazolo[2,3-*a*]pyrimidines (*continued*)

Empirical formula	Substituents	Properties	Refs.
C ₆ H ₇ N ₅ O	2-Amino-5-hydroxy-7-methyl-	m. > 290°.	5
C ₆ H ₇ N ₅ OS	7-Amino-5-hydroxy-2-methylthio-	m. > 290°.	6
C ₇ H ₆ N ₄ O ₃	7-Carboxy-5-hydroxy-6-methyl-	m. > 325°.	32
C ₇ H ₇ ClN ₄	5-Chloro-2,7-dimethyl-	m. 149–50°.	32
C ₇ H ₇ ClN ₄ O	2-Chloromethyl-5-hydroxy-7-methyl-	m. 211–60° (?).	32
C ₇ H ₈ N ₄	5,6-Dimethyl-	m. 91–9° (?).	33
	5,7-Dimethyl-	m. 136° (133°). Ethiodide, m. 229°.	1, 19, 25
	6,7-Dimethyl-	m. 178.0–8.5°.	33
C ₇ H ₈ N ₄ O	7-Ethyl-5-hydroxy-	m. 212–4° (209–11°).	29, 32
	2,7-Dimethyl-5-hydroxy-	m. > 280°; λ _{max} 210, 238 and 272 mμ (ε 23,500, 2,800 and 9,500).	2, 30
	6,7-Dimethyl-5-hydroxy-	m. 304–5° (291–2°); λ _{max} 265 and 298 mμ (ε 4,700 and 12,500).	29, 30, 32
C ₇ H ₈ N ₄ S	7-Methyl-2-methylthio-	m. 125–6°.	28, 33
C ₇ H ₈ N ₄ OS	5-Hydroxy-7-methyl-2-methylthio-	m. 282°.	6
C ₇ H ₈ N ₄ O ₂	5-Hydroxy-2-hydroxymethyl-7-methyl-	m. 275–7°. Hemi-hydrate, m. 227–9°.	32
C ₇ H ₈ N ₄ O ₂ S	5-Carboxymethylthio-7-methyl-	m. 246–7°; λ _{max} 210 and 291 mμ (ε 15,000 and 11,400).	30
C ₈ H ₈ N ₄ O ₃	6-Carbethoxy-7(or 5)-hydroxy-	m. 210–2°; λ _{max} 248 and 291 mμ (ε 5,100 and 9,000).	3, 4, 16, 17, 30, 33
C ₈ H ₈ N ₈	7-Methyl-5-(1,2,4-triazolyl-3-amino)-	m. > 315°.	31
C ₈ H ₉ N ₅ O ₂	7(or 5)-Amino-6-carbethoxy-	m. 198–200°.	3
C ₈ H ₉ N ₅ O ₃	2-Amino-6-carbethoxy-7(or 5)-hydroxy-	λ _{max} 252 and 310 mμ (ε 3,000 and 14,000).	30
C ₈ H ₁₀ N ₄	2,5,7-Trimethyl-	m. 141–2°.	2, 20
	5,6,7-Trimethyl-	m. 135–6°.	1

s-Triazolo[2,3-*a*]pyrimidines (continued)

Empirical formula	Substituents	Properties	Refs.
C ₈ H ₁₀ N ₄ O	5-Hydroxy-7-propyl-	m. 162-3°.	29
	5-Hydroxy-7- <i>iso</i> -propyl-	m. 245-7°.	29
	6-Ethyl-5-hydroxy-7-methyl-	m. 270-1° (268°).	1,19,29
C ₉ H ₇ N ₅ O ₂	2-Amino-7-(2-furyl)-5-hydroxy-	m. 305°.	5
C ₉ H ₁₀ N ₄ O ₂	6-Carbethoxy-7(or 5)-methyl-	m. 103-4°.	3
C ₉ H ₁₀ N ₄ O ₃	6-Carbethoxy-5(or 7)-hydroxy-2-methyl-	λ _{max} 248 and 291 mμ (ε 5,400 and 9,000).	30
C ₉ H ₁₀ N ₄ O ₃ S	6-Carbethoxy-5(or 7)-hydroxy-2-methylthio-	λ _{max} 265 and 308 mμ (ε 6,600 and 16,200).	30
C ₉ H ₁₀ N ₄ O ₄	6-Carbethoxy-5(or 7)-hydroxy-2-hydroxymethyl-	λ _{max} 252 and 298 mμ (ε 5,800 and 10,000).	30
C ₉ H ₁₂ N ₄	2,5,6,7-Tetramethyl-	m. 116-7°.	2
C ₉ H ₁₂ N ₄ O	7-Butyl-5-hydroxy-	m. 150-1°.	29
	5-Hydroxy-7-methyl-6-propyl-	m. 220-1°.	29
	6-Ethyl-5-hydroxy-2,7-dimethyl-	m. 262°.	2
C ₁₀ H ₇ N ₄ O	5-Hydroxy-7-(2-pyridyl)-	m. > 285°.	19
C ₁₀ H ₈ N ₄ O ₂ S	7-(2-Furyl)-5-hydroxy-3-methylthio-	m. 284°.	6
C ₁₀ H ₁₄ N ₄ O	5-Hydroxy-7-pentyl-	m. 147-8°.	29
C ₁₀ H ₁₅ N ₅ O	2-Amino-6-butyl-5-hydroxy-7-methyl-	m. 305°.	5
C ₁₁ H ₈ N ₄	7-Phenyl-	m. 192°.	19
C ₁₁ H ₈ N ₄ O	5-Hydroxy-7-phenyl-	m. 286°.	19,26
C ₁₁ H ₉ N ₄	2-Amino-5-phenyl-	m. 268.5-9°; λ _{max} 339 mμ (ε 15,700).	33
	2-Amino-7-phenyl-	m. 236.5°; λ _{max} 311 mμ (ε 10,500).	33
C ₁₁ H ₁₆ N ₄ O	7-Hexyl-5-hydroxy-	m. 134-6°.	29
C ₁₁ H ₁₆ N ₄ OS	6-Butyl-5-hydroxy-7-methyl-2-methylthio-	m. 212°.	6
C ₁₂ H ₉ ClN ₄	5-Chloro-7-methyl-2-phenyl-	m. 218°.	25
C ₁₂ H ₁₀ N ₄	5(or 7)-Methyl-7(or 5)-phenyl-	m. ~ 134°.	1
C ₁₂ H ₁₀ N ₄ O	7-Benzyl-5-hydroxy-	m. 240°.	32
	5-Hydroxy-2-methyl-7-phenyl-	m. > 293°.	2
C ₁₂ H ₁₈ N ₄ O	7-Heptyl-5-hydroxy-	m. 131-2° (128-30°).	29,32
C ₁₃ H ₁₂ N ₄	3,7(or 3,5)-Dimethyl-5(or 7)-phenyl-	m. 110-1°.	2

(continued)

s-Triazolo[2,3-a]pyrimidines (continued)

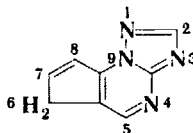
Empirical formula	Substituents	Properties	Refs.
C ₁₃ H ₁₃ N ₅ O	2-Amino-6-benzyl-5-hydroxy-7-methyl-	m. 305°.	5
C ₁₃ H ₂₀ N ₄ O	5-Hydroxy-7-octyl-	m. 124-6°.	29
	2-Heptyl-5-hydroxy-7-methyl-	m. 172°.	32
C ₁₄ H ₁₂ N ₄ O ₃	6-Carbethoxy-7(or 5)-hydroxy-2-phenyl-	—	4
C ₁₄ H ₁₄ N ₄ OS	6-Benzyl-5-hydroxy-7-methyl-2-methylthio-	m. 276°.	6
C ₁₄ H ₂₂ N ₄ O	5-Hydroxy-7-nonyl-	m. 115-8°.	29
C ₁₅ H ₂₄ N ₄ O	7-Decyl-5-hydroxy-	m. 114-6°.	29
C ₁₆ H ₂₆ N ₄ O	5-Hydroxy-7-undecyl-	m. 128-31° (100-1°, a hydrate ?).	29,32
C ₁₇ H ₂₈ N ₄ O	5-Hydroxy-7-methyl-2-undecyl-	m. 163°.	32
C ₁₈ H ₃₀ N ₄ O	5-Hydroxy-7-tridecyl-	m. 90-8°.	29
C ₂₂ H ₃₉ N ₄ O	7-Heptadecyl-5-hydroxy-	m. 87-8°.	29

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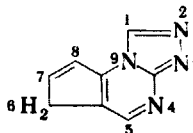
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A-582. 6H-Cyclopenta[*e*]-s-triazolo-[2,3-*a*]pyrimidine

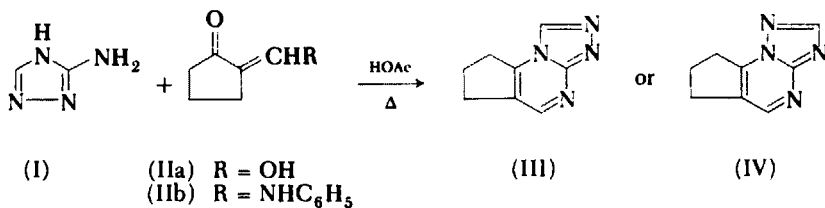


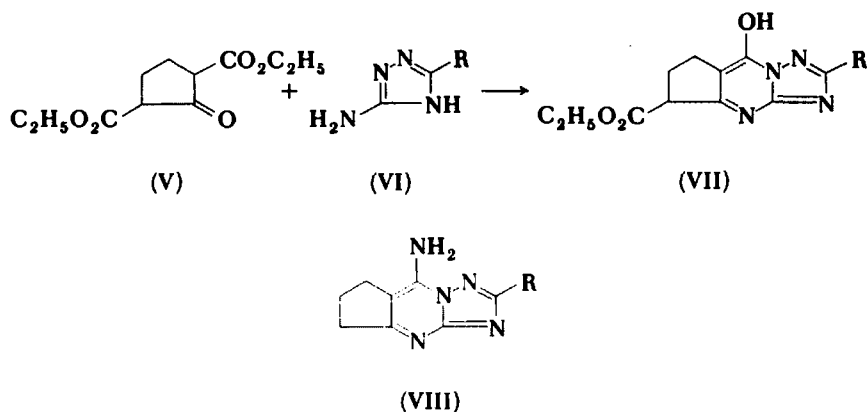
and

A-583. 6H-Cyclopenta[*e*]-s-triazolo-[4,3-*a*]pyrimidine



The reaction of 3-aminotriazole (I) with IIa yields¹ a product (m. 133–4°), which was considered to be either III or (less probably) IV. It was not possible to utilize IIb in this type of re-





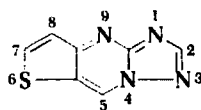
possible that the products assigned structures VII and VIII may be of type III, or the analogous angular derivatives (see Sections A-582/3).

The silver potentiometric titration of IIIa has been examined.⁷

References

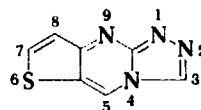
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A-586. Thieno[3,2-*d*]-*s*-triazolo-[2,3-*a*]pyrimidine



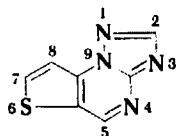
or

A-587. Thieno[3,2-*d*]-*s*-triazolo-[4,3-*a*]pyrimidine*



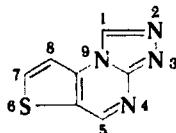
or

**A-588. Thieno[2,3-*e*]-*s*-triazolo-
[1,5-*a*]pyrimidine***

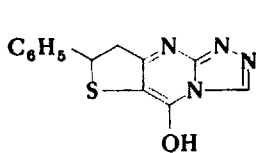
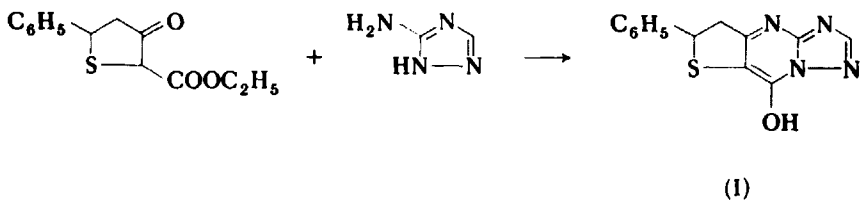


or

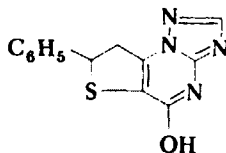
**A-589. Thieno[2,3-*e*]-*s*-triazolo-
[4,3-*a*]pyrimidine***



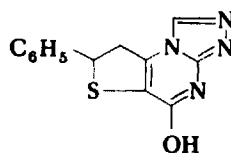
Possibly prepared as shown, and called *8-hydroxy-6-phenyl-thiolano-[4,5-f][1,3,4]triazaindolizine*, compound I was mentioned in patents on photographic fog-inhibitors¹ and toners.² If the product is of the linear type, then structure II also is possible, and the angular structures III and IV must also be considered.



(II)



(III)

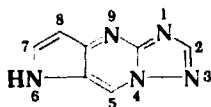


(IV)

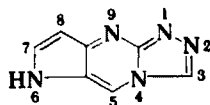
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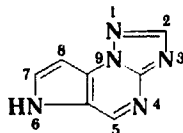
**A-590. 6*H*-Pyrrolo[3,2-*d*]-*s*-triazolo-
[2,3-*a*]pyrimidine**



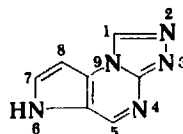
or

A-591. 6H-Pyrrolo[3,2-d]-s-triazolo[4,3-a]pyrimidine*

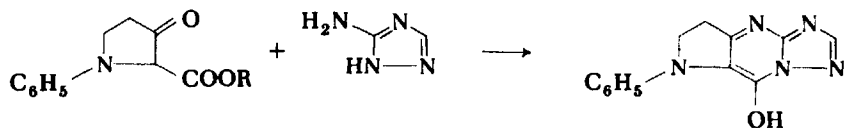
or

A-592. 6H-Pyrrolo[2,3-e]-s-triazolo[1,5-a]pyrimidine*

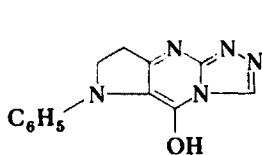
or

A-593. 6H-Pyrrolo[2,3-e]-s-triazolo[4,3-a]pyrimidine*

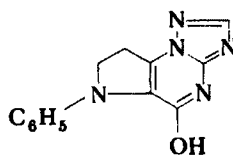
Compound I, possibly prepared as shown, has been mentioned in patents on photographic fog-inhibitors¹ and toners.² It was named *8-hydroxy-7-phenylpyrrolidino[4,5-f][1,3,4]triazaindolizine*, but no other information was given. If prepared as shown, the alternative structures II, III and IV are further possibilities.



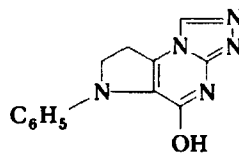
(I)



(II)



(III)

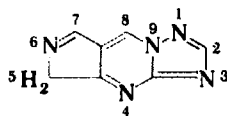


(IV)

References

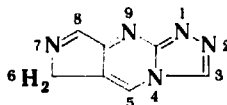
1. Heimbach, U. S. Pat. 2,444,607.
2. Harsh, U. S. Pat. 2,553,500.

A-594. 5*H*-Pyrrolo[3,4-*d*]-*s*-triazolo-
[2,3-*a*]pyrimidine



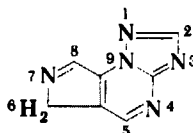
or

A-595. 6*H*-Pyrrolo[3,4-*d*]-*s*-triazolo-
[4,3-*a*]pyrimidine*



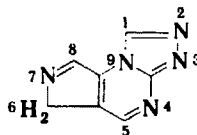
or

A-596. 6*H*-Pyrrolo[3,4-*e*]-*s*-triazolo-
[1,5-*a*]pyrimidine*

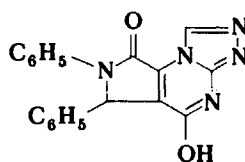
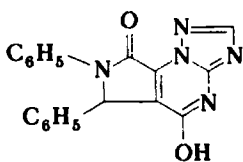
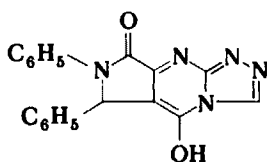
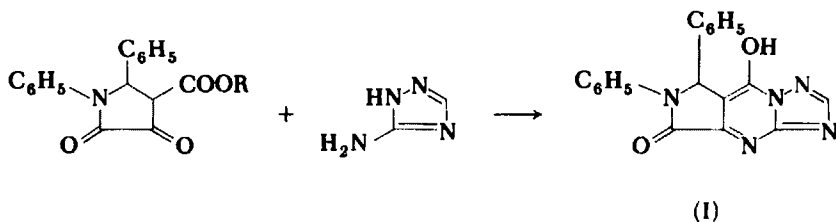


or

A-597. 6*H*-Pyrrolo[3,4-*e*]-*s*-triazolo-
[4,3-*a*]pyrimidine*



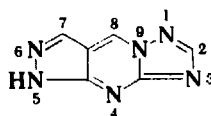
Compound I, which was named *8-hydroxy-5-oxy-6,7-diphenyl-pyrrolidino[3,4-*f*][1,3,4]triazaindolizine*, and possibly was prepared as shown, was mentioned in patents upon photographic fog-inhibitors¹ and toners.² No other information was given, but if the product was synthesized as shown, structures II, III and IV must be considered.



References

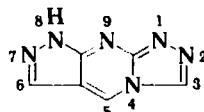
1. Heimbach, U. S. Pat. 2,444,607.
2. Harsh, U. S. Pat. 2,553,500.

A-598. 5*H*-Pyrazolo[3,4-*d*]-*s*-triazolo-
[2,3-*a*]pyrimidine



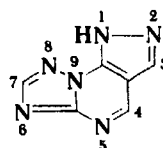
or

A-599. 8*H*-Pyrazolo[3,4-*d*]-*s*-triazolo-
[4,3-*a*]pyrimidine*



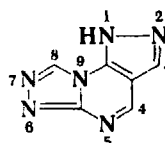
or

A-600. 1*H*-Pyrazolo[4,3-*e*]-*s*-triazolo-
[1,5-*a*]pyrimidine*

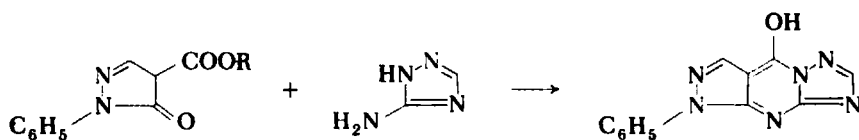


or

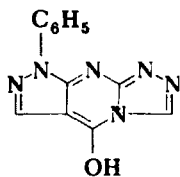
A-601. 1*H*-Pyrazolo[4,3-*e*]-*s*-triazolo-
[4,3-*a*]pyrimidine*



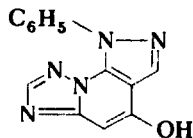
Patents on photographic fog-inhibitors¹ and toners² mention compound I, possibly prepared as shown, which was called 8-*hydroxy-5-phenyl-Δ²-pyrazolidino*[5,4-*f*][1,3,4]triazaindolizine. No further information was reported, but if the product was synthesized as shown, structures II, III and IV also remain possibilities.



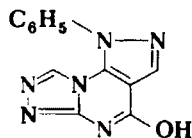
(I)



(II)



(III)

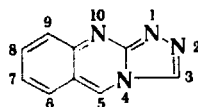


(IV)

References

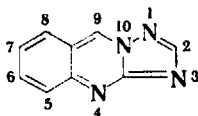
1. Heimbach, U. S. Pat. 2,444,607
2. Harsh, U. S. Pat. 2,553,500.

**A-602. *s*-Triazolo[3,4-*b*]quinazoline
R.I. 1498**



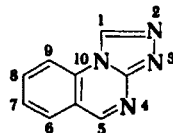
and

A-603. *s*-Triazolo[3,2-*b*]quinazoline



and

A-604. *s*-Triazolo[4,3-*a*]quinazoline*



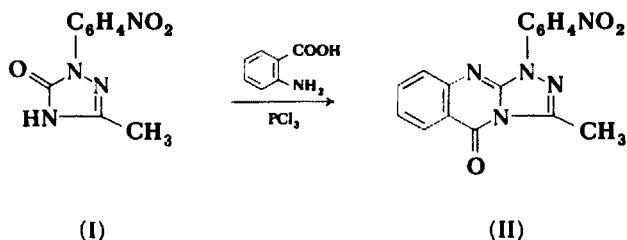
and

A-605. *s*-Triazolo[2,3-*a*]quinazoline*

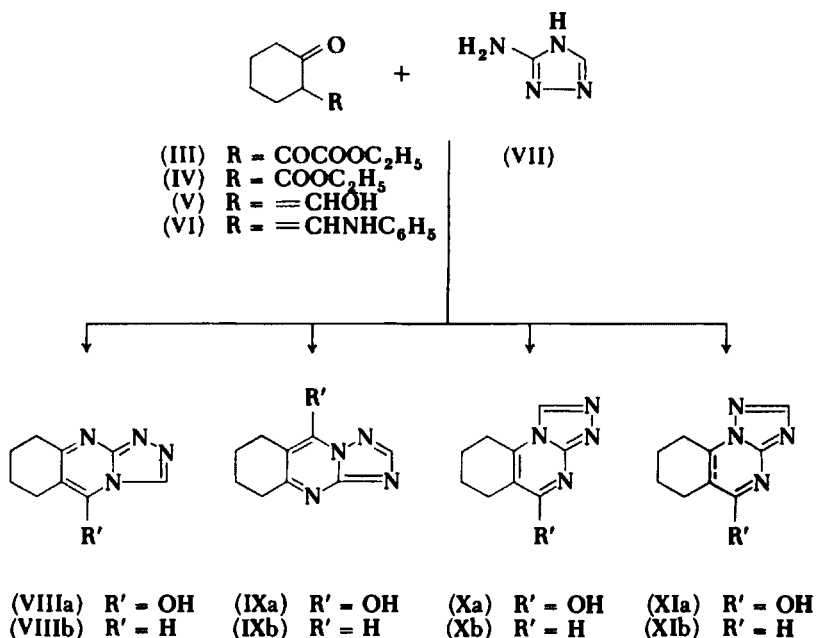


The reaction of acetylurethane with *p*-nitrophenylhydrazine yielded I, which was condensed¹ with anthranilic acid to give a product (brownish-yellow, m. 293°) assigned structure II. The nucleus was called *1,2,4-triazole-4,5-quinazolone*.

The reaction of III with VII yielded² a product (m. 113–6°), which, a priori, might have any of structures VIII–XI (R' =



COOC₂H₅). This ester was converted into an amide (m. 264–6°), and decarboxylation yielded the same product (R' = H, m. 125–6°) obtained from the reaction of VII with V. This identical product (R' = H) was also obtained in three steps from the reaction of IV with VII to yield the hydroxy compound (VIIIa–XIa, m. 279–81°), replacement of the hydroxyl group by chlorine (m.p. 123–4°) and hydrogenolysis of the chlorine atom. The chloro compound was also converted into the diethylaminoethylamino derivative (hydrochloride, m. 204–6°). These products are all thought² to have an angular (either X or XI) rather than linear (VIII or IX) structure, because (1) it was felt² that, in the reaction of VII with V, the hydroxyl

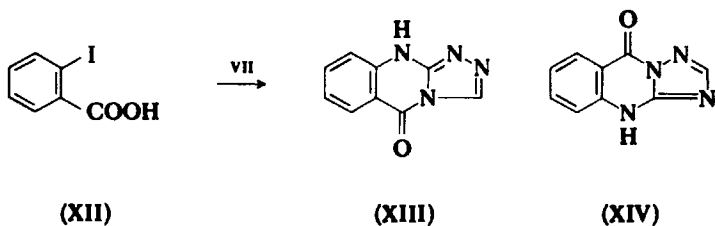


group would react before the carbonyl group with the primary amino group of VII, and (2) from analogy with the reaction of IV and V with aminotetrazole³ (see Section A-649).

When VI was condensed² with VII, the product (VIIIb-XIb, m. 115-8°) obtained was evidently isomeric, but not identical, with the product (v.s.) from the reaction of V and VII. Therefore, this product was considered² to have a linear structure (VIIIb or IXb).

The reaction of IV with guanazole (3,5-diaminotriazole) yielded a product (m. > 295°) formulated⁴ as 2-amino-IXa, and guanazole and 2-methoxymethylenecyclohexanone were reported^{7,8} to yield 2-amino-IXb (m. 317-8°) and "other isomers." Several other incompletely described products, presumably obtained from the reaction of VII with derivatives of IV, were claimed as photographic anti-fogging agents⁵ and toners⁶ and assigned linear structures of type IX.

When VII was condensed with XII, the resulting product (m. 232-7°) was depicted² as XIII or XIV, since the oxygen could



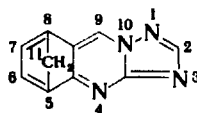
not be replaced by treatment with phosphorus oxychloride or pentachloride. The analogous product from the condensation of 2-amino-tetrazole and XII (see Section A-649) reacted readily with phosphorus oxychloride and was shown to have an angular structure. Another possible explanation for the unreactivity of the first product is that it is a tautomer of XIII or XIV (or their angular counterparts) in which the "extra" hydrogen is located upon one of the triazole ring nitrogen atoms.

Efforts to dehydrogenate Xb (or XIb) by treatment² with sulfur, chloranil, *N*-bromsuccinimide or palladium-charcoal were unsuccessful. When X ($R' = H$ or Cl) was heated with palladium-charcoal, scission of the triazole ring occurred and 2-amino-5,6,7,8-tetrahydroquinazoline was formed.³

References

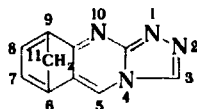
1. Ghosh and Betrabet, *J. Indian Chem. Soc.*, **7**, 899 (1930); *Chem. Zentr.*, **I**, 2059 (1931); *Chem. Abstracts*, **25**, 3651 (1931).
2. Cook, Gentles and Tucker, *Rec. Trav. chim.*, **69**, 343 (1950).
3. Cook, Gentles and Tucker, *Rec. trav. chim.*, **69**, 1201 (1950).
4. Fry, U. S. Pat. 2,566,658.
5. Heimbach, U. S. Pat, 2,444,607.
6. Harsh, U. S. Pat. 2,553,500.
7. Burness, U. S. Pat. 2,837,521.
8. Allen, *et al.*, *J. Org. Chem.*, **24**, 796 (1959).

- A-606. 5,8-Methano-*s*-triazolo[3,2-*b*]-quinazoline**



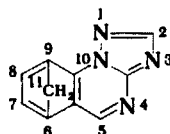
or

- A-607. 6,9-Methano-*s*-triazolo[3,4-*b*]-quinazoline***



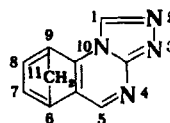
or

- A-608. 6,9-Methano-*s*-triazolo[1,5-*a*]-quinazoline***

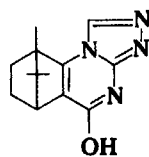
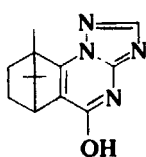
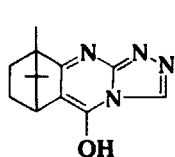
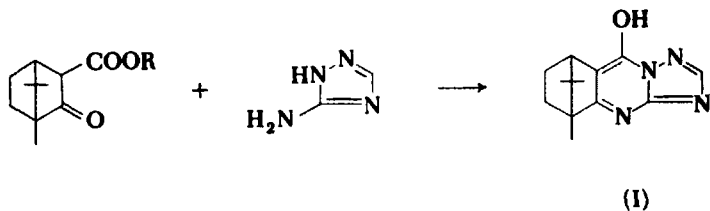


or

- A-609. 6,9-Methano-*s*-triazolo[4,3-*a*]-quinazoline***



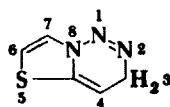
Compound I, presumably prepared as shown, was named *9-hydroxy - 5 - methyl - 5,8 - dimethylmethano-cyclohexano[f][1,3,4]triazaindoline*. No properties or details were reported although it was patented as a photographic fog-inhibitor¹ and toner.² The alternative structures II, III and IV must also be considered.



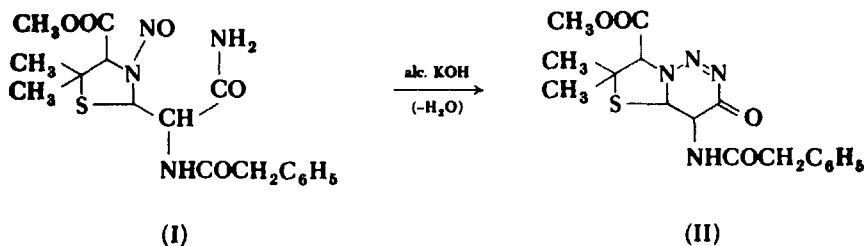
References

1. Heimbach, U. S. Pat. 2,444,607.
2. Harsh, U. S. Pat. 2,553,500.

A-610. 3*H*-Thiazolo[3,2-*c*]-*v*-triazine

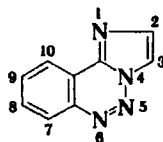


By treating I with alcoholic potassium hydroxide, a product [m. 133–4°; $[\alpha]_D^{23} + 16^\circ$; $\lambda_{\max}$ 265 m μ ($E_{1\text{cm}}^{1\%}$ 420)] thought to be II was obtained.¹

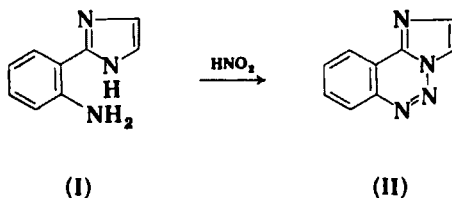


Reference

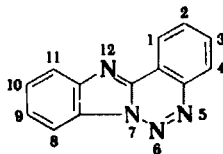
1. Cook and Heilbron, "Thiazolidines" in Clark *et al.*, *The Chemistry of Penicillin*, Princeton University Press, Princeton, New Jersey, 1949, p. 921.

A-611. Imidazo[1,2-c][1,2,3]-benzotriazine. R.I. 1555

Balaban and King¹ treated I with nitrous acid and obtained II (m. 113–4°), the prototype and only example of this ring system.

*Reference*

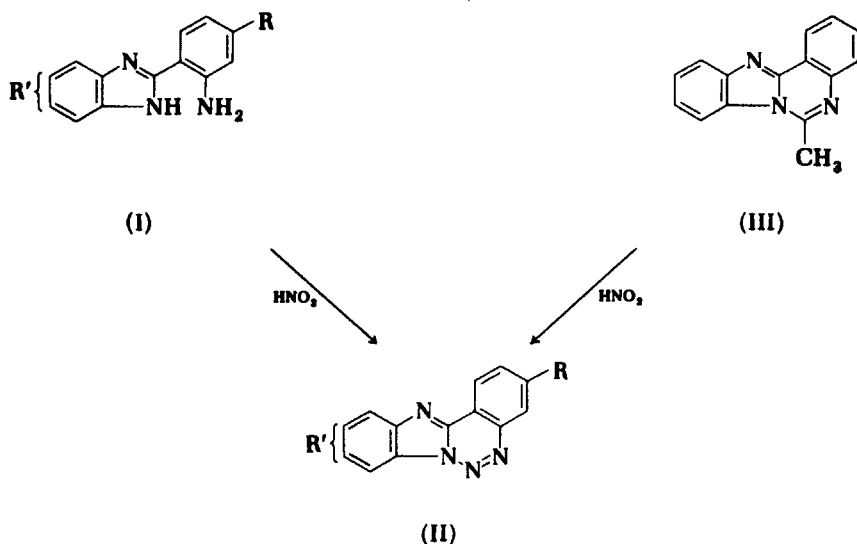
1. Balaban and King, *J. Chem. Soc.*, **127**, 2701 (1925).

A-612. Benzimidazo[1,2-c][1,2,3]-benzotriazole. R.I. 2378

The name (*β-o*)-aminophenylbenzimidazole azimide was applied originally to this system.

v. Niemantowski^{1,2} found that compounds of type I react with nitrous acid to yield² II: IIa, R = R' = H, yellow, m. 207–8°, HCl salt, m. 200°d., H₂AuCl₄ salt, m. 220°d., Br₂ adduct, orange, m. 112°; IIb, R = H, R' = CH₃, yellow, m. 187–8°; IIc, R = CH₃, R' = H, yellow, m. 185°; IId, R = R' = CH₃, yellow, m. 197°. These substances form with bromine, adducts, which regenerate II upon contact with ammonium hydroxide. However, under more vigorous conditions, nuclear bromination occurs giving *x*-bromo-IIa, m. 140°; *x*-bromo-IIb, m. 254° and *x*-bromo-IIc, m. 257°. Reduction of IIa with sodium and alcohol reformed I.

Treatment of III (see Section A-491) with nitrous acid causes³ scission of the pyrimidine ring and produces IIa. When heated with

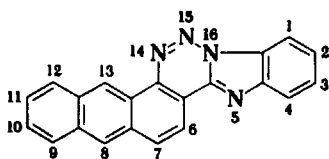


phenolic compounds, II reacts to form the azophenol, and II ($\text{R} = \text{R}' = \text{H}$) is decomposed to 2-(2-hydroxyphenyl)benzimidazole by warm dilute sulfuric acid.

References

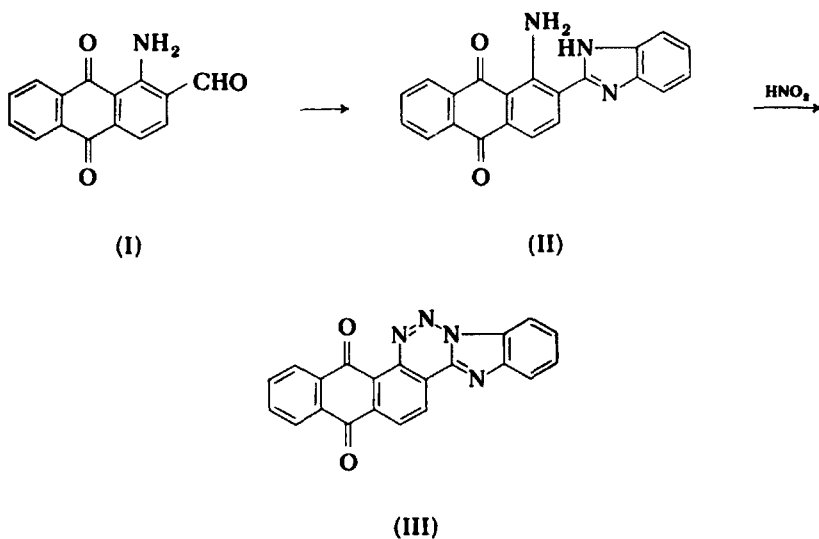
1. v. Niementowski, *Ber.*, **30**, 3062 (1897).
2. v. Niementowski, *Ber.*, **31**, 314 (1898).
3. v. Niementowski, *Ber.*, **32**, 1456 (1899).

A-613. Anthra[1',2',4,5]-*v*-triazino[1,6-*a*]benzimidazole*



The reaction of I with *o*-phenylenediamine yielded¹ II, which, upon treatment with nitrous acid, gave III (yellow, m. $> 300^\circ$; sulfuric acid solution yellow). Compound III dyed cotton a weak yellow-brown with poor substantivity.

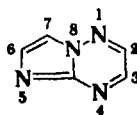
Benzologs of III, made from I and 1,2- and 2,3-naphthylenediamines, showed similar properties.



Reference

1. Roemer, I.G. *Farbenindustrie, A.G.*, 42 *Wissenschaftlicher Austausch der Gruppe IX*, Frankfurt a/M., Feb. 15, 1940; *PB Report No.* 70338, frame 10863; see also *F.I.A.T. Report* 1313, Vol. 3, p. 44.

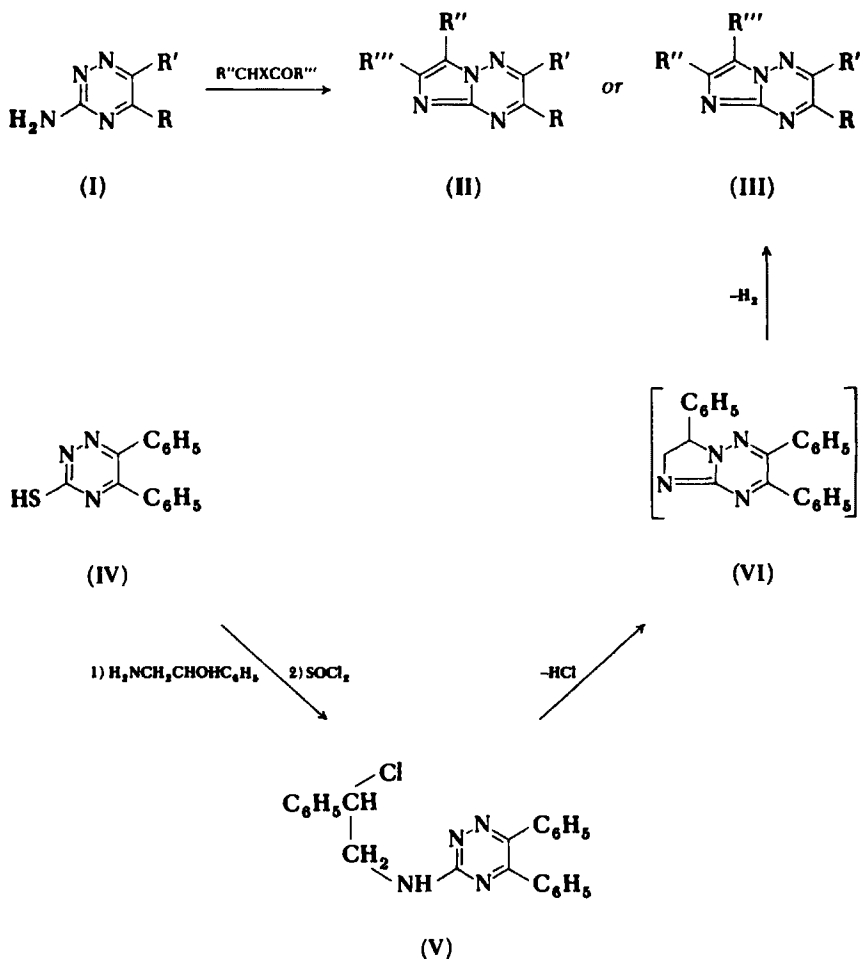
A-614. Imidazo[1,2-*b*]-*as*-triazine*



This nucleus has also been called (2,3,2',3')-imidazolo-1,2,4-triazine, 1,3a,4,7-tetrazaindene and 1,4,7,9-tetrazaindene.

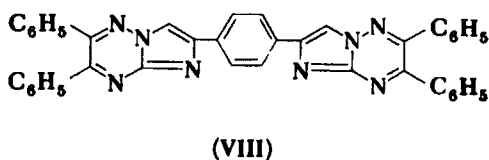
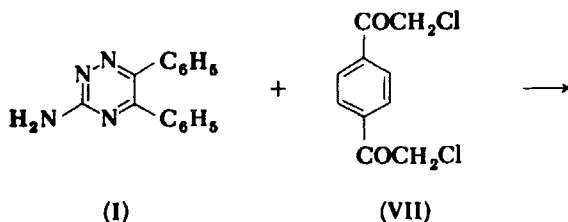
The reaction of 3-amino-*as*-triazines (I) with α -haloketones might lead to products of either type II or III. That the products were of type II ($R' = R'' = H$, $R = R''' = C_6H_5$, *yel.*, *m.* 196°; $R' = R'' = H$, $R = C_6H_5$, $R''' = p\text{-}C_6H_4NO_2$, *yel.* fluorescence, *m.* 258°; $R'' = H$, $R = R' = C_6H_5$, $R''' = p\text{-}C_6H_4COCH_2Cl$, *m.* 162-3°; $R = R' = R'' = C_6H_5$, $R''' = H$, *yel-grn.* fluorescence, *m.* 186°; $R'' = H$, $R = R' = C_6H_5$, $R''' = p\text{-}C_6H_4NO_2$, *grn.-bl.* fluorescence, *m.* 228-9°; $R = R'' = R''' = C_6H_5$, $R' = H$, *grn.* fluorescence, *m.* 227°; $R = R' = R'' = R''' = C_6H_5$, *yel-grn.*

fluorescence, m. 238–9°) was shown¹ by the synthesis of III ($R = R' = R''' = C_6H_5$, $R'' = H$, m. 248–9°). Condensation of IV with 2-phenyl-2-ethanolamine and treatment of the product with thionyl chloride yielded V. Boiling pyridine converted V into VI, which was spontaneously partially dehydrogenated to III ($R'' = H$, $R = R' = R''' = C_6H_5$). This same product was also obtained from



the reaction of I with α -bromophenylacetaldehyde. Compound VIII (m. 340°) was obtained from the condensation of I and VII.

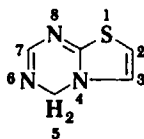
A number of these products were claimed² as fluorescent pigments.



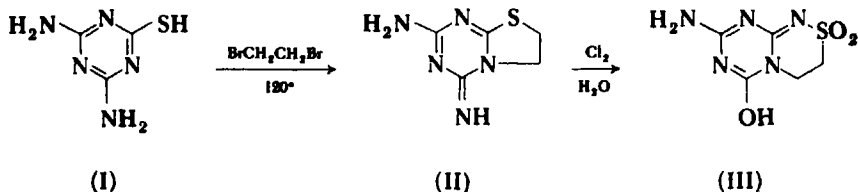
References

1. Fusco and Rossi, *Rend. ist. lombardo sci. Pt. I. Classe sci. mat. e nat.*, **88**, 173 (1955); *Chem. Abstracts*, **50**, 10743 (1956).
2. Fusco and Rossi, *Fr. Pat.* 1,153,100; *Brit. Pat.* 789,850; *Ger. Pat.* 1,026,321; *U. S.* 2,837,520.

A-615. 5*H*-Thiazolo[3,2-*a*]-s-triazine

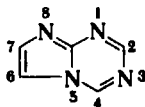


Rathke¹ treated thioammeline (I) with ethylene bromide at 120° and obtained a product, which he considered to be the hydrobromide of II. Chlorination of the hydrochloride of II in hydrochloric acid solution yielded² a new substance, to which he assigned structure III (see Section A-870).

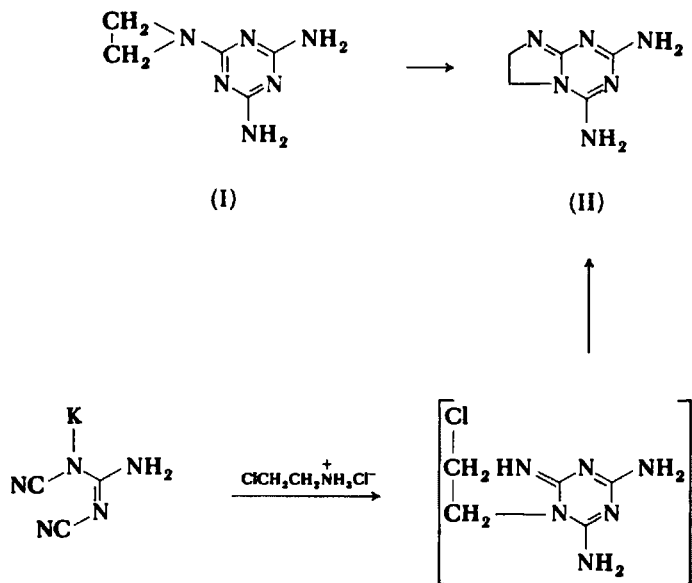


References

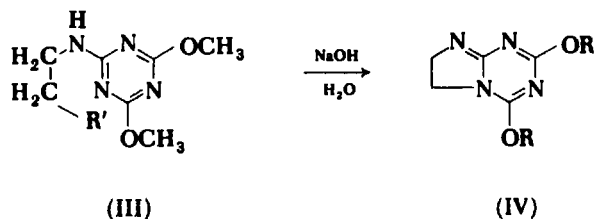
1. Rathke, *Ber.*, **20**, 1059 (1887).
2. Rathke, *Ber.*, **21**, 874 (1888).

A-616. Imidazo[1,2-*a*]-*s*-triazine

When I was heated with triethylamine hydrochloride in acetonitrile (but not in benzene) it was rearranged¹ to II (m. 308–10°; HCl salt, m. >360°), which was also obtained from the reaction of potassium dicyanoguanidine with 2-chlorethylamine hydrochloride.

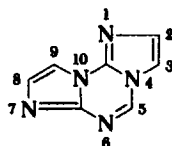


Upon treatment with base, III ($\text{R}' = \text{Cl}$ or OSO_2ONa) was converted into IV (one $\text{R} = \text{H}$ and one $\text{R} = \text{CH}_3$, but which is unknown, m. 229–31°).

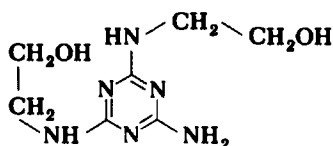


Reference

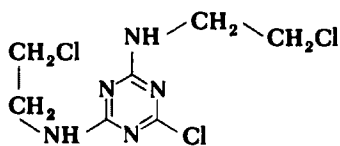
1. Schaefer, *J. Am. Chem. Soc.*, **77**, 5922 (1955).

A-617. Bisimidazo[1,2-*a*, 1',2'-*c*]-*s*-triazine

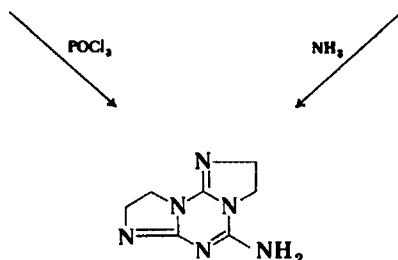
The reaction of I with phosphorus oxychloride gave¹ the dihydrochloride (m. 340–5°d.) of II ($pK_a \sim 3.0$ and ~ 9.0), the monohydrochloride (m. 350°) of which was obtained by treating III with ammonia.



(I)



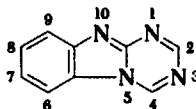
(III)



(II)

Reference

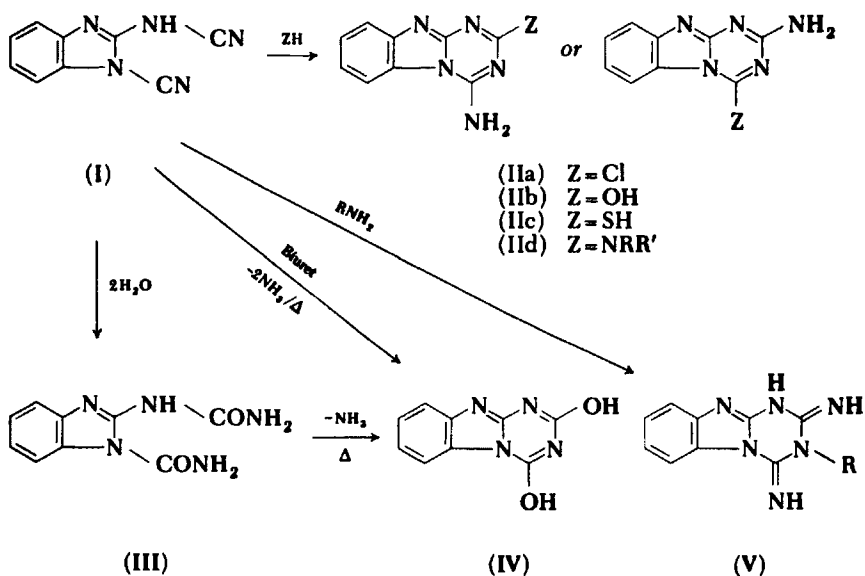
1. Schaefer, *J. Am. Chem. Soc.*, **77**, 5922 (1955).

**A-618. *s*-Triazino[*a*]benzimidazole.
R.I. 1554**

The name *3,4,6-triaza-1,2-benzindolizine* has also been used.

Pierron¹ found that treatment of *o*-phenylenediamine with cyanogen bromide gave a product (I), which he called *o*-phenylene- α,β -dicyanoguanidine. The reactions of this material were subsequently

studied in some detail by Pellizzari.²⁻⁵ He showed that the reaction of I with one mole of a reagent of type ZH (where Z = OH, SH, Cl, NRR', etc.) yielded compounds of type II having one of the two isomeric structures shown. Pierron treated I with two moles of water and obtained the amide III, which lost ammonia when heated and gave phenylenemelanuric acid (IV). This product (IV) could also be obtained¹ by heating I with biuret. The reaction of I with ammonia or primary amines gave V, isomeric with II_d. Hydrolysis of V with dilute acid replaced one of the imino groups by oxygen, giving² isomers of II_b.



Heating II_c with dilute caustic,⁵ or IId (R = R' = H) with dilute acid⁴ hydrolyzed them to *o*-phenyleneammeline (II_b), which in turn was converted³ into IV by the action of nitrous acid. The reaction of II_a with secondary amines gave⁴ IId, while acidic hydrolysis of II_a yielded³ IV. Vigorous hydrolysis of II, IV or V caused scission of the triazine ring to give 2-benzimidazolyurea or 2-benzimidazolyguanidine derivatives.

Commencing with substituted *o*-phenylenediamines, a group of derivatives of IV having substituents in the benz ring was prepared, and these were claimed⁶ as fog inhibitors for photographic emulsions.

As is readily apparent, most of the compounds discussed are capable of existing in two or more tautomeric modifications. The precise structure of none is known with certainty, and they are shown here, for convenience's sake, with the maximum number of endocyclic double bonds. Most of the simpler hydroxy and amino derivatives are infusible or have very high melting points.

Derivatives of *s*-Triazino[*a*]benzimidazole

Empirical formula	Substituents	Properties	Refs.
C ₉ H ₄ Br ₂ N ₄ O ₂	6,8(or 7,9)-Dibromo-2,4-dihydroxy-	—	6
C ₉ H ₅ BrN ₄ O ₂	7(or 8)-Bromo-2,4-dihydroxy-	—	6
C ₉ H ₅ ClN ₄ O ₂	7(or 8)-Chloro-2,4-dihydroxy-	m. > 320°.	6
C ₉ H ₆ N ₄ O ₂	2,4-Dihydroxy-	m. > 320°. Dec. without m. on Pt. foil @ 300°.	1,3,6
C ₉ H ₆ ClN ₅	4(or 2)-Amino-2(or 4)-chloro-	m. > 220°.	3,4
C ₉ H ₇ N ₅ O	4(or 2)-Amino-2(or 4)-hydroxy-	—	3,5
C ₉ H ₇ N ₅ S	4(or 2)-Amino-2(or 4)-mercapto-	d. > 300°.	5
C ₉ H ₈ N ₆	2,4-Diamino-	m. > 300°.	2,4
C ₉ H ₈ N ₆ O	2,3-Diamino-4-hydroxy-	m. 303°. HCl salt, m. 289°. Benzylidene deriv., m. > 300°.	2
C ₉ H ₉ N ₇	2,3,4-Triamino-	d. 283°.	2
C ₁₀ H ₆ N ₄ O ₄	7(or 8)-Carboxy-2,4-dihydroxy-	—	6
C ₁₀ H ₈ N ₄ O ₂	2,4-Dihydroxy-7(or 8)-methyl-	m. > 320°.	6
C ₁₀ H ₈ N ₄ O ₃	2,4-Dihydroxy-7(or 8)-methoxy-	—	6
C ₁₃ H ₁₁ N ₅ O	2(or 4)-Anilino-4(or 2)-hydroxy-	—	4
	2-Amino-4(3 <i>H</i>)-oxo-3-phenyl-	m. 292° d. Nitrate, m. 225° d.	2
C ₁₃ H ₁₂ N ₆	2-Amino-4(3 <i>H</i>)-imino-3-phenyl-	m. 241°.	2
	4(or 2)-Amino-2(or 4)-anilino-	m. > 300°.	4
C ₁₆ H ₁₃ N ₅ O	2-(Methylanilino)-4-hydroxy-	—	4
C ₁₆ H ₁₄ N ₆	4-Amino-2-(methylanilino)-	—	4

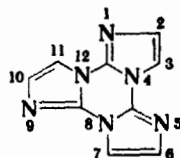
References

- Pierron, *Ann. Chim. et Phys.*, [8] **15**, 145 (1908).
- Pellizzari, *Gazz. chim. ital.*, **51**, I, 89 (1921).
- Pellizzari, *Gazz. chim. ital.*, **52**, I, 199 (1922).
- Pellizzari, *Gazz. chim. ital.*, **54**, 177 (1924).

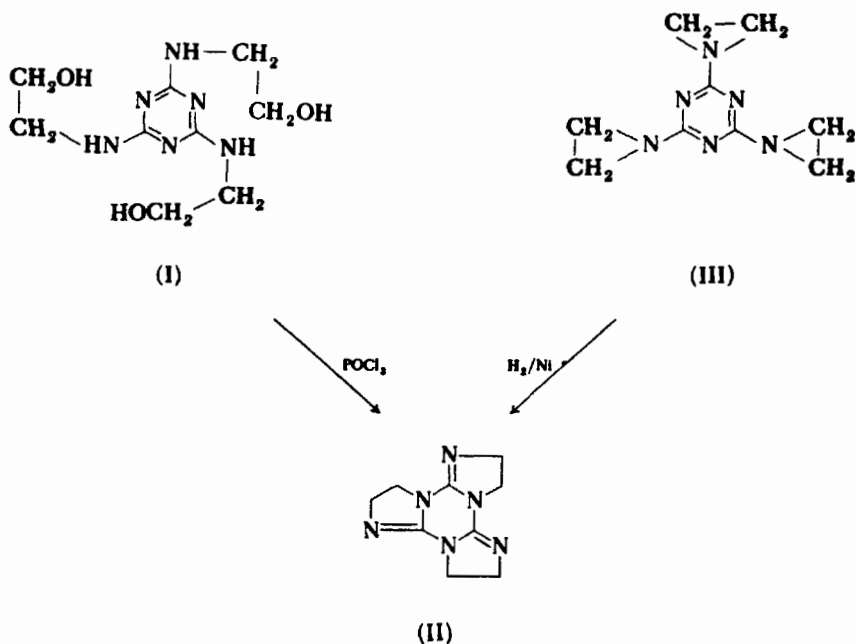
5. Pellizzari, *Gazz. chim. ital.*, **54**, 451 (1924).

6. Heimbach and Clark, U. S. Pat. 2,444,609.

A-619. Trisimidazo[1,2-*a*, 1',2'-*c*, 1'',2''-*e*]-*s*-triazine



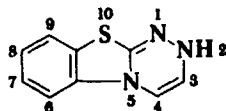
Compound II (m. 322–4°) was obtained¹ by the cyclization of I with phosphorus oxychloride. It was also formed via an unusual rearrangement of III in the presence of hydrogen and Raney nickel. The presence of both the catalyst and hydrogen was required, and III was not isomerized by heat alone.



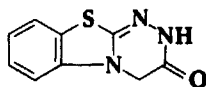
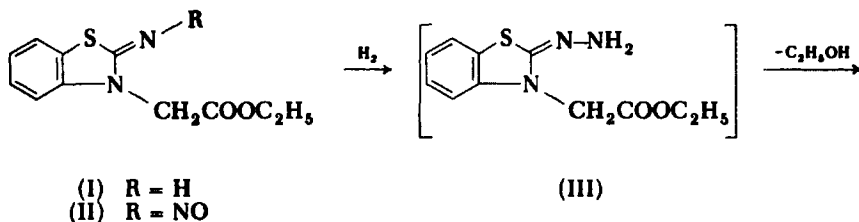
Reference

1. Schaefer, *J. Am. Chem. Soc.*, **77**, 5922 (1955).

**A-620. 2*H*-[1,2,4]Triazino-
[3,4-*b*]benzothiazole**



While studying the condensation of chloroacetic ester with 2-aminobenzothiazole, Allen and Van Allen¹ obtained I, which was nitrosated to II. This gave, upon reduction, a product (m. 260°) thought to be IV, formed presumably, via the intermediate III.

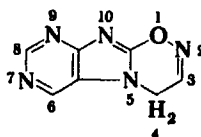


(IV)

Reference

1. Allen and Van Allen, *J. Org. Chem.*, **13**, 603 (1948).

**A-621. 4*H*-Pyrimid[4',5',4,5]imidaz-
[1,2-*e*]-1,2,5-oxadiazine***

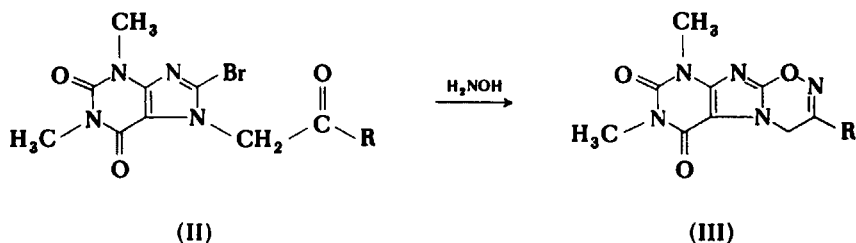


This ring system has been called *pyrimido*(4,5-*d*)4'(*H*),5',6'(*H*)-*oxadiazine*-1',2',5'-(5',6'-*b*)-*imidazole*, and numbered as shown in I.



(I)

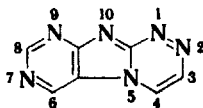
The reaction of II with hydroxylamine yields first the oxime, which, through loss of hydrogen bromide, gives III ($R = CH_3$, m. $\sim 320^\circ$ d.; $R = C_6H_5$, m. 260° d.). See Section A-622.



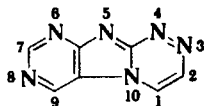
Reference

1. Zelnick, Pesson, and Polonovski, *Bull. soc. chim. France*, **1956**, 888.

A-622. Pyrimid[4',5'-4,5]imidazo-[2,1-c]-*as*-triazine*

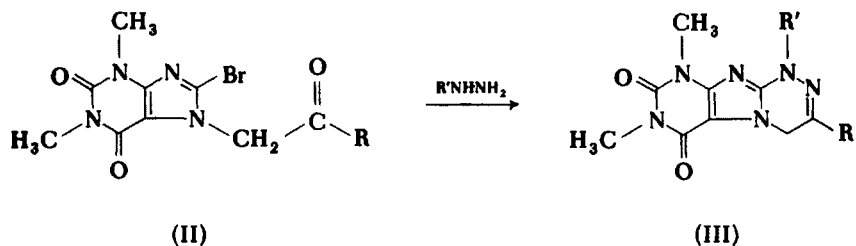


This nucleus has been called *pyrimido(4,5-d)-3',4'-(H)-as-triazine-(3',4'-b)imidazole*, and numbered as shown in I.



(I)

The reaction of 7-acetonyl- (or phenacyl)-8-bromotheophylline (II) with hydrazines yields^{1,2} products of structure III ($R = CH_3$,

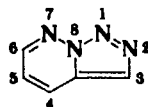


$R' = H$, sublimes above 310° ; $R = R' = CH_3$, m. 278° ; $R = C_6H_5$, $R' = H$, m. $\sim 310^\circ$). From III ($R' = H$) the cyanoethyl and acetyl derivatives were prepared (III, $R = CH_3$, $R' = CH_2CH_2CN$, m. $210-1^\circ$; $R = CH_3$, $R' = Ac$, m. $\sim 310^\circ$; $R = C_6H_5$, $R' = Ac$, m. 275°). See Section A-621.

References

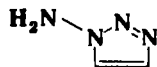
1. Polonovski, Pesson and Zelnik, *Compt. rend.*, **236**, 2519 (1953).
2. Zelnick, Pesson and Polonovski, *Bull. soc. chim. France*, **1956**, 888.

A-623. *v*-Triazolo[3,4-*b*]pyridazine*

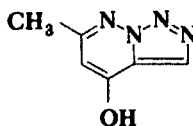


The name *1,2,7-triazaindolizine* has been used.

The preparation of II from I, presumably by condensation with acetoacetic ester, has been mentioned¹ by Birr (no details given).



(I)

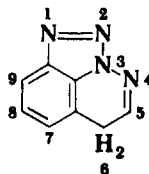


(II)

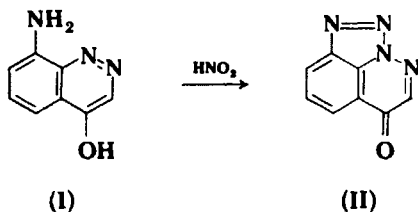
Reference

1. Birr, *Z. wiss. Phot.*, **47**, 2 (1952).

A-624. 6*H-v*-Triazolo[4,5,1-*ij*]cinnoline



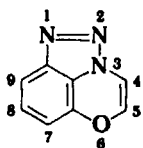
Treatment of I with nitrous acid yielded¹ II (m. $159-60^\circ$), which was called *1:8-azo-1:4-dihydrocinnol-4-one*. See Section A-537.



Reference

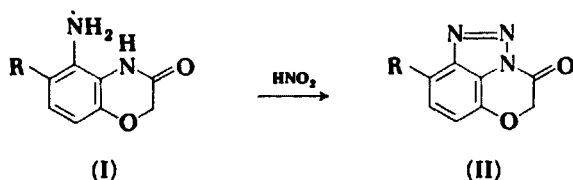
1. Schofield and Theobald, *J. Chem. Soc.*, **1949**, 2404.

A-625. Triazolo[1,5,4-*de*][1,4]-benzoxazine*



The name *4,5-azophenmorpholine* was used by Beilstein's *Handbuch*.

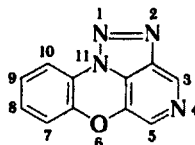
Treatment of I ($R = H$ or $AsO(OH)_2$) with nitrous acid yielded II ($R = H$, ¹ m. 204°; $R = AsO(OH)_2$, ² m. 247°).



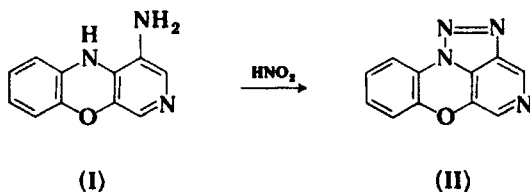
References

1. Newbery and Phillips, *J. Chem. Soc.*, **1928**, 3046.
2. Newbery, Phillips and Stickings, *J. Chem. Soc.*, **1928**, 3051.

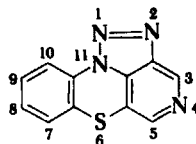
A-626. 4-Azatriazolo[*kl*]phenoxazine



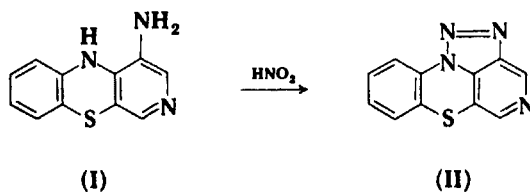
The reaction of I with nitrous acid yielded ¹ II (m. 171° d.), which was named *3-azaphenoxazine-5,6-diazole*.

*Reference*

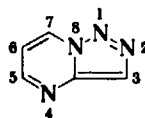
1. Petrow and Rewald, *J. Chem. Soc.*, **1945**, 313.

A-627. 4-Azatriazolo[*kl*]phenothiazine

The treatment of I with nitrous acid is reported¹ to produce II (m. 199–200°).

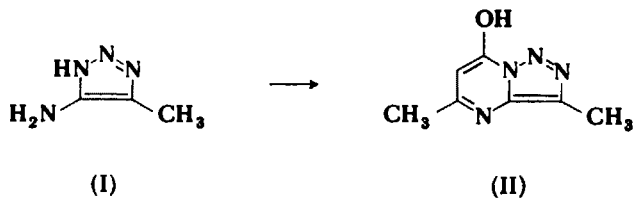
*Reference*

1. Petrow and Rewald, *J. Chem. Soc.*, **1945**, 591.

A-628. *v*-Triazolo[3,4-*a*]pyrimidine*

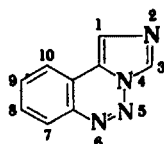
The name *1,2,4-triazaindolizine* has been used.

The preparation of II from I, presumably by condensation with acetoacetic ester, has been claimed¹ by Birr (no details given).

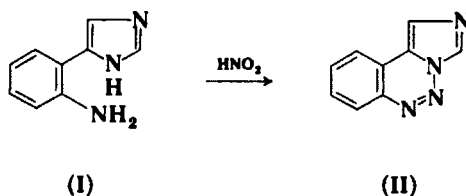
*Reference*

1. Birr, *Z. wiss. Phot.*, **47**, 2 (1952).

A-629. Imidazo[1,5-c][1,2,3]-benzotriazine*

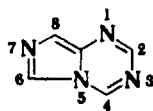


Treatment of I with nitrous acid yielded¹ II, but no further details were offered.

*Reference*

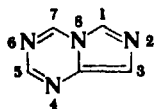
1. Balaban and King, *J. Chem. Soc.*, **127**, 2701 (1925).

A-630. Imidazo[1,5-a]-s-triazine.*
R.I. 741



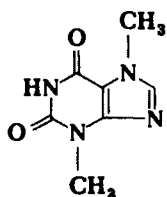
The above name is suggested in place of the ambiguous *imidazo-s-triazine* used by the *Ring Index*. In the decennial index to volumes 21-30 of *Chemical Abstracts*, this ring system was numbered as shown in I.

Fischer and Frank¹ treated theobromine (II) with chlorine in chloroform solution, and obtained a product, which was hydrolyzed

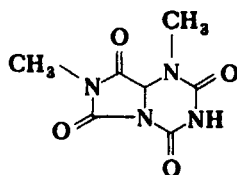


(I)

by cold water to a substance, $C_7H_8N_4O_5$, called "theobromuric acid," and reduction of this with hydriodic acid and phosphorus gave "hydrotheobromuric anhydride" (m. 264° d., cor.). Biltz, Heyn, Mundt and Damm² re-examined these substances and suggested structure III for the "anhydride." The "anhydride" could be converted into the acid or esters, which were assigned structure IV. Oxidation of III with chromic acid yielded² methylparabanic acid (V). Some further evidence regarding the accuracy of structures III and IV would be welcome.

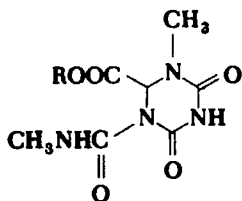


(II)



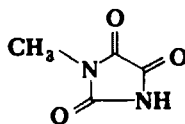
(III)

ROH



(IV)

[O]

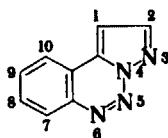


(V)

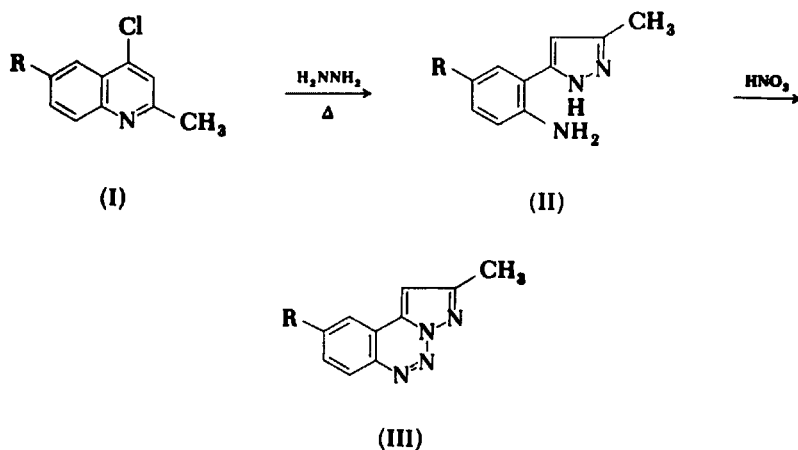
References

1. Fischer and Frank, *Ber.*, **30**, 2604 (1897).
2. Biltz, Heyn, Mundt and Damm, *Ber.*, **67**, 1856 (1934).

**A-631. Pyrazolo[2,3-*c*][1,2,3]-
benzotriazine**



The vigorous reaction of hydrazine with 4-chloroquinaldine (I, R = H) yielded a product at first thought¹ to be 4-quinaldylhydrazine. This structure was questioned,² and it was suggested³ (but disproved⁴) that the product was 3,4-diaminoquinaldine. It was recently shown⁵ that the product is actually II (R = H), formed by scission of the pyridine ring. Treatment of II with nitrous acid gave a product first thought² to be 4-azidoquinaldine, but now known⁵ to be III (R = H, m. 126°). Homologs (R = OCH₃, m. 186°, and

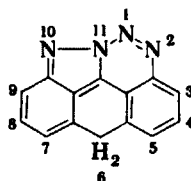


R = OC₂H₅, m. 212°) were also obtained.² Reduction of III with stannous chloride opens the triazine ring and yields 2-(5-methyl-3-pyrazolyl)-phenylhydrazine, while 3-methyl-5-phenylpyrazole results from the oxidation of III with copper acetate in aqueous acetic acid.

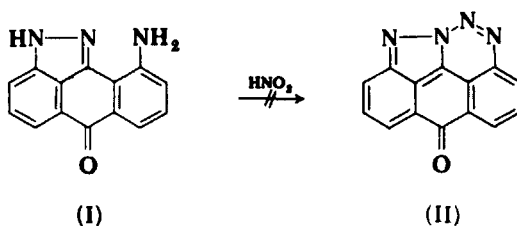
References

1. Marckwald and Chain, *Ber.*, **33**, 1895 (1900).
2. Koenigs and von Loesch, *J. prakt. Chem.*, **143**, 59 (1935).
3. Backeberg and Friedmann, *J. Chem. Soc.*, **1938**, 972.
4. Koenigs and Freund, *Ber.*, **74**, 1085 (1941).
5. Koenigs and Freund, *Chem. Ber.*, **80**, 143 (1947).

A-632. 6H-Benz[de]indazolo[4,3,2-hij]-[1,2,3]benzotriazine*



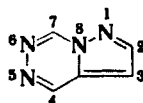
Baumann and Schwechten attempted¹ to obtain II by diazotization of I, but the diazonium salt intermediate always decomposed to give other products.



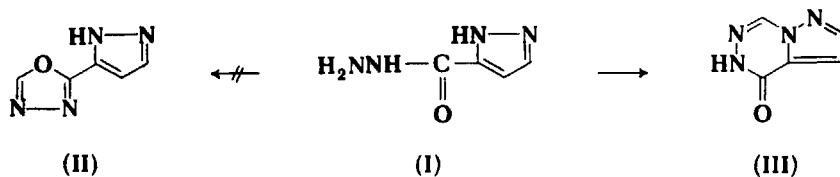
Reference

1. Baumann and Schwechten, *I.G. Farbenindustrie, A.G., 34 Wissenschaftlicher Austausch der Gruppe IX*, Leverkusen, October 25/6, 1935; *PB Report No. 70339*, frames 11319-11324.

A-633. Pyrazolo[1,5-d]-as-triazine



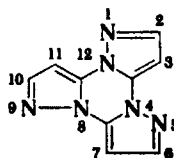
Condensation of I with ethyl orthoformate yielded a product (m. 265°) thought¹ to have structure III, rather than the expected II.



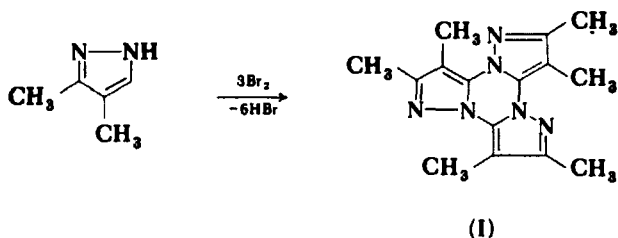
Reference

1. Ainsworth, *J. Am. Chem. Soc.*, **77**, 1148 (1955).

A-634. Tripyrazolo[1,5-a, 1',5'-c, 1'',5''-e]-s-triazine



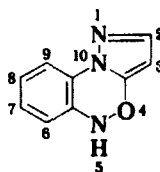
From the bromination (by bromine in chloroform, *N*-bromosuccinimide in chloroform or hypobromous acid in acetic acid) of 3,4-dimethylpyrazole, several products were obtained,¹ including one ($C_{15}H_{18}N_8$, m. 278°) assigned structure I. It could not be hydrogenated over a platinum oxide catalyst, nor could it be brominated. With methyl sulfate it gave a monomethyl bisulfate salt (m. $206-9^\circ$ d.), which, with base, gave the monomethyl hydroxide (m. $237-8^\circ$). Treatment of this with acetic anhydride gave an acetate (m. $175-6^\circ$).



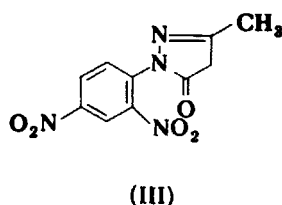
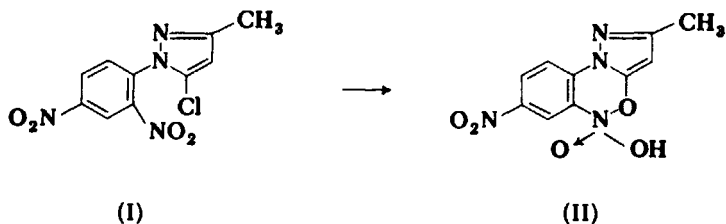
Reference

1. Hüttel, Wagner and Jochum, *Ann.*, **593**, 179 (1955).

A-635. 5H-Pyrazolo[3,2-c][2,1,4]-benzoxadiazine. R.I. 1552

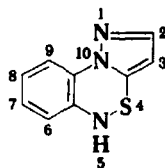


Treatment of I with potassium hydroxide or methoxide, followed by acidification, gave a product (m. 126° , yellow potassium salt), to which Rojahn and Fegeler assigned¹ structure II. The possibility of the product having structure III does not seem to have been eliminated, however. See Sections A-636/7.

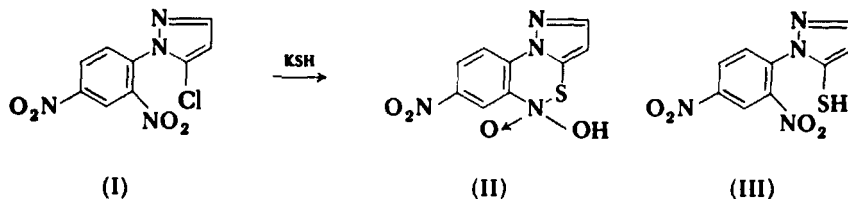
*Reference*

1. Rojahn and Fegeler, *Ber.*, **63**, 2510 (1930).

A-636. 5*H*-Pyrazolo[3,2-*c*][2,1,4]-benzothiadiazine. R.I. 1553

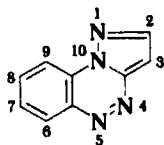


The reaction of I with potassium sulfhydrate in ethanol yields a red potassium salt from which a yellow product (m. 179°) is obtained on acidification.¹ Structure II was postulated for this product, but further evidence excluding the normal dinitrothiol structure (III) would be welcome. See Sections A-635 and A-637.

*Reference*

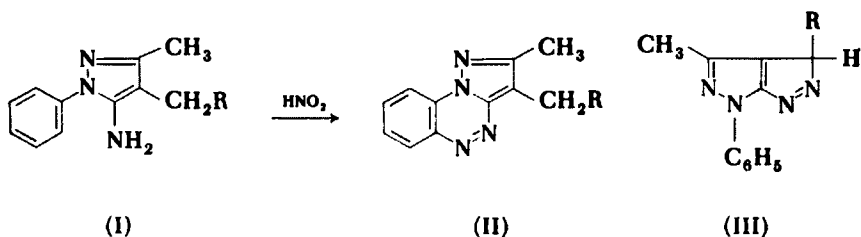
1. Rojahn and Fegeler, *Ber.*, **63**, 2510 (1930).

A-637. Pyrazolo[3,2-c][1,2,4]-benzotriazine. R.I. 1556

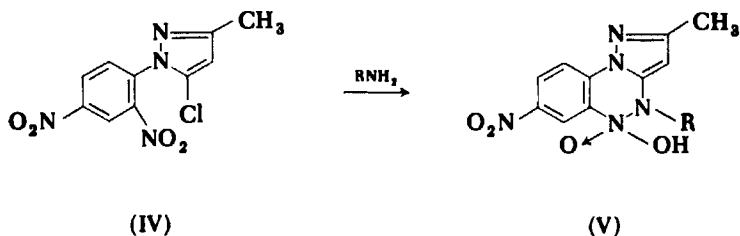


This nucleus has also been called *pyrazobenzotriazine* and *benzo-(2'.1':3.4)pyrazolo(1''.5'':5.6)-1,2,5-triazine*.

Mohr¹ diazotized I, and poured the diazonium sulfate solution into boiling water to obtain brownish-yellow products thought to be of type II ($R = H$, b_{15-17} 208–15°, b_{30} 225–6°, m. 145°; $R = CH_3$, b_{14} 210°, m. 106°; $R = C_6H_5$, m. 128–30°, silver salt, orange, m. 169–70°). Compound II ($R = H$) was not reduced by zinc and acid or by sodium amalgam. The alternative structure III has not been eliminated definitely for these products.



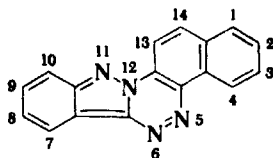
Rojahn and Fegeler² treated IV with various amines and obtained yellow products to which they assigned structure V ($R = H$, m. 204°; $R = CHO$, m. 286°; $R = C_6H_5$, m. 190°; $R = C_6H_5NH$, m. 216°; $R = p-CH_3C_6H_4$, m. 166°). The cyclic structure V was proposed for these products (which ordinarily one would expect to be merely IV with the chlorine replaced by $RNH-$) to account for the unexpected properties (when $R = H$ the product does not form a hydrochloride or picrate and cannot be acylated). The evidence for structure V seems unconvincing. See Sections A-635/6.



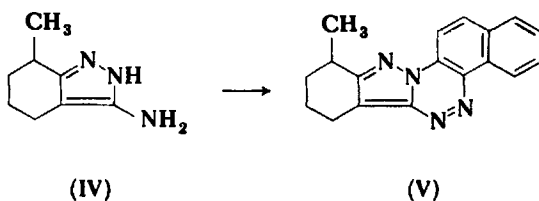
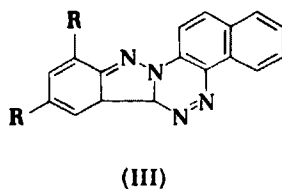
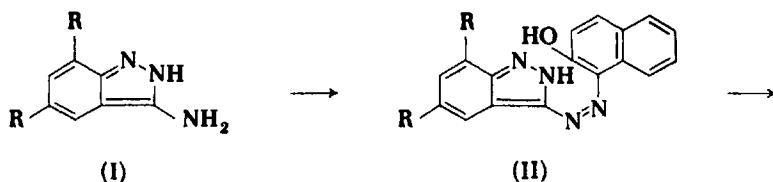
References

1. Mohr, *J. prakt. Chem.*, [2]90, 509 (1914).
2. Rojahn and Fegeler, *Ber.*, 63, 2510 (1930).

A-638. Indazolo[3,2-*c*]naphtho[2,1-*e*]-triazine. R.I. 3037



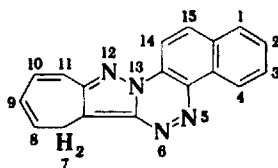
Bamberger found^{1,2} that when I was diazotized and coupled with β -naphthol, the red intermediate azo dye II readily dehydrated to give a yellow product of structure III ($R = H$, m. 250–1°; $R = CH_3$, m. 267°). Later it was shown³ that IV similarly could be converted into V (m. 152–4°).



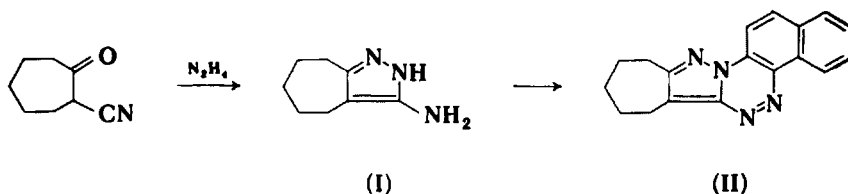
References

1. Bamberger, *Ber.*, 32, 1797 (1899).
2. Bamberger and Goldberger, *Ann.*, 305, 339 (1899).
3. v. Auwers, Bahr and Frese, *Ann.*, 441, 68 (1925).

**A-639. 7*H*-Cyclohepta[3,4]pyrazolo-
[5,1-*c*]naphtho[2,1-*e*]-*as*-triazine**



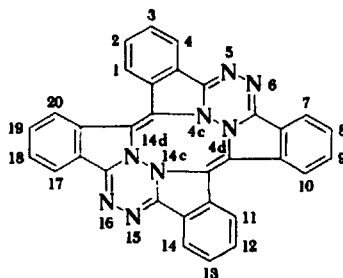
When I was diazotized and coupled to β -naphthol, a red azo dye was obtained, which was readily dehydrated by boiling ethanol to a yellow substance (m. 176–7°) of structure II. See Section A-638.



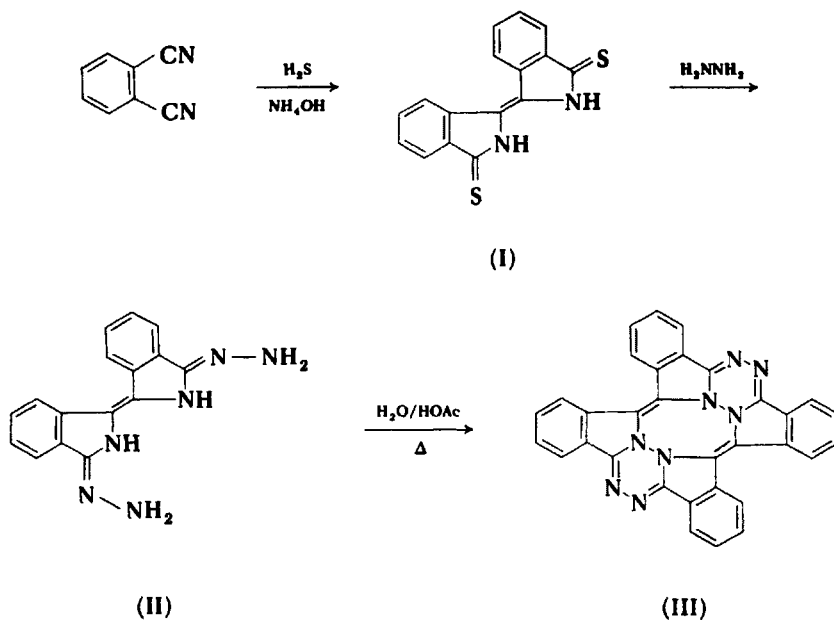
Reference

1. Iwanoff, *Chem. Ber.*, **87**, 1600 (1954).

**A-640. 4*c*,4*d*,5,6,14*c*,14*d*,15,16-Octaza-
tetrabenzo[*b,h,b'h'*]cycloöcta-
[1,2,3,4-*jkl*, 5,6,7,8-*j'k'l'*]di-
as-indacene***



Treatment of phthalonitrile with ammonia and hydrogen sulfide yields I, which is converted by treatment with hydrazine into II. When II was heated with aqueous acid, ammonia (not hydrazine) was lost, and a dark blue substance (brassy reflex, vigorous d. $\sim 300^\circ$), provisionally assigned structure III, was produced.¹

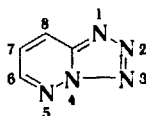
*Reference*

1. Drew and Kelley, *J. Chem. Soc.*, **1941**, 637.

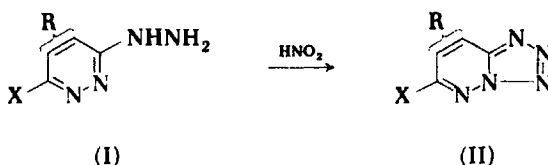
CHAPTER VIII

Fused 5/6 Ring Systems with Four or More Extra Heteroatoms

A-641. Tetrazolo[*b*]pyridazine



Several compounds of type II ($R = H$, $X = Cl$, m. 107° ; $R = H$, $X = OCH_3$, m. 154.5° ; $R = CH_3$, $X = Cl$, m. 97° ; $R = CH_3$, $X = OCH_3$, m. 108°) were obtained¹ from the reaction of I with nitrous acid. It is uncertain whether the group R is in the 7 or 8 position.

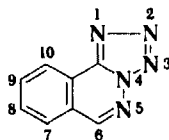


Treatment of II ($R = H$, $X = Cl$) with hydrazine gave² the 6-hydrazino compound (m. 230.5°), while palladium catalyzed reduction of the chloro compound yielded the prototype (II, $R = X = H$, m. 104° ; HCl salt, m. 151°).

References

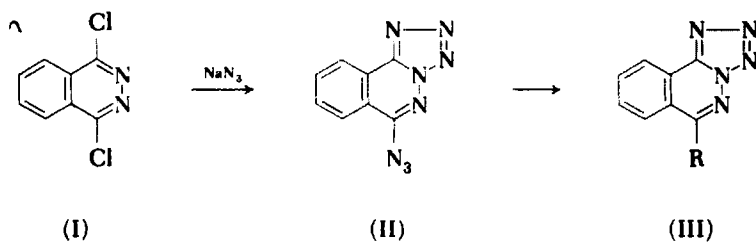
1. Takahayashi, *J. Pharm. Soc. Japan*, **75**, 1242 (1955); *Chem. Abstracts*, **50**, 8655 (1956).
2. Takahayashi, *J. Pharm. Soc. Japan*, **76**, 765 (1956); *Chem. Abstracts*, **51**, 1192 (1957).

A-642. Tetrazolo[*a*]phthalazine.
R.I. 1473



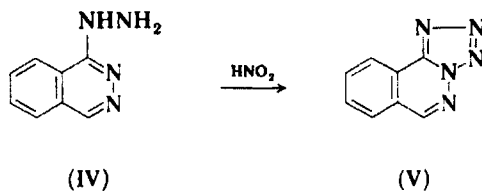
The older name is *tetrazolo[5,4-*a*]phthalazine*.

Stollé and Storch¹ treated dichlorophthalazine (I) with sodium azide and obtained II (m. 152°). The azido group showed no inclination to cyclize to a second tetrazole ring. Treatment of II with various reagents yielded III (R = OH, m. 258°; R = OAc, m. 165°; R = OCH₃, m. 211°; R = OC₂H₅, m. 187°; R = Cl, m. 195°;



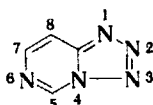
R = NH₂, m. 305°, R = NAc₂, m. ~260°). The reaction of II with sodium alkoxides yielded the methoxy and ethoxy compounds, or, under slightly different conditions, the hydroxy derivative, which in turn reacted with phosphorus pentachloride to give the chloro compound from which, by ammonolysis, the amine was obtained.

Recently, Druey and Ringier² prepared the prototype (V, m. 209–10°) by treatment of IV with nitrous acid.

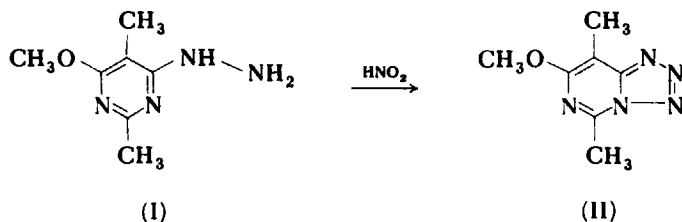


References

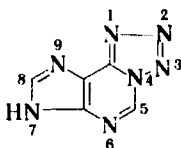
1. Stollé and Storch, *J. prakt. Chem.*, **135**, 128 (1932).
2. Druey and Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).

A-643. Tetrazolo[c]pyrimidine

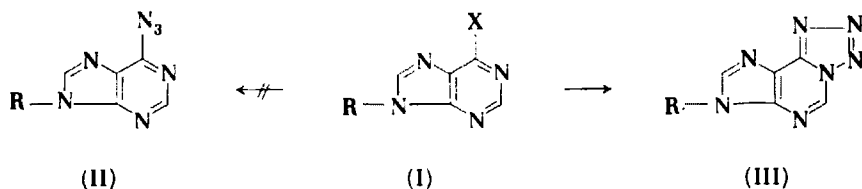
The treatment of I with nitrous acid yielded¹ II (m. 68.0–8.5°)

*Reference*

1. Shiho, Tagami, Takahayashi and Honda, *J. Pharm. Soc. Japan*, **76**, 804 (1956); *Chem. Abstracts*, **51**, 1196 (1957).

A-644. 7H-Tetrazolo[i]purine*

Treatment of the hydrazine I ($\text{R} = \text{H}$, $\text{X} = \text{NHNH}_2$) with nitrous acid, or of the chloro derivative (I, $\text{R} = \text{H}$, $\text{X} = \text{Cl}$) with sodium azide, produced a product [m. 185°, pK_a 7.60 in water, λ_{max} 250, 258 and 286 $\text{m}\mu$ (ϵ 4,580, 5,050 and 7,380)] thought¹ to be the azido derivative II. Hydrogenation of this product over a palladium-charcoal catalyst was without effect, but use of a Raney nickel catalyst yielded¹ adenine (6-aminopurine), which also resulted when the compound was boiled with dilute hydrochloric acid.

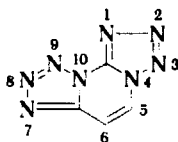


Recently, however, examination² of the infrared spectrum of this product disclosed it to be a tetrazole rather than an azide, and it therefore is assigned structure III (R = H). The related riboside [III, R = β -D-ribofuranosyl, m. 222° d., $[\alpha]_D^{32}$ $-12 \pm 3^\circ$ (in 1*N* hydrochloric acid), $\lambda_{\max}$ 251, 260 and 287 m μ (ϵ = 4,970, 4,900 and 7,930)] was similarly prepared² from I (R = β -D-ribofuranosyl, X = NHNH₂).

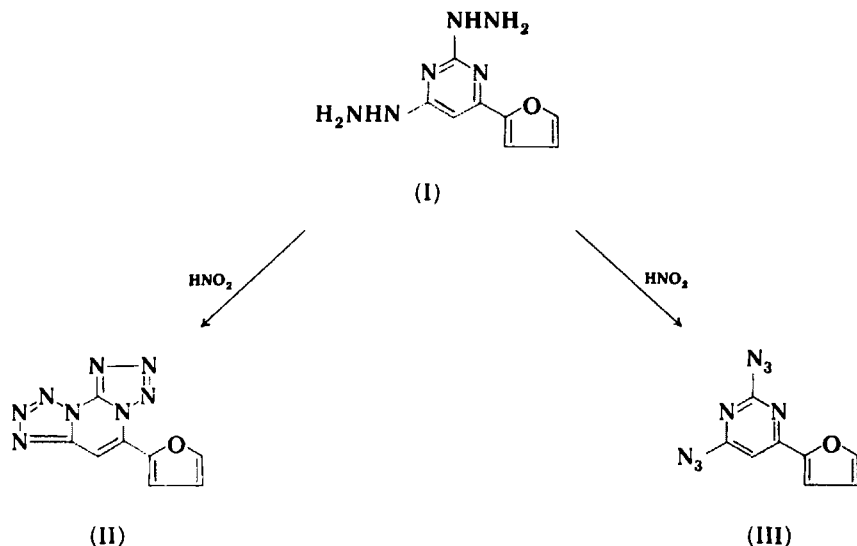
References

1. Bendich, Giner-Sorolla and Fox in Wolstenholme and O'Connor, Editors, *Ciba Foundation Symposium on the Chemistry and Biology of Purines*, Little, Brown & Co., Boston, 1957, p. 3.
2. Johnson, Thomas and Schaeffer, *J. Am. Chem. Soc.*, **80**, 699 (1958).

A-645. Ditetrazolo[*a,c*]pyrimidine



Andrisano claimed¹ to have obtained II (pale yellow, m. 122°) from the reaction of I with nitrous acid. However, Benson, Hartzel and Otten² were unable, on repeating this experiment, to obtain



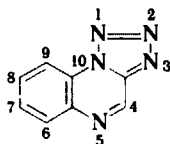
Andrisano's product. They obtained, instead, a substance (m. 93°) having structure III.

The failure of two five-membered rings to cyclize, in this manner, to yield a fused 5/6/5 ring system has previously been noted (see Sections A-575, A-642, etc.).

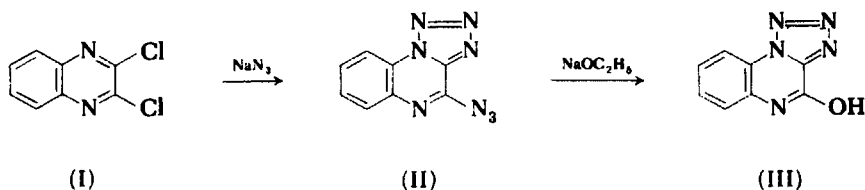
References

1. Andrisano, *Boll. sci. fac. chim. ind. univ. Bologna*, **5**, 45 (1944-7); *Chem. Abstracts*, **44**, 3904 (1950).
2. Benson, Hartzel and Otten, *J. Am. Chem. Soc.*, **76**, 1858 (1954).

A-646. Tetrazolo[*a*]quinoxaline.
R.I. 1475



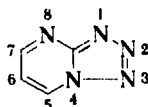
Stollé and Hanusch¹ treated I with sodium azide and obtained II (m. 265°). Cyclization of the azido group to a second tetrazole ring could not be achieved. Sodium ethoxide converted II into III (m. 288°).



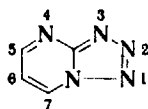
Reference

1. Stollé and Hanusch, *J. prakt. Chem.*, **136**, 9 (1933).

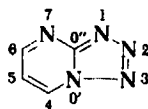
A-647. Tetrazolo[*a*]pyrimidine.
R.I. 671



This nucleus has also been called *tetrazolo[1,5-*a*]pyrimidine*, *1,2,3,4-tetrazaindolizine*, and *1,2,3-tetrazolo-7.0'-pyrimidine* with, for the latter two, the numbering shown in I and II, respectively.

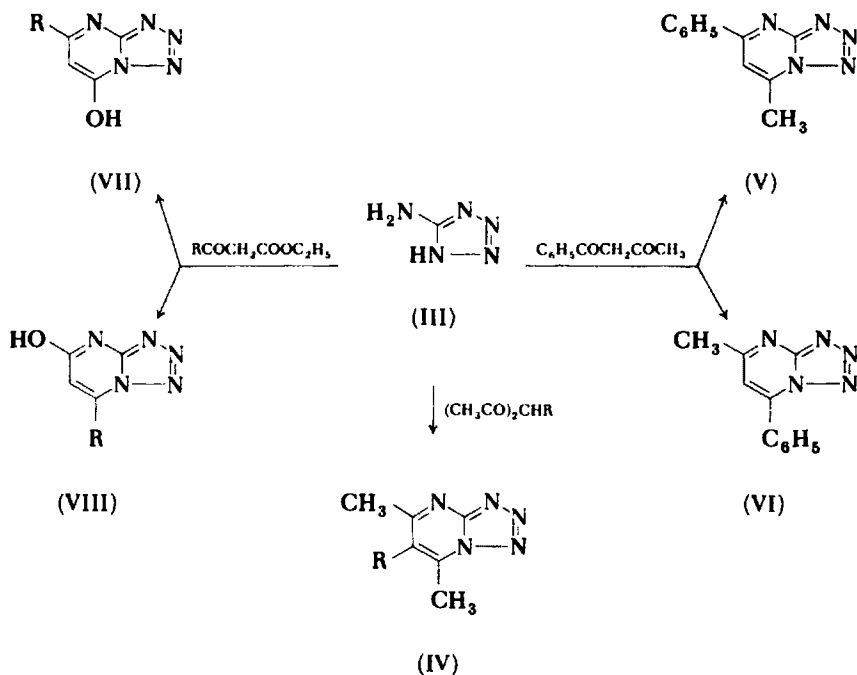


(I)



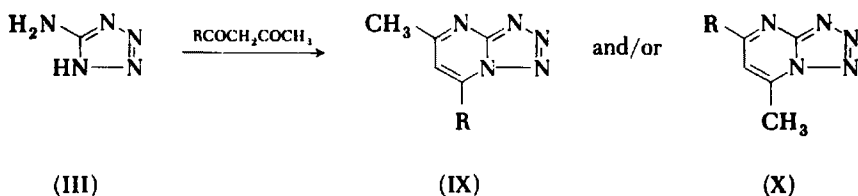
(II)

Bülow¹ treated aminotetrazole (III) with 1,3-diketones and obtained IV ($R = H$, m. $151-2^\circ$; $R = CH_3$, m. $123.0-3.5^\circ$). The reaction with benzoylacetone yielded a product (m. 185°), for which Bülow shows structure V, but since he refers to it in different places as the 6-phenyl-4-methyl, 6-methyl-5-phenyl and 2-methyl-5-phenyl derivative, his concept of its structure is unclear. The product is, however, in all probability either V or VI. Similarly, from the reaction of III with acetoacetic and benzoylacetic esters, are obtained products (m. $258-60^\circ$ d. [253° , $246-7^\circ$] and 261° d., respectively), assigned structure VII. The probable accuracy of this choice is indicated by the recent synthesis^{7,10} of VII ($R = CH_3$) from 2-hydrazino-4-hydroxy-6-methylpyrimidine, and its conversion via the 5-chloro-7-methyl compound¹⁰ (m. $106.5-7.5^\circ$) to 7-methyl-

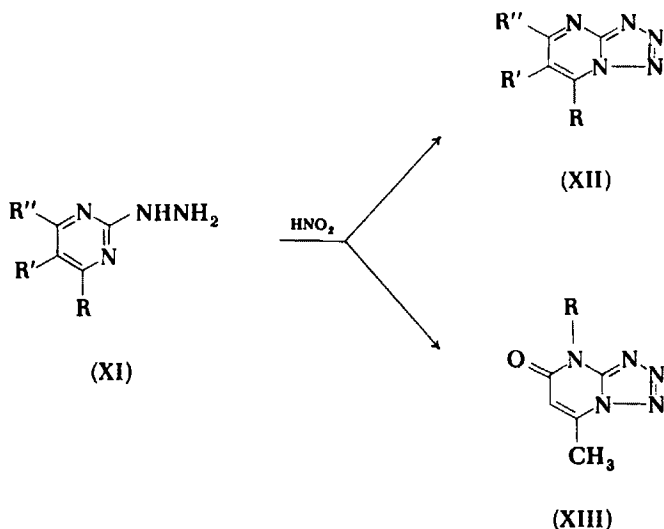


tetrazolo[*a*]pyrimidine (m. 134°), also obtained⁹ by condensing III with 1,1-dimethoxy-3-butanone.

The condensation of III with acetylpyruvic acid yielded² an acidic product (m. 173–4°; diethylamide, m. 126–7°), which was assigned structure IX (R = COOH), although X would seem equally possible. From the condensation of III with 7-diethylamino-hepta-2,4-dione, Dewar³ isolated a mixture of picrates [of presumably IX and X, R = CH₂CH₂CH₂N(C₂H₅)₂], from which one (m. 145–6°) was obtained in pure condition.



Recently, Shirakawa⁸ prepared a number of tetrazolo[*a*]pyrimidines (XII, R = R' = R'' = H, m. 121–3°; R = CH₃, R' = R'' = H, m. 135–6°; R = R'' = CH₃, R' = H, m. 153–4°; R = CH₃, R' = H, R'' = OH, m. 253° d; R = CH₃, R' = H, R'' = OCH₃, m. 163–5°; R = NH₂, R' = CN, R'' = H, m. 223° d. and XIII, R = CH₃, m. 177–9°; and R = CH₂C₆H₅, m. 174.5–6.5°) by treating 2-pyrimidylhydrazines (XI) with nitrous acid. The similarity



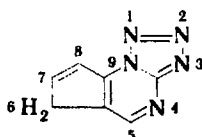
of the melting point of the monomethyl derivative to that^{9,10} (v.s.) of the 7-methyl compound suggests the possibility that some of Shirakawa's products may be the isomers (of structure XII) having the R and R'' groups reversed.

The ultraviolet absorption spectra of IV (R = H)⁴ and VII (R = CH₃)⁷ have been measured, and the potentiometric titration of various derivatives was studied.⁵ The utility of compounds of structure VII in photographic emulsions has been discussed.⁶

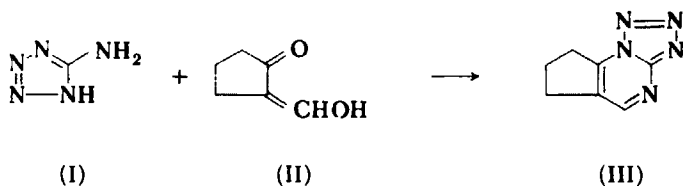
References

1. Bülow, *Ber.*, **42**, 4429 (1909).
2. Ettel and Nosek, *Collection Czechoslov. Chem. Commun.*, **15**, 335 (1950).
3. Dewar, *J. Chem. Soc.*, **1944**, 615.
4. Nachod and Steck, *J. Am. Chem. Soc.*, **70**, 2819 (1948).
5. Kikuchi and Akiba, *J. Soc. Sci. Phot. (Japan)*, **18**, 20 (1955); *Chem. Abstracts*, **50**, 2331 (1956).
6. Birr, *Z. wiss. Phot.*, **50**, 107 and 124 (1955); *Chem. Abstracts*, **50**, 9911 (1956).
7. Bower and Doyle, *J. Chem. Soc.*, **1957**, 727.
8. Shirakawa, *Jap. Pat.* 777 ('57); *Chem. Abstracts*, **52**, 4699 (1958).
9. Burness, *U. S. Pat.* 2,837,521.
10. Allen *et al.*, *J. Org. Chem.*, **24**, 796 (1959).

A-648. 6H-Cyclopenta[*e*]tetrazolo-[4,5-*a*]pyrimidine



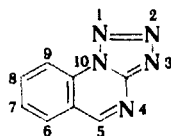
The reaction of 5-aminotetrazole (I) with II yielded¹ III (m. 152–3°), although the analogous 5-hydroxy compound could not be obtained from I and 2-carbethoxycyclopentanone. See Sections A-584/5.



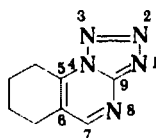
Reference

1. Cook, Gentles and Tucker, *Rec. trav. chim.*, **69**, 1201 (1950).

A-649. Tetrazolo[*a*]quinazoline.
R.I. 1474

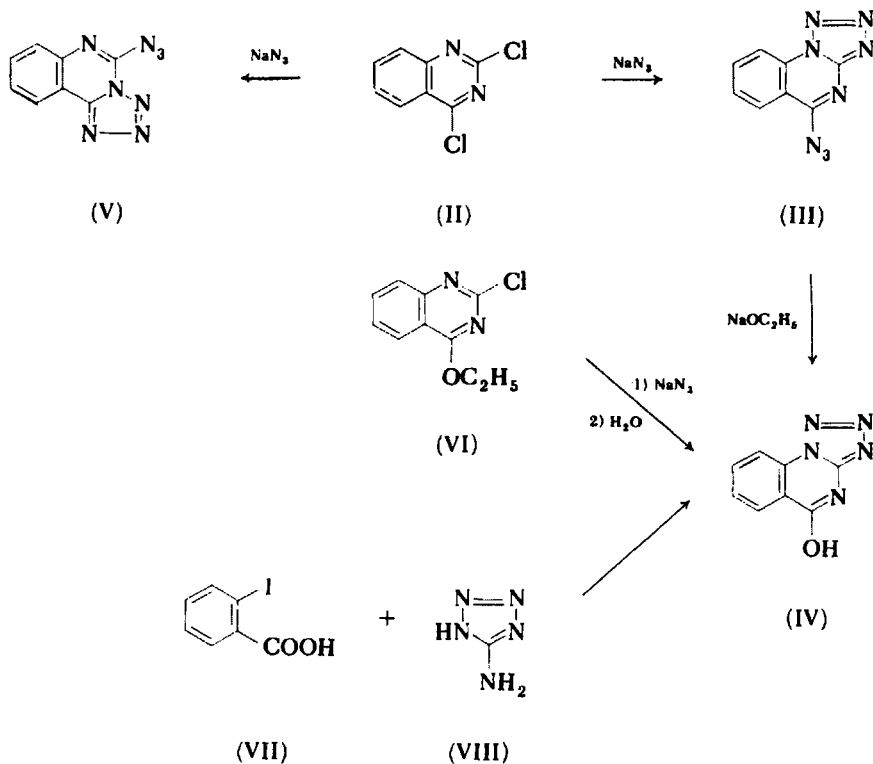


The 6,7,8,9-tetrahydro derivative of this nucleus has been called *5,6-tetramethylene-1,2,3,8-tetrazaindolizine* and numbered as shown in I.



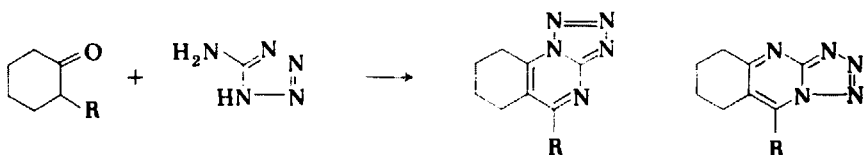
(I)

Stollé and Hanusch¹ treated II with sodium azide and obtained a product (m. 145° d.), considered to be either III or V. The azido



group was replaced by a hydroxyl group when the compound was treated with sodium ethoxide, and this hydroxy compound (m. 243°) could also be prepared² from VI, a fact which excludes structure V from consideration as the initial product. It was also found possible³ to obtain this substance, although as a minor product, from the condensation of VII and VIII. The product was assigned² structure IV, although the corresponding *linear* structure does not appear to have been eliminated, or even considered, and in view of the preparation of the product from VII and VIII, the linear structure seems quite reasonable. The 5-chloro derivative (m. $184-5^{\circ}$) was obtained³ by treating IV with phosphorus oxychloride.

The reaction of IX and X with 5-aminotetrazole yields products thought,³ by analogy to the reaction of IX and X with 3-amino-1,2,4-triazole (see Sections A-584/5), to have the angular structure XI rather than the linear structure XII. Thus from IX was obtained XIa



(IX) $\text{R} = \text{CHO}$

(X) $\text{R} = \text{COOC}_2\text{H}_5$

(XIa) $\text{R} = \text{H}$

(XIb) $\text{R} = \text{OH}$

(XIc) $\text{R} = \text{Cl}$

(XIId) $\text{R} = \text{C}_6\text{H}_5\text{NH}$

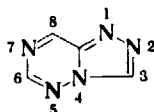
(XIe) $\text{R} = \text{HN}(\text{CH}_2)_2\text{N}(\text{C}_2\text{H}_5)_2$

(XII)

($\text{R} = \text{H}$, m. $122-3^{\circ}$), while X gave XIb ($\text{R} = \text{OH}$, m. 200° d.). Treatment of XIb with phosphorus oxychloride gave XIc ($\text{R} = \text{Cl}$, m. 97.9°), which reacted with amines to yield XIId ($\text{R} = \text{C}_6\text{H}_5\text{NH}$, m. $192-4^{\circ}$) and XIe ($\text{R} = (\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{N}$, m. $220-2^{\circ}$), and which could be dehalogenated to XIa.

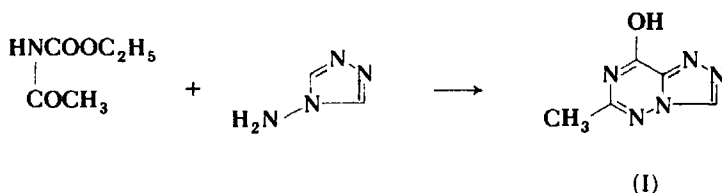
References

1. Stollé and Hanusch, *J. prakt. Chem.*, **136**, 9 (1933).
2. Stollé and Hanusch, *J. prakt. Chem.*, **136**, 120 (1933).
3. Cook, Gentles and Tucker, *Rec. Trav. Chim.*, **69**, 1201 (1950).

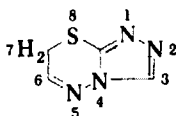
A-650. *s*-Triazolo[3,4-*f*]-*as*-triazine *

The name *2,3,5,7-tetrazaindoline* has been used.

The preparation, as shown, of I has been suggested by Birr,¹ but no further information is available.

*Reference*

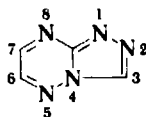
1. Birr, *Z. wiss. Phot.*, **47**, 2 (1952).

A-651. *7H-s*-Triazolo[3,4-*b*][1,3,4]-thiadiazine

The reaction of I with phenacyl bromide or with bromoacetal gave products considered¹ to have structure II ($R = R' = C_6H_5$, m. 214–5°; $R = CH_3$, $R' = C_6H_5$, m. 186–7°; $R = CH_3$, $R' = H$, m. 144°).

*Reference*

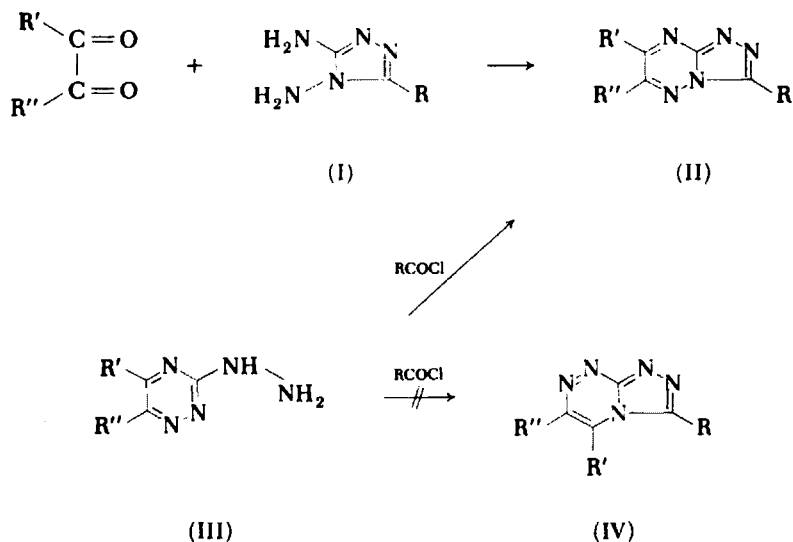
1. Hoggarth, *J. Chem. Soc.*, **1952**, 4811.

A-652. *s*-Triazolo[4,3-*b*]-*as*-triazine

This nucleus has also been called *1:2:4:7:9-pentaaazaindene* and *2,3,4,7-tetraazaindizine*.

Hoggarth found^{1,2,3} that the reaction of 3,4-diamino-*s*-triazoles (I) with α,β -diketones readily produced compounds of type II. This reaction was extended⁴ to use the thio and mercapto derivatives of I ($R = SCH_3$ and SH) and the more readily available guanazine (I, $R = NH_2$). Guanazine, however, failed to condense⁴ with glyoxal or alloxan.

An alternative synthesis⁵ commences with 3-hydrazino-1,2,4-triazines (III) and constructs the triazole ring by reaction with acid chlorides. Such a reaction might, a priori, lead either to II or to the isomeric compound IV. That products of type II result was shown⁵ by comparison with the product (II, $R = R' = R'' = C_6H_5$) obtained by Hoggarth.



Treatment⁴ of II ($R' = R'' = C_6H_5$, $R = SH$ or SCH_3) with hot alcoholic ammonia or with potassium amide failed to yield the 3-amino derivative. Oxidation of II ($R = CH_2OH$, $R' = C_6H_5$,

$R'' = H$) yielded⁵ the carboxylic acid II ($R = COOH$, $R' = C_6H_5$, $R'' = H$).

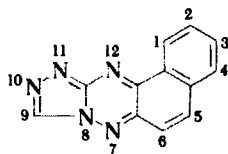
Derivatives of Type II

R	R'	R''	Properties	Refs.
H	OH	CH ₃	m. 266°.	5
NH ₂	OH	CH ₃	m. 317-8°.	4
NH ₂	CH ₃	CH ₃	Yel., m. 299-300°.	4
H	C ₆ H ₅	H	m. 252-3°.	5
COOH	C ₆ H ₅	H	m. 229-30°.	5
CH ₃	C ₆ H ₅	H	m. 127°.	5
CH ₂ OH	C ₆ H ₅	H	m. 230-2°.	5
C ₆ H ₅	CH ₃	CH ₃	Yel., m. 203°.	1
CH ₂ OC ₂ H ₅	C ₆ H ₅	H	m. 171-2°.	5
<i>p</i> -CH ₃ OC ₆ H ₄	CH ₃	CH ₃	Yel., m. 215°.	2
CH=C(CH ₃) ₂	C ₆ H ₅	H	m. 253°.	5
NH ₂	<i>p</i> -C ₆ H ₄ Cl	<i>p</i> -C ₆ H ₄ Cl	Red, m. 229-31°.	4
H	C ₆ H ₅	C ₆ H ₅	Or.-red, m. 182-3°.	3
SH	C ₆ H ₅	C ₆ H ₅	Or., m. 304.5-6.5°.	4
NH ₂	C ₆ H ₅	C ₆ H ₅	Red, m. 263-4°.	4
CH ₃ S	C ₆ H ₅	C ₆ H ₅	Yel., m. 201-3°.	3,4
C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	Yel., m. 250°.	1,5
<i>p</i> -CH ₃ OC ₆ H ₄	C ₆ H ₅	C ₆ H ₅	Yel., m. 247°.	3

References

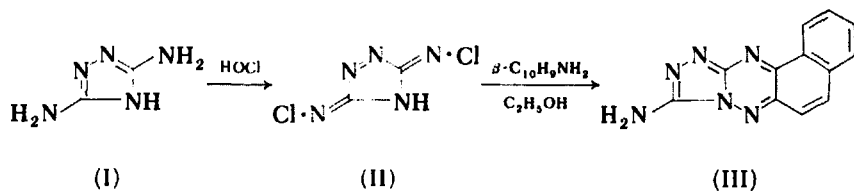
1. Hoggarth, *J. Chem. Soc.*, **1950**, 614.
2. Hoggarth, *J. Chem. Soc.*, **1950**, 1579.
3. Hoggarth, *J. Chem. Soc.*, **1952**, 4817.
4. Taylor, Gumprecht and Vance, *J. Am. Chem. Soc.*, **76**, 619 (1954).
5. Fusco and Rossi, *Rend. inst. lombardo sci. Pt. I. Classe sci. mat. e nat.*, **88**, 173 (1955); *Chem. Abstracts*, **50**, 10742 (1956).

**A-653. Naphtho[1,2-*e*]-s-triazolo-
[4,3-*b*]-as-triazine. R.I. 2344**



Stollé and Dietrich¹ treated guanazole (I) with hypochlorous acid and isolated a yellow *N*-chloro compound, which they con-

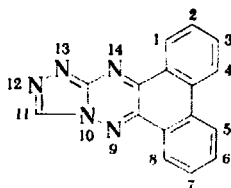
sidered to be II. This reacted with β -naphthylamine to yield a brownish-red product (m. 285°), which has a free amino group, since it could be diazotized and coupled to R-salt. This product was thought to have structure III, although no real evidence in support of either structure II or III was adduced.



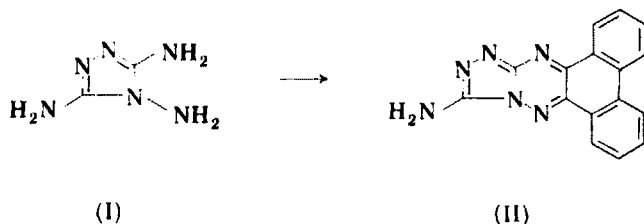
Reference

1. Stollé and Dietrich, *J. prakt. Chem.*, **139**, 193 (1934).

A-654. Phenanthro[9,10-*e*]-*s*-triazolo-[4,3-*b*]-*as*-triazine *

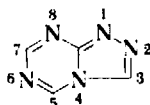


The condensation of guanazine (I) with phenanthraquinone yielded ¹ II (red, m. 334-6°).

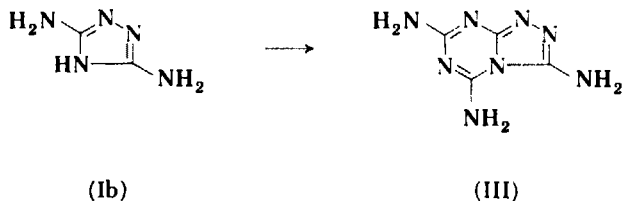
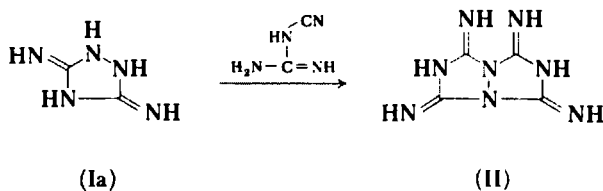


Reference

1. Taylor, Gumprecht and Vance, *J. Am. Chem. Soc.*, **76**, 619 (1954).

A-655. *s*-Triazolo[4,3-*a*]-*s*-triazine

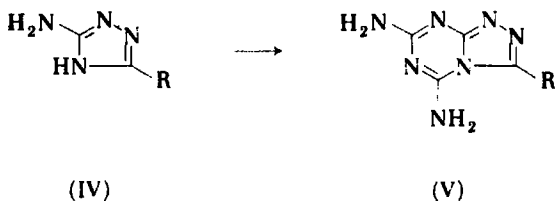
Pellizzari and Roncagliolo heated¹ guanazole (Ia or Ib) with dicyandiamide and obtained a product called *guanazoguanazole*, to which they assigned structure II. In similar fashion a group of related products was prepared (see Section A-182). Recently, in view of evidence that structure Ib better represents the structure of guanazole, Kaiser, Peters and Wystrach proposed² structure III for *guanazoguanazole*. They demonstrated the probable presence of a



triazine nucleus in this substance by isolating cyanuric acid as the major product of its oxidation with acidic permanganate. Furthermore, *guanazoguanazole* yielded a mixture of di- and triacetyl derivatives¹ and a tribenzoyl derivative,² as would be expected from structure III, whereas II would be expected to form tetra- and possibly penta- or hexaacyl derivatives. See Section A-658.

Similarly, 5-substituted 3-amino-*s*-triazoles (IV) react^{2,3} with dicyandiamide to yield V (R = methyl, d. 345–6°; R = *n*-amyl, d. 315–6°; R = heptadecyl, d. 219–220°; R = phenyl, d. 375–6°). It is possible that a group of compounds prepared (see Section A-658) similarly by Birr⁴ are also of this type.

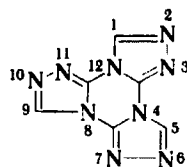
It is also possible that certain degradation products (see Section A-656) of *pyroguanazole* contain this nucleus.



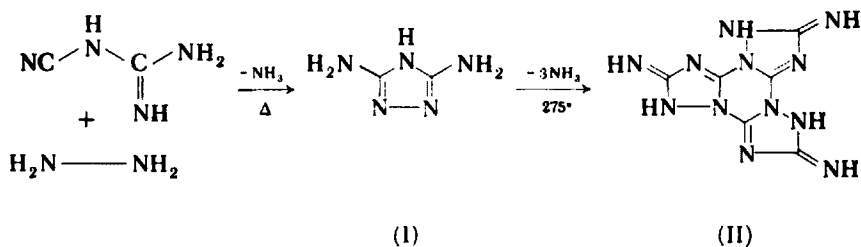
References

1. Pellizzari and Roncagliolo, *Gazz. chim. ital.*, **31**, I, 477 (1901); *Chem. Zentr.*, **II**, 588 (1901).
2. Kaiser, Peters and Wystrach, *J. Org. Chem.*, **18**, 1610 (1953).
3. Kaiser, U. S. Pat. 2,473,797.
4. Birr, *Z. wiss. Phot.*, **47**, 2 (1952).

A-656. Tris-*s*-triazolo[4,3-*a*, 4',3'-*c*, 4'',3''-*e*]-*s*-triazine

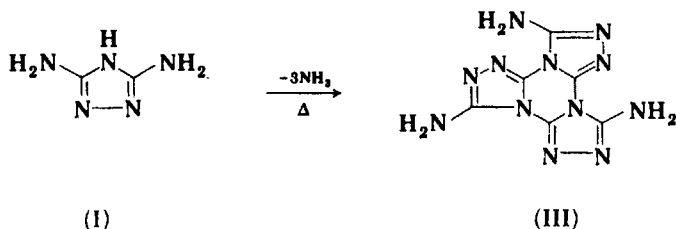


By heating dicyandiamide with hydrazine, Hofmann and Ehrhart¹ obtained an infusible white solid, which was called *pyroguanazole*, *melmazine* or *tridesaminoguanazole*. They later² found that pyroguanazole could be obtained by simply heating guanazole (I), an intermediate in the first reaction, and they assigned structure II to pyroguanazole. See Section A-659.



Since the permanganate oxidation of pyroguanazole was known² to yield cyanuric acid and nitrogen, Kaiser, Peters and Wystrach³ considered structure II untenable. They argued that oxidation of II to yield nitrogen would necessarily involve cleavage of the triazine

ring so that no cyanuric acid should be obtained, and to account for the formation of both degradation products, they proposed structure III for pyroguanazole.

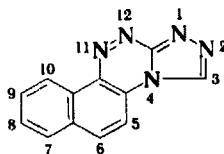


No really characteristic or well-defined derivatives of pyroguanazole are known, although a number of its reactions were reported,² and two of its degradation products are discussed in Sections A-655 and A-658.

References

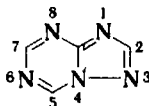
1. Hofmann and Ehrhart, *Ber.*, **44**, 2713 (1911).
2. Hofmann and Ehrhart, *Ber.*, **45**, 2731 (1912).
3. Kaiser, Peters and Wystrach, *J. Org. Chem.*, **18**, 1610 (1953).

A-657. Naphtho[2,1-*e*]-*s*-triazolo-[3,4-*c*]-*as*-triazine*



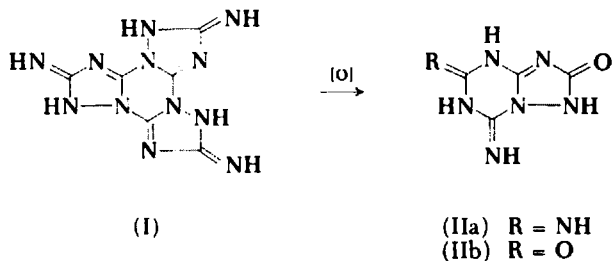
See Section A-660.

A-658. *s*-Triazolo[2,3-*a*]-*s*-triazine. R.I. 701

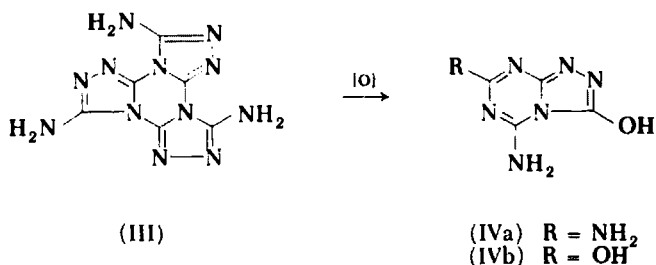


This nucleus is also called *1,3,4,6-tetrazaindolizine*.

From the pyrolysis of guanazole, Hofmann and Ehrhart obtained a substance called *pyroguanazole*, to which they assigned¹ structure I (see Section A-656). From its degradation they obtained two products, which they assigned structures IIa and IIb.

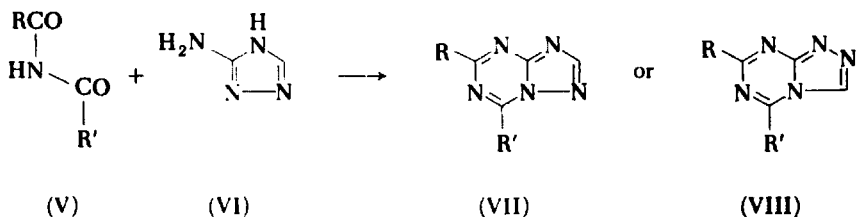


However, in view of suggestion² that pyroguanazole has structure III, it is possible that these products may be represented by structures IVa and IVb. See Section A-655.



In Section A-182, the possibility was advanced that substances known as *imidurazoguanazole* and *urazoguanazole* may have structures IVa and IVb, respectively. Inadequate characterization of both of these substances and of Hofmann and Ehrhart's products precludes a comparison now, but an examination should readily provide evidence of their identity or non-identity.

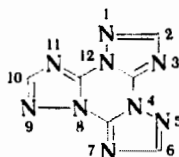
Birr³ suggests that the reaction of aminotriazole (VI) with reagents of type V (such as acetylurethane, diacetimide, iminodicarboxylic ester, dicyanamide, cyanourethane, etc.), forms products of structure VII or VIII. No details are given. See Section A-655.



References

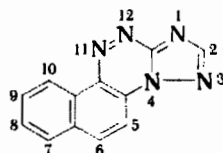
1. Hofmann and Ehrhart, *Ber.*, **45**, 2731 (1912).
2. Kaiser, Peters and Wystrach, *J. Org. Chem.*, **18**, 1610 (1953).
3. Birr, *Z. wiss. Phot.*, **47**, 2 (1952).

**A-659. Tris-*s*-triazolo-*s*-triazine.
R.I. 2230**

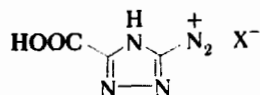


The above name was used by the *Ring Index*. A more precise name is *tris-s-triazolo[2,3-*a*, 2',3'-*c*, 2'',3''-*e*]-s-triazine*. See Section A-656.

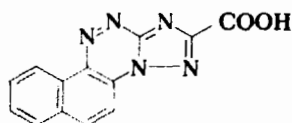
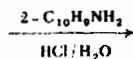
**A-660. Naphtho[2,1-*e*]-*s*-triazolo
[5,1-*c*]-*as*-triazine**



When the diazonium salt I was coupled into β -naphthylamine, and the resulting acidic mixture boiled for several hours, a pale yellow solid formed, which was assigned¹ structure II. No further

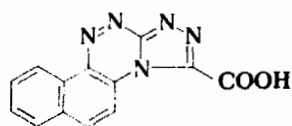


(I)



(II)

or



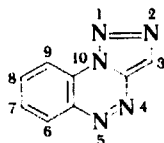
(III)

description of the product was given, nor was any evidence to exclude the alternative structure III. See Section A-663.

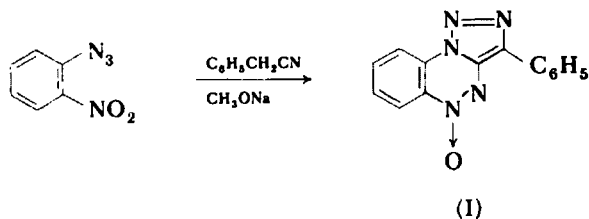
Reference

1. Morgan and Grimm, U. S. Pat. 2,515,728.

A-661. Benzo[*e*]-*v*-triazolo[4,3-*c*]-*as*-triazine*



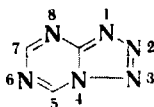
Condensation of *o*-nitrophenyl azide with phenylacetone nitrile yielded¹ an orange product ($C_{14}H_9N_5O$, m. $220-2^\circ$ or $218-9^\circ$ d.) thought to have structure I.



Reference

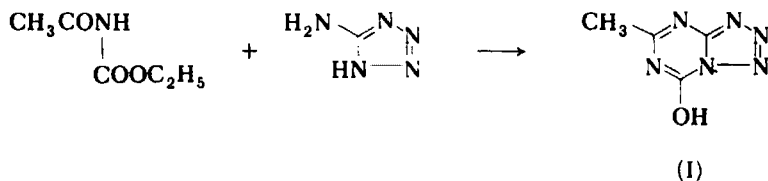
1. Lieber, Chao and Rao, *J. Org. Chem.*, **22**, 654 (1957).

A-662. Tetrazolo-*s*-triazine*



The name *1,2,3,4,6-pentazaindolizine* has been used.

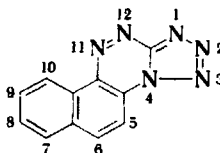
The condensation of aminotetrazole with acetylurethane has been proposed¹ as a synthesis of I.



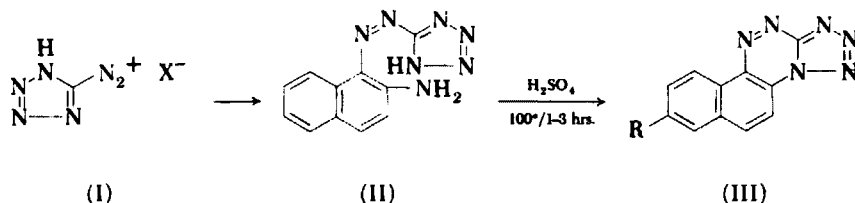
Reference

1. Birr, *Z. wiss. Phot.*, **47**, 2 (1952).

A-663. Naphtho[2,1-*c*]tetrazolo[*c*]-*as*-triazine



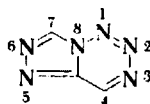
When I was coupled into β -naphthylamine, and the resulting red azo-compound (II) was heated with sulfuric acid, the initial red color of the solution changed slowly to yellow, and III (R = H) was isolated¹ in 50–75% yield. A sulfo derivative (III, R = SO₃H) was similarly obtained. No further description of these products was given.



Reference

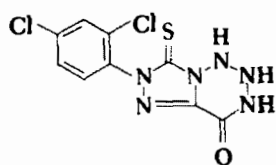
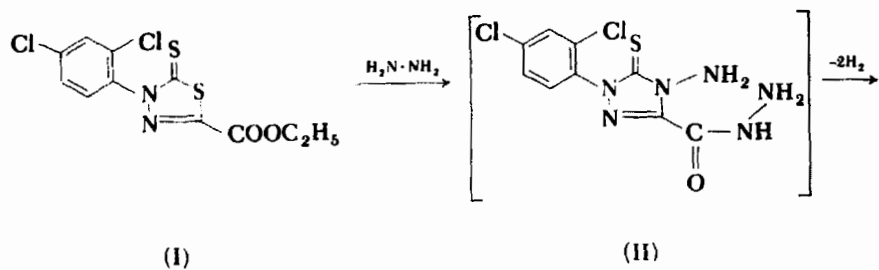
1. Morgan and Grimm, U. S. Pat. 2,515,728.

**A-664. *s*-Triazolo[4,3-*d*]-*v*-tetrazine.
R.I. 700**



This nucleus has been called *1,3,4-triazolo-1,2-tetrazine*.

Bülow and Seidel¹ treated I with hydrazine and obtained a product (sinters at 191–2°, m. 196–7° d., and decomposes on standing), to which they assigned structure III. It was presumably formed by the oxidation of II. However, the properties of the product and the analytical data given are more closely in accord with structure II than III, and it seems probable that structure III is incorrect.



(III)

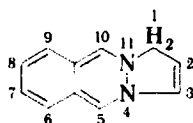
Reference

1. Bülow and Seidel, *Ber.*, **57**, 357 (1924).

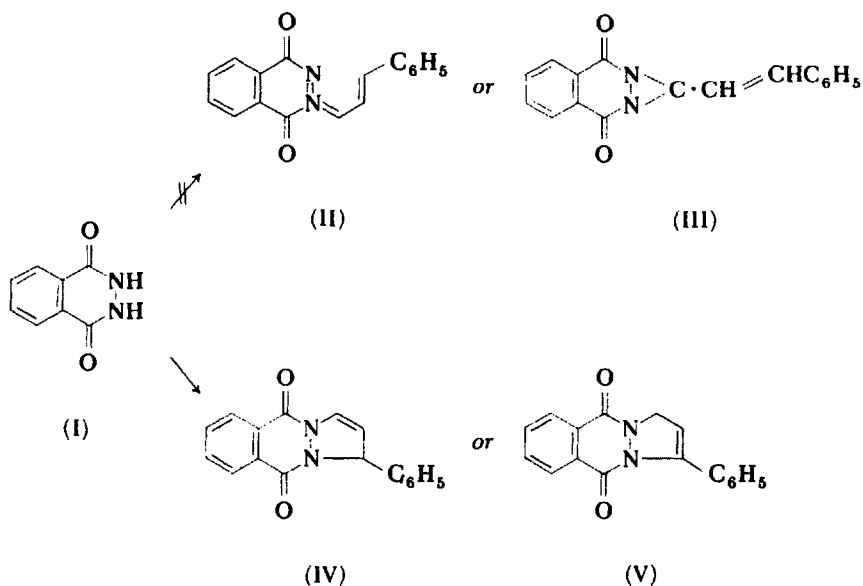
CHAPTER IX

Fused 5/6 Ring Systems With Two Bridgehead Nitrogen Atoms

A-665. 1*H*-Pyrazolo[1,2-*b*]phthalazine.
R.I. 1564



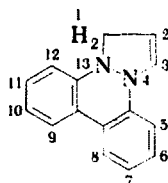
The reaction of I with cinnamaldehyde yielded a product, which Radulescu considered¹ to have one of the unlikely structures II or III. While studying the chemistry of I, Drew and Hatt² repeated this reaction and obtained a yellow product (m. 224-8°) thought to be either IV or its tautomer V. The product turns green upon exposure to light.



References

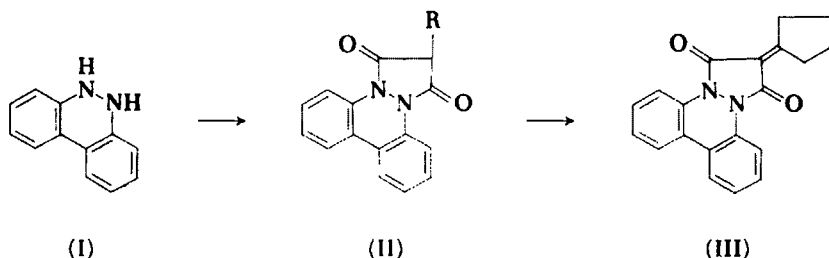
1. Radulescu, *Bull. Soc. Chim. Roumania*, **8**, 120 (1926); *Chem. Zentr.*, **II**, 258 (1927).
2. Drew and Hatt, *J. Chem. Soc.*, **1937**, 16.

A-666. 1H-Benzo[c]pyrazolo[1,2-a]-cinnoline



The name *pyrazolidino[1,2-f]benzo[c']cinnoline* has been used.

The condensation of I or its mono- or di-*N*-acetyl derivatives with malonic esters or chlorides yields^{1,2} II, which, when R = H, may be alkylated in the 2-position or condensed with cyclic ketones to yield, e.g., III. Some of these products are said² to possess analgesic ac-



tivity, and the alkali salts of others are claimed² to aid the solution in water of other sparingly soluble substances.

Products of Structure II

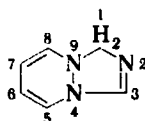
Empirical formula	Where R represents	Properties	Refs.
C ₁₅ H ₁₀ N ₂ O ₂	Hydrogen	m. 210–2° (205–7° d.).	1,2
C ₁₆ H ₁₂ N ₂ O ₂	Methyl	m. 205–6°.	2
C ₁₇ H ₁₄ N ₂ O ₂	Ethyl	Lt. yel., m. 145°.	2
C ₁₈ H ₁₄ N ₂ O ₂	Allyl	m. 123°.	2
C ₁₈ H ₁₆ N ₂ O ₂	<i>n</i> -Propyl	Pale yel., m. 117–8°.	2
	<i>i</i> -Propyl	m. 149°.	2
C ₁₉ H ₁₈ N ₂ O ₂	<i>n</i> -Butyl	m. 140° (136–8°, 125–8°).	1,2
	<i>sec</i> -Butyl	m. 103°.	2

Products of Structure II (*continued*)

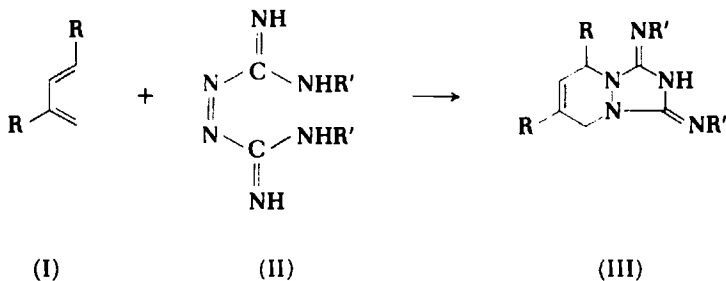
Empirical formula	Where R represents	Properties	Refs.
C ₂₀ H ₁₄ N ₂ O ₃	Furfuryl	m. 147°.	2
C ₂₀ H ₁₆ N ₂ O ₂	Cyclopentylidene	m. 193-4°.	2
C ₂₀ H ₁₈ N ₂ O ₂	Cyclopentyl	m. 124-5°.	2
C ₂₀ H ₁₈ H ₂ O ₃	Tetrahydrofurfuryl	m. 115°.	2
C ₂₀ H ₂₀ N ₂ O ₃	3-Methoxybutyl	Pale yel., m. 105°.	2
C ₂₁ H ₁₈ N ₂ O ₂	Cyclohexylidene	Red, m. 136°.	2
C ₂₁ H ₂₀ N ₂ O ₂	Cyclohexyl	Pale yel., m. 165°.	2
C ₂₁ H ₂₀ N ₂ O ₃	Tetrahydropyranyl-2-methylene	Pale yel., m. 128-9°.	2
C ₂₁ H ₂₂ N ₂ O ₂	n-Hexyl	m. 112°.	2
C ₂₁ H ₂₂ N ₂ O ₃	n-Butoxyethyl	m. 71-2°.	2
C ₂₂ H ₁₆ N ₂ O ₂	Benzyl	m. 190°.	2
C ₂₃ H ₁₈ N ₂ O ₃	Phenoxyethyl	Pale grn., m. 153-4°.	2

References

1. Kühne and Erlenmeyer, *Helv. Chim. Acta*, **38**, 531 (1955).
2. Matter, U. S. Pat. 2,778,829; Brit. Pat. 794,775; Ger. Pat. 1,071,708.

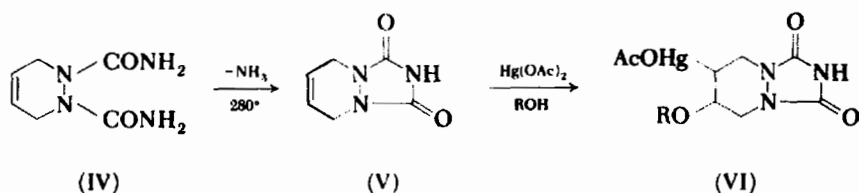
A-667. 1*H*-s-Triazolo[*a*]pyridazine

By the reaction of dienes (I, R = H or CH₃) with II (R' = H or NO₂), good yields of III (R = R' = H, nitrate, m. 261.2°; R =



CH₃, R' = H, nitrate, m. 196.5-196.8°; picrate, m. 253.4-4.2°; R = CH₃, R' = NO₂, m. 258.5-60.6°) were obtained.^{1,2}

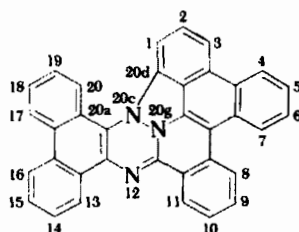
In a very similar synthesis, IV was obtained^{3,4} from the condensation of butadiene with azodicarboxamide. Heating IV gave V (m. 244–7°), which was named *1,6,8-triazabicyclo[4.3.0]-3-nonene-7,9-dione*. With alkyl halides V yielded 2-alkyl homologs, and a group of mercury derivatives of structure VI also was prepared.



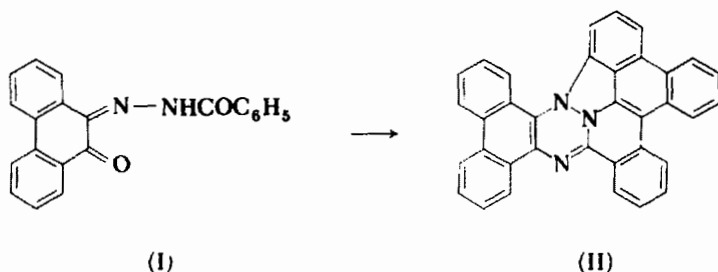
References

1. Wright, *Can. J. Chem.*, **30**, 62 (1952); *Chem. Abstracts*, **47**, 3793 (1953).
2. MacKenzie, Rodgman and Wright, *J. Org. Chem.*, **17**, 1666 (1952).
3. Clarke and Gubitz, U. S. Pat. 2,813,865.
4. Clarke, U. S. Pat. 2,813,866.

A-668. 12,20c,20g-Triazabenz[*p*]indeno-[1,2,3,4-*defg*]phenanthro[9,10-*b*]-chrysene*



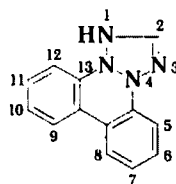
Heating I for three hours with ammonium acetate in acetic acid produced¹ a yellow crystalline solid (m. > 360°; deep blue color in sulfuric acid), tentatively assigned structure II.



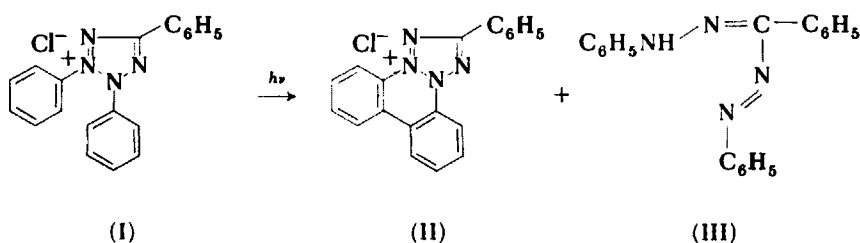
Reference

1. Laasko, Robinson and Vandrewala, *Tetrahedron.*, **1**, 103 (1957).

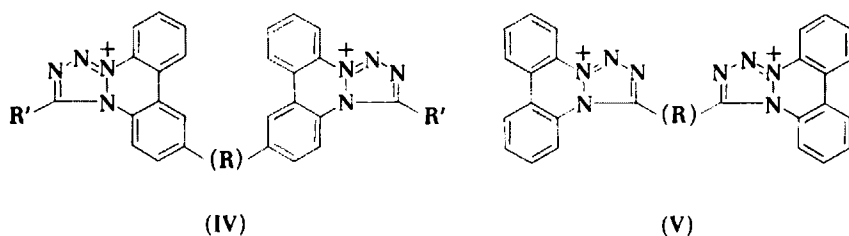
A-669. 1H-Benzo[c]tetrazolo[2,3-a]-cinnoline



Because of their unusual properties, much interest has recently been focused (see review¹) upon tetrazolium salts such as I. It was found that irradiation of aqueous solutions of I with sunlight, or better ultraviolet light, yielded² the formazan (III) together with the strongly fluorescent II. In alcoholic solution II was the sole product,

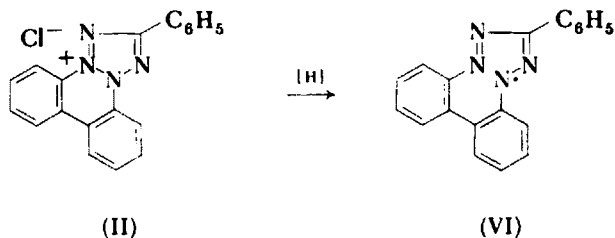


and was obtained³ in almost quantitative yield. Numerous derivatives of II were thus obtained from analogs of I, including complex molecules⁵⁻⁷ such as IV and V.



The rather unexpected structure (II) was demonstrated by its degradation (on zinc dust distillation) to carbazole and benzonitrile and (upon reduction with zinc and acid) to benzo[c]cinnoline. The action of numerous reducing agents upon II was studied⁴ and it was

found that several (best: sodium hydrosulfite) convert II (and its homologs) to highly colored paramagnetic free radicals, perhaps best represented by structure VI, although undoubtedly of hybrid character.

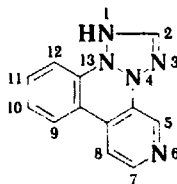


In view of the existence of an excellent recent review¹ of tetrazolium salts, and because the presence of a pentavalent nitrogen atom puts these salts outside the intended scope of this book, no tabulation of these compounds is presented here. The influence of polycyclic hydrocarbons as oxidation catalysts in the formation of I and II from III has been studied.⁹

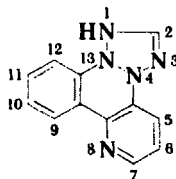
References

1. Nineham, *Chem. Rev.*, **55**, 355 (1955).
2. Weygand and Frank, *Z. Naturforsch.*, **3b**, 377 (1948); *Chem. Abstracts*, **43**, 5313 (1949).
3. Hausser, Jerchel and Kuhn, *Chem. Ber.*, **82**, 195 (1949).
4. Kuhn and Jerchel, *Ann.*, **578**, 1 (1952).
5. Jerchel and Edler, *Chem. Ber.*, **88**, 1284 (1955).
6. Jerchel and Fischer, *Chem. Ber.*, **88**, 1595 (1955).
7. Jerchel and Fischer, *Chem. Ber.*, **89**, 563 (1956).
8. Jerchel and Fischer, *Ann.*, **590**, 216 (1954).
9. Garzia and Dansi, *Ann. chim. (Rome)*, **45**, 31 (1955); *Chem. Abstracts*, **50**, 4102 (1956).

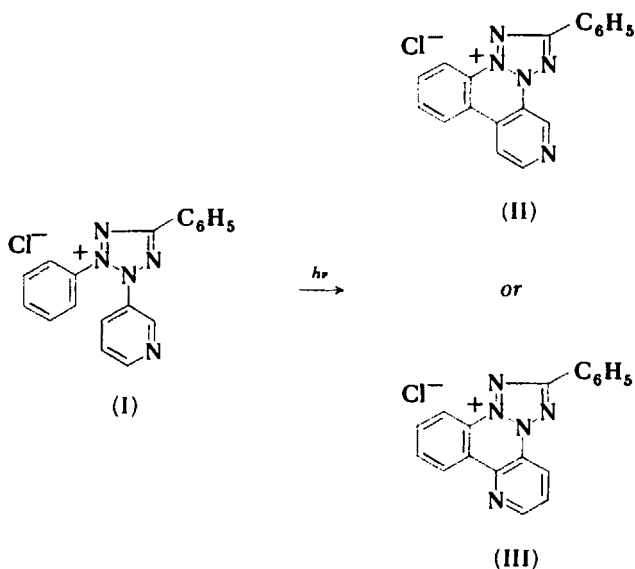
A-670. 1H-Pyrido[3,4-c]tetrazolo-[2,3-a]cinnoline*



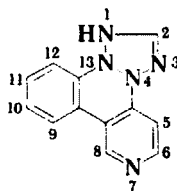
or

A-671. 1H-Pyrido[3,2-c]tetrazolo-[2,3-a]cinnoline*

The photoirradiation of I yielded¹ a product (m. 312°d.), which probably has either structure II or III. It behaves similarly to its analogs. See Sections A-669 and A-672.

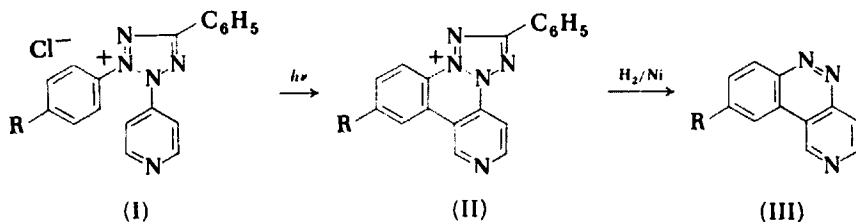
*Reference*

1. Jerchel and Fischer, *Chem. Ber.*, **89**, 563 (1956).

A-672. 1H-Pyrido[4,3-c]tetrazolo-[2,3-a]cinnoline*

Irradiation of solutions of the tetrazolium salts I (R = H or CH₃) with ultraviolet light yields¹ II (R = H, m. 245-7°; R =

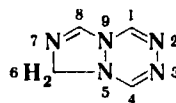
CH_3 , m. 240°d .). Reduction of II with hydrosulfite yields olive-colored free radicals analogous to those formed by the benzo[*c*]tetrazolo-[2,3-*a*]cinnolinium salts (see Section A-669). Hydrogenation of II over a Raney nickel catalyst causes scission of the tetrazole ring and yields 3,9,10-triazaphenanthrenes (III).



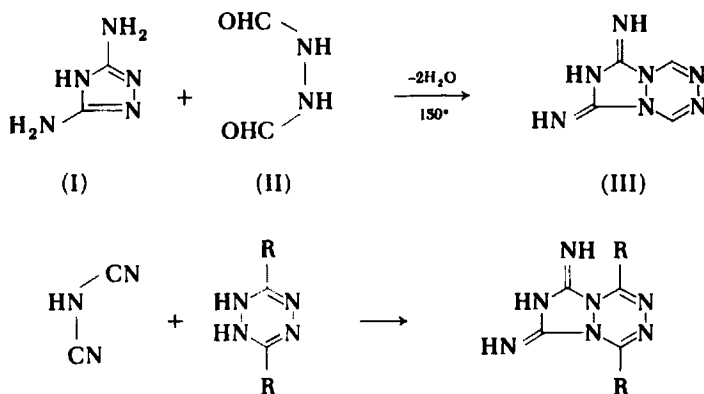
Reference

1. Jerchel and Fischer, *Chem. Ber.*, **89**, 563 (1956).

A-673. 6*H*-*s*-Triazolo[1,2-*a*]-*s*-tetrazine



The reaction of guanazole (I) with II yielded¹ a white solid, decomposing at high temperatures, which was assigned structure III. Further evidence in favor of this structure would be welcome. For example, analogs of III might possibly be formed by the interaction of 1,2-dihydrotetrazines and dicyanamide.



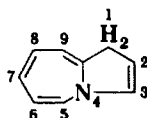
Reference

1. Papini and Checchi, *Gazz. chim. ital.*, **82**, 735 (1952); *Chem. Abstracts*, **47**, 12371 (1953).

CHAPTER X

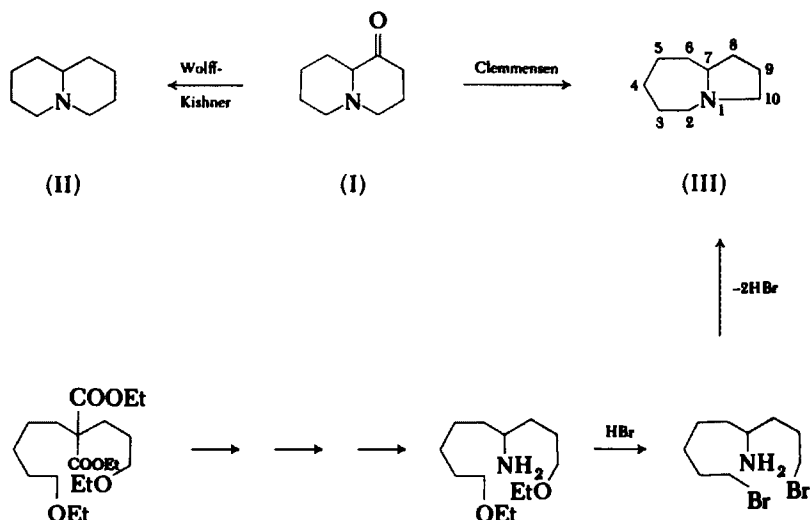
Fused 5/7 and Larger Ring Systems

A-674. 1*H*-Pyrrolo[1,2-*a*]azepine.
R.I. 889M



The perhydrogenated nucleus has been called *1-azabicyclo[0.3.5]-decane* (numbered as shown in III) and *norlupinane B*.

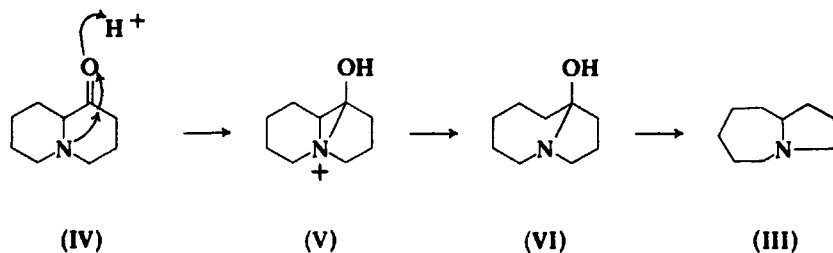
While investigating the structure of the lupine alkaloids, Clemo and Ramage¹ found that quinolizidin-1-one (I, see Section A-721) underwent the Wolff-Kishner reduction to yield norlupinane (II, quinolizidine), identical with that obtained from lupinine. However, the Clemmensen reduction of I gave a product (norlupinane B) isomeric but not identical with II. At first this was regarded^{1,2} as a case



of *cis-trans* isomerism analogous to that occurring in the decalins. A number of ketones related to I were found by Clemo and his co-workers²⁻⁵ to yield similar pairs of isomeric bases when subjected to the two different reductions.

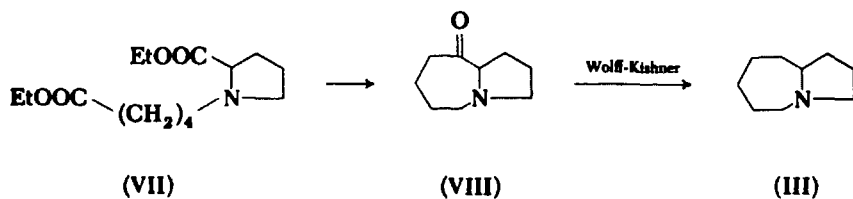
Unconvinced that compounds (such as II) with a bridgehead nitrogen atom could exhibit isomerism of the *cis-trans* decalin type, Prelog and Seiwert⁶ proposed the alternative formula III for the Clemmensen reduction product of I. They were able to prove the validity of this proposal by synthesizing III as shown.

At this point Leonard and his associates became interested in the rearrangement, and their studies in this field have been the subject of numerous papers. They devised several syntheses for 1-azabicyclo[0.3.5]decanes, and were able to show that it was the ring containing the carbonyl group which contracted during the rearrangement. It was also found that III is formed as the minor product of the electrolytic reduction⁷ of I, while the major product is 5-hydroxyazacyclodecane. The mechanism of these reductive rearrangements has been discussed by Prelog,⁶ Leonard⁸ and Wilson.⁹ Under the acidic reaction conditions of the Clemmensen reduction, a concerted displacement reaction (such as is depicted in IV) leading to V, is thought⁹ to follow attack on the carbonyl oxygen by a proton. Reductive scission of the original bridgehead C—N bond then leads to VI, which yields III by further reduction.

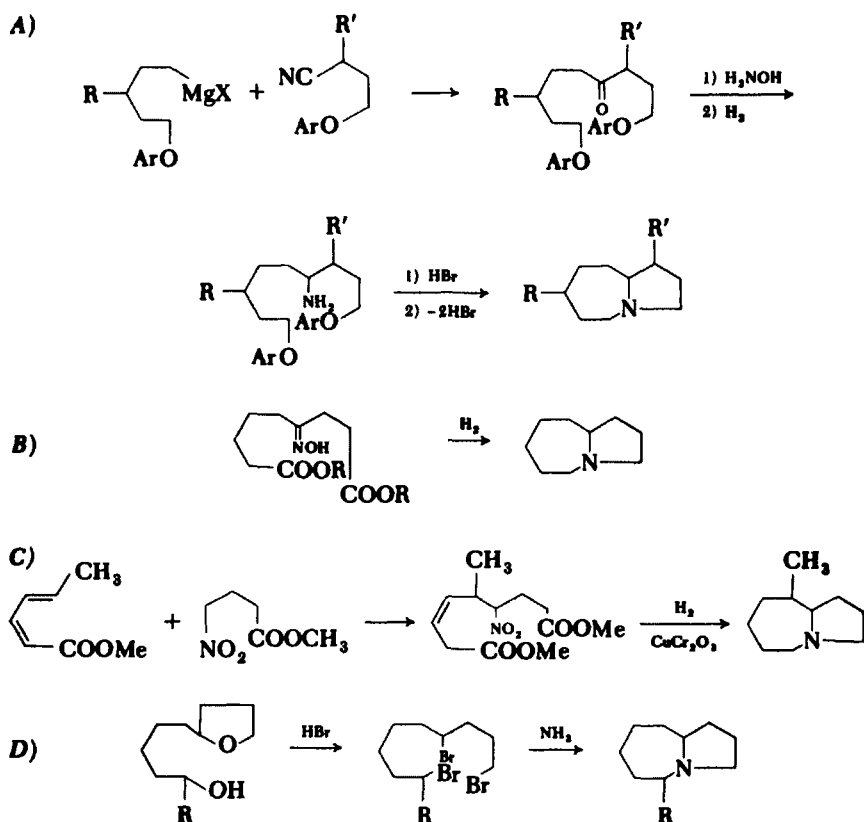


Leonard and Wildman¹⁰ obtained the ketone VIII by the Dieckmann cyclization of VII followed by decarboxylation. The ketone was converted by a Wolff-Kishner reduction into III, while the Clemmensen reduction yielded II.

Three other methods (A, B, C) were developed by Leonard, *et al.*^{8, 11, 12} for the synthesis of 1-azabicyclo[0.3.5]decanes, while a

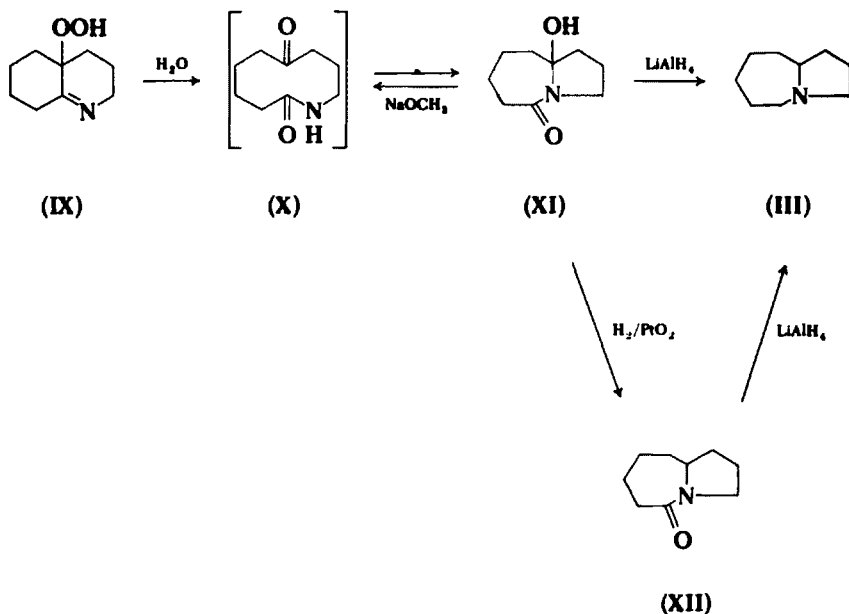


variation (D) of the synthesis used by Prelog and Seiwert⁶ has been elaborated by Seiwert.^{13, 14}

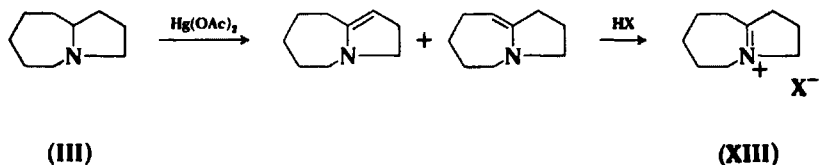


Recently, Withop and Cohen^{15, 16} demonstrated that the peroxide IX readily rearranges in solution to the ketolactam X, which then undergoes *in situ* a transannular addition reaction to give XI. Catalytic reduction of XI gives XII, which can be further reduced by lithium

aluminum hydride to III, also obtainable from XI with this reagent.



Despite the rather large number of papers dealing with the synthesis of III and its methyl homologs, the chemistry of the pyrrolo-[1,2-*a*]azepines has been little studied. Although this ring system may be regarded as 3*a*-azazulene, only one unsaturated derivative has been described. Treatment of III with mercuric acetate produces¹⁷ a mixture of the Δ^6 - and Δ^7 -dehydro derivatives. This mixture yields homogeneous salts of structure XIII.



The only other reaction reported for III is its conversion⁶ into 1-methylazacyclodecane by the Hoffman degradation followed by hydrogenation of the resulting olefin.

Derivatives of Octahydropyrrolo[1,2-*a*]azepine

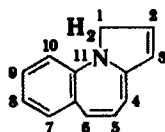
Empirical formula	Substituents	Properties	Refs.
$C_9H_{13}N$	Δ^6 - and Δ^7 -Dehydro-	b_{18} 78–80°, n_D^{20} 1.500.	17
$C_9H_{15}NO$	5-Oxo-	Oil. HCl salt subl. 95°, m. 103–5°.	15,16
	9-Oxo-	b_{12} 105–6°. Picrate, m. 170–1°. Picrolonate, m. 165–6°.	10
$C_9H_{15}NO_2$	9 α -Hydroxy-5-oxo-	m. 109.0–9.5°.	15,16
$C_9H_{17}N$	Unsubstituted	$b_{0.5}$ 45°, b_{14} 71.0–3.5° (75° and 80°), b_{17} 79–80°; n_D^{20} 1.4822. Picrate, m. 217.0–7.5° (213°, 213–4°, 214–5°, 214.8–5°). Picrolonate, m. 191–2° (191.5°, 189°). Methiodide, m. 282.5–3.0° (279–80°, 281°, 282–3°, 283°). Aurichloride, m. 170°.	1,3,6–8, 11,13, 15,16
$C_{10}H_{19}N$	1-Methyl-	b_1 56–7°. Picrate, m. 182° (181–2°). Picrolonate, m. 189° (189–90°).	4,8
	5-Methyl-	b_{12} 82°. Picrate, m. 196°. Picrolonate, m. 157°.	14
	7-Methyl-	b_1 47–8°. Picrate, m. 189°. Picrolonate, m. 138–9° (138°). Methiodide, m. 181°.	5,8
	9-Methyl-	b_{33} 91–2°; n_D^{20} 1.4790. Picrate, m. 192–3° (188.5–9.5°). Picrolonate, m. 200–2° d.	12
$C_{11}H_{19}NO_2$	8-Carbomethoxy-	$b_{0.5}$ 102–5°. Picrate, m. 187°.	2

References

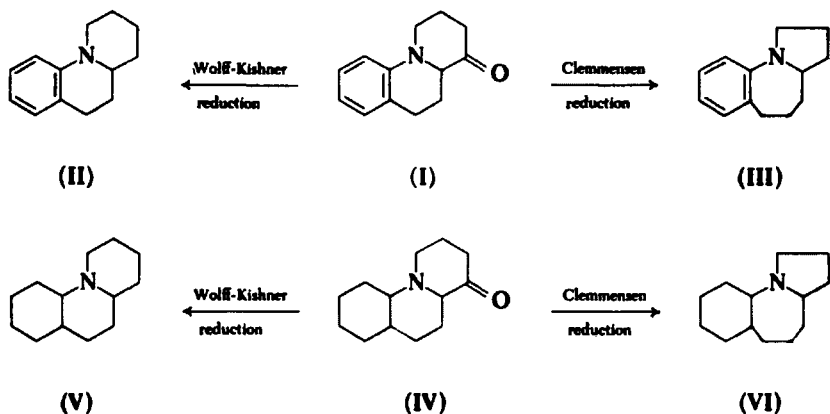
1. Clemo and Ramage, *J. Chem. Soc.*, **1931**, 437.
2. Clemo, Ramage and Raper, *J. Chem. Soc.*, **1931**, 3190.
3. Clemo, Metcalfe and Raper, *J. Chem. Soc.*, **1936**, 1429.
4. Clemo and Metcalfe, *J. Chem. Soc.*, **1937**, 1518.
5. Clemo, Cook and Raper, *J. Chem. Soc.*, **1938**, 1183.
6. Prelog and Seiwert, *Ber.*, **72**, 1638 (1939).
7. Leonard, Swann and Figueras, *J. Am. Chem. Soc.*, **74**, 4620 (1952).
8. Leonard and Wildman, *J. Am. Chem. Soc.*, **71**, 3089 (1949).

9. Wilson, *Chem. and Ind.*, **1955**, 200.
10. Leonard and Wildman, *J. Am. Chem. Soc.*, **71**, 3100 (1949).
11. Leonard and Goode, *J. Am. Chem. Soc.*, **72**, 5404 (1950).
12. Leonard, Felley and Nicolaides, *J. Am. Chem. Soc.*, **74**, 1700 (1952).
13. Seiwerth, *Arhiv. Kem.*, **24**, 21 (1952); *Chem. Abstracts*, **49**, 340 (1955).
14. Orešćanin-Majhofer and Seiwerth, *Monatsh.*, **84**, 777 (1953); *Chem. Abstracts*, **48**, 12137 (1954).
15. Witkop and Cohen, *XIV International Congress of Pure and Applied Chemistry*, Zurich, 1955, Abstracts, p. 134.
16. Cohen and Witkop, *J. Am. Chem. Soc.*, **77**, 6595 (1955).
17. Leonard, Middleton, Thomas and Choudhury, *J. Org. Chem.*, **21**, 344 (1956).

A-675. 1H-Pyrrolo[1,2-a][1]benzazepine*



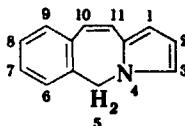
In 1938 Clemo, Cook and Raper¹ subjected the ketones I and IV to the Clemmensen reduction and obtained products which were thought to be II (b_1 120°; picrate, m. 142°; picrolonate, m. 175°) and V (b_1 100–10°; picrate, m. 128–30°). Recently, Leonard and his co-workers made an extensive study of the reduction of cyclic ketones related to I and IV, and of the rearrangements thereby encountered. As a result of this, Leonard and Wildman² have reformulated Clemo's two products as III and VI, respectively. Compounds II and V are obtained from the ketones I and IV by the Wolff-Kishner reduction. Compound III was named *benzo[b]-1-azabicyclo-[5.3.0]decane* (see Section A-674).



References

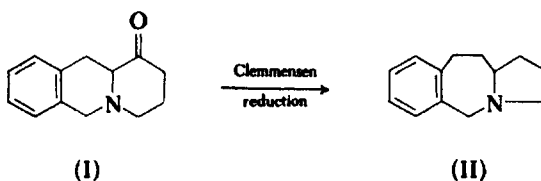
1. Clemo, Cook and Raper, *J. Chem. Soc.*, **1938**, 1318.
2. Leonard and Wildman, *J. Am. Chem. Soc.*, **71**, 3089 (1949).

A-676. 5*H*-Benzo[*e*]pyrrolo[1,2-*a*]-azepine



The 1,2,3,10,11,11*a*-hexahydro derivative of the above nucleus has been named *benzo[*c*]-1-azabicyclo[5.3.0]decane*.

Compound II ($b_{0.6}$ 100–2°; $n_D^{20.8}$ 1.5565; picrate, m. 191–2°) was obtained¹ by the Clemmensen reduction of I (see Section A-728). It was also found among the products of the electrolytic reduction of I (see Section A-674).

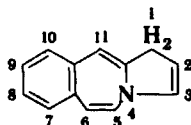


The 7,8-dimethoxy homolog of II may have been obtained in a similar manner.²

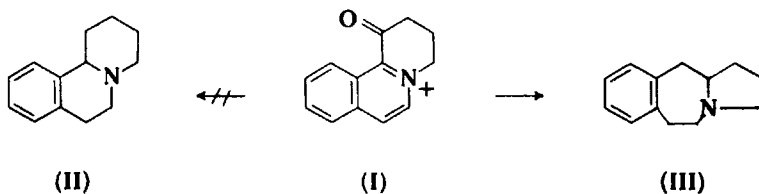
References

1. Leonard, Swann and Fuller, *J. Am. Chem. Soc.*, **76**, 3193 (1954).
2. Sugimoto, *J. Pharm. Soc. Japan*, **64**, No. 9A, 27 (1944); *Chem. Abstracts*, **45**, 8535 (1951).

A-677. 1*H*-Pyrrolo[1,2-*a*][3]-benzazepine*



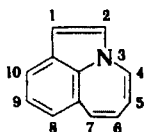
The Clemmensen reduction of I yielded¹ a base (picrate, m. 184°) evidently not identical with II (see Section A-725). In view of the course of this reaction in related systems (see Sections A-674/6, A-681, A-882, etc.), one might expect this product to have structure III, although no claim to this effect was made.¹



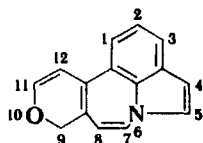
Reference

1. Prasad and Swan, *J. Chem. Soc.*, **1958**, 2024.

A-678. Azep[*h,i*]indole

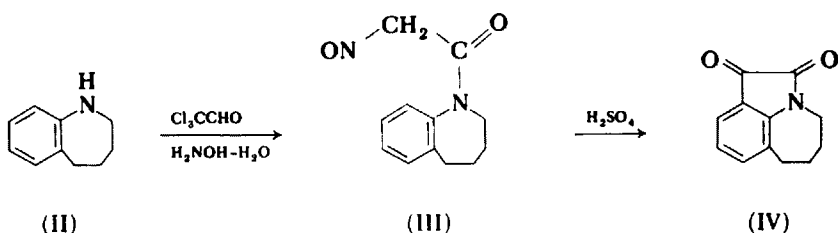


Derivatives of this ring system (or more specifically of I, which was named *9H-pyrano[3,4-d]pyrrolo[3,2,1-jk][1]benzazepine* by *Chemical Abstracts*) were found by Boekelheide, *et al.*^{1-4,6} among the degradation products of the *Erythrina* alkaloids.



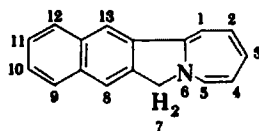
(I)

By treatment of II with chloral and hydroxylamine, Astill and Boekelheide⁵ obtained a 68% yield of III, which was converted in 30% yield into IV (orange, m. 155.0–5.5°; $\lambda_{\max}$ 249, 310 and 440 μ with $\log \epsilon$ 4.43, 3.62 and 2.86, respectively).

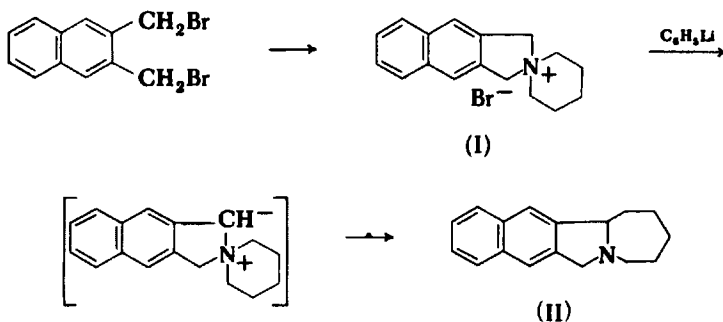


References

1. Grundon and Boekelheide, *J. Am. Chem. Soc.*, **75**, 2537 (1953).
2. Grundon, Sauvage and Boekelheide, *J. Am. Chem. Soc.*, **75**, 2541 (1953).
3. Boekelheide, Weinstock, Grundon, Sauvage and Agnello, *J. Am. Chem. Soc.*, **75**, 2550 (1953).
4. Boekelheide and Grundon, *J. Am. Chem. Soc.*, **75**, 2563 (1953).
5. Astill and Boekelheide, *J. Am. Chem. Soc.*, **77**, 4079 (1955).
6. Boekelheide and Prelog, "Indole Alkaloids," in Cook, *Progress in Organic Chemistry*, Vol. 3, Academic Press, New York, 1955, p. 218.

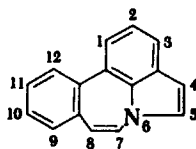
A-679. 7*H*-Azepo[*a*]benz[*f*]isoindole

While investigating the Stevens rearrangement, Wittig and Ludwig¹ found that I was converted into II (m. 101–2°) by reaction with phenyl lithium.



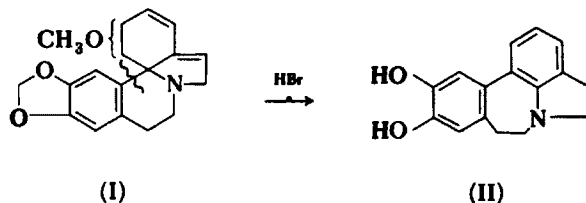
Reference

1. Wittig and Ludwig, *Ann.*, **589**, 55 (1954).

A-680. Indolo[7,1-*ab*][3]benzazepine

Treatment of the alkaloid *erythraline* (proposed structure I, see Section A-201) with hydrobromic acid yields *apoerysopine* (II), the

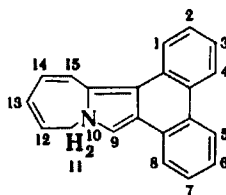
dimethyl ether of which has recently^{1,2} been synthesized. These derivatives are the only examples of this ring system.



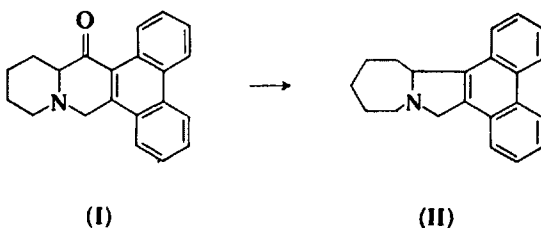
References

1. Wiesner, Valenta, Manson and Stonner, *J. Am. Chem. Soc.*, **77**, 675 (1955).
2. Valenta and Wiesner, *Chem. & Ind.*, **1954**, 402.

A-681. 11*H*-Phenanthra[9',10'-3,4]-pyrrolo[1,2-*a*]azepine*



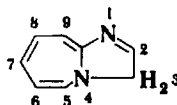
The Clemmensen reduction of I (see Section A-769) yielded¹ II (m. 164°).



Reference

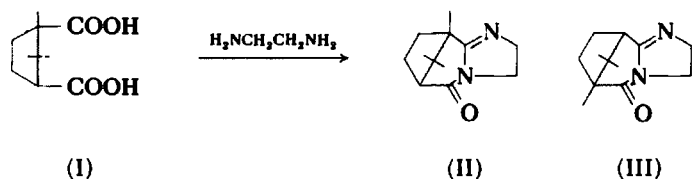
1. Marchini and Belleau, *Can. J. Chem.*, **36**, 581 (1958).

A-682. 3*H*-Imidazo[1,2-*a*]azepine. R.I. 886

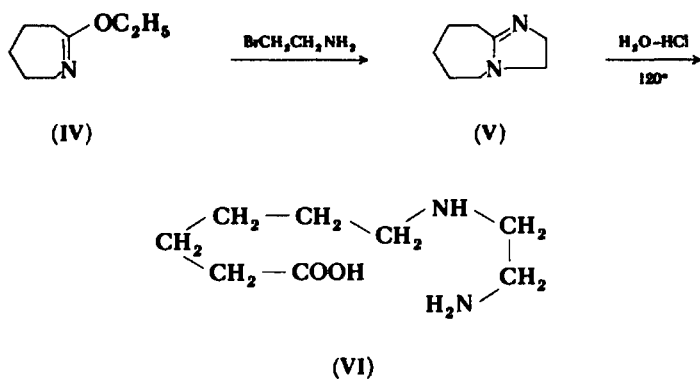


By condensing camphoric acid (I) with ethylenediamine, Bockmühl and Schwarz¹ obtained a product (m. 65°; HCl salt, m. 283°)

to which they assigned structure II. The same product was said to result from the reaction of camphorimide with 2-bromethylamine or of *N*-(2-bromomethyl)-camphorimide with ammonia. No mention was made of the possible alternative structure III, although the condensation of camphoric acid with *o*-phenylenediamine reportedly gave both possible products (the benz homologs of II and III, see Section B-60).



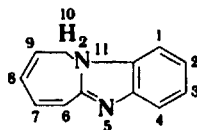
Stollé, Merkle and Hanusch² found that treatment of IV with 2-bromomethylamine hydrobromide yielded V (hydrobromide, m. 172° ; picrate, yellow, m. 166°) in the same fashion that ethyl benzimidate yielded 3,4-dihydro-2-phenylimidazole. Hydrolysis of V with concentrated hydrochloric acid produced VI.



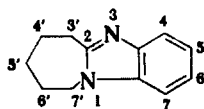
References

1. Bockmühl and Schwarz, Ger. Pat. 408,183; *Frdl.*, **14**, 1288 (1926).
2. Stollé, Merkle and Hanusch, *J. prakt. Chem.*, **140**, 59 (1934).

A-683. 10*H*-Azepino[1,2-*a*]-benzimidazole*

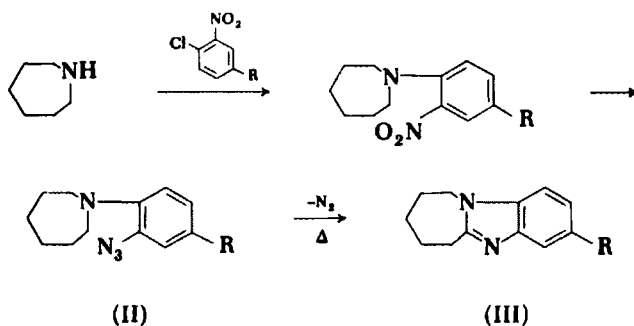


Derivatives of this nucleus have been called *hexahydroazepino-(1':2'-1:2)benzimidazoles*, and numbered as shown in I.



(I)

By an extension of his work on the synthesis of benzimidazopyridines (see Section A-274), Saunders¹ converted hexahydroazepine into azides such as II, which decomposed with loss of nitrogen when heated in nitrobenzene solution, yielding III (R = H, m. 125–6°; methiodide, m. 232–4°; R = Cl, m. 107–9°; HCl salt, sinters



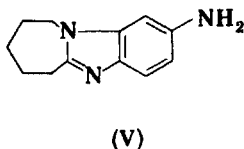
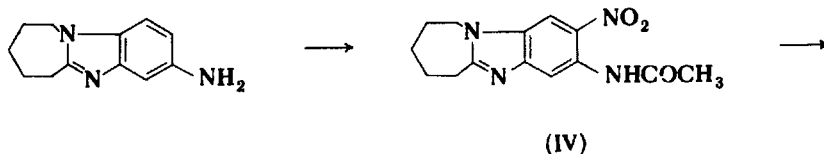
at 225°, m. 259–61°; methiodide, m. 273–4°; R = NO₂, m. 174–5°).

Chlorination of the 3-chloro compound (III, R = Cl) in chloroform gave an adduct, which was decomposed by boiling water, with loss of hydrogen chloride, to a 3,*x*-dichloro derivative (m. 176–7°).

Hydrogenation of the 3-nitro compound (III, R = NO₂) gave the 3-amine (m. 180.5–1.0°, acetyl derivative, m. 254–5°; urethane, m. 238–40°; urethane methiodide, m. 270–2°d.; *N*-(2-hydroxy-3-

naphthoyl) derivative, m. 310–1°). A few other more complex derivatives of this amine were described by Saunders.¹ Diazotization of the amine and decomposition of the rather stable diazonium salt yielded the 3-hydroxy compound (m. 295–6°).

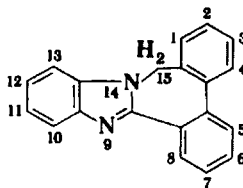
Nitration of the 3-acetamido compound yielded the 3-acetamido-2-nitro derivative (IV, m. 190–1°), in turn converted into 3-amino-2-nitro-7,8,9,10-tetrahydro-6*H*-azepo[*a*]benzimidazole (m. 295–6°). This substance was deaminated by diazotization and treatment with hypophosphorus acid, to yield the 2-nitro compound (m. 196–7°), which was hydrogenated over Raney nickel to the corresponding amine (V, m. 198–9°).



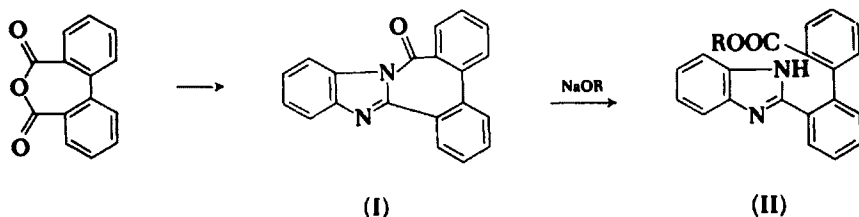
Reference

1. Saunders, *J. Chem. Soc.*, **1955**, 3275.

A-684. 15*H*-Dibenzo[*c,e*]benzimidazo[1,2-*a*]azepine. R.I. 3182



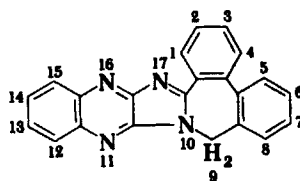
Bistrzycki and Fassler¹ prepared I (colorless, m. 177–8°) by treating diphenic anhydride with *o*-phenylenediamine. Compound I was cleaved by sodium ethylate or sodium hydroxide to II (R = C₂H₅ or Na).



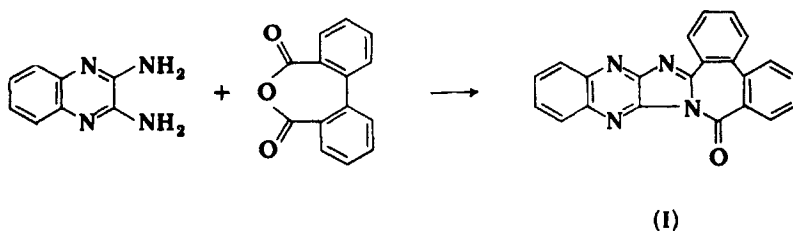
Reference

1. Bistrzycki and Fassler, *Helv. Chim. Acta*, **6**, 519 (1923).

**A-685. 9H-Dibenzo[*c,e*]quinoxalo-
[2',3',4,5]imidazo[1,2-*a*]azepine.
R.I. 3566**



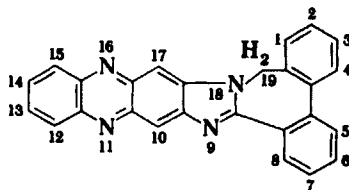
Sircar and Pal¹ treated 2,3-diaminoquinoxaline with diphenic anhydride and obtained yellow-brown needles of I, which was named *o*-diphenoylene- α,β -quinoxalinoimidazole.



Reference

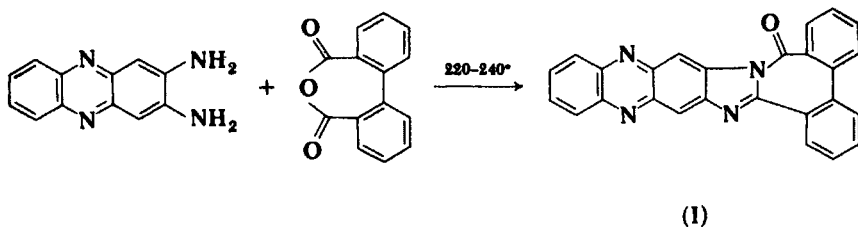
1. Sircar and Pal, *J. Indian Chem. Soc.*, **9**, 527 (1932); *Chem. Zentr.*, **I**, 1947 (1933); *Chem. Abstracts*, **27**, 1882 (1933).

**A-686. 19H-Dibenzo[*c,e*]quinoxalo-
[2',3',5,6]benzimidazo[1,2-*a*]-
azepine. R.I. 3744**



Compound I (greenish-yellow, m. $> 290^\circ$; red solution in sulfuric acid) was prepared by Sircar and De¹ by heating 2,3-diaminophena-

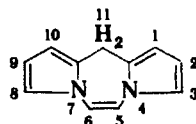
zine with diphenic anhydride. It was named *o*-diphenylene-2,3-phenaziminazole.



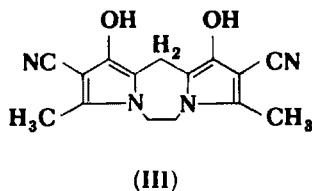
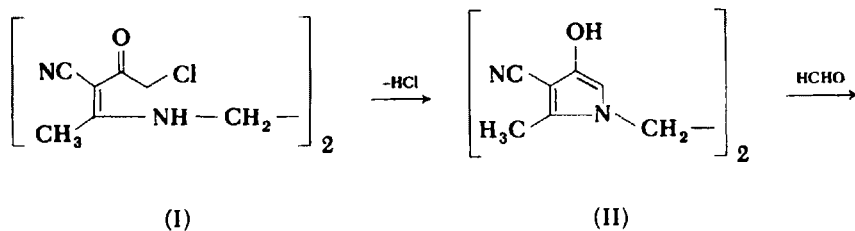
Reference

1. Sircar and De, *Quart. J. Indian Chem. Soc.*, **2**, 312 (1925); *Chem. Zentr.*, **I**, 2697 (1926); *Chem. Abstracts*, **20**, 1805 (1926).

A-687. 11*H*-Dipyrrolo[*d,g*][1,4]diazepine. R.I. 1466

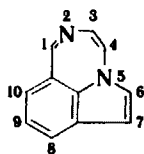


Benary¹ reported that treatment of I with ammonia yielded the bispyrrole II, which was unstable, but which on treatment with formaldehyde yielded III, a red-brown, uncrystallizable solid. Further investigation of these structures seems indicated.

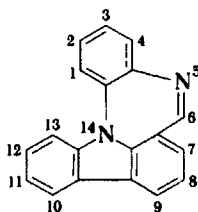


Reference

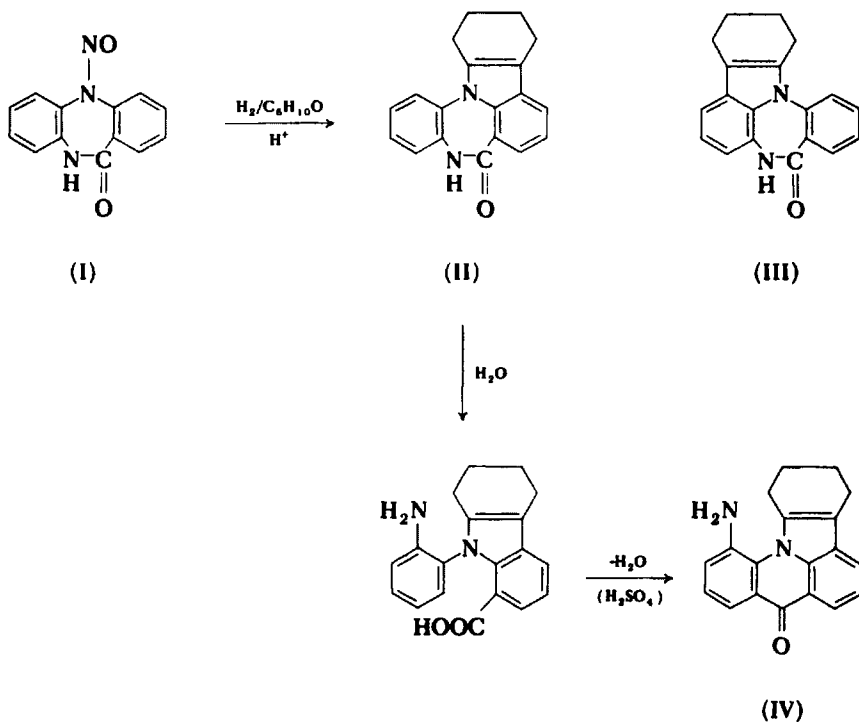
1. Benary, *Ber.*, **60**, 1826 (1927).

A-688. [1,4]-Diazepino[6,5,4-*hi*]indole*

See [1,4]-diazepino[3,2,1-*hi*]indole (Section A-690).

A-689. [1,5]Benzodiazepo[3,2,1-*jk*]-carbazole. R.I. 3183

Linnell and Perkin¹ found that the reduction of I with zinc and acid in the presence of cyclohexanone yielded II (m. 204°). The reaction undoubtedly involves reduction of I to the hydrazine, which

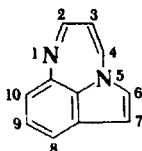


then forms the hydrazone of cyclohexanone, and this in turn undergoes a Fischer indole synthesis to yield II. An alternative formulation (III) of the product was rejected because alkaline cleavage of the product and treatment of the resulting amino acid with sulfuric acid gave IV (see Section A-236). Under these conditions the amino acid formed by alkaline cleavage of III could only revert to III.

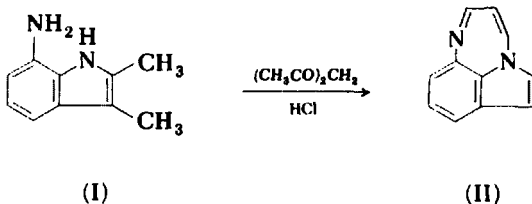
Reference

1. Linnell and Perkin, *J. Chem. Soc.*, **125**, 2451 (1924).

A-690. 1,4-Diazepino[3,1-*hi*]indole

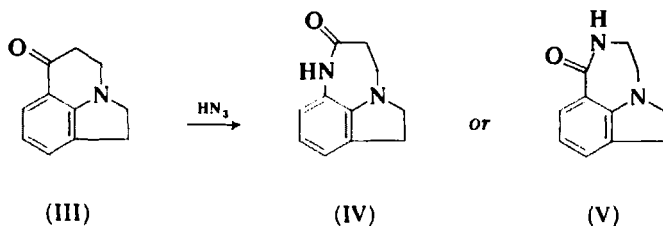


The condensation of I with acetylacetone in hydrochloric acid solution gave¹ an 88% yield of II (colorless, orange-red fluorescence,



m. 213.0–3.5°; HCl salt, yellow, green fluorescence, m. 353–5°d.). The ultraviolet spectrum was recorded.

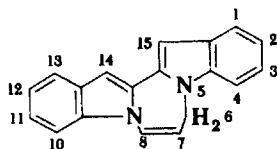
Treatment of 6-oxolilolidine (III, see Section A-197) with hydrazoic acid afforded² a yellow product (m. 140–1°, $\lambda_{\max}$ 227, 263, 310 and 353 μ m (log ϵ 4.19, 3.71, 3.49 and 3.40)) probably having structure IV, although V cannot be excluded.



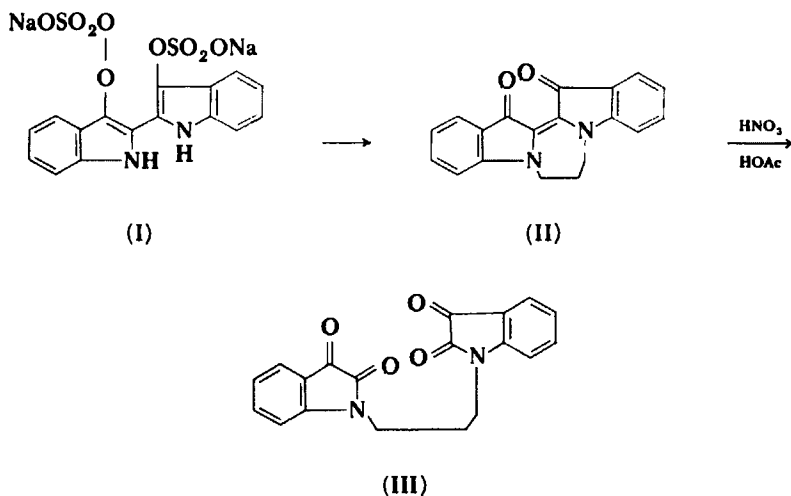
References

1. Maitlis, *Proc. Chem. Soc.*, **1957**, 354.
2. Astill and Boekelheide, *J. Org. Chem.*, **23**, 316 (1958).

**A-691. 6*H*-Diindolo[1,2-*a*, 2',1'-*c*]-
diazepine***



While indigo and its analogs are resistant to *N*-alkylation, it was found by Pummerer and Meininger¹ that a derivative of the leuco form (the commercially available "Indigosol," I) readily underwent alkylation. By means of this technique they were able to prepare a number of *N*-alkylated indigos, including II (trimethyleneindigo, brown-violet prisms or tablets with a metallic reflex, m. 220.5°).

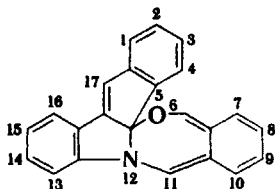


Since the indigo system in II is constrained in the abnormal *cis*-configuration, the yield and the stability of II are both lower than in the case of other (*trans*) *N,N'*-dialkylindigos. Nitric acid converts II into III.

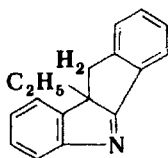
Reference

1. Pummerer and Meininger, *Ann.*, **590**, 173 (1954).

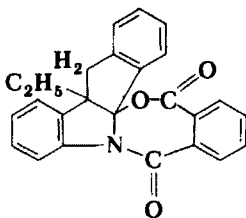
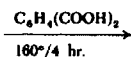
A-692. [2,4]Benzoxazepo[4,3-*a*]indeno-
[1,2-*b*]indole. R.I. 3490



Leuchs and Philpotts¹ heated I with phthalic anhydride, and obtained a product (m. 200–1°) thought to be II. *Chemical Abstracts* assigned to II the name: 5-*o*-carboxybenzoyl-10*a*-ethyl-10,10*a*-dihydro-indeno[1,2-*a*]indol-5*a*(5)-*ol* lactone.



(I)

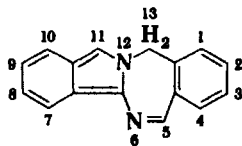


(II)

Reference

1. Leuchs and Philpotts, *Ann.*, **461**, 27 (1928).

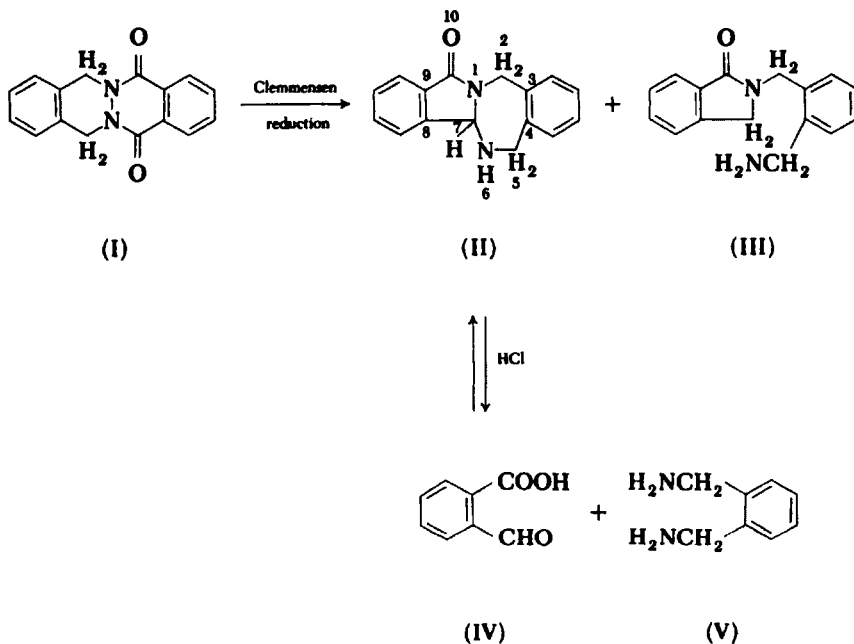
A-693. 13*H*-Isoindolo[2,1-*b*][2,4]benzo-
diazepine



Hatt and Stephenson¹ showed that the Clemmensen reduction of I (see Section A-874) yielded II (m. 254–5°d.; hydrochloride, m. 273–6°, acetyl derivative, m. 193.5–4.0°; benzoyl derivative, m. 168.5–9.5°; *N*-nitroso derivative, m. 204°; *N*-methyl derivative, m.

207–9°) and III. Acid hydrolysis of II yielded IV and V, from which Stephenson² resynthesized II.

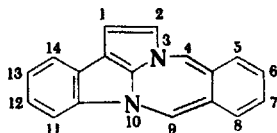
Compound II was named^{1,2} *10-keto-1:6-diaza-3:4-8:9-dibenzo-bicyclo[5,3,0]deca-3:8-diene* and numbered² as shown.



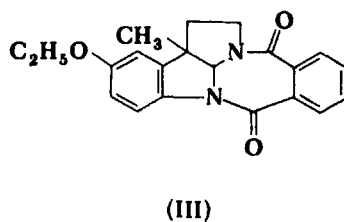
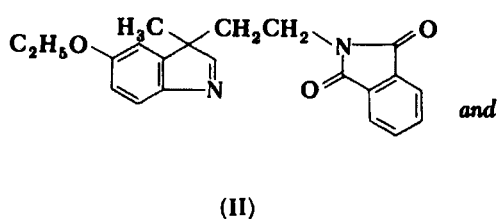
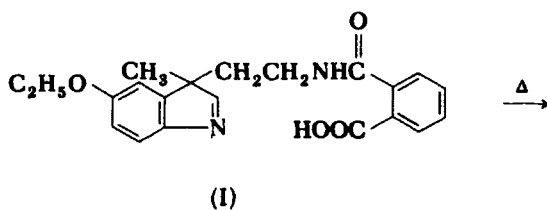
References

1. Hatt and Stephenson, *J. Chem. Soc.*, **1952**, 199.
2. Stephenson, *J. Chem. Soc.*, **1952**, 5024.

A-694. Pyrrolo[3',2',3,2; 2',1'-c]indolo-[1,2-b][2,4]benzodiazepine.
R.I. 3018



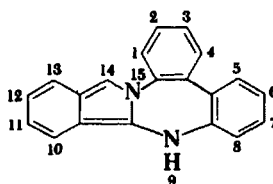
Robinson and Sugimoto¹ found that heating I in xylene solution yielded some II, but chiefly *N,N'*-phthaloyldinoreserethole (III, m. 218–9°). Compound III was stable to refluxing alcoholic potash but was converted by an acetic-hydrochloric acid mixture into equal amounts of II and an unidentified base.



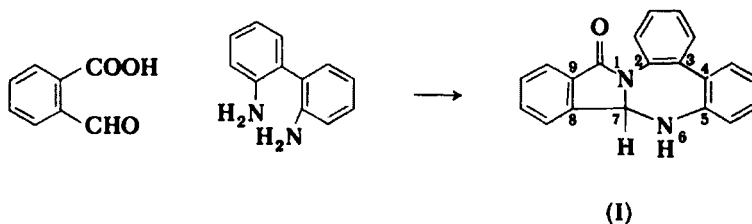
Reference

1. Robinson and Suginome, *J. Chem. Soc.*, **1932**, 304.

A-695. 9H-Dibenzo[*d,f*]isoindolo-[2,1-*a*][1,3]diazepine.



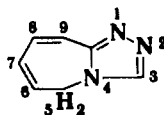
By condensing phthalaldehydic acid with 2,2'-diaminobiphenyl, Stephenson¹ prepared I (colorless, m. 245–7°; *N*-acetyl derivative, m. 221.5–2.0°; *N*-nitroso derivative, m. 198.5–200.5°d.), which she named *10-keto-1:6-diaza-2:3-4:5-8:9-tribenzobicyclo[5.3.0]deca-2:4:8-triene*, and numbered as shown.



Reference

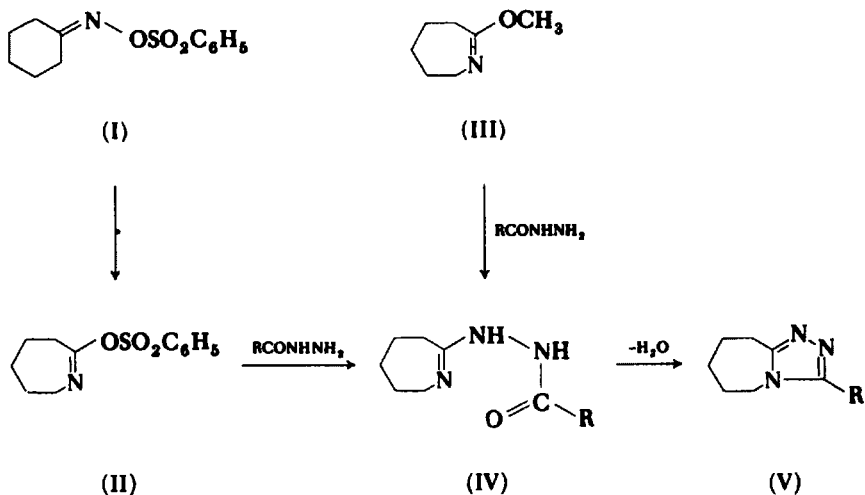
1. Stephenson, *J. Chem. Soc.*, 1952, 5024.

A-696. 5*H*-*s*-Triazolo[4,3-*a*]azepine*



The names 3,4- and 4,5-pentamethylene-1,2,4-triazole have been applied to the 6,7,8,9-tetrahydro derivatives of this ring system.

Scheuing and Walach found¹ that certain oxime esters or lactim esters (such as I and II) reacted with acylhydrazines to yield *s*-triazole derivatives (V). Phosphorus oxychloride may replace benzene sulfonyl chloride in forming the esters used in these reactions.² It seems probable that oxime esters (I) undergo, initially, a Beckmann rearrangement to lactim esters (II), which then react with the acylhydrazines to yield amidrazones of type IV, from which the triazoles (V)



are formed by dehydration. Recently, lactim ethers (III) have been shown^{3,4} to undergo this reaction.

Homologs of III have been used to prepare related systems, and similar reactions have been employed in the synthesis of Metrazole (see Sections A-143, A-476, A-703 and A-716).

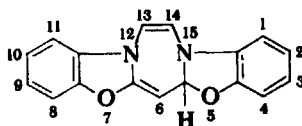
6,7,8,9-Tetrahydro-5H-azepo[2,1-a]-s-triazoles

Substituents	Properties	Refs.
Unsubstituted	m. $\sim 65^\circ$; $b_{0,2}$ 181° , b_{16} $239-41^\circ$. HCl salt, m. $228-30^\circ$.	3,4
3-OH	m. $182-3^\circ$.	3,4
3-CH ₃	m. (hydrate) 62° or (anhydr.) $111-2^\circ$ (108°); b_{10} 210° , b_{15} 236° . HCl salt, m. $213-5^\circ$.	1,3,4
3-CONH ₂	m. 191° . HCl salt d. 245° .	3,4
3-CH ₂ CN	m. $112-3^\circ$ (111°). HCl salt, m. 244° .	3,4
3-C ₂ H ₅	m. 41° ; $b_{0,05}$ 164° .	3
3-CH ₂ OCH ₃	b_{13} 226 . HCl salt, m. 157° .	3,4
3-(2-Furyl)	m. 152° .	3,4
3,3'-(CH ₂) ₄	m. 140° .	3,4
3-CH ₂ CH(CH ₃) ₂	m. 50° ; $b_{0,4}$ 183° .	1
3-(3-Pyridyl)	m. $81-2^\circ$.	3,4
3-(4-Pyridyl)	HCl salt, m. $248-55^\circ$.	3,4
3-(2,4-C ₆ H ₃ Cl ₂)	m. 131° .	3,4
3-(4-C ₆ H ₄ Cl)	m. 171° .	3,4
3-(4-C ₆ H ₄ NO ₂)	m. $184-5^\circ$.	3,4
3-C ₆ H ₅	m. 133° .	3,4
3-(2-C ₆ H ₄ OH)	m. $260-5^\circ$.	3,4
3-(4-C ₆ H ₄ NH ₂)	m. 211° .	3
3-(2-C ₆ H ₄ OCH ₃)	m. 161° .	3
3-(4-C ₆ H ₄ OCH ₃)	m. 158° .	3,4
	m. 102° ; b_{14} 230° .	1
Δ^8 -3,8-Diisopropyl-5-methyl		
3-(3-Hydroxy-2-naphthyl)	m. 309° ($306-8^\circ$).	3,4

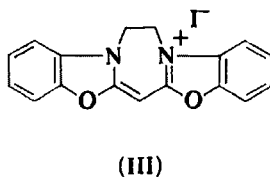
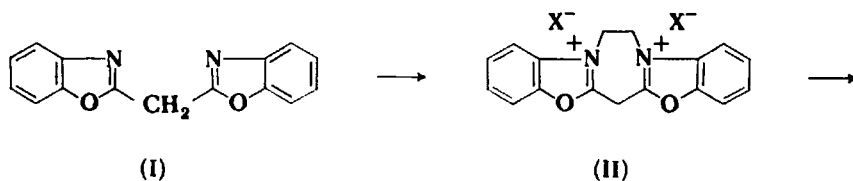
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2. C. H. Boehringer Sohn, A.G., Ger. Pat. 543,026; *Frdl.*, **18**, 3057 (1933).
3. Petersen and Tietze, *Chem. Ber.*, **90**, 909 (1957).
4. Petersen, Tietze and Wirth, Ger. Pat. 1,025,881.

**A-697. 5aH-Bisbenzoxazolo-
[3,2-d, 2',3'-g][1,4]diazepine**



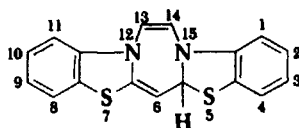
Treatment of I with ethylene *p*-toluenesulfonate produced the intermediate II, which was converted¹ (e.g. by means of triethylamine and sodium iodide) into III (yellow needles, m. > 325°).



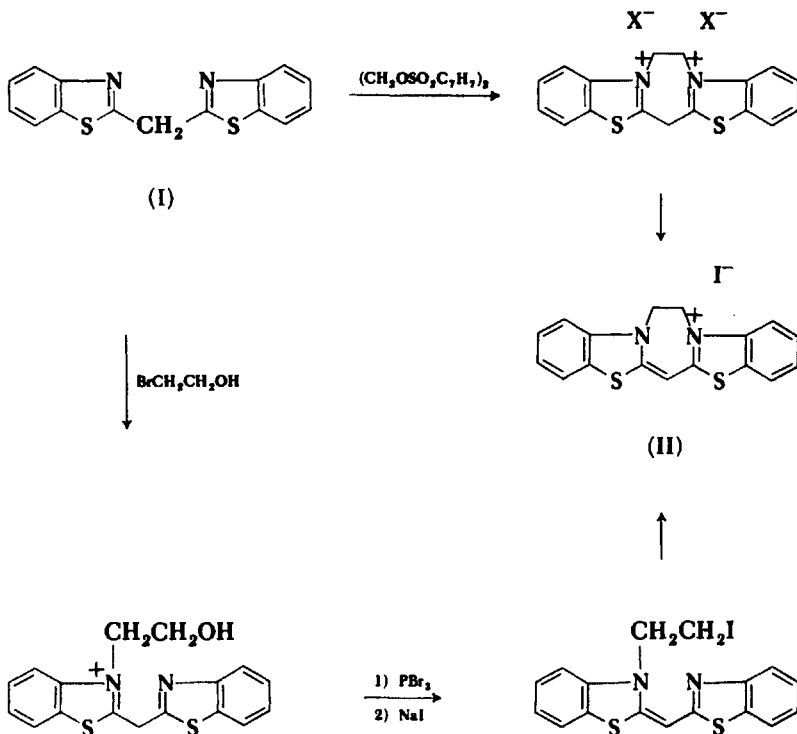
References

1. Brooker and Sprague, U. S. Pats. 2,478,367 and 2,541,400; Brit. Pat. 610,064; *Chem. Abstracts*, **43**, 7845 (1949).

**A-698. 5aH-Bisbenzothiazolo-
[3,2-d, 2',3'-g][1,4]diazepine**



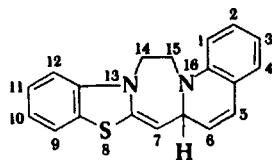
Brooker and Sprague¹ have described the synthesis of II (m. > 330°) by two slightly different routes starting from I.



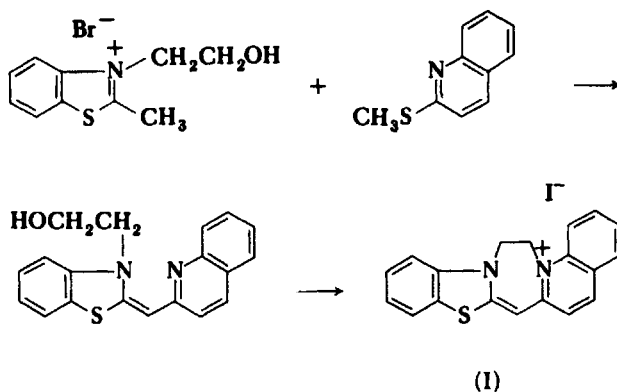
Reference

1. Brooker and Sprague, U. S. Pats. 2,478,367 and 2,541,400; Brit. Pat. 610,064; *Chem. Abstracts*, **43**, 7845 (1949).

A-699. 6aH-Benzothiazolo[3,2-d]quino- [2,1-g][1,4]diazepine



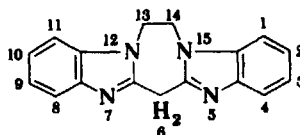
As one of several photographic sensitizing agents containing the diazepine nucleus, Brooker and Sprague¹ prepared I (red, m. 320–5, sensitization maximum at 520 mμ) by the route shown.



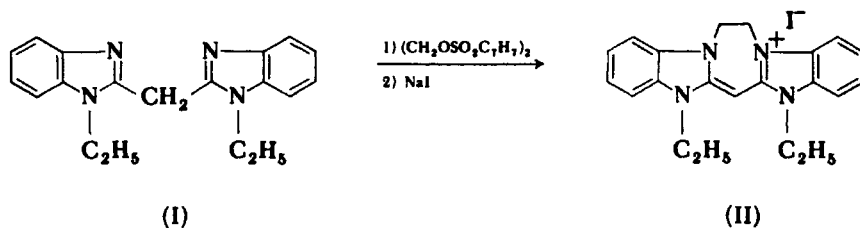
Reference

1. Brooker and Sprague, U. S. Pat. 2,541,400; Brit. Pat. 610,064; *Chem. Abstracts*, **43**, 7845 (1949).

A-700. 6*H*-Bisbenzimidazo- [1,2-*d*, 2',1'-*g*][1,4]diazepine



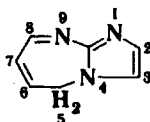
By treating I with ethylene *p*-toluenesulfonate followed by sodium iodide, Brooker obtained¹ II (tan crystals, m. $\sim 325^\circ$). Ethanolic solutions of II are reported to show a strong blue fluorescence.



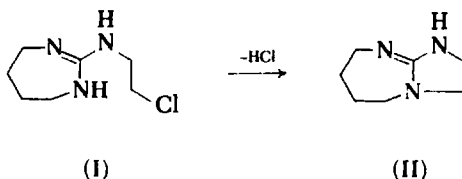
Reference

1. Brooker, U. S. Pat. 2,479,152; Brit. Pat. 618,889; *Chem. Abstracts*, **44**, 4813 (1950).

A-701. 5*H*-Imidazo[1,2-*a*][1,3]-diazepine*



Dehydrochlorination of I yielded¹ II (m. 109–11°; picrate, m. 216–8°), which was named Δ^9 -1,4,9-triazabicyclo[5.3.0]decene. Nitration

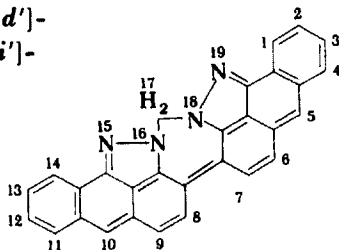


of II gave the 1-nitro derivative as the nitrate salt (m. 166.5–7.5°). See Sections A-146 and A-516.

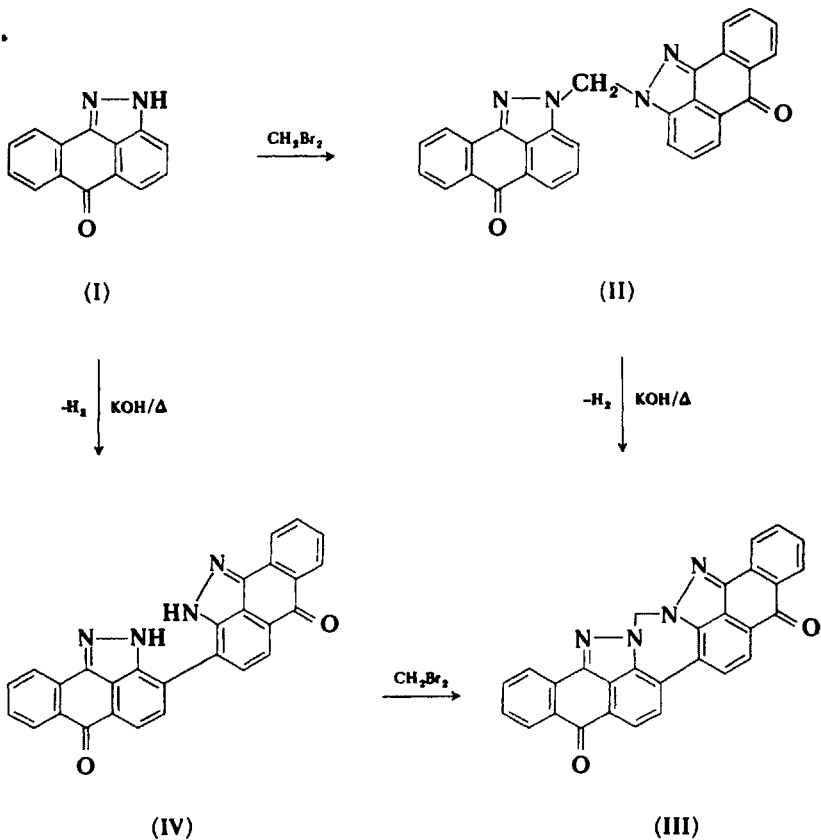
Reference

1. McKay and Kreling, *Can. J. Chem.*, **35**, 1438 (1957).

A-702. 17*H*-Dinaphtho[1,2,3-*cd*, 1',2',3'-*c'd'*]-[1,3]diazepinobis[6,7,1-*hi*, 5,4,3-*h'i'*]-indazole*



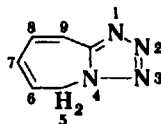
When pyrazolanthrone (I) is alkylated with methylene bromide, a product thought¹ to have structure II results. Alkaline fusion of II yields a yellow dye (blue vat; red sulfuric acid solution), which may have structure III, although no structure was suggested by Nawiasky and Krause.¹ The alkylation of “pyrazolanthrone yellow” (IV) with methylene bromide to yield III has evidently not been described. See Section A-711.



Reference

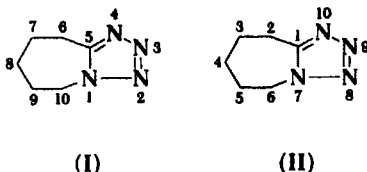
1. Nawiasky and Krause, Ger. Pat. 457,579; *Frdl.*, **16**, 1370 (1931). U. S. Pat. 1,920,426.

A-703. 5H-Azepotetrazole. R.I. 879



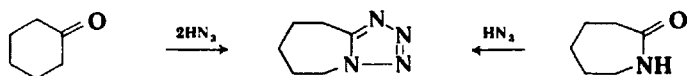
The only reported derivatives of this ring system are the 6,7,8,9-tetrahydro compounds, which have been named *1,5-pentamethylenetetrazoles* (numbered as shown in I), *pentylenetetrazoles*, α,β -cyclopentamethylenetetrazoles, *1,2,3,3a-tetrazacyclohepta-8a,2-cyclopentadienes*

and 7,8,9,10-tetrazabicyclo[5.3.0]-8,10-decadienes (numbered as shown in II). In addition, the unsubstituted 6,7,8,9-tetrahydro-5*H*-azepo-



tetrazole has received, because of its medicinal use (v.i.), a number of proprietary names such as *Metrazole*, *Leptazole*, *Cardiazole*, *Tetracor*, etc., the first of which is recognized by *Chemical Abstracts*.

Metrazole was apparently first obtained by K. F. Schmidt¹ and the Knoll A. G., who were studying the preparation of amides and nitriles by the treatment of aldehydes and ketones with hydrazoic acid. The reaction of a wide variety of compounds containing unsaturated ($>C=C<$ as well as $>C=N-$, $-C\equiv N$, $>C=O$, etc.) linkages with hydrazoic acid has come to be known as the Schmidt reaction, and was reviewed by Wolff.² Cyclohexanone, on treatment with one mole of hydrazoic acid, yields ϵ -caprolactam, and Metrazole is formed in only small quantities as a by-product.¹ However, if the amount of hydrazoic acid is increased to at least two moles, Metrazole becomes the major product and can be obtained³ in a yield of about 70%. These reactions are conducted in the presence of

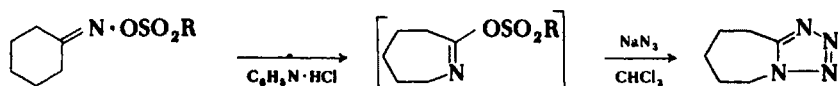


mineral acid, which appears to be necessary, since Burke and Herbst⁴ found that lactams do not react with pure hydrazoic acid to give tetrazoles, although the imino chlorides obtained from the lactams with phosphorus pentachloride do give tetrazoles with pure hydrazoic acid. The reactions of imino chlorides were studied by v. Braun and Heymons,⁵ and the intermediates and mechanisms of these reactions were discussed by Herbst *et al.*^{4,6}

Since ϵ -caprolactam is the product of the Beckmann rearrangement of cyclohexanone oxime, it was soon found⁷ that the oxime could replace the ketone in the synthesis of Metrazole. The reaction, conducted as before in the presence of a solvent and a mineral acid,

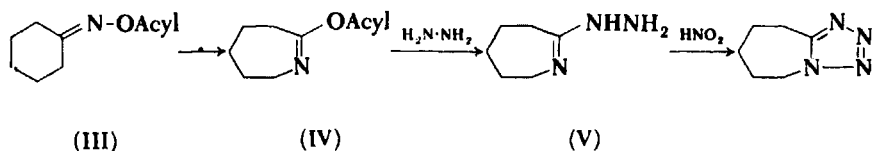
gave higher yields of Metrazole and had the further advantage of requiring but one mole of hydrazoic acid. It is still the most generally useful reaction for the preparation of Metrazole and its derivatives.^{6, 7, 9, 10, 30}

A number of modifications of this basic method were patented, but do not seem to have been used widely. It was found possible to avoid the presence of mineral acid and the use of free hydrazoic acid by treating the benzenesulfonyl^{11, 12} or phosphoryl^{12, 13} esters of cyclohexanone oxime or ϵ -caprolactim with salts of hydrazoic acid. The reaction of the potassium salt of the monosulfuric acid ester of cyclohexanone oxime with aqueous sodium azide was claimed⁷ to give a 70% yield of Metrazole. The lactim ester was postulated as



the intermediate in these reactions.¹² Lactim ethers (imido ethers)¹⁴ and thioethers³² also react with hydrazoic acid to yield tetrazoles. Recently, Metrazole was prepared^{35, 36} by the reaction of ϵ -thio-caprolactam with aluminum azide (prepared *in situ* by the reaction of aluminum chloride with sodium azide in benzene solution). It was mentioned earlier that lactim chlorides (imino chlorides) react with hydrazoic acid to yield Metrazole analogs.⁴ Knoll, A.G.¹⁵ also found that more drastic treatment of ϵ -caprolactam with phosphorus pentachloride replaced the α -hydrogen atoms as well as the lactim hydroxyl group, leading to 9,9-dichlorotetrahydroazepotetrazole.

The only recorded method for the synthesis of Metrazole which avoids completely the use of azides or hydrazoic acid is patented by Knoll, A.G.¹⁶ Oxime or lactim esters, such as III or IV, were found to yield "hydrazidines" (V) on treatment with hydrazine, and on further reaction with nitrous acid, Metrazole was formed in about 70% yield.



The earlier work in this field was concerned largely with the preparation of Metrazole itself, and only recently have very many Metrazole homologs been described. The reaction of substituted cyclohexanones (or their oximes) with hydrazoic acid raises the question of the formation of isomeric products. A 4-substituted cyclohexanone would, of course, yield only a 7-substituted metrazole, but a 3-substituted cyclohexanone could yield either a 6- or 8-substituted metrazole and, similarly, a 2-substituted cyclohexanone might give either a 5- or 9-substituted product. v. Braun and Heymons⁵ treated 2-methylcyclohexanone with hydrazoic acid and obtained a product which they considered (probably correctly⁶) to be the 5-methyl homolog. From 3-methylcyclohexanone oxime a methyl homolog, presumably either the 6 or 8 isomer was obtained.²⁶ Burke and Herbst⁴ showed, by synthesizing both isomers via the corresponding ϵ -caprolactams, that treatment of 3-ethyl-5-methylcyclohexanone oxime yielded only 6-methyl-8-ethyl compound on treatment with hydrazoic acid. Further work is needed to demonstrate beyond doubt the structures of the several other substituted Metrazoles which have been prepared from 3- and 3,5-substituted cyclohexanones.

Metrazole and its analogs having at least one hydrogen in the 9-position react with phenyllithium or phenylsodium, followed by carbonation, to give the 9-carboxylic acid derivatives.¹⁷ Heating Metrazole in a sealed tube with concentrated hydrochloric acid degrades it to pentamethylenediamine, nitrogen and carbon dioxide.^{18,19} Reduction of Metrazole with lithium aluminum hydride affords³⁴ a 66% yield of hexamethyleneimine.

Metrazole is a white crystalline solid, m. 59°, which may be distilled at reduced pressure. While it does not form salts with most acids, it does form quaternary salts with alkyl halides and sulfonates,^{6,20} and complexes with a number of salts.^{19,21} Extremely insoluble complexes are formed between Metrazole and mercuric or cuprous chlorides, which are of value in the isolation and identification of Metrazole and its homologs. While Metrazole itself is extremely water-soluble, its simple homologs are very much less soluble,⁶ a property which reduces their utility as therapeutic agents.

The considerable literature concerning the pharmacologic activity and therapeutic applications of Metrazole and its derivatives in

the treatment of cardiac conditions and schizophrenia has not been included in the bibliography. For a review of this subject a pharmacology text such as Goodman and Gilman²² should be consulted. The physiological action of Metrazole has been described in graphic detail.²³ Alkyl substitution in the azepine ring of Metrazole produces products of reduced activity.^{24,25}

Derivatives of Metrazole

Empirical formula	Substituents	Properties	Refs.
C ₆ H ₈ Cl ₂ N	9,9-Dichloro-	m. 87°.	15
C ₆ H ₁₀ N ₄	Unsubstituted	m. 59° (59-60°; 57-8°; 90-1°). b _{0.15} 180-90°, b ₁₀ 192°, b ₁₂ 194°. Methiodide, m. 175-180°; methyl benzenesulfonate, m. 145-6°; ethobromide m. 95°; HgCl ₂ complex, m. 175°.	1,3,7-9,11-14, 16,18-21, 28-30,32, 34,36
C ₆ H ₁₁ N ₅	9-Amino-	HCl salt, m. 254-5° d. Urethane, m. 83.5-4.5°.	33
C ₇ H ₁₀ N ₄ O ₂	9-Carboxy-	m. 147-8°. Amide, two forms, m. 137.5-9° and 178.0-9.5°. Hydrazide, m. 158-9°.	17,33
C ₇ H ₁₂ N ₄	5-Methyl-	m. 31-2° (30.5°); b ₁₅ 185-6°.	5,6,8,24
	6-(8?)-Methyl-	—	25,26
	7-Methyl-	m. 43-4° (~45°).	6,8,24-26
	8 (6?)-Methyl-	m. 53-4°.	6,25,26
	9-Methyl-	—	17,25
C ₈ H ₁₂ N ₄ O ₂	9-Carboxy-7-methyl-	m. 136-8°.	17
	9-Carboxy-8-methyl-	m. 105-27° d.	17
	9-Carboxy-9-methyl-	m. 128-30°.	17

Derivatives of Metrazole (*continued*)

Empirical formula	Substituents	Properties	Refs.
$C_8H_{14}N_4$	6,8-Dimethyl-	m. 156°.	6,25
$C_9H_{14}N_4O_2$	8(6?)-Carboxy-6,8-dimethyl-	d. 238°. Methyl ester, m. 114-5°.	10,25
$C_9H_{16}N_4$	6,6(8?),8-Trimethyl-	m. 115-7°.	6,25
	6-Ethyl-8-methyl-	m. 79.5-80.5°.	4
	8-Ethyl-6-methyl-	m. 87-8°.	4,6,25
	7-(2-Propyl)-	m. 48-9°.	6,25
$C_{10}H_{16}N_4$	5,8(or 6,9)-Dimethyl-methano-5(or 9)-methyl-"Thujonetetrazole"	"Camphortetrazole," m. 242-3°.	27,31
		From β -thujone oxime; m. 93.5°.	27
$C_{10}H_{16}N_4O_2$	8(6?)-Carboxy-6,6(8?), 8-trimethyl-	m. 263-4° d. Methyl ester, m. 131-2°.	10,25
	8(6?)-Carboxy-6(8?)-ethyl-8(6?)-methyl-	m. 161-2°.	10,25
$C_{10}H_{18}N_4$	7-(2-Butyl)-	Methyl ester, m. 68-9°.	
	7-(<i>t</i> -Butyl)-	m. 70-1°.	6,25
		m. 132.5-3.5°.	6,25
		Methyl benzene-sulfonate, m. 171.5-2.5°.	
	8-Methyl-5-(2-propyl)-	m. 49.0-9.5°.	6,25
	8(6?)-Methyl-6(8?)-propyl-	m. 64.5-5.5°.	6,25
	8(6?)-Methyl-6(8?)-(2-propyl)-	m. 135°.	6,25
$C_{10}H_{18}N_6O$	9-Carbohydrazido-7,7,9-trimethyl-	m. 207-9°.	33
$C_{11}H_{18}N_4O_2$	7-(<i>t</i> -Butyl)-9-carboxy-	m. 153-4°.	17
	8(6?)-Carboxy-8(6?)-methyl-6(8?)-propyl-	m. 174.5-5.5°.	10
		Methyl ester, b, 163-5°.	
	8(6?)-Carboxy-8(6?)-methyl-6(8?)-(2-propyl)-	m. 201.0-1.5°.	10,25
		Methyl ester, m. 76.5-7.5°.	
$C_{11}H_{20}N_4$	7-Cyclohexyl-	m. 92-3°.	6,25
	7-(<i>t</i> -Amyl)-	m. 73-4°.	6,25

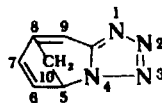
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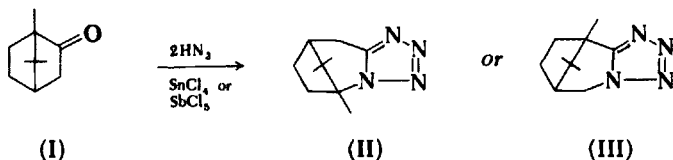
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**A-704. 5,8-Methano-5*H*-azepotetrazole.
R.I. 1310R**



Treatment of camphor (I) with hydrazoic acid yields¹ a product (II or III m. 242–3°) called “camphortetrazole.” Structure II seems more probable than III, but no definite proof is available. The

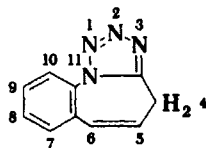


physiological action² of II is similar to that of Metrazole (see Section A-703).

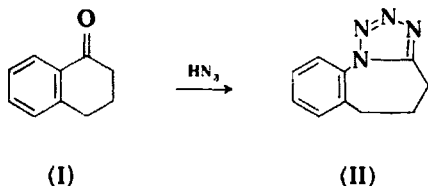
References

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A-705. 4*H*-Tetrazolo[*a*][1]benzazepine*



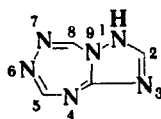
Application of the Schmidt tetrazole synthesis to I yielded¹ II (m. 104.0–4.5°), the ultraviolet spectrum of which was compared with those of related products.



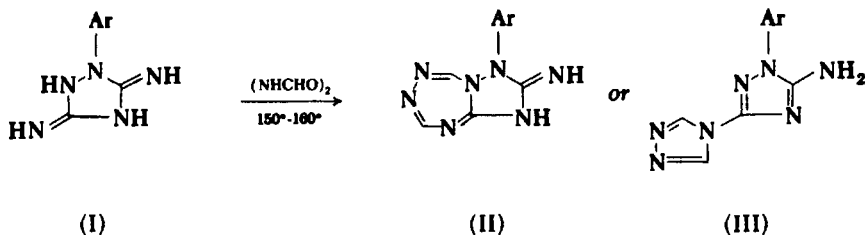
Reference

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A-706. 1*H*-s-Triazolo[2,3-*d*][1,2,4,6]-tetrazepine



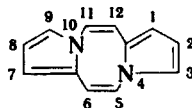
Compounds thought to have either structure II or III were claimed by Papini and Checchi¹ to have been prepared, as shown, from I. Structure II was preferred to III because hydrolysis of the products regenerated I. When Ar is phenyl, the product melts at 256–8°; when Ar is *p*-tolyl, the product melts at 265°.



Reference

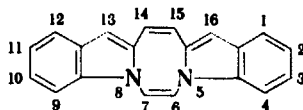
1. Papini and Checchi, *Gazz. chim. ital.*, **82**, 735 (1952); *Chem. Abstracts*, **47**, 12370 (1953).

A-707. Dipyrrolo[1,2-*a*, 1',2'-*e*][1,5]-diazocine*



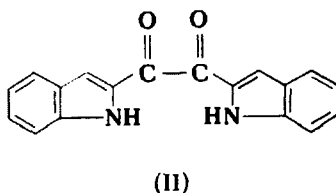
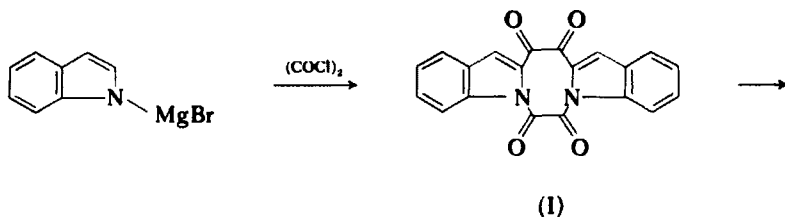
See 1-azabicyclo[2.2.1]heptane (Section B-20).

A-708. Diindolo[1,2-*d*, 2',1'-*h*][1,4]-diazocine. R.I. 3022



The reaction of oxalyl chloride upon indole magnesium bromide was studied by Sanna,¹ who obtained in very small yield (together

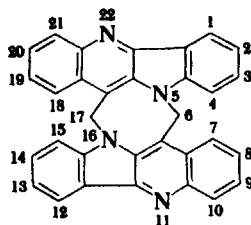
with other products) an ethanol-insoluble product (yellow scales, m. 320°), which he called *1,3-bisindil* and formulated as I. Because of the limited amount available the product was not analyzed, but it was ascertained that it did not form a silver salt and that it was hydrolyzed to II by concentrated caustic solution. Further confirmation of structure I would be desirable.



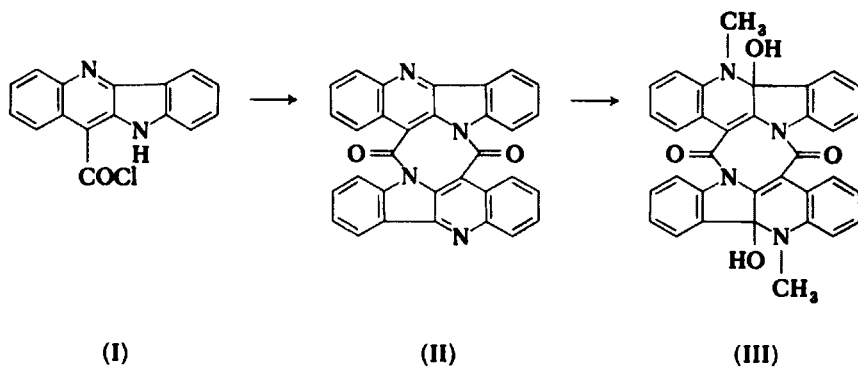
Reference

1. Sanna, *Gazz. chim. ital.*, **52**, II, 165 (1922); *Chem. Zentr.*, **I**, 1452 (1923); *Chem. Abstracts*, **17**, 1639 (1923).

A-709. Diquindolo[10,11-*ab*, 10', 11'-*ef*]-[1,5]diazocine



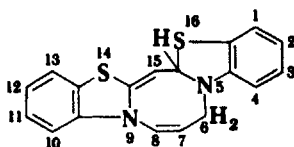
Holt and Petrow^{1,2} obtained II (pale yellow, m. $365-7^\circ$) by heating I in nitrobenzene. Hot aqueous alkali cleaves II to the acid corresponding to I, while dimethyl sulfate and bases convert II into a product (m. about 173°d.) probably having structure III.



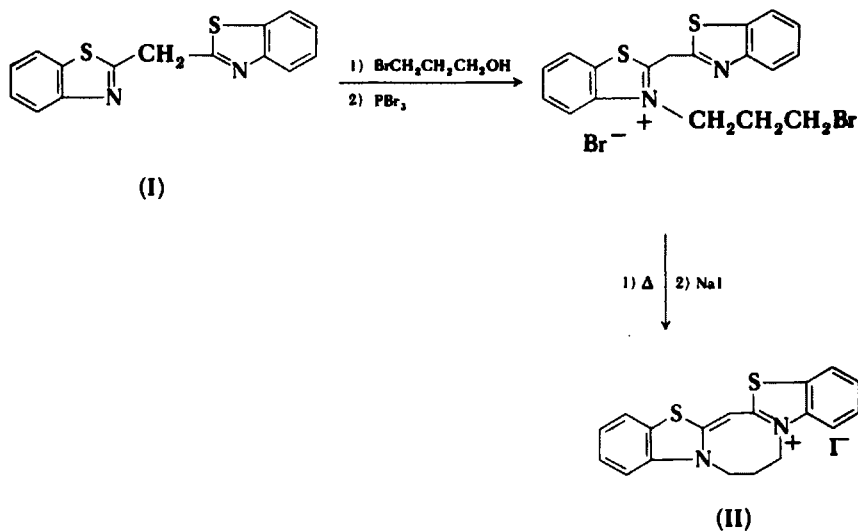
References

1. Holt and Petrow, *J. Chem. Soc.*, **1947**, 607.
2. Holt and Petrow, *J. Chem. Soc.*, **1948**, 919.

**A-710. 6*H*,15*aH*-Bisbenzothiazolo-
[3,2-*a*, 2',3'-*d'*][1,5]diazocine**



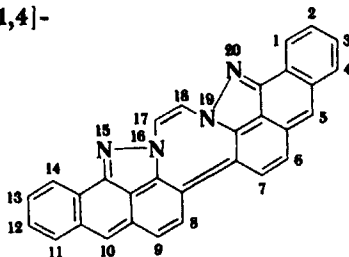
Treatment of I as shown is reported¹ to yield II (yellow, m. 300–3°), which has been patented as a photographic sensitizing agent.



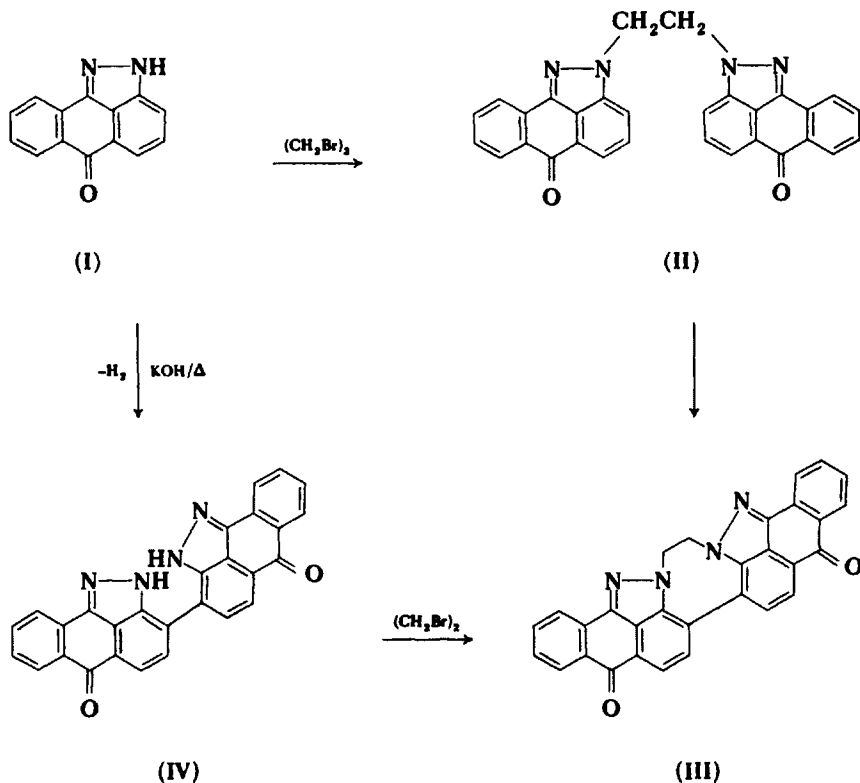
Reference

1. Brooker and Sprague, U. S. Pat. 2,541,400; Brit. Pat. 610,064; *Chem. Abstracts*, 43, 7845 (1949).

A-711. Dinaphtho[1,2,3-*cd*, 1',2',3'-*c'd'*][1,4]-diazocinobis[7,8,1-*hi*, 6,5,4-*h'i'*]-indazole*



Alkylation of pyrazolanthrone (I) with ethylene bromide was reported by Nawiasky and Krause¹ to yield II, which on alkaline fusion yielded an orange dye (blue vat, red sulfuric acid solution). No struc-

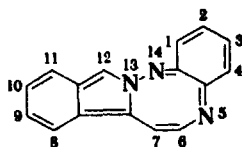


ture was assigned¹ to this product, although it may have structure III. If so, its synthesis from "pyrazolanthrone yellow" (IV) would seem feasible, but this has not been reported. See Section A-702.

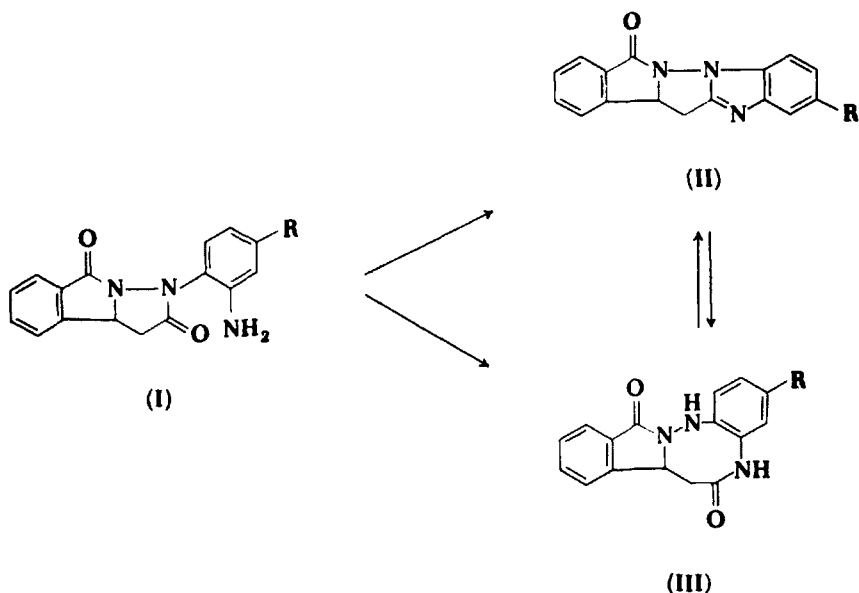
Reference

1. Nawiasky and Krause, Ger. Pat. 457,579; *Frdl.*, **16**, 1370 (1931). U. S. Pat. 1,920,426.

A-712. Benz[*c*]isoindolo[1,2-*h*][1,2,5]-triazocine. R.I. 2584

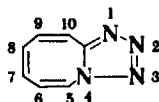


Rowe and his co-workers^{1,2} found that I (see Section A-120), where R = H or CH₃, yielded II (see Section A-121) when heated just to the boiling point in 50% sulfuric acid, but that longer refluxing of the mixture gave III (R = H, not characterized; R = CH₃, m. 231°; picrate, m. 226°). Furthermore, II could be converted into III by refluxing with 50% sulfuric acid, while III (when R = CH₃, but not when R = H or Cl) was converted into II by treatment with phosphorus trichloride in toluene.

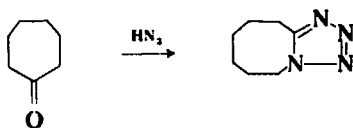


References

1. Rowe, Davey, Garforth, Levin, Pask and Peters, *J. Chem. Soc.*, **1935**, 1796.
2. Rowe, Haigh and Peters, *J. Chem. Soc.*, **1936**, 1098.

A-713. Tetrazolazocine. R.I. 897

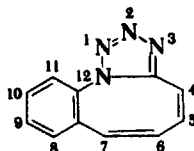
To see if cyclic ketones larger than cyclohexanone would yield Metrazole (see Section A-703) analogs on treatment with hydrazoic acid, Ruzicka, Goldberg and Hürbin¹ investigated cycloheptanone, and obtained I (b_{0.1} 135–40°, m. 66–8°).



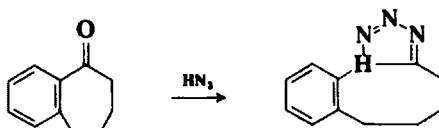
(I)

Reference

1. Ruzicka, Goldberg and Hürbin, *Helv. Chim. Acta.*, **16**, 1335 (1933).

A-714. Tetrazolo[*a*][1]benzazocine

By treating benzosuberone (I) with hydrazoic acid, Huisgen¹ obtained compound II (m. 119.0–20.5°). The ultraviolet spectrum of II was compared² with those of related products.



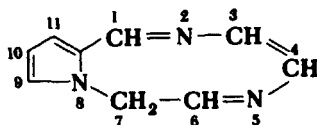
(I)

(II)

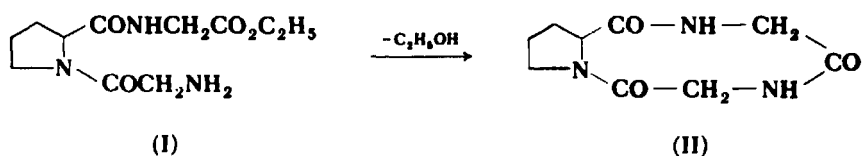
References

1. Huisgen, *Ann.*, **574**, 171 (1951).
2. Huisgen and Ugi, *Ann.*, **610**, 57 (1957).

A-715. 7H-Pyrrolo[1,2-*a*][1,4,7]-triazonine*



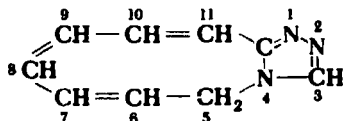
When a solution of glycyl-DL-prolylglycine (I) in ethanolic triethylamine was allowed to stand for two years, traces of crystalline material identified as II were obtained.¹



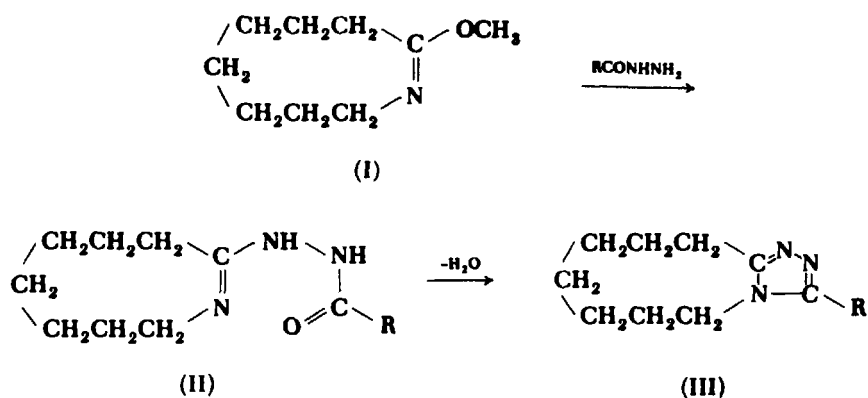
Reference

1. Smith, *J. Chem. Soc.*, **1957**, 3985.

A-716. 5H-*s*-Triazol[4,3-*a*]azonine*



Hexahydro derivatives of structure III ($R = H$, $b_{0.1}$ 167°; $R = CH_3$, m. 40°, $b_{0.6}$ 172°, hydrochloride, m. 168°; $R = OH$, m. 112°;



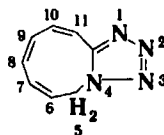
$R = \text{CONH}_2$, m. 177° ; $R = \text{CH}_2\text{OCH}_3$, $b_{0.2}$ 188° ; $R = -(\text{CH}_2)_4-$, m. 112° ; $R = 3\text{-pyridyl}$, m. 104° ; $R = 4\text{-pyridyl}$, m. 119° , hydrochloride, m. 216° ; $R = \text{phenyl}$, m. 113°) were obtained,^{1,2} via the intermediate amidrazones (II), from the condensation of the lactim methyl ether I with acylhydrazones.

Several related systems have been prepared by means of this type of reaction (see Sections A-143, A-476 and A-696).

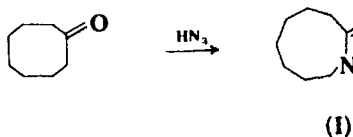
References

1. Petersen and Tietze, *Chem. Ber.*, **90**, 909 (1957).
2. Petersen, Tietze and Wirth, Ger. Pat. 1,025,881.

A-717. 5H-Tetrazolazonine. R.I. 900



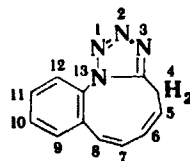
Treatment of cyclooctanone with hydrazoic acid yielded¹ I ($b_{0.1}$ $145-6^\circ$).



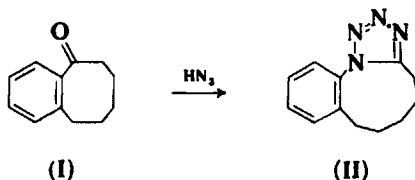
Reference

1. Ruzicka, Goldberg and Hürbin, *Helv. Chim. Acta*, **16**, 1335 (1933).

A-718. 4H-Tetrazolo[*a*][1]benzazonine*



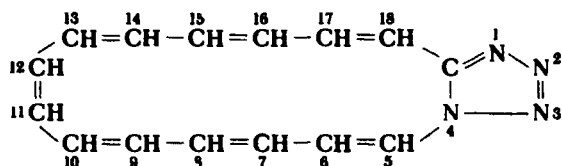
The reaction of I with hydrazoic acid gave¹ II (m. $110-1^\circ$), the ultraviolet spectrum of which was compared with those of related products.



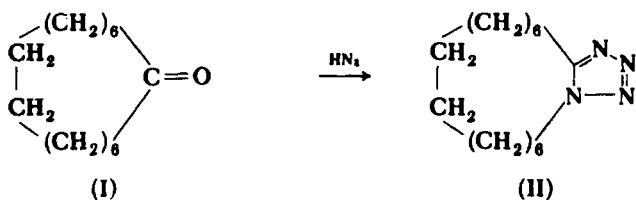
Reference

1. Huisgen and Ugi, *Ann.*, **610**, 57 (1957).

A-719. Tetrazoloazacyclohexadecine.* R.I. 901



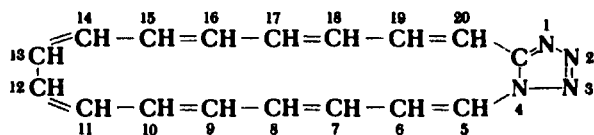
The action of hydrazoic acid upon I is reported¹ to yield II ($b_{0.1}$ 180–5°, m. 97–8°).



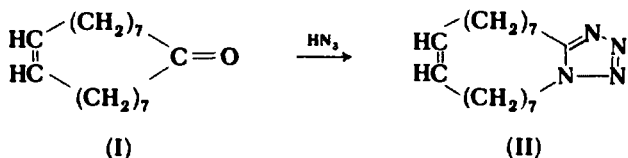
Reference

1. Ruzicka, Goldberg and Hürbin, *Helv. Chim. Acta*, **16**, 1335 (1933).

A-720. Tetrazoloazacyclooctadecine.* R.I. 902



Subjection of civetone (I) to the hydrazoic acid tetrazole synthesis yielded¹ II ($b_{0.4}$ 225–35°, m. 90–1°).



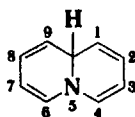
Reference

1. Ruzicka, Hürbin, Goldberg and Furter, *Helv. Chim. Acta*, **18**, 659 (1935).

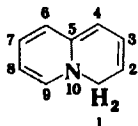
CHAPTER XI

Fused 6/6 Ring Systems with No Extra Heteroatom

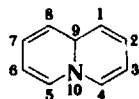
A-721. *9aH*-Quinolizine. R.I. 1011



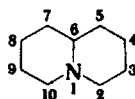
The *2H*- and *4H*-tautomers and the quinolizinium cation have received, respectively, *Ring Index Numbers* 1009, 1010 and 1012. The alternative names *pyridocoline* and *pyrido*[1,2-*a*]*pyridine* have been used, as has the numbering shown in I and II. The perhydro derivative may be called *1-azabicyclo*[0.4.4]*decane* (III), but has been given the trivial names *norlupinane*, *quinolizidine* and *piperidocoline*.



(I)



(II)



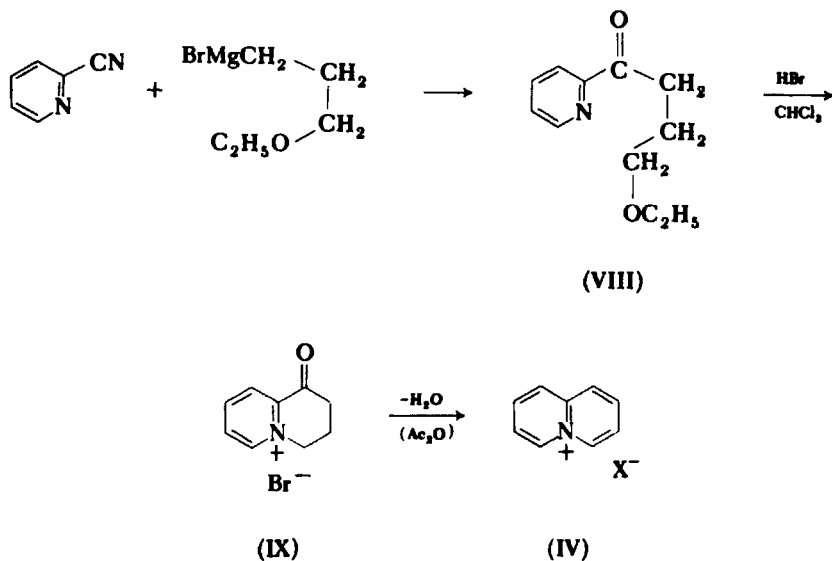
(III)

The chemistry of quinolizine and its homologs recently was reviewed,¹ and the relationships to various alkaloids^{2,3} were discussed. Many of the references to this ring system are concerned with the sparteine and lupine alkaloids, and these papers have not been included in the discussion which follows, nor has every quinolizine derivative been included in the table.

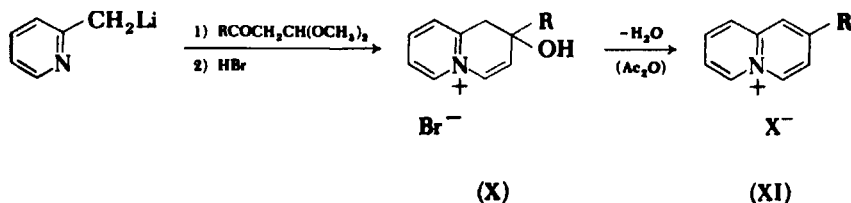
I. Dehydroquinolizinium Salts and Quinolizines

Although Diels *et al.* had described more complex derivatives (v.i.) some two decades earlier, the first synthesis of simple de-

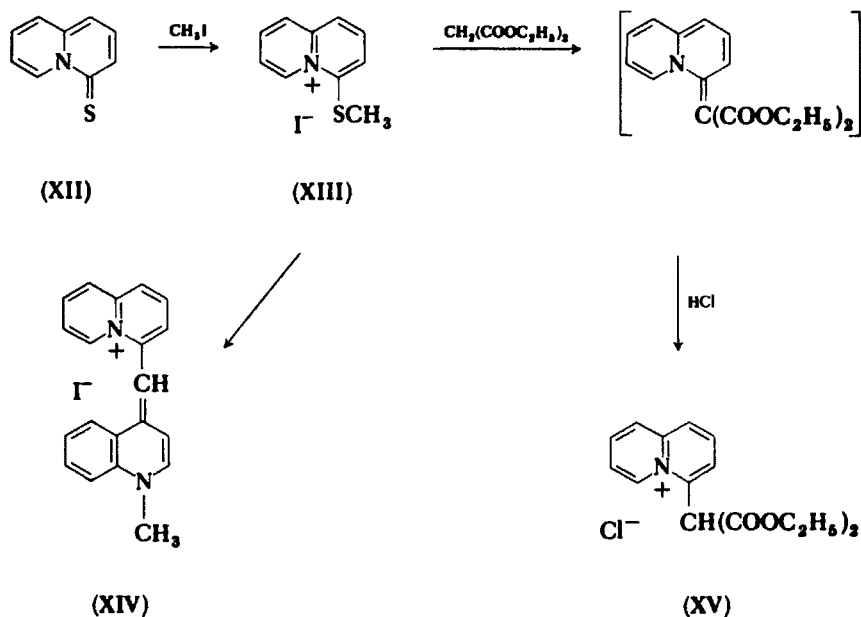
To avoid this troublesome dehydrogenation step, Glover and Jones⁹ prepared VIII in 62% yield, as shown, and cyclized it to IX in 73% yield. Dehydration of IX gave⁵¹ a 96% yield of dehydroquinolizinium picrate (IV).



An improved synthesis of 2-substituted dehydroquinolizinium salts (XI), which also avoids the dehydrogenation step, was devised¹⁰ recently. Treatment of picolyl lithium with β,β -dimethoxyethyl ketones followed by hydrobromic acid afforded carbinols of structure X in yields of 21–32%. Dehydration of X readily produced XI, presumably in high yield.



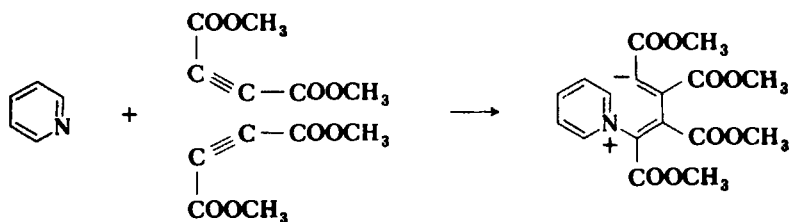
The reaction of XII with methyl iodide produced¹¹ the dehydroquinolizinium salt XIII, which was converted by reaction with lepidine methiodide or malonic ester into, respectively, XIV or XV.



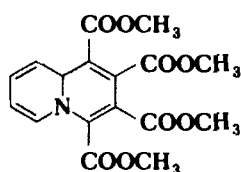
2-Methyldehydroquinolinizinium iodide has been condensed⁵² with *p*-dimethylaminobenzaldehyde to yield a styryl derivative.

In the early 1930's, Diels and his co-workers began a series of detailed investigations into the reactions, under different conditions, of dimethyl acetylenedicarboxylate with pyridine and its homologs. At room temperature, in ethereal solution, the reaction with pyridine yields¹²⁻¹⁴ three products: a "labile red adduct" (XVI) a "stable yellow adduct" (XVII) and "Kashimoto's compound" (XVIII). The labile red adduct is readily isomerized to the stable yellow adduct by the action of hot polar solvents (e.g. methanol, acetonitrile or 50% acetic acid). Attempts to substantiate the structures assigned disclosed an array of complex transformations. Three reviews^{1,15,16} have surveyed briefly some of these reactions.

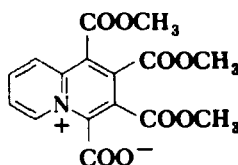
The reaction of XVII with nitric acid gave a salt formulated¹³ as XIX, which was hydrolyzed by water to the hydroxyquinolinizine XX. Treatment of XX with pyridine yielded Kashimoto's compound (XVIII), while perchloric acid converted XX into the dehydroquinolinizinium perchlorate XXI. Compound XXI also resulted¹³ from the



(XVI)



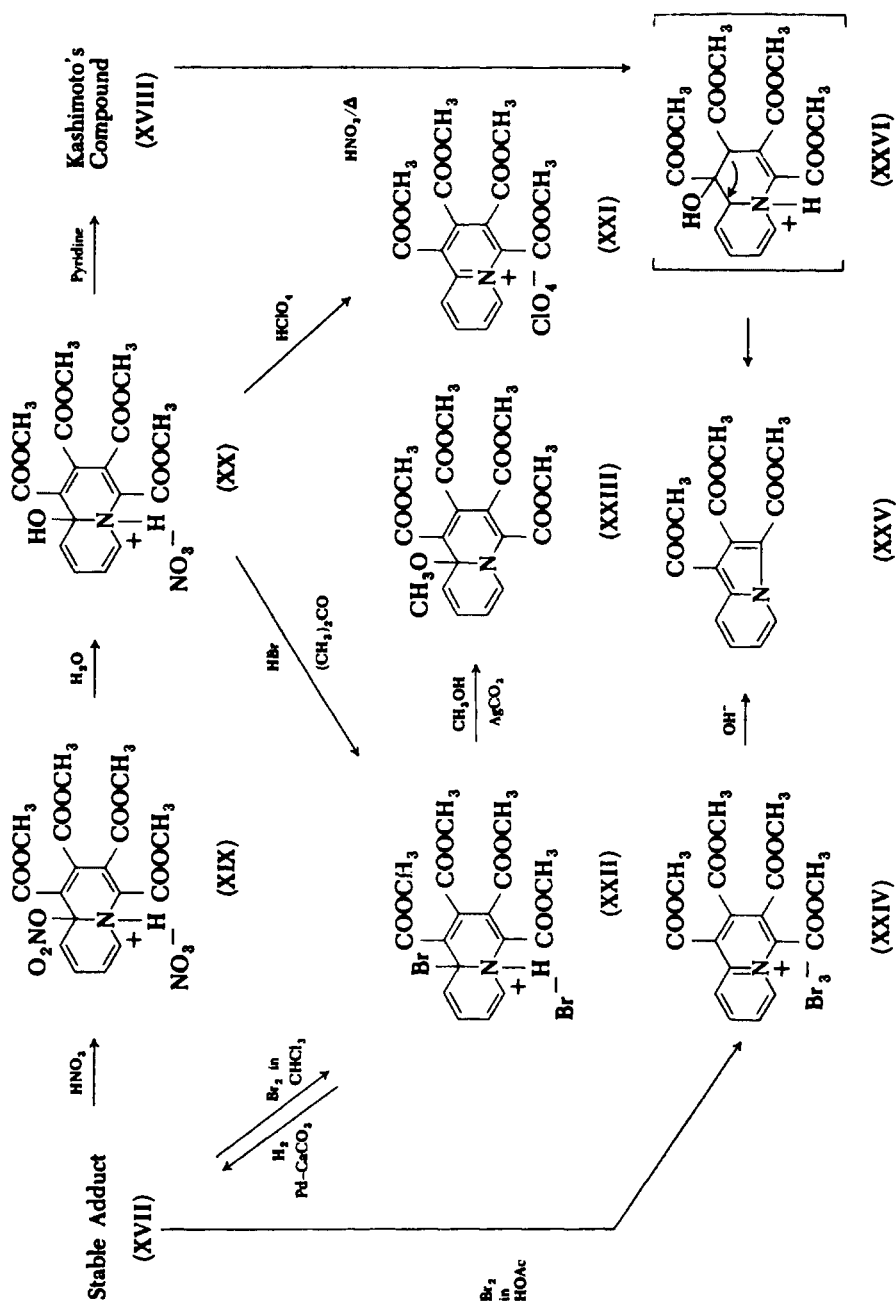
(XVII)



(XVIII)

treatment of Kashimoto's compound with sodium methoxide in methanol. Hydrogen bromide in acetone converted XX into the 9a-bromo compound XXII, which also could be obtained by the direct bromination of XVII in chloroform. The bromine could be removed by catalytic reduction to reform XVII, or it could be displaced by a methoxyl group to yield XXIII, while treatment of XXII with pyridine produced Kashimoto's compound (XVIII). Bromination of the stable adduct (XVII) in acetic acid yielded¹³ another dehydroquinolizinium salt (XXIV), which could be transformed into either XIX or XXI. However, when XXIV was treated with pyridine, or hot water, or soda solution, the elements of methyl glyoxalate were lost and the pyrrocoline ester XXV was obtained. The latter substance also resulted^{12,13} when the stable adduct (XVII) was heated with dilute nitric acid, and its formation was postulated to occur via the intermediate XXVI, although other routes may be envisioned.

While these transformations present an internally consistent picture, and appear, on the whole, to have been accepted^{1,15,16} without question, there are one or two disquieting features, and some evidence for the actual presence of a quinolizine (or dehydroquinolizin-



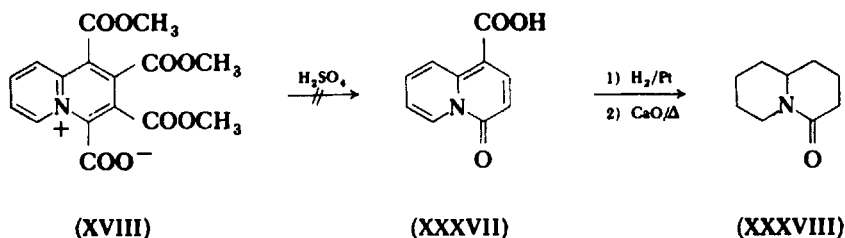
ium) nucleus in these products would be welcome. Modern physical methods of analysis should be of assistance. One anomalous piece of information is the reported¹² catalytic hydrogenation of the stable adduct (XVII) to yield a *tetrahydro* derivative. While pyrrocolines are known to yield tetrahydro derivatives, it is more difficult to reconcile this behavior with a quinolizine structure. Another source of concern is the frequency with which pyrrocoline derivatives have been obtained from degradation reactions upon XVII and XVIII.

Considerable study was devoted by Diels and his colleagues to the stepwise saponification and decarboxylation of the stable adduct. Heating the latter in phenol or in formic acid yielded a tricarbomethoxy compound formulated^{12,13} as XXVII, and treatment of this with hot aqueous potassium hydroxide solution afforded a dicarboxylic acid thought to be XXVIII. Decarboxylation of this acid was reported^{12,13} to yield quinolizine, and after hydrogenation, quinolizidine. However, the physical constants of the latter substance and its picrate were not in accord with the literature values, and Diels and Schrum¹⁷ demonstrated the final product to be 3-methyloctahydropyrrocoline (see Section A-183). They also reformulated the triester (XXVII) as XXXII. Thus the intermediates XXVIII-XXXI should be written correctly as XXXIII-XXXVI.

When the stable adduct (XVII) was boiled with dilute hydrochloric acid, a monocarboxylic acid resulted, and catalytic hydrogenation of this yielded a product thought^{12,13} to be a quinolizidine-carboxylic acid. Decarboxylation gave a base having a picrolonate melting at 181°. Now this obviously is not quinolizidine (the picrolonate of which melts at 249°), and one is tempted to formulate it as a methyloctahydropyrrocoline. Of the three possible choices, the picrolonate of the (least likely) 2-methyl isomer is unknown; that of the 1-methyl isomer melts at 198°, while 3-methyloctahydropyrrocoline yields two picrolonates: m. 216° and 166-8°. Further information is needed, therefore, to establish the structure of the base.

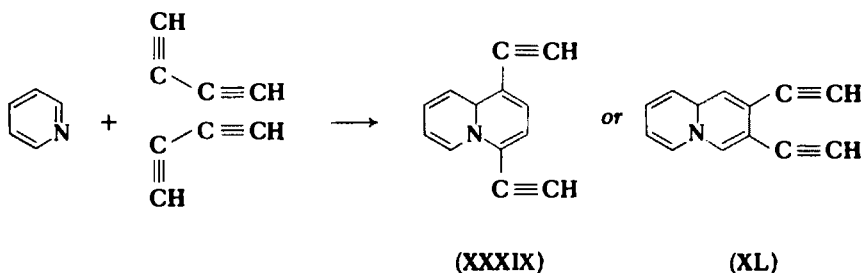
Another discrepancy occurs in the acid hydrolysis of Kashimoto's compound (XVIII). Sulfuric acid hydrolysis yielded a substance formulated¹³ as XXXVII, which could be hydrogenated and decarboxylated to yield a compound said to be XXXVIII. However,

reduction of the latter substance with sodium and amyl alcohol was reported¹³ to yield octahydropyrrocoline! Further, it has been shown¹⁸ recently, by the unequivocal synthesis of XXXVII, that the initial hydrolysis product is not this substance.



In similar reactions dimethyl acetylenedicarboxylate has been condensed with α -picoline,¹⁹ stilbazole,²⁰ quinoline (Section A-729), quinaldine (Section A-77), isoquinoline (Section A-725) and phenanthridine (Section A-735). Products postulated to be the 6-methyl and 6-styryl homologs of XVII were obtained in the first two instances. However, as has been indicated previously, the acceptability of these structures would be enhanced by further evidence.

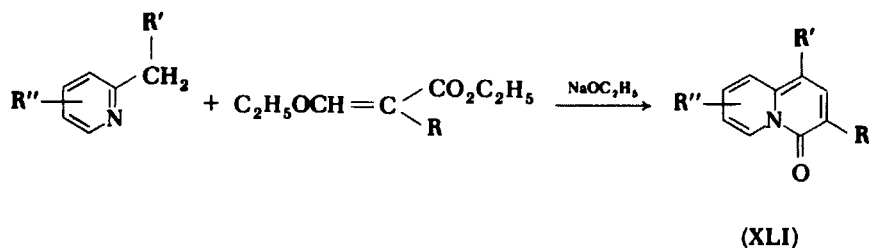
Schneider²¹ found that passage through pyridine of gas streams containing diacetylene, yielded colored solutions containing an adduct for which he suggested structure XXXIX (or XL), although no real evidence for these structures was offered.



Quinolizine itself has never been prepared. As mentioned earlier, the claims of Diels *et al.* to its preparation were later withdrawn. An attempt⁶ to obtain it by heating compound VI (X = I) with sodium acetate yielded only 2-(buta-1,3-dienyl)-pyridine.

A synthesis of 4*H*-quinolizin-4-ones announced by Boekelheide and Lodge¹⁸ in 1951 has been modified and extended, and it has

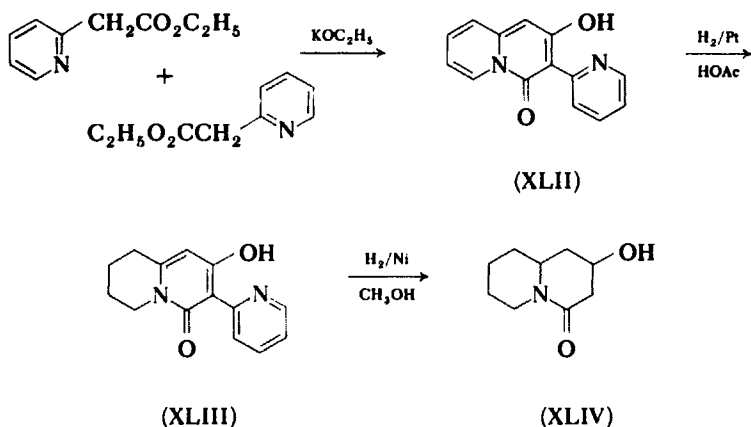
found considerable utility in various attempts to prepare cytosine.²²⁻⁵ 2-Picolines or 2-pyridylacetic esters, etc., are condensed with ethoxymethylenemalononic esters or their derivatives to yield products^{11, 18, 22-7} of structure XLI. Mild alkaline hydrolysis of esters



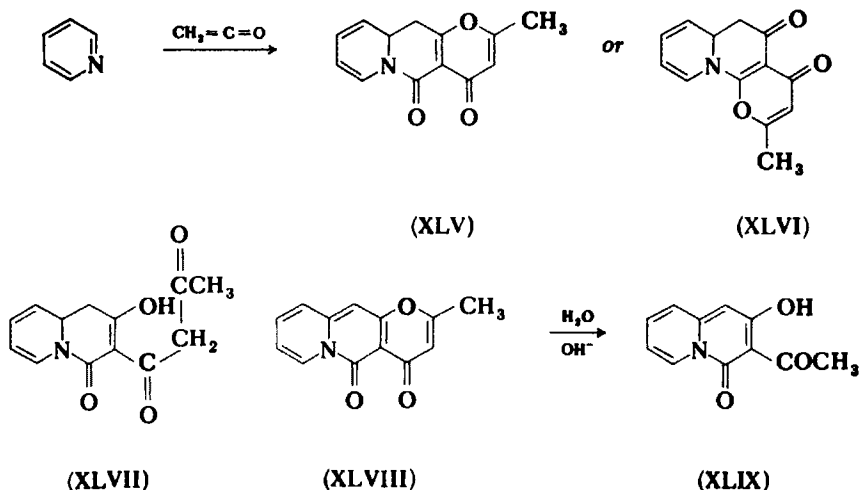
of structure XLI ($\text{R} = \text{R}' = \text{COOC}_2\text{H}_5$) causes^{18, 24} saponification of only the ester group in the 3-position, and heating the diester with 6*N* hydrochloric acid causes simultaneous decarboxylation of this group. More vigorous conditions result^{11, 18} in saponification or removal of both ester groups, however. High-temperature hydrogenation of XLI over a Raney nickel catalyst yields the 4-quinolizidone homologs, and a carbalkoxy group, if present in the 3-position, suffers hydrogenolysis.²⁷ Perhydrogenation without hydrogenolysis is accomplished with the use of Adams catalyst. Under acidic conditions with this catalyst it is also possible to obtain the 6,7,8,9-tetrahydro compounds. The carbonyl group of 4-quinolizone was unaffected by lithium aluminum hydride.¹⁸

The self-condensation of 2-pyridylacetic ester was shown^{28, 29} to yield XLII, while the mixed condensation with ethyl phenylacetate afforded the 3-phenyl homolog of XLII. Hydrogenation of XLII over a platinum catalyst produced the tetrahydro compound XLIII, which underwent both reduction and hydrogenolysis of the pyridyl substituent, yielding XLIV when treated with hydrogen and Raney nickel.

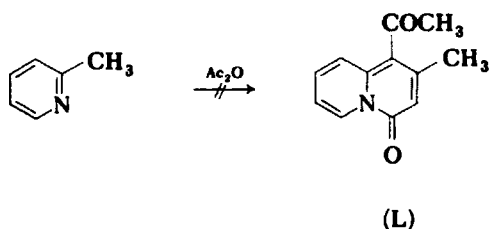
While dimethylketene was reported³⁰ to react with pyridine or collidine to yield only unstable, oily products, the passage of ketene into pyridine produced³¹ a bright yellow crystalline substance. This reaction was re-examined³² and structures XLVI or (more probably) XLV were proposed for the yellow product. Hydrolysis of the yellow substance gave a compound thought to be XLVII. Catalytic reduction yielded a dihydro compound, while heating with palladium-



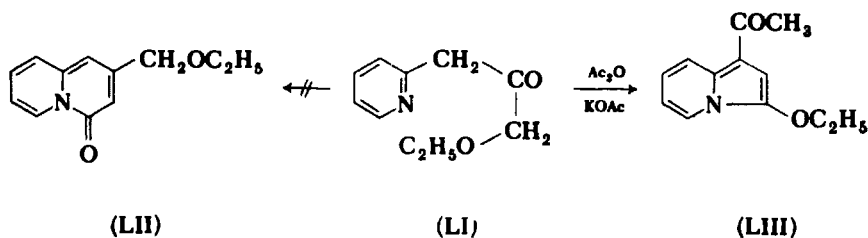
charcoal caused the loss of two atoms of hydrogen to yield XLVIII (or possibly the angular analog). Hydrolysis of XLVIII yielded XLIX. Hydrogenation of XLIX over platinum in ethyl acetate gave the 6,7,8,9-tetrahydro derivative, whereas more vigorous conditions (in acetic and hydrochloric acids) also reduced the acetyl function to an ethyl group.



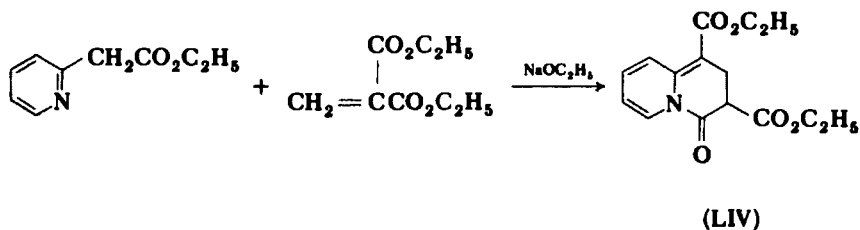
Formula XLIX recalls L, the structure proposed originally³³ for the compound "picolide" prepared from acetic anhydride and α -picoline. Picolide is now known to be a pyrrocoline derivative (see Section A-183, part I-3).



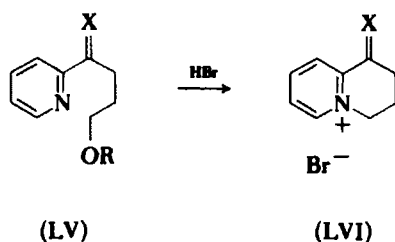
Treatment of LI (prepared by the reaction of 2-picolyl lithium with ethyl ethoxyacetate) with acetic anhydride yielded a product thought³⁴⁻⁶ to be LII, which was employed in the reported synthesis of *dl*-2-lupinine. An authentic synthesis of the latter compound was described³⁷ recently however, and the original dehydration product was demonstrated to have structure LIII.



The reaction of ethyl 2-pyridylacetate with methylenemalonate ester was reported³⁸ to afford a 6.5% yield of compound LIV.

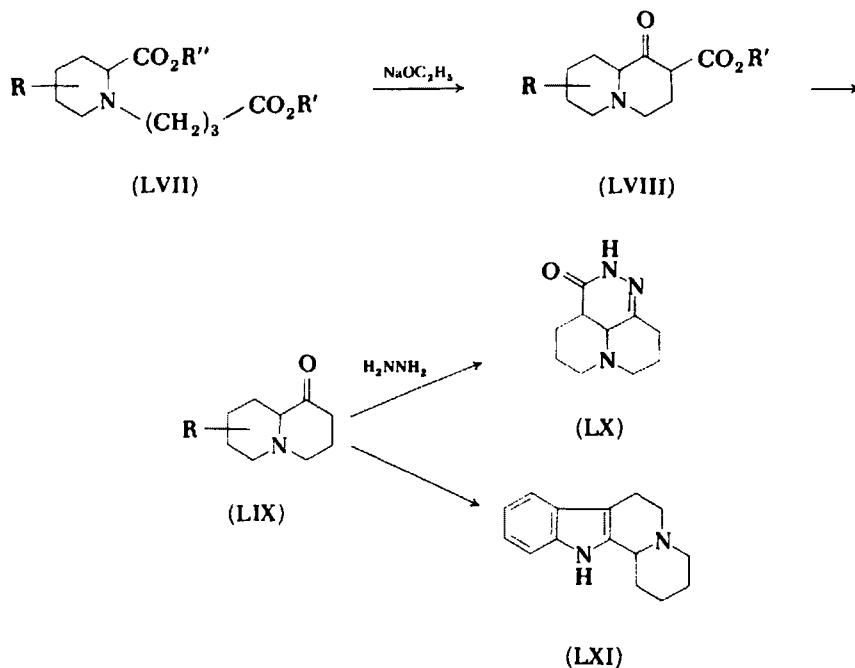


Salts of type LVI ($X = H_2$ or O) may be obtained³⁹⁻⁴¹ by treating pyridines of structure LV ($R = H$ or C_2H_5 ; $X = H_2, O$ or NH) with hydrobromic acid. The ketone LVI ($X = O$) has been converted, via the phenylhydrazone, into an indoloquinolizine⁴⁰⁻¹ (see Section A-753) by means of the Fischer indole synthesis.



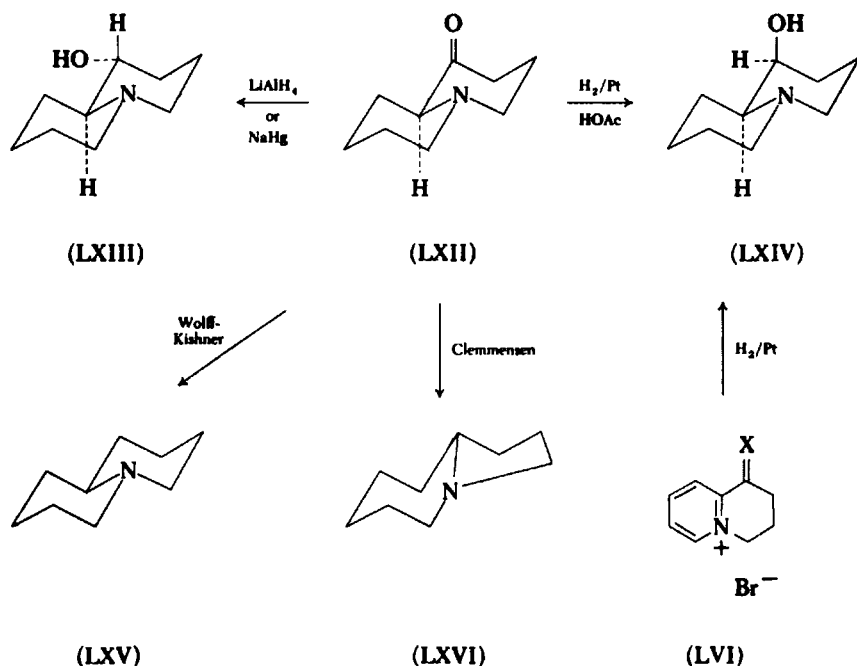
II. Quinolizidones

The only method which has been employed⁴²⁻⁸ for the preparation of 1-quinolizidones (LIX) is the Dieckmann condensation of esters such as LVII. Generally, the reaction products were converted directly into LIX, without isolation of the intermediate keto-ester (LVIII), and yields in the range of 70–80% are normal. The use of LVII in which R represents a 3-carbethoxy group afforded⁴³ a mixture of 1-quinolizidone with the expected 9-carbethoxy-1-quinolizidone. The reaction of this latter compound with hydrazine produced



LX (see Section A-734). The phenylhydrazone of LIX ($R = H$) underwent^{45,50} the Fischer indole reaction to produce LXI (see Section A-753).

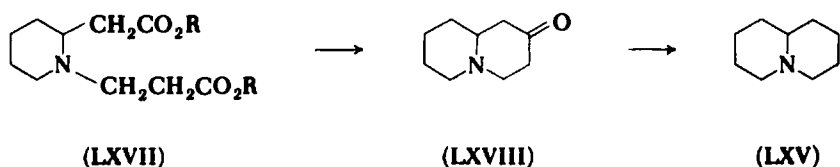
Reduction of LVIII ($R = H$) with sodium borohydride gave³⁷ the corresponding 1-hydroxy ester, probably with the two substituents in the *trans* configuration. Lithium aluminum hydride^{53,54} or sodium amalgam⁵⁵ reduction of LXII yielded a racemate thought to be the *trans* epimer LXIII, while catalytic hydrogenation gave⁵⁴ (a mixture⁵⁵ containing) the *cis* racemate LXIV. The configurations were assigned by analogy with the alcohols obtained in the reduction of *trans*-1-decalone. The *cis* epimer also was obtained⁵⁵ by hydrogenating LVI ($X = O$).



Reduction of 1-quinolizidones by the Clemmensen technique was, at first, thought^{42,43} to yield the corresponding quinolizidine (e.g., LXV). However, it was soon found^{4,44} that the Wolff-Kishner reduction yielded an "isomeric" product. The Clemmensen reduction product then was shown by Prelog and Seiwert⁵⁶ to have structure

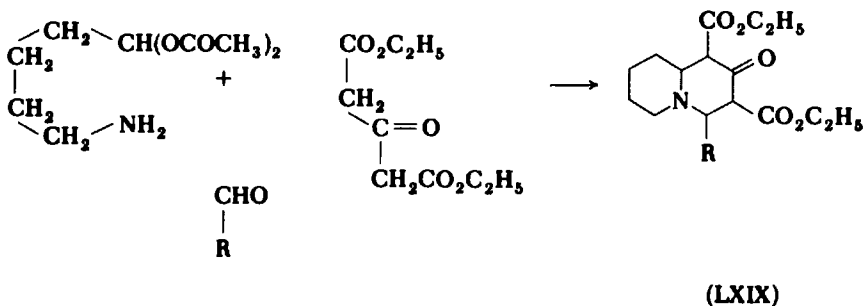
LXVI (see Section A-674) formed by transannular interaction⁵⁷ between the nitrogen and the carbonyl group during reduction. This type of rearrangement was studied extensively by Leonard and his colleagues, who found it characteristic of α -aminoketones. Thus it was concluded that all 1-quinolizidones would yield 1-azabicyclo-[5.3.0]decanes when reduced by the Clemmensen method. About 5% of LXVI also is formed during the electrolytic reduction⁴⁷ of LXII, although the major product (59% yield) is 1-azacyclodecane-5-ol. Treatment of LXII with methyl Grignard reagent gave⁴⁸ 1-hydroxy-1-methylquinolizidine in 73% yield.

Dieckmann cyclization of LXVII afforded^{48,58,59} (in 75% yield) 2-quinolizidone (LXVIII), which underwent a normal Clemmensen reduction to quinolizidine. Oxidation^{6,29} of 2-hydroxyquinolizidine

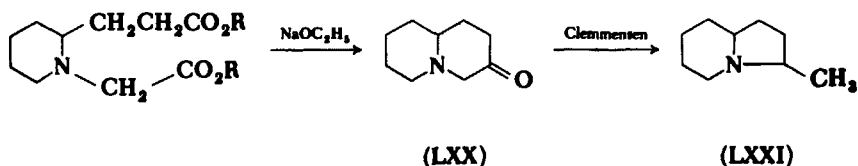


with chromic anhydride also has been used to prepare LXVIII. The reaction of LXVIII with methyl lithium produced⁴⁸ the corresponding methyl carbinol in 28% yield.

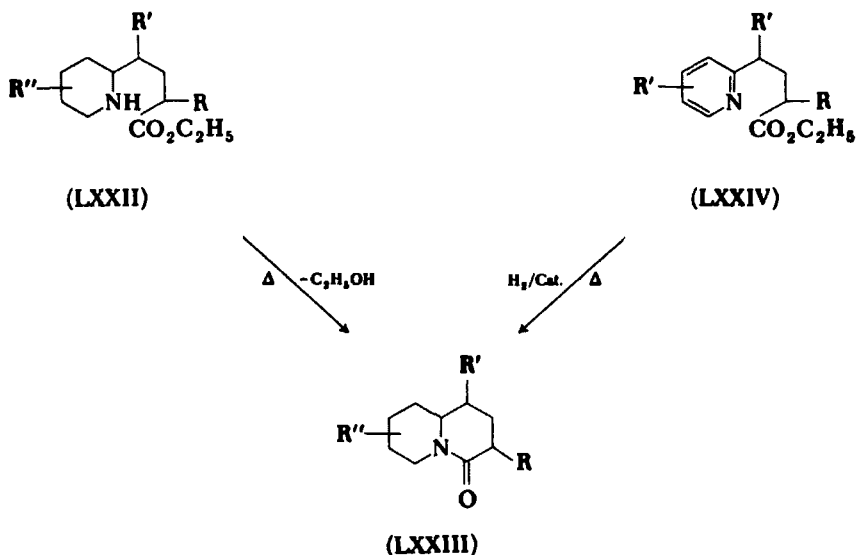
In a synthesis analogous to that used to prepare octahydropyrrocolin-7-ones (see Section A-183, part IV-2-d), δ -aminovaleraldehyde was condensed in buffered ethanolic solution with diethyl acetonedicarboxylate and various aldehydes to yield⁶⁰ LXIX. Hydrolysis and decarboxylation afforded the corresponding 4-substituted 2-quinolizidones.



The only reported 3-quinolizidone is LXX, prepared as shown via the Dieckmann cyclization.^{58,61} The Clemmensen reduction of LXX originally was thought⁵⁸ to yield quinolizidine, but was shown⁹⁶ subsequently to produce 3-methyloctahydropyrrocoline (LXXI). Reduction of LXX with lithium aluminum hydride afforded⁵³ 3-hydroxyquinolizine in 89% yield.



An early and still important synthesis of 4-quinolizidones⁶¹⁻⁶ (LXXIII) consists of the thermal dehydration of γ -(2-piperidyl)-butyric acids and esters (LXXII). A somewhat simpler variation, developed by Boekelheide and Rothchild,⁶⁸⁻⁹ involves the catalytic hydrogenation (over either Raney nickel or platinum oxide) of the corresponding pyridyl esters (LXXIV) at a temperature sufficiently high to cyclize the intermediate piperidyl esters (LXXII). Reduction of LXXIV where $\text{R} = \text{CO}_2\text{C}_2\text{H}_5$ at too high a temperature (180°) causes hydrogenolysis of the ester function, and in cases where

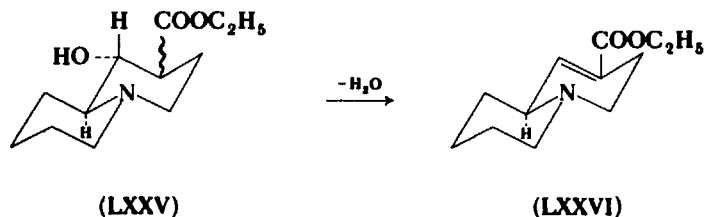


R is capable of reduction (as are, for example, acetyl and cyano groups), quinolizidines derived from its reduction also may be formed.^{69,70} As mentioned earlier, 4-quinolizidones may be obtained via catalytic reduction of products of type XLI, etc.

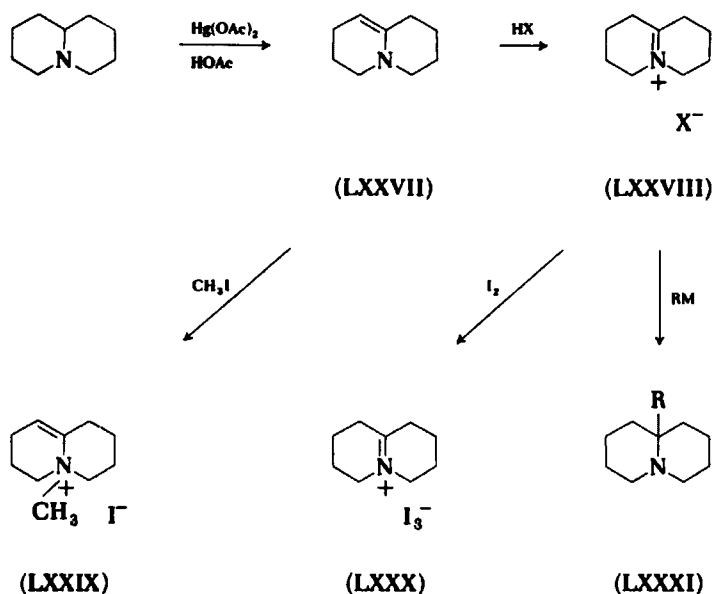
Lithium aluminum hydride has been used to reduce the ester function of carbethoxy-4-quinolizidones with^{26,39,71} and without²⁷ concomitant reduction of the ring carbonyl group. Electrolytic reduction has been employed for 4-quinolizidones^{65,67} and 4-quinolizidinethione.⁶³ Methyl Grignard reagent reacts with 4-quinolizidone⁴⁸ and its 2-methyl homolog⁶¹ giving, after dehydration, good yields of the 4-methyl- Δ^3 -dehydroquinolizidines. Treatment of LXXIII with hydrogen bromide may cause scission of the lactam bond.²³ Mercuric acetate produced⁷² no dehydrogenation in 4-quinolizidone.

III. Hexahydroquinolizines

These substances have been prepared in two fashions: by the dehydration of hydroxyquinolizidines, and by the mercuric acetate dehydrogenation of quinolizidines. The structures of the products obtained by the first method are governed, obviously, by the stereochemistry of the quinolizidinol, and only in relatively simple cases has it been possible to control the dehydration so as to obtain a single hexahydroquinolizine. For example, dehydration of LXXV yielded³⁷ LXXVI, and pyrolysis of *trans*-1-acetoxyquinolizidine produced⁵³ Δ^1 -dehydroquinolizidine. Dehydration of the mixtures of carbinols resulting⁴⁸ from the reaction of Grignard reagents or alkyl lithium compounds with quinolizidones, leads to mixtures of hexahydroquinolizines in all cases except those of the 4-isomers,^{48,61} which, of course, yield only Δ^3 -dehydroquinolizidines. Interestingly, dehydration of either 1- or 3-hydroxyquinolizidine appears⁷⁵ to yield Δ^2 -dehydroquinolizidine.



The second of the two methods has been studied extensively by Leonard and his co-workers.^{48,53,74,75} Heating quinolizidine with mercuric acetate in acetic acid was shown⁵³ to yield Δ^9 -dehydroquinolizidine (LXXVII), although the latter, with acids, forms salts having the $\Delta^{5(10)}$ structure (LXXVIII). The Δ^9 form reacts normally with methyl iodide to form⁵³ a salt of structure LXXIX. With iodine, salts of type LXXVIII yield a triiodide salt (LXXX), while with other reactants such as mercaptans, potassium cyanide, alkyl lithium compounds or Grignard reagents, adducts of structure LXXXI are produced.⁷⁴ The nitrile function of LXXXI (R = CN) is labile,⁷⁴ and is displaced by a methyl group when treated with methyl Grignard reagent, while the reaction of LXXXI (R = CN) with iodine yields LXXX. Reduction of LXXVIII with lithium alumi-



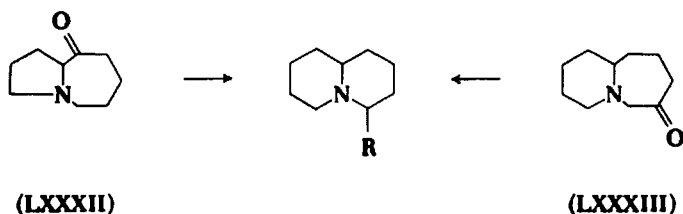
num hydride readily yielded⁵³ quinolizidine, while no reduction of the Δ^9 compound (LXXVII) occurred under these conditions. The infrared and ultraviolet spectra of the Δ^1 , $\Delta^{5(10)}$ and Δ^9 isomers have been found useful^{53,74} in distinguishing their structures.

Salts corresponding to structure LXXVIII have been obtained⁴⁸ from the action of mercuric acetate upon the four methylquinolizidines. The previously-mentioned 4-methyl- Δ^3 -dehydroquinolizidine

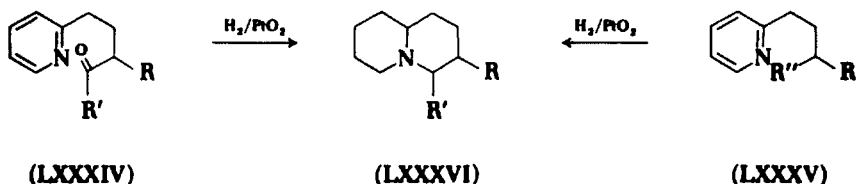
exhibits prototropic tautomerism analogous to that shown by LXXVII, and with acids yields⁴⁸ 4-methyl- Δ^4 -dehydroquinolizinium salts. These salts form adducts with the same types of reagents (e.g. potassium cyanide) as does LXXVIII.

IV. Quinolizidines

As mentioned earlier, quinolizidines are readily obtained by catalytic hydrogenation (over platinum) of the corresponding dehydroquinolizinium salts.^{6,7,10,52} Similar reductions have been applied to hexahydroquinolizines,^{37,48,61} to dihydroquinolizinium salts³⁹ and (with lithium aluminum hydride or sodium borohydride) to quinolizidones.^{26,29,37,39,53,67,71} Reduction of quinolizidones by the Wolff-Kishner technique produces authentic quinolizidines. However, as has been discussed previously, the Clemmensen reduction of 1- and 3-quinolizidones (but not 2-quinolizidones) leads to products of ring contraction. Utilization of this type of rearrangement has been made to prepare^{76,94} quinolizidine and its 4-methyl homolog from, respectively, LXXXII and LXXXIII.

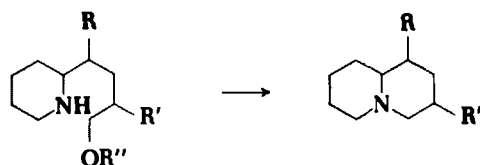


A method explored by Boekelheide and his colleagues^{69,70,77} consists of the reductive cyclization of pyridines of types LXXXIV and LXXXV ($R'' = \text{CN}$). In many instances mixtures of products resulted, particularly when R was a group (such as cyano or carboxy) capable of participating in the cyclization reaction, although in favorable cases good yields of LXXXVI were obtained. Hydrogenation of LXXXV ($R = R'' = \text{CO}_2\text{C}_2\text{H}_5$) over a copper



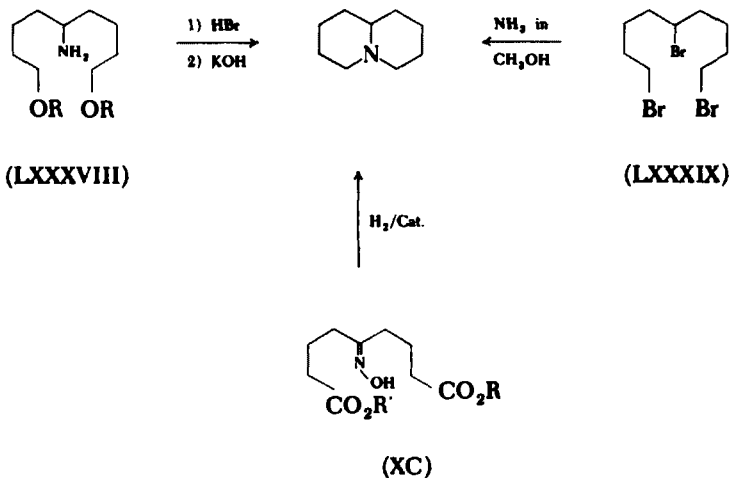
chromite catalyst at 250° produced⁶⁸ quinolizidine in 65% yield. Similar hydrogenolyses of substituents in the 3-position have been commented upon in Part II of this Section.

A synthesis of quinolizidines first employed by Clemo, Morgan and Raper⁴⁹ has been utilized several times by Winterfeld and his collaborators.⁷⁹⁻⁸³ Alcohols or phenyl ethers of structure LXXXVII ($R'' = H$ or C_6H_5) have been cyclized by the action of heat (in the case of alcohols) or by treatment with hydrogen bromide, phosphorus tribromide or phosphorus pentabromide. When the latter reagents are employed, hydroxyl groups, if present, are replaced by bromine.



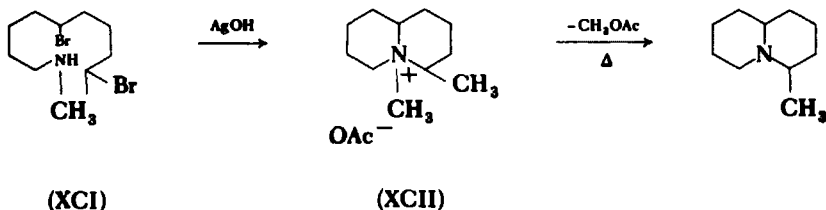
(LXXXVII)

Quinolizidine itself has been obtained by the cyclization of diethyl⁸⁴ or diphenyl⁸⁵ ethers of type LXXXVIII, by the ammonolysis of 1,5,9-tribromononane (LXXXIX),⁸⁶ and by the hydrogenation of XC over a copper chromite catalyst.⁸⁷

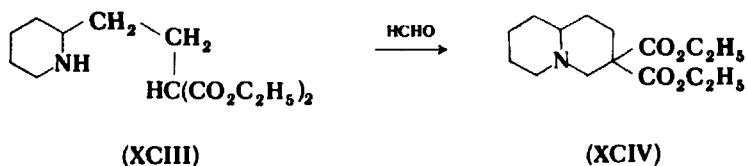


(XC)

Treatment of XCI with silver oxide yielded⁸⁸ XCII, which was converted into 4-methylquinolizidine upon pyrolysis.

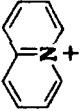
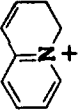
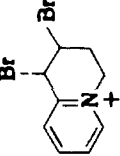
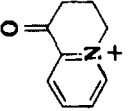


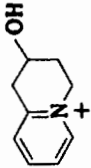
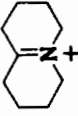
In an apparently unique application of the Pictet-Spengler synthesis to the quinolizidine series (although numerous benz homologs have thus been prepared), XCIV was obtained⁶⁷ from XCIII.



As was implied in Part II of this Section, the stable conformation of the quinolizidine nucleus has been postulated⁸⁹ to be the *trans* chair-chair form by analogy with decalin. Thus 9*a*-monosubstituted quinolizidines will exist as a single racemic mixture, while the 1-, 2-, 3- and 4-monosubstituted compounds will be capable of yielding two diastereoisomeric forms. This has been illustrated by the careful work of Leonard *et al.*^{48,53,76} who isolated all the racemates of the various monomethylquinolizines. In some cases it has been possible⁹⁰ to epimerize the less stable axial isomer to the more stable (equatorial) conformation (often referred to as the "epi" form).

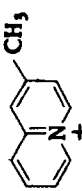
As mentioned earlier, the quinolizidine ring system is present in several groups of alkaloids^{2,3} some of which have been found of therapeutic value. The absence of curariform activity in simple quinolizidine salts has been reported,⁶⁹ and a number of quinolizidine derivatives were prepared and examined for antimalarial activity.^{92,93,102}

Quinolinizine Derivatives			
Empirical formula	Substituents or structure	Properties	Ref.
C_9H_7NO	4-Oxo-(4H)-	Yel., m. 71-2°. HCl salt, m. 135-40°. Picrate, m. 136-7°.	18
C_9H_7NS	4-Thio-(4H)-	Yel., m. 98-100°.	11,18
C_9H_8N		Bromide, m. 260-1°; λ_{max} 225, 274, 284, 310, 317 and 324 $m\mu$ (log ϵ 4.23, 3.42, 3.43, 4.00, 3.95 and 4.16). Dibromiodide, or., m. 182-4°. Iodide, d. 220-30° indef. (m. 206-12°). Perchlorate, m. 289.0-9.6° (285-8°). Picrate, m. 181.0-1.5° (180-1°, 179°).	6,7,9, 51,52
$C_9H_{10}N$		Bromide, m. 207-8°. Iodide, yel., m. 183-6° d. Tri-iodide, magenta, m. 133° d. Picrate, m. 133.0-3.5°.	6,7,52
$C_9H_{10}Br_2N$		Iodide, or., m. 141.5-2.5°, λ_{max} 211 and 311 $m\mu$ (log ϵ 4.43 and 3.94).	7,52
$C_9H_{10}NO$		Bromide, m. 205° (198°, 197°); phenylhydrazone, or.-brn., m. 271°; 2,4-DNPH $\cdot C_2H_5OH$, or.-yel., m. 192° d.; 2,4-DNPH $\cdot 3HOAc$, yel., m. 249-50°. Iodide phenylhydrazone, yel., m. 239°. Iodide m -methoxyphenylhydrazone, m. 255°. Picrate, m. 161-2° (147-8°); phenylhydrazone, or.-red, m. 225° d.	9,40,41, 55

$C_9H_{11}NO$	4(4 <i>H</i>)-Oxo-5,6,7,8-tetrahydro-	$b_{0,0}$ 110–20°; m. 46–7°, λ_{max} 235 and 311 m μ (ϵ 5700 and 7260). Picrate, m. 107°.	22
$C_9H_{12}NO$		Bromide, m. 169–70°. Iodide, m. 162.0–2.5°.	6,7
$C_9H_{13}N$	3,4,6,7,8,9-Hexahydro-9 <i>aH</i> -	b_{20} 75–6°; n_D^{28} 1.4917. HI salt, m. 209–10°. Picrate, m. 178–9°.	53
	1,4,6,7,8,9-Hexahydro-9 <i>aH</i> -	b_{12} 72°; n_D^{27} 1.4908. HI salt, m. 214.5–5.0°. Picrate, m. 196–7°.	75
$C_9H_{13}NO$	2,3,6,7,8,9-Hexahydro-4 <i>H</i> -	b_{18} 80°; n_D^{28} 1.5116. Methiodide, m. ~278° d.	53
	Perhydro-1-oxo-	b_4 95°, b_{14} 107°, b_{17} 110°. Picrate, m. 167–8°. Methiodide, m. 210°. Semicarbazone, m. 215° (230°, 214°).	42,43,45, 47,48, 53,55
	Perhydro-2-oxo-	b_1 74–6°, b_5 64–6°, b_{16} 142–4°; n_D^{20} 1.4916. . Picrate, m. 211° (209–11°, 209–10°, 208–10°).	6,29,48, 58–60
	Perhydro-3-oxo-	$b_{0,65}$ 62–3°; n_D^{20} 1.4926. Picrate, m. 180–2° d.	53,58,96
	Perhydro-4-oxo-	$b_{0,6}$ 83–5°, $b_{1,5}$ 97°, b_2 84–6°, b_3 105° (118°); n_D^{28} 1.5055. Hydrobromide, m. 195–7°, Hydrochloride, m. 146–7° (144–6°, 143–5°, 142–3°).	22,47,48, 61,63, 64,68, 69
$C_9H_{15}NS$	Perhydro-4-thio-	b_3 162°; m. 80°.	63
$C_9H_{15}NO_2$	Perhydro-2-hydroxy-4-oxo-	b_{13} 215°.	29
$C_9H_{16}N$		Iodide, m. 273–5°. Triiodide, maroon, m. 155–6°. Perchlorate, m. 234–5° d. Picrate, m. 108–9°.	53,74

(continued)

Quinolinizine Derivatives (continued)

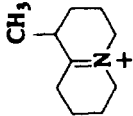
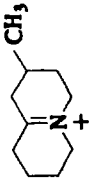
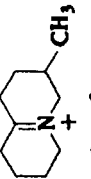
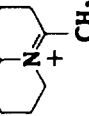
Empirical formula	Substituents or structure	Properties	Refs.
$C_9H_{17}N$	Perhydro- (Quinolinizidine, Norlupinane)	b_{11} 69–70°, b_{14} 74–6°, b_{18} 79°, b_{21} 84°, b_{25} 80–2°, b_{34} 84–5°, b_{40} 91°, b_{748} 165–9°; n_D^{20} 1.4796 (1.4794). HCl salt, m. indef. (~260°, ~200°). HI salt, m. 241.5–2.0° (189–92°). $HClO_4$ salt, m. 149–50°. Chloroaurate, m. 168–9° (167–8°). Picrate, m. 198–9° (199–200°, 197.5–8.5°, 197–9°, 197°, 196–8°, 194°, 193°). Picrolonate, m. 249° (245°, 244–5°). Methiodide, m. 333–5° (333°, 329–30°, 322°, 321–2°, 321°, 309–11°). <i>Cis</i> form: b_{24} 137–9°; m. 74–5° (81°). HBr salt, m. 232–3°. Picrate, m. 177–8.5°. <i>Trans</i> form: b_{18} 127–30°; m. 72° (71–2°). HBr salt, m. 243–4°. Picrate, m. 174–6°. Mixed <i>cis-trans</i> picrates, m. 169–75°.	6,53,58, 59,63, 68,69, 71,84–87,94
$C_9H_{17}NO$	Perhydro-1-hydroxy-	b_{13} 127–30°; m. 92°. HCl salt, m. 266–9°. Picrate, m. 166–7°. Phenylcarbamate, m. 146–7°. b_{14} 128°. HI salt, m. 214–5°. Picrate, m. 161.5–2.5°.	54,55 53–55 54 6,29 53
$C_{10}H_7NO_3$	1-Carboxy-4(4H)-oxo-	Methyl ester, <i>yel.</i> , m. 162–3°. Ethyl ester, <i>lt. yel.</i> , m. 117–8°. Hydrazide, <i>yel.</i> , m. 230–40° d.	18
$C_{10}H_9NO$	6-Methyl-4(4H)-oxo-	<i>Lt. yel.</i> , m. 48.5–50.5°.	11
$C_{10}H_{10}N$		Bromide, m. 185–6°. Dibromiodide, <i>or.</i> , m. 100–1°. Perchlorate, m. 110.5°; λ_{max} 226, 285.5, 312, 320 and 326 $m\mu$ ($\log \epsilon$ 4.32, 3.50, 4.10, 4.03 and 4.30). Picrate, m. 162° (161°).	10,51,52

	Bromide, m. 189°; $\lambda_{\max}$ 230, 280, 314, 320 and 328 μ ($\log \epsilon$ 4.28, 3.41, 4.03, 3.96 and 4.25). Picrate, m. 182°.	51
	Picrate, m. 135.0-5.5° (135°).	7,51
	Iodide, lt. yel., m. 171-3°.	11
	Bromide, m. 198-9°. Iodide, m. 204-5°. Picrate, m. 134.5-5.5°.	7
	Bromide, 2,4-DNPH, yel., m. 182° d.	51
	Bromide, m. 205° d.; $\lambda_{\max}$ 275 μ ($\log \epsilon$ 3.93). Picrate, m. 157°.	51

(continued)

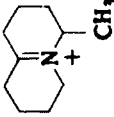
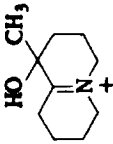
Quinoline Derivatives (continued)

Empirical formula	Substituents or structure	Properties	Refs.
		Bromide, m. 170-1°; λ_{max} 275 m μ (log ϵ 3.75). Picrate, m. 146°.	51
		Bromide, m. 156-8°.	10
$\text{C}_{10}\text{H}_{14}\text{NO}$		Bromide, m. 174-5°. Iodide, m. 174-5°. Picrate, m. 172-3°.	7
$\text{C}_{10}\text{H}_{15}\text{N}_2$		Dipicrolonate, m. 128°.	39
$\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}$		m. 137°.	49
$\text{C}_{10}\text{H}_{16}\text{N}_2$ $\text{C}_{10}\text{H}_{17}\text{N}$	9a-Cyanoperhydro-1-Methyl- $\Delta^{1(9a)}$ and Δ^9 -hexahydro-2-Methyl- Δ^1 and Δ^2 -hexahydro-	b_{16} 118-9°; n_D^{21} 1.4893. Picrate, m. 128-9°. (Mixture), $b_{4,5}$ 64°; n_D^{23} 1.5186. (Mixture ?), $b_{3,5}$ 64°; n_D^{20} 1.4950. Picrate, m. 148.0-9.3°.	74 48 48

$C_{10}H_{17}NO$	3-Methyl- $\Delta^{1(9a)}$ and Δ^2 -hexahydro-4-Methyl- Δ^3 -hexahydro-2-Methyl-1-oxoperhydro-	(Mixture), b_5 67°; n_D^{20} 1.4910. Unstable, b_{22} 101°. $b_{0,2}$ 70-5°, b_1 80°. Picrate, m. 176°. Methiodide, m. 167°.	48 48 48, 95
	8-Methyl-1-oxoperhydro-4-Methyl-2-oxoperhydro-2-Methyl-4-oxoperhydro-1-Carboxyperhydro-	b_{15} 115-20°. Picrate, m. 178° d. b_1 85°. Picrate, m. 189°. b_2 107°. Chloroplatinate, d. 175°. Two forms: m. 178-80° (chloroaurate, m. 178-82°), and m. 260-1° d. Ethyl ester, $b_{0,5}$ 91-3°; perchlorate, m. 175-6°; picrate, m. 189-90°. Methiodide, m. 153-4°.	44 60 61 82, 83
	3-Carboxyperhydro-4-Carboxyperhydro-	m. 206°. Methyl ester, $b_{0,6}$ 85°; methiodide, m. 230°. b_2 80-4°; n_D^{20} 1.4912.	71 78
		Perchlorate, m. 252-3°.	48
$C_{10}H_{18}N$		Perchlorate, m. 205-6°.	48
		Perchlorate, m. 211-2°.	48
		Perchlorate, m. 176-7°. Picrate, m. 135-6°.	48

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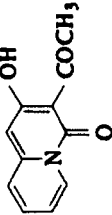
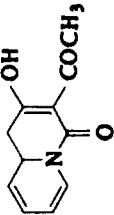
Quinoline Derivatives (continued)

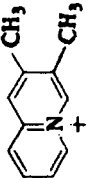
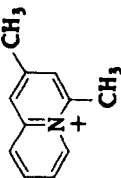
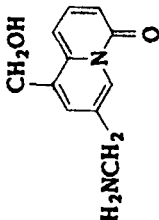
Empirical formula	Substituents or structure	Properties	Refs.
		Perchlorate, m. 241-2°.	48
C ₁₀ H ₁₈ BrN	1-Bromomethylperhydro-	Two forms: A, b ₁ 107°. Picrate m. 144°. Picrolonate, m. 169°. Methiodide, m. 186°. B, b ₁ 107°. Picrate, m. 135-6° (135°). Picrolonate, m. 202° (198-9°). Methiodide, m. 216°. b _{0,001} 50-1°; b ₁₈ 138-41°. Picrate, m. 154-6° (146-51°).	49,93,98, 101
	3-Bromomethylperhydro-		39,80
C ₁₀ H ₁₈ ClN	1-Chloromethylperhydro-	b ₁₂ 127°. Picrate, m. 145-6°. Chloroaurate, m. 138-9°. Chloroplatinate, m. 198-9°.	98,101
C ₁₀ H ₁₈ IN	1-Iodomethylperhydro-	HI salt, m. 214-5°. Picrate, m. 132°.	101
C ₁₀ H ₁₈ NO		Perchlorate, m. 220-1°.	48
C ₁₀ H ₁₈ N ₂ O	3-Aminomethyl-4-oxoperhydro-	b ₂ 120-3°; n _D ²⁰ 1.5070. Picrate, m. 188-90°.	70
C ₁₀ H ₁₉ N	1-Methylperhydro-	Two forms: A, b ₁₃ 79-81.5°; n _D ²⁰ 1.4740. Picrate, m. 192.5-3.5°. B, b ₁₃ 85-7°; n _D ²⁰ 1.4757. Picrate, m. 161-2°.	48,53,99
	2-Methylperhydro-	Two forms: A, b ₁ 47-8°, b ₁₂ 80°. Picrate, m. 151-2° (150-1°, 150°). Picrolonate, m. 197° (194-5°).	44,48,52

		Methiodide, m. 212°. <i>B</i> , <i>b</i> ₁ 58°, <i>b</i> _{12,3} 80.5°; <i>n</i> _D ^{21°} 1.4778, <i>n</i> _D ^{23°} 1.4776. Picrate, m. 160–1° (158°, 154–6°). Picrolonate, m. 226.5–8° (219°). HBr salt, m. 221–3°.	10,48,95
	3-Methylperhydro-	Two forms: <i>A</i> , <i>b</i> ₁₄ 77.5°; <i>n</i> _D ^{20°} 1.4757. Picrate, m. 194.5–5.5°. Picrolonate, m. 248–50° d. <i>B</i> , <i>b</i> ₁₄ 80.5–1°; <i>n</i> _D ^{20°} 1.4738. Picrate, m. 183–4°. Picrolonate, m. 208–9° d.	53
	4-Methylperhydro-	Two forms: <i>A</i> , <i>b</i> ₁₃ 79°; <i>n</i> _D ^{19°} 1.4813, <i>n</i> _D ^{20°} 1.4806. Picrate, m. 195° (191–5°, 191–3°, 190–1°). Methopicrate, m. 261°. <i>B</i> , <i>n</i> _D ^{20°} 1.4814. Picrate, m. 187° (182–4°, 165°). Methopicrate, m. 213°. HBr salt, m. 315°.	7,48,69, 76,88 60,76,88
	9a-Methylperhydro-	<i>b</i> ₂₀ 95–6°; <i>n</i> _D ^{28°} 1.4859. Picrate, m. 261.5–2° (259.5–61.5°). Picrolonate, m. 244.5–5.5°. HI salt, m. 215–7°.	53,74
C ₁₀ H ₁₉ NO	1-Hydroxymethylperhydro-	<i>dl</i> -Lupinine, <i>b</i> ₁ 107°; m. 59° (57–8°). Picrate, m. 127° (124–5°). Picrolonate, m. 203–4° (203°). Methiodide, m. 303° d. (298–301° d., 287–8° d.). Benzoate, m. 48–9°. Benzoate hydrochloride, m. 208°.	18,49,70, 97
	2-Hydroxymethylperhydro-	<i>dl</i> -Epilupinine, <i>b</i> ₁ 122°. Picrate, m. 139°. Picrolonate, m. 225°. Methiodide, m. 248°. m. 74–6°; <i>n</i> _D ^{22°} 1.5053–1.5066. Picrate, m. 144.5–5°. Picrolonate, m. 171.5–3°. <i>p</i> -Nitrobenzoate, m. 97–9°.	49 37

(continued)

Quinoline Derivatives (continued)

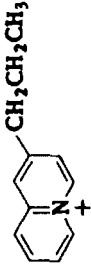
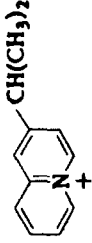
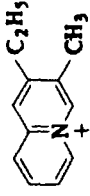
Empirical formula	Substituents or structure	Properties	Refs.
	3-Hydroxymethylperhydro-	<i>dl</i> -3-Lupinine: b_2 101-9°, b_4 115-7°; m. 59° (61-2°, 39, 67, 70, 57-8°, 54-7°). Picrate, m. 126-7° (126°). Picrolonate, m. 226-7°. Methiodide, m. 249-50°. Phenylcarbamate, m. 114-5° (92.0-2.5°, 66°). <i>dl</i> -3-Epilupinine, m. 30°. <i>dl</i> - α -4-Lupinine, m. 44.5-6°. <i>dl</i> - β -4-Lupinine, m. 16-18.5°. b_1 70°; m. 96-7°. Picrate, m. 122-3°. $b_{0,2}$ 73-5°; m. 55.5-6.5°. m. 104-6°. $b_{1,1}$ 126°, b_2 140-1°. Picrate, m. 217-8°. b_3 80-93°. Dipicrate, m. 205°. Dipicrolonate, m. 249.5°.	71, 79 67 81 48 48 37 91, 100 39
$C_{10}H_{19}NO_2$ $C_{10}H_{20}N_2$	4-Hydroxymethylperhydro- 1-Hydroxy-1-methylperhydro- 2-Hydroxy-2-methylperhydro- 1-Hydroxy-2-hydroxymethylperhydro- 1-Aminomethylperhydro- 3-Aminomethylperhydro-		
$C_{11}H_9NO_3$		Yel., m. 194.5-5.5° d.; λ_{max}^{MeOH} 289, 315 and 405 m μ (log ϵ 3.90, 3.46 and 3.90).	32
$C_{11}H_{11}NO_3$		Lt. yel., m. 56-7°; λ_{max} 264 and 331 m μ (log ϵ 3.99 and 3.83).	32
$C_{11}H_{11}NO_3$	2,3-Dicarboxy-6,7,8,9-tetrahydro-4(4H)-oxo-	m. $\sim$ 240° d.; λ_{max} 252 and 337 m μ (ϵ 7,600 and 9,550). Diethyl ester, m. 124-5°, λ_{max} 265 and 333 m μ (ϵ 16,600 and 10,500).	22

$C_{11}H_{12}N$		Dibromiodide, α -, m. 160° d. Picrate, m. 216° d.	52
		Picrate, m. $150-1^\circ$.	52
$C_{11}H_{12}N_2O_2$		Oil.	25
$C_{11}H_{13}NO_3$	1-Carbomethoxy-6,7,8,9-tetrahydro-4(4H)-oxo-3-Acetyl-2-hydroxy-6,7,8,9-tetrahydro-4(4H)-oxo-3-Ethyl-2-hydroxy-6,7,8,9-tetrahydro-4(4H)-oxo-8-Carbomethoxy-1-oxoperydro-9-Carbomethoxy-1-oxoperydro-1-Carbomethoxy-4-oxoperydro-3-Carbomethoxy-4-oxoperydro-1-Cyanomethylperhydro-	m. $139-40^\circ$. m. $104.0-4.5^\circ$; λ_{max}^{MeOH} 232,269 and 331 $m\mu$ ($\log \epsilon$ 3.96, 3.50 and 4.15). 2,4-DNPH, red, m. $214-5^\circ$ d. m. $230-1^\circ$; λ_{max}^{MeOH} 289 $m\mu$ ($\log \epsilon$ 3.87). $b_{0,2}$ $104-6^\circ$; n_D^{20} 1.4954. Picrate, m. $152.5-4.5^\circ$. $b_{0,3}$ $127-30^\circ$. m. $70-1^\circ$. b_2 $162-5^\circ$. ω -Cyanolupinane, b_1 $108-12^\circ$. Picrate, m. $150-1^\circ$. Methiodide, m. $241-2^\circ$. ω -Cyanoeplupinane, b_2 $120-5^\circ$. Picrate, m. $207-8^\circ$.	18 32 32 46 43 18 18,39 93

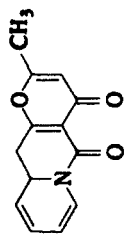
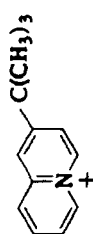
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Quinoline Derivatives (continued)

Empirical formula	Substituents or structure	Properties	Refs.
$C_{11}H_{19}N$	4-Cyano-4-methylperhydro-	b_{18} 130°; n_D^{25} 1.4878.	48
	9a-Cyano-4-methylperhydro-	b_{20} 121°; n_D^{25} 1.4882.	48
	1,2,6,7,8,9-Hexahydro-2,4-dimethyl-9aH-	b_{22} 115°. HI salt, d. 237°.	61
$C_{11}H_{19}Br_2N$ $C_{11}H_{19}NO$	1,3-Bisbromomethylperhydro-	$b_{0.1}$ 145-50°. Unstable.	26
	3-Ethyl-4-oxoperhydro-	$b_{0.5}$ 125-8°; n_D^{23} 1.4957.	69
	7,9-Dimethyl-4-oxoperhydro-	b_{10} 160°.	62
	1-Acetoxyperhydro-	$b_{0.1}$ 78-9°; n_D^{29} 1.4790. HI salt, m. 223-5°.	53
		Picrate, m. 172-4°.	
$C_{11}H_{19}NO_2$	3-Carboxy-4-methylperhydro-	Yel., m. 203-5°. Ethyl ester, $b_{1.5}$ 105-20°; n_D^{22} 1.480.	69
		Picrate, m. 127.5-8.5°.	
	3-(1-Hydroxyethyl)-4-oxoperhydro-	$b_{1.5}$ 145-55°; n_D^{20} 1.5090.	69
	2-Carbomethoxy-8-hydroxyperhydro-	m. 127-32°.	46
	7,9-Bishydroxymethyl-4-oxoperhydro-	Yel. oil.	27
$C_{11}H_{21}N$	3-Ethylperhydro-	b_{20} 104-8°; n_D^{21} 1.4735. HCl salt, m. 198-9°.	69
		Picrate, m. 156-7°.	
	9a-Ethylperhydro-	b_{25} 115°. Picrate, m. 220-1°.	74
$C_{11}H_{21}NO$	2,4-Dimethylperhydro-	b_{69} 127°. HCl salt, d. 280°. Perchlorate, d. 228°.	61
		Picrate, m. 142.5°. Methiodide, m. 168°.	
	1-(2-Hydroxyethyl)-perhydro-	b_2 124-5°. Methiodide, m. 205-7°.	93
	3-Hydroxymethyl-4-methylperhydro-	$b_{0.8}$ 98-110°; n_D^{19} 1.5072. Benzyl bromide salt, m. 179.5-80.5°.	69
$C_{11}H_{21}NO_2$ $C_{11}H_{22}N_2$	1,3-Bishydroxymethylperhydro-	$b_{0.1}$ 165-75°. Chloroaurate, m. 157-9°.	26
	1-Methylaminomethylperhydro-	b_{11} 128-9°. Styrphnate, m. 260° d.	100

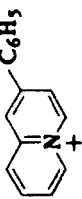
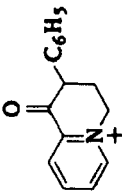
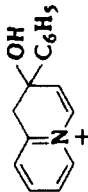
$C_{12}H_9NO_3$	1,3-Dicarboxy-6-methyl-4(4 <i>H</i>)-oxo-1-Carbomethoxy-3-carboxy-4(4 <i>H</i>)-oxo-3-Carbethoxy-4(4 <i>H</i>)-oxo-	Yel., d. 263–75°. Diethyl ester, yel., m. 124–8°. Yel., m. 210–5° with slow d. > 185°. $b_{0,0}$ 150°; m. 115°; $\lambda_{\max}$ 254 and 406 $m\mu$ (ϵ 12,600 and 22,100).	11 18 24
$C_{12}H_{11}NO_3$			10
$C_{12}H_{14}N$		Bromide, m. 133–5°.	52
		Picrate, m. 156–7°.	5,52
$C_{12}H_{19}NO_2$	2-Carboxy-3,4,6,7,8,9-hexahydro-9 <i>H</i> -	Chloride, $\lambda_{\max}$ 263, 275, 312.5 and 326 $m\mu$ (log ϵ 3.24, 3.28, 3.98 and 4.09). Dibromide, or., m. 222–4°. Picrate, m. 189.5°.	37
$C_{12}H_{19}NO_3$	2-Carboxy-1-oxoperhydro-1-Carboxy-4-oxoperhydro-3-Carboxy-4-oxoperhydro-	HCl salt, m. 194–5°.	37,42,48 70 65,67–69, 71
$C_{12}H_{20}ClNO_2$	2-Carboxy-1-chloroperhydro-	$b_{0,1}$ 115°, b_{15} 155°.	37
$C_{12}H_{21}N$	1-Allylperhydro-	b_2 155–8°; n_D^{20} 1.4949.	93
$C_{12}H_{21}NO$	1-Propionylperhydro-1,2,6,7,8,9-Hexahydro-3-(1-hydroxyethyl)-4-methyl-9 <i>H</i> -	$b_{0,1}$ 150–3°, $b_{0,15}$ 149°, $b_{0,5}$ 145–55°; n_D^{22} 1.5022; gives neg. $FeCl_3$ test. HCl salt, m. 143–5°.	83 69
$C_{12}H_{21}NO_2$	1-Carboxyperhydro-	HCl salt, m. 136–7°.	37
		<i>Epi</i> form, picrate, m. 132–3°.	93
		Picrate, m. 212–3° d.	83
		$b_{0,5}$ 92–100°; n_D^{21} 1.4931	69
		b_1 95–100°. Picrate, m. 137.5–8°.	70

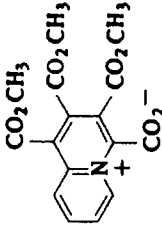
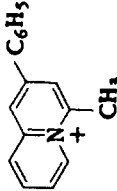
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$C_{13}H_{11}NO_3$		Yel., m. 205-7°; λ_{max}^{MeOH} 243 and 332 $m\mu$ (log ϵ 4.05 and 3.75).	31,32
$C_{13}H_{11}NO_4$	3-Acetoacetyl-2-hydroxy-4(4H)-oxo-	Lt. yel., m. 132-3.5°; λ_{max} 288, 315 and 408 $m\mu$ (log ϵ 4.10, 3.88 and 4.00).	32
$C_{13}H_{12}N_2O_4$	3-Carboethoxy-1-carboxamido-4(4H)-oxo-	d. > 260°.	22
$C_{13}H_{13}NO_3$	Dihydro deriv. of $C_{13}H_{11}NO_3$ (q. v.)	m. 242-3° (240-2° d.); λ_{max}^{MeOH} 243 and 295 $m\mu$ (log ϵ 4.05 and 3.62).	31,32
$C_{13}H_{13}NO_4$	3-Acetoacetyl-9a,1-dihydro-2-hydroxy-4(4H)-oxo-	Lt. yel., m. 126-7°; λ_{max}^{MeOH} 264 and 332 $m\mu$ (log ϵ 4.06 and 3.98).	31,32
$C_{13}H_{14}N_2O_3$	3-Aminomethyl-1-carboethoxy-6(6H)-oxo-	Gum. Benzoate, m. 100-2°.	25
$C_{13}H_{15}NO_4$	Dihydro deriv. of $C_{13}H_{13}NO_4$ (q. v.)	m. 120.0-0.5°; λ_{max}^{MeOH} 268, 275 and 291 $m\mu$ (log ϵ 4.12, 4.12 and 4.14).	32
$C_{13}H_{16}N$		Picrate, m. 184°.	52
$C_{13}H_{19}NO_5$	2,8-Dicarboethoxy-1-oxoperhydro-7,9-Dicarboethoxy-4-oxoperhydro-	m. 77-9°.	46
$C_{13}H_{21}NO_2$	3-Carboethoxy-1,2,6,7,8,9-hexahydro-4-methyl-9aH-	$b_{0.1}$ 165-80°; λ_{max} 270 $m\mu$ (ϵ 700). $b_{0.8}$ 129-32°; n_D^{20} 1.5426.	27 69
$C_{13}H_{23}NO_2$	1-Carboethoxymethylperhydro-	ω -Carboethoxylupinane: b_3 125-9°.	93
$C_{13}H_{23}NO_3$	7,9-Bismethoxymethyl-4-oxoperhydro-	ω -Carboethoxypilupinane: b_2 120-2°.	27

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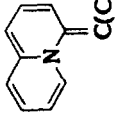
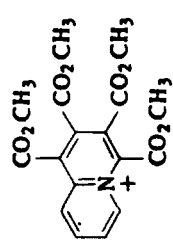
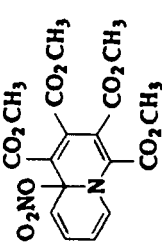
Quinolizine Derivatives (continued)

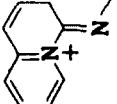
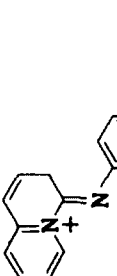
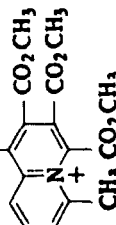
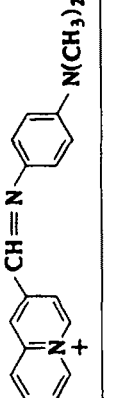
Empirical formula	Substituents or structure	Properties	Refs.
$C_{14}H_{10}N_2O_2$	2-Hydroxy-3-(2-pyridyl)-4(4H)-oxo-	Yel., m. 181-2°. HCl salt, m. 230-40°. Picrate, m. 237-8°.	29
$C_{14}H_{13}NO_3$	3-Carbethoxy-1-carbomethoxy-4(4H)-oxo-	Yel., m. 159-60°.	18
$C_{14}H_{14}N_2O_2$	6,7,8,9-Tetrahydro-2-hydroxy-3-(2-pyridyl)-4(4H)-oxo-	m. 123-4°. Picrate, m. 228-9°. <i>p</i> -Toluenesulfonate, m. 134°.	29
$C_{14}H_{22}N_2$	9 α -(2-pyridylmethyl)-perhydro-	b _{0,3} 137°; m. ~50°. Dipicrate, m. 152.5-3.5°. Monomethiodide, m. 212-3°.	74
$C_{14}H_{23}NO_3$	3-Carbethoxy-3-ethyl-4(4H)-oxoperhydro-	b _{0,8} 140-5°; n_D^{22} 1.4891.	69
$C_{14}H_{25}NO_2$	1-(2-Carbethoxyethyl)-perhydro-	b ₂ 136-40°. Methiodide, m. 109-11°.	93
$C_{15}H_{12}N$		Bromide, m. 193-4°. Perchlorate, m. 168-9.5° (168°); 10,51,52 λ_{max} 263 and 342 m μ (log ϵ 4.18 and 4.37). Picrate, m. 171° (168-70°, 168°).	
$C_{15}H_{14}NO$		Bromide, m. 196°; λ_{max} 246, 286 and 377 m μ (log ϵ 3.95, 3.86 and 3.92).	51
$C_{15}H_{15}NO_3$		Bromide, m. 150-3°. Perchlorate, m. 145-6°.	10
$C_{15}H_{15}NO_5$	1,3-Dicarbethoxy-4(4H)-oxo-	Yel., m. 132-3° (131.2°, 130°); λ_{max} 265, 342.5 and 395 m μ (ϵ 15,200, 9,600 and 16,300).	18,22,25, 26
$C_{15}H_{16}N_2O_4$	1,3-Dicarbethoxy-4(4H)-imino-	Or., m. 128°. HCl salt, m. 178-9° d.	25
$C_{15}H_{17}NO_5$	1,3-Dicarbethoxy-2,3-dihydro-4(4H)-oxo-	Yel., m. 120-1°.	38
$C_{15}H_{19}NO$	3-Phenyl-4-oxoperhydro-	b _{0,02} 163-8°.	66

$C_{15}H_{19}NO_5$	1,3-Dicarbethoxy-6,7,8,9-tetrahydro-4(4H)-oxo-	m. 124-5°; λ_{max} 265 and 333 $m\mu$ (ϵ 16,600 and 10,500).	22
$C_{15}H_{21}N$	3-Phenylperhydro-	$b_{0,4}$ 115-20°, $b_{1,5}$ 122-45°, b_{4-5} 127°. Two picrates, m. 152-3° (152°) and m. 171-2°.	66,70
	4-Phenylperhydro-	$b_{0,5}$ 87-9°; n_D^{20} 1.5392. Picrate, m. 213-4°. Methiodide, m. 152-9°.	77
$C_{15}H_{23}N$	9 α -Benzylperhydro-	$b_{0,3}$ 117-9°; m. 60-2°. Picrate, m. 203-4°.	74
$C_{15}H_{23}NO_5$	1,3-Dicarbethoxy-2-oxoperhydro-	Decomp. upon distillation.	60
	1,3-Dicarbethoxy-4-oxoperhydro-	One form, m. 80-1°.	26
$C_{15}H_{25}NO_4$	3,3-Dicarbethoxyperhydro-	$b_{0,5}$ 122-3°.	67
$C_{15}H_{28}N_2$	1-(1-Piperidinomethyl)-	b_{12} 170°. Styphnate, m. 232°.	100
$C_{15}H_{28}N_2O$	3-(2-Diethylaminoethyl)-4-oxoperhydro-	b_4 170-3°.	65
$C_{15}H_{30}N_2$	3-(2-Diethylaminoethyl)-perhydro-	b_2 115-8°. Picrate, m. 143°. Picrolonate, m. 212°. Chloroaurate, m. 174°.	65
$C_{16}H_{13}NO_8$		Kashimoto's compound. Grn.-yel. (yel. fluoresc. in UV), m. 186-7°.	12,13
$C_{16}H_{14}N$		Picrate, m. 226° d.	52
$C_{16}H_{14}N_2O_5$	3,9-Dicarbethoxy-7-cyano-4(4H)-oxo-	m. 130-2°	25
$C_{16}H_{15}NO_7$	3-Carbethoxy-7,9-dicarbomethoxy-4(4H)-oxo-	Yel., m. 151°; λ_{max} 420 $m\mu$ (ϵ 20,500).	24,27

(continued)

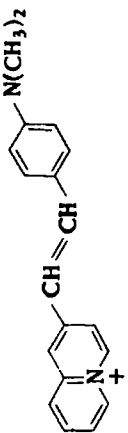
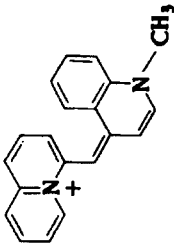
Quinolinizine Derivatives (continued)

Empirical formula	Substituents or structure	Properties	Refs.
$C_{16}H_{17}NO_4$	 $C(CO_2C_2H_5)_2$	HCl salt, m. 125–30° d.	11
$C_{16}H_{19}NO_5$	3-Carbethoxy-7,9-bismethoxymethyl-4(4H)-oxo-	m. 131°.	24,27
$C_{16}H_{23}NS$	9a-(p-Tolylthio)-perhydro-	m. 61–3°	74
$C_{16}H_{24}N_2$	1-Anilinomethylperhydro-	b ₁₅ 215–6°. Picrate, m. 159–60°.	100
$C_{16}H_{25}NO_5$	1,3-Dicarbethoxy-4-methyl-2-oxoperhydro-	b _{0.001} 140°. Picrolonate, m. 160°.	60
$C_{17}H_{16}NO_8$		Perbromide (Br ₃ ⁻), or., m. 129–30° d. Perchlorate, yel. m. 201°.	13
$C_{17}H_{16}BrNO_8$	9a-Bromo-1,2,3,4-tetracarboxymethoxy-9aH-	HBr salt, m. 101–2°.	13
$C_{17}H_{16}N_2O_{11}$		Nitrate, m. 110–1° (103–5°).	12,13

$C_{17}H_{17}NO_8$ $C_{17}H_{17}NO_9$	1,2,3,4-Tetracarboxymethoxy-9 <i>aH</i> - 9 <i>a</i> -Hydroxy-1,2,3,4-tetracarboxymethoxy- 9 <i>aH</i> - 	m. 187-8°. Chloroplatinate, m. 197-8° d. Nitrate, m. 92-3°.	12,13,17 13.
$C_{17}H_{18}N_3$		Iodide, red-brn., m. 224-5° d.	52
$C_{17}H_{19}NO_5$	1,3-Dicarboxy-7,9-dimethyl-4(4 <i>H</i>)- oxo-	m. 102°; λ_{max} 271.5, 343 and 413 $m\mu$ (ϵ 14,800, 8,100 and 18,500).	24
$C_{17}H_{19}NO_7$	1-Carboxy-3-carboxy-7,9-bis- methoxymethyl-4(4 <i>H</i>)-oxo-	m. 128°; λ_{max} 265, 342 and 408 $m\mu$ (ϵ 13,600, 6,900 and 17,500).	24
$C_{17}H_{21}NO_8$	1,2,3,4-Tetracarboxymethoxy- <i>x,x,x,x</i> - tetrahydro-9 <i>aH</i> -	Yel., m. 144°.	12
$C_{17}H_{24}N_2O$ $C_{17}H_{29}NO_4$	3-(4-Acetamidophenyl)-perhydro- 1-(2,2-Dicarboxyethyl)-perhydro-	Picrate, m. 220-2°. b_3 175-8°. Methiodide, m. 149-50°.	66 93
$C_{18}H_{18}NO_8$		Perbromide, brn., m. 135° d.	19
$C_{18}H_{18}N_3$		Iodide, dk. brn., m. 230-2°.	52

(continued)

Quinolinizine Derivatives (continued)

Empirical formula	Substituents or structure	Properties	Refs.
$C_{18}H_{19}NO_8$	1,2,3,4-Tetracarbomethoxy-6-methyl-9aH-	Lt. α ., m. 234° d.	19
$C_{18}H_{19}NO_9$	1,2,3,4-Tetracarbomethoxy-9a-methoxy-	Or., m. 160°. HBr salt, yel., m. 102-3° d.	13
$C_{18}H_{21}NO_7$	3,7,9-Tricarbethoxy-4(4H)-oxo-	Yel., m. 151°; λ_{max} 420 m μ (ϵ 20,500).	24
$C_{18}H_{23}NO_2$	3-Carbethoxy-1,2,6,7,8,9-hexahydro-4-phenyl-9aH-	$b_{0,3}$ 141-9°; n_D^{20} 1.5707.	77
$C_{18}H_{25}NO_2$	3-Carbethoxy-4-phenylperhydro-	$b_{1,2}$ 138-43°; n_D^{20} 1.5312. Picrate, m. 139-41°.	77
$C_{18}H_{32}N_2O_3$	3-Carbethoxy-3-(2-diethylaminoethyl)-perhydro-	$b_{0,1}$ 188-93°; Picrolonate, m. 200-2°.	65
$C_{19}H_{19}N_2$		Iodide, red, m. 316°.	52
$C_{19}H_{23}NO_7$	1,3-Dicarbethoxy-7,9-bismethoxymethyl-4(4H)-oxo-	m. 75°.	24
$C_{20}H_{17}N_2$		Iodide, deep red, m. 270-2°; λ_{max} 545 m μ (log ϵ 4.5).	11
$C_{20}H_{25}NS$	9a-(1-Naphthylmethylthio)-perhydro-	m. 98-9°.	74
$C_{21}H_{23}NO_9$	7,9-Bisacetoxymethyl-1,3-dicarbethoxy-4(4H)-oxo-	m. 134°; λ_{max} 265, 352 and 410 m μ .	24

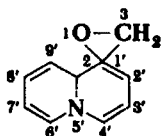
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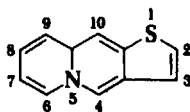
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A-722. Spiro[oxirane-2,1'[1]-quinolizine]. R.I. 1226

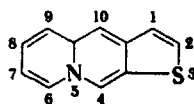


See under quinolizine (Section A-721).

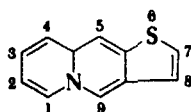
A-723. Thieno[2,3-*b*]quinolizine*



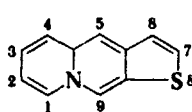
and

A-724. Thieno[3,2-*b*]quinolizine*

The numbering shown in I and II, respectively, was proposed for these systems.

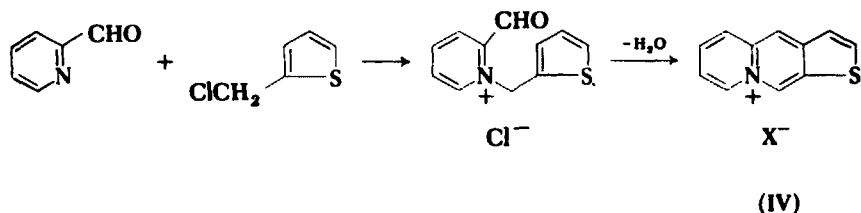
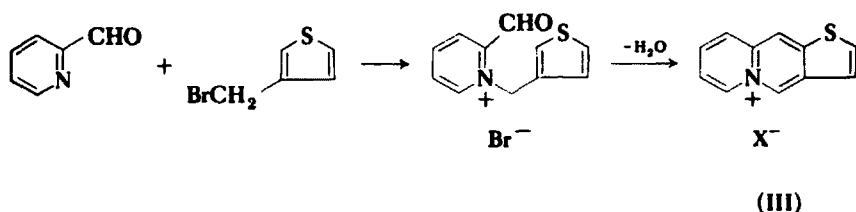


(I)



(II)

By application of the general method devised by Bradsher and Beavers¹ for the synthesis of benzo[*b*]quinolizinium salts (see Section A-728), the thienoquinolizinium salts III ($X = \text{Br}$, yel., m. 227–8°; $X = \text{picrate}$, yel., m. 213–4°) and IV ($X = \text{Br}$, yel., m. 216–7°; $X = \text{picrate}$, yel., m. 210.5–1°) were obtained.² The former was prepared in about 70% yield, whereas the yield of IV ($X = \text{Br}$) was only about 4%.

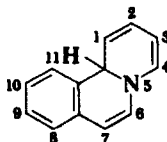


The structures were established by means of infrared and ultra-violet spectra (which closely resemble that of benzo[*b*]quinolizinium perchlorate¹) and by the Raney nickel desulfurization-reduction of III to the known 3-ethylquinolizidine (see Section A-721).

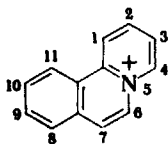
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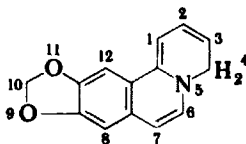
A-725. 11*b*H-Benzo[*a*]quinolizine.
R.I. 1957



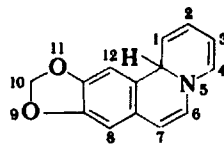
In addition to the tautomers of this structure and the dehydroquinolizinium cation (I, *R.I.* 1958), the following related structures will be considered under this heading: 4*H*-[1,3]benzodioxolo[5,6-*a*]-quinolizine (II, *R.I.* 2402), 12*b**H*-[1,3]benzodioxolo[5,6-*a*]quinolizine (III, *R.I.* 2402F) and their salts (*R.I.* 2402M). The benzoquinolizines



(I)

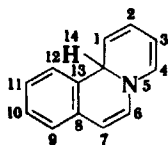


(II)

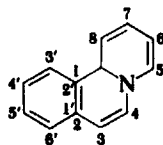


(III)

are also referred to as *benzpyridocolines*, and numbered as shown in IVa, while some of the Japanese workers use the numbering shown in IVb.



(IVa)

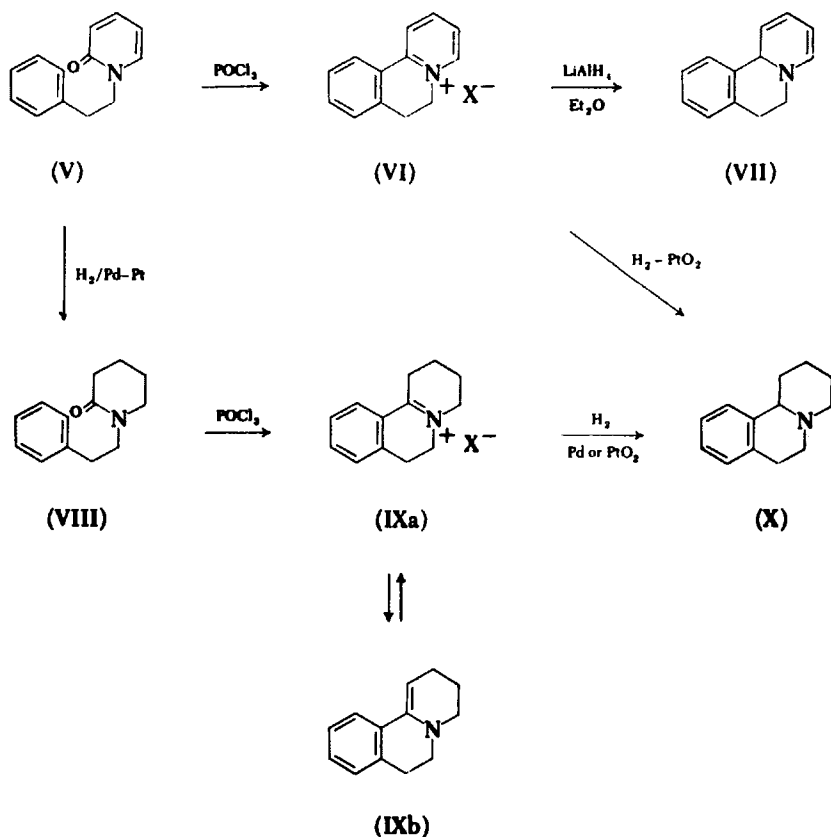


(IVb)

A number of the alkaloids of *ipêcac*^{1,2} (e.g., *emetine*) contain this nucleus, as do some of the degradation products of the *corydalis* alkaloids.^{2,3} The work on these alkaloids will not be reviewed here as it recently has been thoroughly discussed.^{1-5,36}

By far the most frequently employed preparative method for this ring system is Sugawara's cyclodehydration of 1-arylethylene-2-pyri-

ones (or 2-piperidones), which is, in fact, a variant of the Bischler-Napieralski reaction.⁶ While trying to convert quinolizinium salts of type VI into the dihydroquinolizine VII, a variety of reduction conditions were studied.^{7,8} Catalytic hydrogenation of compounds such as VI invariably gave hexahydro derivatives (X). In the presence of aqueous alkaline reducing agents, (and aqueous alkalis in general) VI reverted to V. The use of lithium aluminum hydride finally afforded the unstable VII (oil, methiodide, d. 174–5°). It had been suggested⁹ that the cyclization of V to VI required the presence of activating substituents in the phenyl ring. However, the example which evoked this theory was the 5-carboxy analog of V, and its anomalous behavior (it yields the intermediate 2-chloropyridinium salt but fails to cyclize) must result from the negative nature and the position of the substituents in the pyridine ring, since cyclizations of

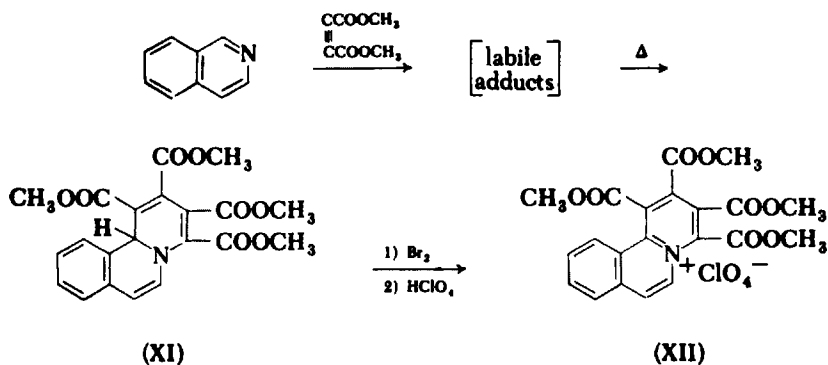


this type are now well known.^{7, 10} A number of derivatives of type VI (an incomplete listing) are given in Table A.

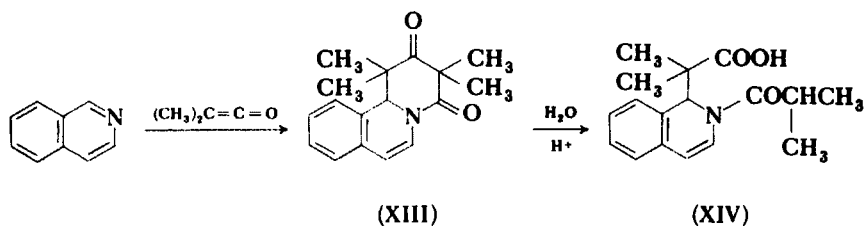
An analogous synthesis involves the cyclization of piperidone derivatives of type VIII. The salt resulting from this cyclization is invariably written as IXa, although recently certain *bases* prepared from the salts were assigned structure IXb. In view of the recent work by Leonard²⁸ demonstrating that quinolizidine bases analogous to IXb give salts having structures similar to IXa (see Section A-721) it seems likely that both structures IXa and IXb may be correct, and that they represent, respectively, the salts, and their bases (see also Witkop³³). A partial listing of compounds with structures IXa and IXb is given in Table B.

Table C shows some representative 1,2,3,4,6,7-hexahydrobenzo-[a]quinolizines (X). It has been shown that these compounds undergo the Hofmann degradation with rupture of the 5-6 bond.

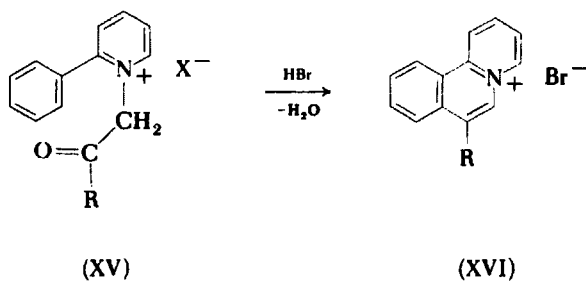
A few other syntheses of the benzo[a]quinolizine nucleus are known. Diels, *et al.*^{12, 30} treated isoquinoline with acetylenedicarboxylic ester, and obtained two isomeric "labile" adducts, which, when heated, each gave the same product ($C_{21}H_{19}NO_8$, vermilion, m. 231° d.), thought to be XI. Catalytic reduction of XI gave a *tetra*-hydro (!) compound (colorless, m. 217°) and treatment of XI with bromine produced the compound $C_{21}H_{18}Br_3NO_8$ (d. 140°), which gave 1,2,3-tricarbomethoxybenz[e]pyrrocoline (see Section A-192) when treated with base. The compound $C_{21}H_{18}Br_3NO_8$, upon treatment with perchloric acid, gave the perchlorate (yel., d. 215°) of a new base, possibly XII. The oxidative degradation of XI afforded quinaldic acid N-oxide.



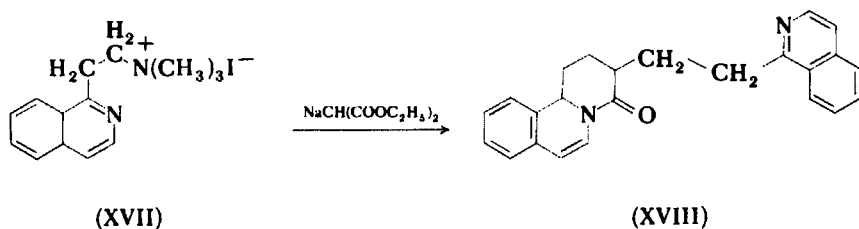
When isoquinoline was treated with dimethylketene, compound XIII (m. 105°) was obtained.¹³ Acidic hydrolysis of XIII gave XIV. See Section A-729.



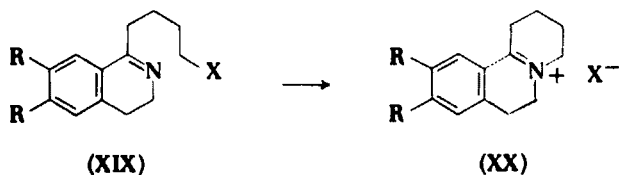
Bradsher and Beavers¹⁴ found that refluxing compounds such as XV ($\text{R} = \text{CH}_3$ or C_6H_5) with hydrobromic acid produced the quinolizinium bromides (XVI, $\text{R} = \text{CH}_3$ or C_6H_5).



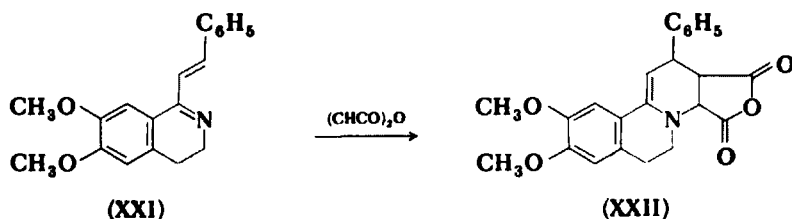
Treatment of XVII with sodiummalonic ester gave a product (yel., m. 206–9°; picrate, m. 200–2°) thought¹⁵ to be XVIII.



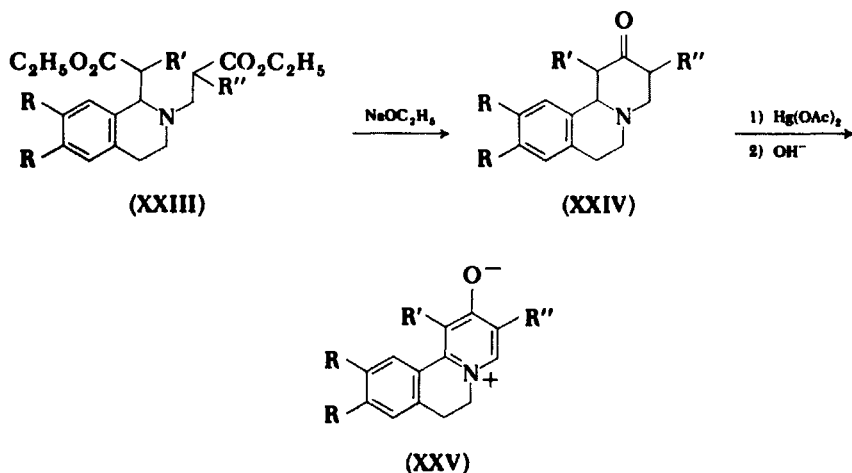
A good method, which has been little used, is the cyclization of 1-(δ -haloalkyl)isoquinolines or 3,4-dihydroisoquinolines, and which, in the latter case, yields compounds such as XX²² ($\text{R} = \text{OCH}_3$ —see Table B).



Tomimatsu³⁷ achieved a novel synthesis of this ring system in preparing XXII by the Diels-Alder reaction of XXI with maleic anhydride.



In the course of work directed towards synthesis of the *emeline* alkaloids, a number of 2-oxo- derivatives (XXIV) were obtained³⁹⁻⁴¹ by the Dieckmann cyclization of esters of type XXIII. These ketones have not been listed in the tables. Oxidation of XXIV ($R = OCH_3$, $R' = H$, $R'' = C_2H_5$) yielded⁴⁰ the anhydro compound XXV (m. 224–5°).



During studies upon the *yohimbe* alkaloids and related products, Prasad and Swan⁴³ prepared XXVII (m. 223–4°; phenylhydra-

zone bromide, m. 279°, chloride, m. 243–6°, nitrate, m. 237° and picrate, m. 200°) by treatment of XXVI with hydrobromic acid. A Clemmensen reduction of XXVII produced a substance, evidently not identical with the simple hexahydro compound X, which may have structure XXVIII (see Section A-677). The phenylhydrazone of XXVII was recovered unchanged from an attempted Fischer indole reaction.

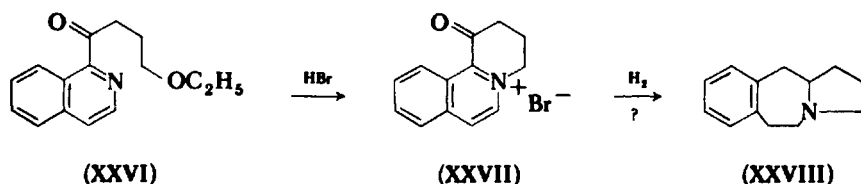
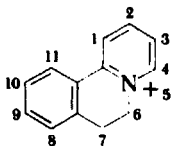


Table A. Derivatives of



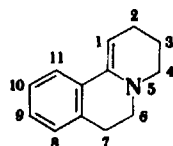
Empirical formula	Substituents	Properties and comments	Refs.
C ₁₃ H ₁₂ N	Unsubstituted	Iodide, yel., m. 191–2° d.; picrate., m. 137°; chloroplatinate, d. 193.0–4.5°; bisulfite, m. 210–1° d.	7,8,10
C ₁₄ H ₁₂ N	6,7-Dehydro-7-methyl-	Bromide, m. 283° d. Iodide, m. 267–8° d. Picrate, yel., m. 230.0–0.5°.	14
C ₁₄ H ₁₂ NO ₂	9,10-Methylenedioxy-	Iodide, yel., m. 191°.	7,16,17
C ₁₅ H ₁₆ NO ₂	8,9-Dimethoxy-	Iodide, yel., d. 182°; picrate, m. 135–6°.	18
	8,11-Dimethoxy-	Chloride, yel., m. 63°; iodide, yel., m. 156.0–7.5°.	18,19
C ₁₆ H ₁₈ NO ₂	10,11-Dimethoxy-8-methyl-	Iodide, yel., m. 186.5–7°.	18,19
C ₁₇ H ₁₆ NO ₄	2-Carbethoxy-9,10-methylenedioxy-	Iodide, d. 162°.	20
	3-Carbethoxy-9,10-methylenedioxy-	Iodide, Yel. m. 224–5° d. (d. 210–2°).	9,31

(continued)

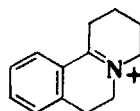
Table A (continued)

Empirical formula	Substituents	Properties, and comments	Refs.
$C_{18}H_{15}N_2O_2S$	3-(2'-methyl-4'-thiazolyl)-9,10-methylenedioxy-	Iodide, m. 190-3° d.	29
$C_{18}H_{20}NO_4$	3-Carbethoxy-9,10-dimethoxy-	Iodide, softens ~200°, m. 223-4° d.	9
$C_{19}H_{15}N$	6,7-Dehydro-7-phenyl-	Bromide, m. 276-7°. Perchlorate, m. 190-2°. Picrate, yel., m. 197.5-8.2°.	14
$C_{19}H_{21}N_2O_2$	9,10-Methylenedioxy-3-(1'-methyl-2'-pyrrolidyl)-	Chloride, viscid yel. oil.	21

Table B. Derivatives of

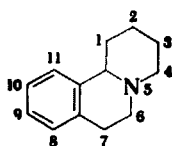


or



Empirical formula	Substituents	Properties and comments	Refs.
$C_{14}H_{16}NO_2$	9,10-Methylenedioxy-	Iodide, d. 251-2°.	27
$C_{15}H_{20}NO_2$	9,10-Dimethoxy-	Chloride, m. 197-8°; picrate yel., m. 185-6°.	22
	9,10-Dimethoxy-(?)	Picrate, yel., d. 179-80°	23,24
$C_{16}H_{22}NO_2$	9,10-Dimethoxy-4-methyl-	b ₁ 160-70°; picrate, m. 153-4°.	11
$C_{17}H_{20}NO_4$	3-Carbethoxy-9,10-methylenedioxy-	Iodide, yel., m. 197°.	31
$C_{17}H_{24}NO_2$	9,10-Dimethoxy-3,4-dimethyl-	b _{0,01} 135-40°; picrate, m. 137-9°.	11
$C_{18}H_{24}NO_4$	2-Carbethoxy-9,10-dimethoxy-	Iodide, m. 182-4°.	34,35
$C_{19}H_{26}NO_4$	3-Carbethoxy-9,10-dimethoxy-1-methyl-	Chloride, yel., m. 177-8°.	25
$C_{21}H_{24}NO_2$	9,10-Dimethoxy-2-phenyl-	Iodide, oil. Picrate, m. 211-2° d.	37
$C_{21}H_{30}NO_4$	2-(Carbethoxymethyl)-3-ethyl-9,10-dimethoxy-	Iodide, m. 257-8°.	32
$C_{23}H_{21}NO_5$	9,10-Dimethoxy-2-phenyl-2,3-dicarboanhydride	Oil. Picrate, m. 218-20° d.	37

Table C. Derivatives of



Empirical formula	Substituents	Properties and comments	Refs.
$C_{13}H_{17}N$	Unsubstituted	Oil, HCl salt, m. 214–6°; picrate, m. 148.0–8.5° (123°) picrolonate, yel., m. 205°; methiodide, m. 179–80°.	7,10
$C_{14}H_{17}NO_2$	9,10-Methylenedioxy-	HCl salt, m. 213°; HI salt, m. 198°; chloroplatinate, d. 223–4°; methiodide, m. 164° d.	16,17,27
$C_{14}H_{18}N_2O_2$	2-Amino-9,10-methylene-dioxy-	Di-HCl salt, d. 230°.	20
	3-Amino-9,10-methylene-dioxy-	Di-HCl salt, m. 253°.	26,31
$C_{14}H_{19}N$	7-Methyl-	HBr salt, m. 199°.	14
$C_{15}H_{20}N_2O_2$	3-Aminomethyl-9,10-methylenedioxy-	Di-HCl salt, m. 255–6°.	31
$C_{15}H_{21}NO_2$	8,9-Dimethoxy-	Oil; HI salt, m. 170°; picrate, yel., m. 147.5°.	18
	9,10-Dimethoxy-	b ₁₅ 225°; m. 59–60°; HCl salt, m. 235–7° d.; picrate, m. 172–4° (179–80°); perchlorate, m. 185°. Two methiodides: m. 228° and 244–5°.	22–24
	8,11-Dimethoxy-	Oil, picrate, or.-yel., m. 127–8.5°; methiodide, m. 158–9°.	18
$C_{16}H_{21}NO_2$	11-Ethyl-2,3-methylene-dioxy-	Picrate, m. 168–71°.	42
$C_{16}H_{22}N_2O_2$	2-Dimethylamino-9,10-methylenedioxy-	Di-HCl salt, m. > 300°.	20
	3-Dimethylamino-9,10-methylenedioxy-	HCl salt hydrate, m. 176–7°. Di-HCl salt, m. 261° d.	31

(continued)

Table C (continued)

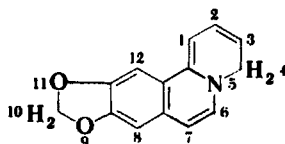
Empirical formula	Substituents	Properties and comments	Refs.
$C_{16}H_{23}NO_2$	9,10-Dimethoxy-4-methyl-	b ₁ 150-5°; HCl salt, m. 214-7° d.; picrate, m. 181-3°.	11
	9,10-Dimethoxy-8-methyl-	Oil; HI salt, m. 225-6°.	18
$C_{17}H_{21}NO_4$	2-Carbethoxy-9,10-methylenedioxy-	m. 92°; HCl salt, d. 251°; hydrazide, d. 206°.	20
	3-Carbethoxy-9,10-methylenedioxy-	Exists as two diastereoisomeric racemates: (a) m. 97-8°; hydrazide, m. 174-6°; acid hydrochloride, m. 249-50°; amide, m. 237-8°, and (b) gummy hydrazide, m. 224-5°.	26,31
$C_{17}H_{25}NO_2$	9,10-Dimethoxy-3,4-dimethyl-	b ₀₀₁ 130-5°; HCl salt, m. 217-9° d.; picrate, m. 197-9°.	11
$C_{18}H_{21}N_2O_2S$	3-(2-Methyl-4-thiazolyl)-9,10-methylenedioxy-	m. 167-9°	29
$C_{18}H_{28}NO_4$	2-Carbethoxy-9,10-dimethoxy-	Oil. Hydrazide, m. 204-7°.	34,35
$C_{19}H_{25}NO_3$	3-(Isobutyl)-9,10-dimethoxy-2-oxo-	Sedative action similar to that of reserpine.	38
$C_{19}H_{26}N_2O_2$	9,10-Methylenedioxy-3-(1'-methyl-2'-pyrrolidyl)-	Di-HCl salt, m. 198-9°; chloroplatinate, m. 172-5° (168-72°).	21
$C_{19}H_{27}NO_4$	3-Carbethoxy-9,10-dimethoxy-1-methyl-	m. 115-6°.	25
$C_{21}H_{25}NO_2$	9,10-Dimethoxy-2-phenyl-	Oil. Chloroplatinate, m. 128-9° d.	37
$C_{21}H_{31}NO_4$	2-(Carbethoxymethyl)-3-ethyl-9,10-dimethoxy-	HCl salt, m. 195-6°.	32
$C_{23}H_{25}NO_6$	2,3-Dicarboxy-9,10-dimethoxy-2-phenyl-	Oil. Methiodide, m. 177-8°. Anhydride, oil.	37
$C_{24}H_{22}N_2O_4$	3-(6,7-Methylenedioxy-2-quinolyl)-9,10-methylenedioxy-	Picrolonate, m. 157-8° d.	29

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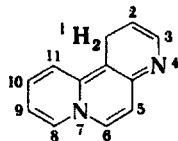
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A-726. 4*H*-[1,3]Benzodioxolo[5,6-*a*]-quinolizine. R.I. 2402

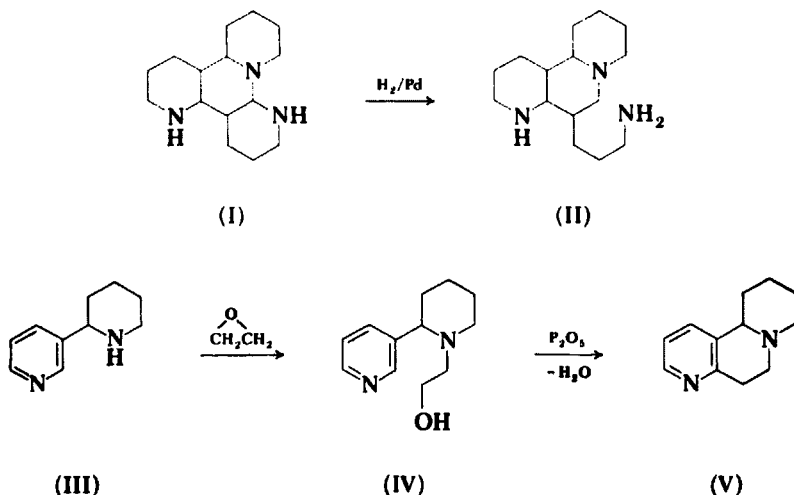


See 11*bH*-Benzo[*a*]quinolizine, Section A-725.

A-727. 1*H*-Pyrido[3,2-*a*]-quinolizine



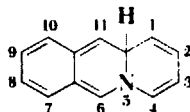
The catalytic hydrogenation of aldotripiperidine (I, see Section A-736) is reported¹ to yield II (m. 64–6°), while V (m. 53–4°) is claimed^{2,3} to be formed via IV from *anabasin* (III).



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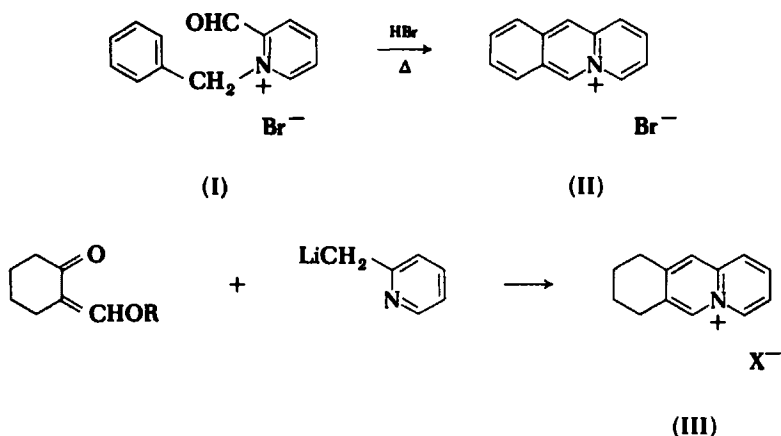
A-728. 11aH-Benzo[b]quinolizine.
R.I. 1951



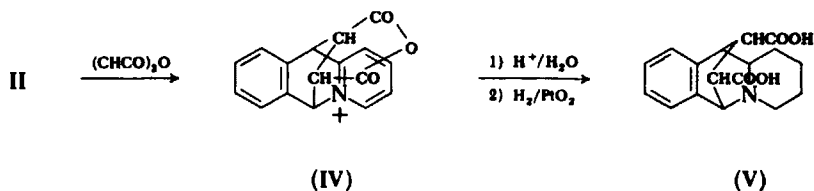
This nucleus has also been called *benz-2,3-pyridocoline*, and the name *acridizium* has been proposed for the dehydro quaternary salts (e.g., II).

When I was heated in 48% hydrobromic acid, cyclodehydration occurred, yielding^{1,10} the benzo[b]quinolizinium salt (II). The synthesis, as shown, of the tetrahydro analog (III) had previously been reported.² Oxidation of II with potassium permanganate gave phthalic acid.

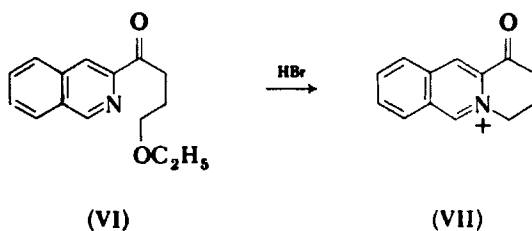
Irradiation of II yielded¹⁴ a 6(6*H*),11(11*H*)-dimer (dibromide, m. 260–4°; dinitrate, m. 228–30°; diperchlorate, m. 294°; dipicrate,



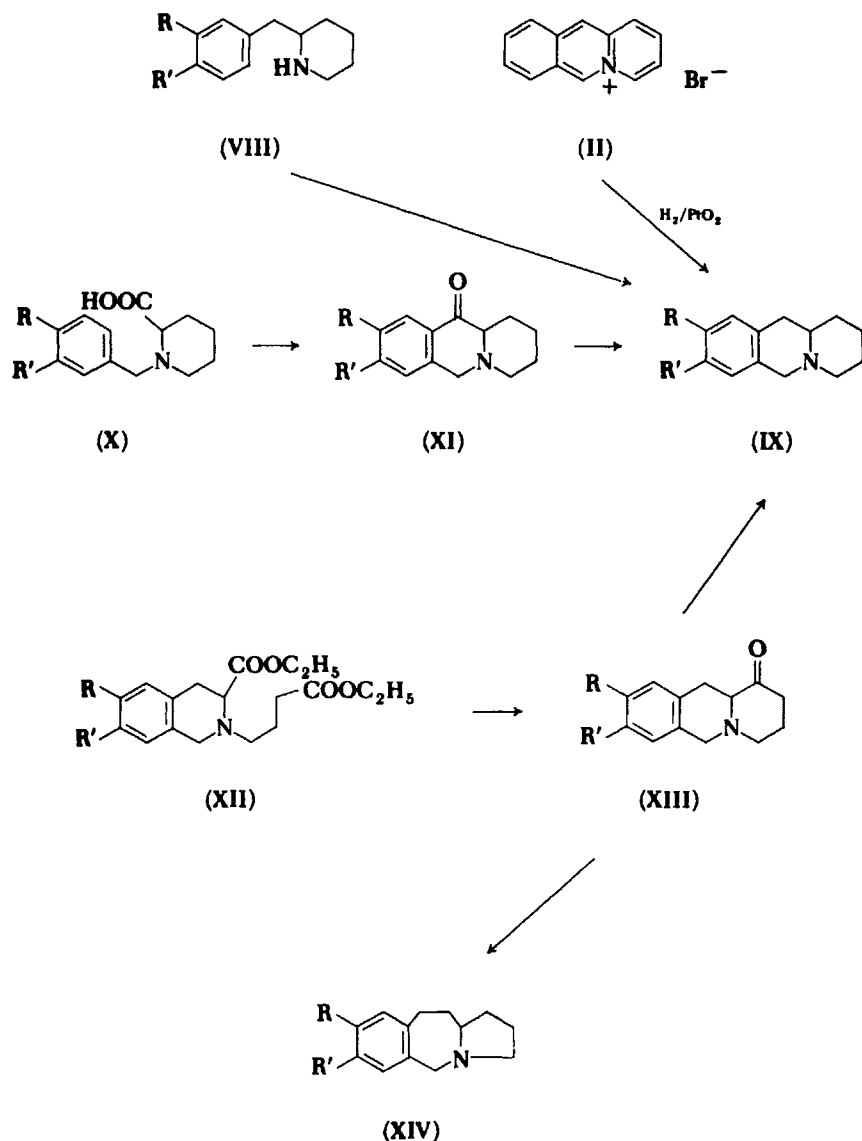
m. 280–3°), analogous to that obtained in this manner from anthracene. The similarity between II and the latter compound was illustrated further by the reaction¹⁵ of II with maleic anhydride to yield IV. The acid and esters derived from IV were thought to have the *cis* configuration, while *trans* esters were obtained from the condensation of II with maleic (or fumaric) esters. Hydrogenation of the *cis* acid yielded V.



In an extension of a synthesis used to prepare the quinolinizinium homolog (see Section A-721), compound VI was cyclized^{16,17} by treatment with acid, producing VII. The octahydro homolog of VII was obtained¹⁷ similarly.



Catalytic hydrogenation of II yielded^{1,10} the hexahydro compound IX ($R = R' = H$), which had been reported⁸ to result from the reaction of 2-benzylpiperidine (VIII, $R = R' = H$) with formaldehyde. Compound IX ($R = R' = H$) was also thought⁹ to result from the Wolff-Kishner reduction of XIII ($R = R' = H$). The



Clemmensen reduction of XIII ($R = R' = \text{OCH}_3$) gave a product reported³ to be IX ($R = R' = \text{OCH}_3$), but which, in view of the work of Leonard *et al.*,^{4,9} probably is of type XIV ($R = R' = \text{OCH}_3$). Compound IX ($R = R' = \text{OCH}_3$) was also obtained by the Wolff-Kishner reduction^{3,12} of XI ($R = R' = \text{OCH}_3$) and by the treatment¹¹ of VIII ($R = R' = \text{OCH}_3$) with formaldehyde¹² or with formic acid, then with phosphorus oxychloride and finally with zinc and acid.¹¹ Other examples of these structures were prepared by analogous reactions.

Several ketones of type XIII were obtained by the Dieckmann cyclization of XII. From ethyl *cis*-decahydroisoquinoline-3-carboxylate the perhydro analog (m. 103–4°; hydrochloride, m. 208–10°) of XIII was prepared,¹³ converted into the phenylhydrazone (m. 127–9°) and 3-methoxyphenylhydrazone (m. 119–21°), and these were transformed by the Fischer indole reaction to *dl*-allo- and epialloyohimbanes and their 11-methoxy homologs. Similar reactions were conducted upon VII and its octahydro homolog.^{16,17}

Benzo[*b*]quinolizinium Salts

Empirical formula	Substituents or structure	Properties	Refs.
$\text{C}_{13}\text{H}_{10}\text{N}$	Unsubstituted	Bromide, hydrate, yel., m. 239–40° d.; λ_{max} 242, 361, 379.5 and 399 μ in EtOH (log ϵ 4.68, 3.99, 4.01 and 3.93). Perchlorate, m. 205–6.2°. Picrate, m. 216–8°.	1,10
$\text{C}_{13}\text{H}_{12}\text{NO}$	1,2,3,4-Tetrahydro-1-oxo-	Bromide, m. 243° (234°). Picrate, m. 180°. Phenylhydrazone bromide, or., d. 285° (m. 360°); iodide, m. 281° (265–7°) d. <i>m</i> -Methoxyphenylhydrazone iodide, yel., m. 262° d.	16,17
$\text{C}_{13}\text{H}_{14}\text{N}$	7,8,9,10-Tetrahydro-	Perchlorate, m. 187.1–7.8°. Picrate, m. 237–8°.	2
$\text{C}_{13}\text{H}_{16}\text{NO}$	1,2,3,4,7,8,9,10-Octahydro-1-oxo-	Bromide, oily. Phenylhydrazone bromide, or., m. 285° d.	17
$\text{C}_{14}\text{H}_{12}\text{N}$	7-Methyl-	Bromide, yel., m. 270–5°. Perchlorate, m. 232.9–3.2°.	1,10
	9-Methyl-	Bromide, yel., m. 191–3°. Perchlorate, m. 203–5°.	1,10

Benzo[*b*]quinolizinium Salts (*continued*)

Empirical formula	Substituents or structure	Properties	Refs.
C ₁₇ H ₁₂ NO ₃	II-Maleic anhydride adduct	Bromide, m. 244-6°, λ_{max} 263 m μ (log ϵ 3.62).	15
C ₁₇ H ₁₄ NO ₄	II-Maleic acid adduct (cis-)	Perchlorate, m. 299.5-300.5°.	15
C ₁₉ H ₁₈ NO ₄	II-Dimethyl maleate adduct (cis-)	Perchlorate, m. 249-50°.	15
	II-Dimethyl- maleate adduct (trans-)	Perchlorate, m. 298.5-9° d.	15
C ₂₁ H ₂₂ NO ₄	II-Diethyl maleate adduct (cis-)	Perchlorate, m. 262-3°.	15
	II-Diethyl maleate adduct (trans-)	Perchlorate, m. 182.5-3.5°.	15

1,2,3,4,6,11-Hexahydro-11*aH*-benzo[*b*]quinolizines

Empirical formula	Substituents	Properties	Refs.
C ₁₃ H ₁₃ NO	1-oxo-	Or., m. 99-100° (92-6°). Oxime, m. 207-8°. Oxime HCl salt, m. 221°. Phenylhydrazone, m. 92-4°. <i>p</i> -Nitrophenylhydrazone, m. 197.9-8.8°.	5,6
C ₁₃ H ₁₃ NO ₂	8,9-Dihydroxy-	HBr salt, m. 307-8° d. MeBr, m. 298° d. MeSCN, m. 232-3°.	11
C ₁₃ H ₁₇ N	Unsubstituted	Oil, b_{15} ~160°. HBr salt, m. 241.5-3.2° d. Picrate, m. 177° (161-2°, 163.8-5°).	8-10
C ₁₄ H ₁₇ NO ₂	9-Methoxy-1-oxo-	Or.-yel., m. 123-4°. HCl salt, m. 195.6°. Oxime, m. 223-4°. Phenylhydrazone, m. 88-90°.	7
	8,9-Methylenedioxy-	m. 135-6°. Picrate, m. 164-5° d. Methiodide, m. 293-4° d. Methyl thiocyanate, m. 190-2°.	11

(continued)

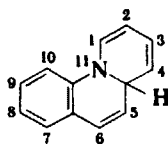
1,2,3,4,6,11-Hexahydro-11aH-benzo[b]quinolizines (*continued*)

Empirical formula	Substituents	Properties	Refs.
C ₁₄ H ₁₉ NO ₂	1-Hydroxy-9-methoxy-	Exists in two modifications: <i>A</i> , m. 166°. Picrate, m. 144-5°. Acetate, m. 118°. <i>B</i> , m. 138-40°. Acetate, m. 86-7°.	
C ₁₅ H ₁₉ NO ₃	8,9-Dimethoxy-1-oxo-	—	3
	8,9-Dimethoxy-11-oxo-	—	3
C ₁₅ H ₂₁ NO ₂	8,9-Dimethoxy-	m. 108-9° (101-2°). HCl salt, m. 232-4°. Picrate, m. 209-10° d. Picrolonate, m. 230° d. Methiodide, m. 251-2°. Methyl methosulfate, m. 263°. Methyl thiocyanate, m. 182-3°.	3,11,12
C ₁₆ H ₁₉ NO ₃	2-Carbethoxy-1-oxo-	HCl salt, m. 192-4° d.	6
C ₁₇ H ₁₉ NO ₄	Compound V	Perchlorate, m. 236-7°.	15

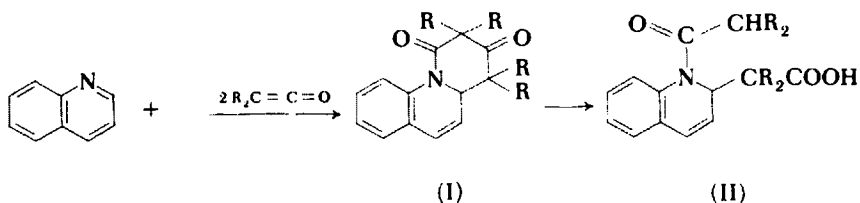
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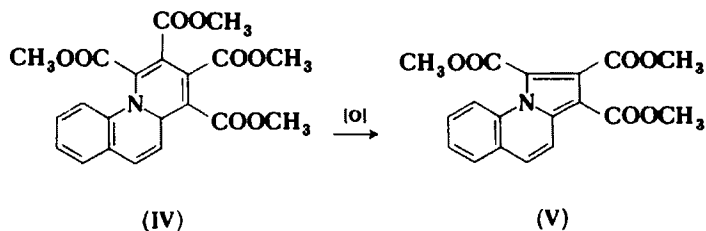
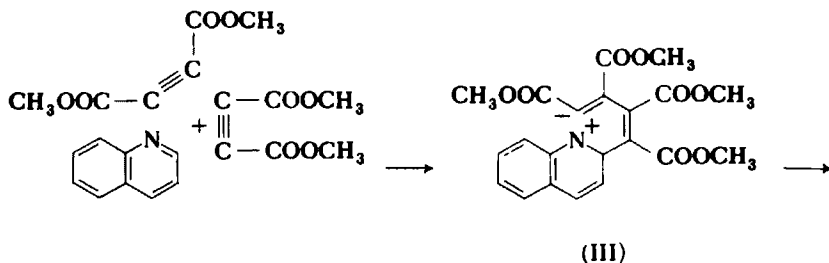
A-729. 4aH-Benzo[c]quinolizine.
R.I. 1959



The first examples of this ring system were described by Staudinger and his co-workers,¹⁻⁴ who treated quinoline with various ketenes and obtained compounds of structure I. These substances underwent reversible pyrolytic cleavage to yield the reactants, and on hydrolysis, gave acids such as II.

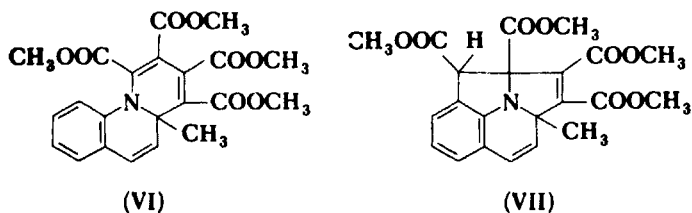


By treating quinoline with acetylenedicarboxylic ester, Diels and Alder,⁵ obtained a "labile yellow adduct" which they considered to have structure III. When III was treated with acids; or was heated, it yielded the "stable adduct" IV, which, in contrast to III, did not react with diazomethane and was not reduced by hydrogen with

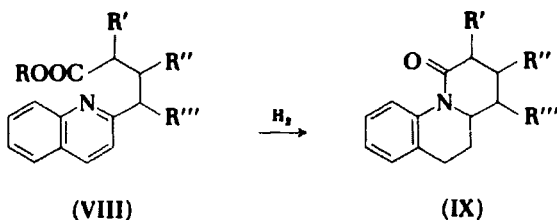


palladium or platinum catalysts. Strong aqueous potassium hydroxide degraded IV to quinaldine (a fact which casts some doubt upon the accuracy of structure IV), whereas milder hydrolyses yielded carboxylic acids. Oxidation of IV with chromic acid or with dilute nitric acid resulted in ring contraction, similar to that shown by the quinolizine analog (see Section A-721), to V. Considerable effort was expended by Diels and his co-workers in elucidating the structures and reactions of these compounds and a more extensive discussion of this work is given in the section on quinolizine (A-721).

The reaction of quinaldine with acetylenedicarboxylic ester yielded a product at first thought⁵ to be VI but later¹³ shown to be VII (see Section A-77).

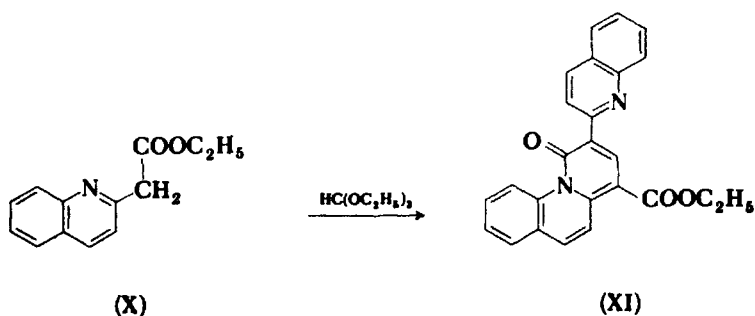


Another method employed for the preparation of this ring system involves the reduction of γ -(2-quinolyl)butyric acids (VIII).^{6,7} The intermediate tetrahydroquinolylbutyric acids spontaneously lactamize to IX.

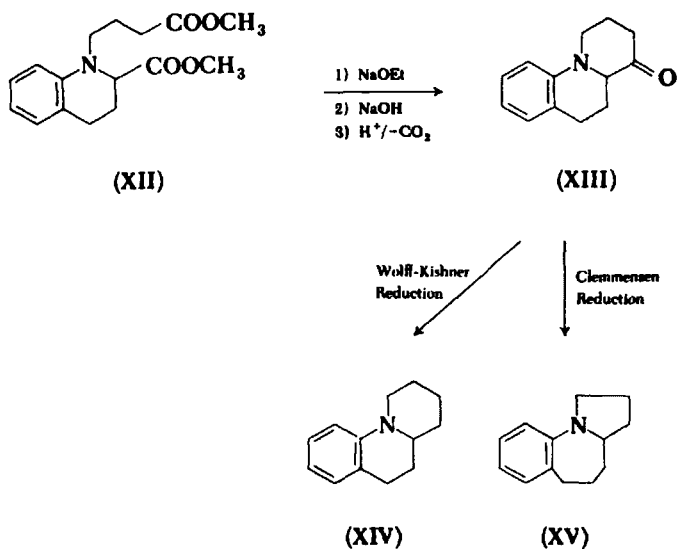


The synthesis of XI is reported by Clemo and Nath,⁸ who condensed two moles of 2-quinolylacetic ester (X) with orthoformic ester.

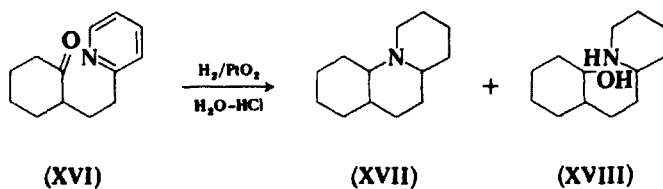
The Dieckmann condensation was used by Clemo, Cook and Raper⁹ to convert XII into XIII. The reduction of XIII by the Wolf-Kishner method afforded the normal compound XIV,⁹ whereas the Clemmensen reduction of XIII produced⁹ a compound later



shown¹⁰ to be XV. Similarly, the perhydro analog of XIII was converted⁹ into XVII and the perhydro analog of XV.

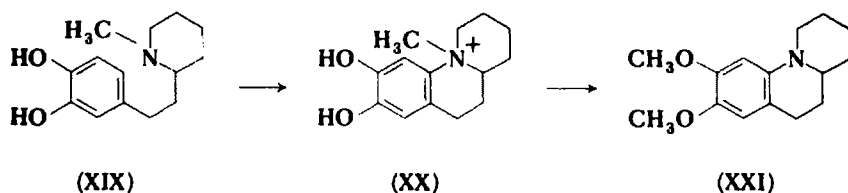


A perhydro derivative (XVII) of this nucleus was described by Jampolsky and Solodar,¹⁴ who reduced XVI catalytically. Some XVIII was also obtained in this reduction, but was not, apparently,

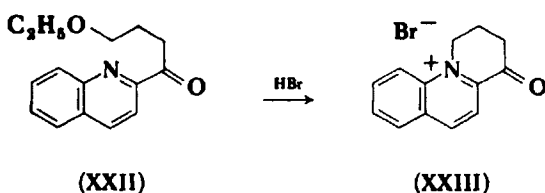


an intermediate in the formation of XVII, as XVIII could not be converted into XVII. The properties of XVII thus prepared differ from those of the product obtained by Clemo, Cook and Raper,⁹ and it is evidently a second of the four possible racemic modifications of XVII.

A further synthesis has been mentioned by Sugasawa, Sugimoto and Nakata,¹¹ who obtained XX and XXI from XIX.



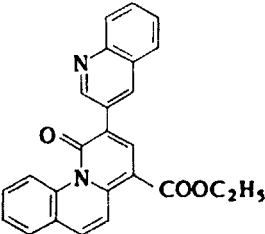
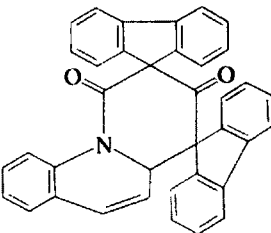
Recently, the ketone XXIII (m. 116–8°; phenylhydrazone bromide, m. 260°, chloride, m. 257–8°, nitrate, m. 257–8° and picrate, m. 245°) was prepared¹⁵ from XXII. The phenylhydrazone of XXIII was recovered unchanged from an attempted Fischer indole reaction.



Derivatives of 4aH-Benzo[c]quinolizine

Empirical formula	Substituents or structure	Properties and comments	Refs.
C ₁₃ H ₁₃ NO	1,2,3,4,5,6-Hexahydro-4-oxo-	Unstable yel. oil, b ₁ 160°.	9
C ₁₃ H ₁₇ N	1,2,3,4,5,6-Hexahydro-	Yel. oil, b ₁ 120°. Picrate, yel., m. 174°.	9
C ₁₃ H ₂₁ NO	1,2,3,4,5,6,6a,7,8,9,10,10a-Dodecahydro-4-oxo-	Lt. yel. oil, b ₁ 130° Picrolonate, lt. yel., m. 216°.	9
C ₁₃ H ₂₃ N	1,2,3,4,5,6,6a,7,8,9,10,10a-Dodecahydro-	A. Oil, b ₁ 100–10°. B. Oil, b _{0,5} 71–4°; n _D ²⁴ 1.5080. Picrate, m. 178–80°. Forms two methiodides, m. ~185–6° and ~242–9°.	9 14

Derivatives of 4aH-Benzo[c]quinolizine (*continued*)

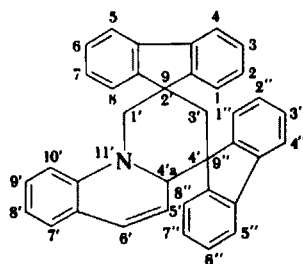
Empirical formula	Substituents or structure	Properties and comments	Refs.
C ₁₄ H ₁₇ NO	1,2,3,4,5,6-Hexahydro-4-methyl-1-oxo-	m. 80°.	6
C ₁₅ H ₂₁ NO ₂	1,2,3,4,5,6-Hexahydro-8,9-dimethoxy-	Unstable oil.	11
C ₁₆ H ₁₉ NO ₃	2-Carbethoxy-1,2,3,4,5,6-hexahydro-1-oxo-	m. 99-101°, b _{0.2} 188-90°, n_D^{21} 1.5551.	7
C ₁₇ H ₁₈ NO ₂	1,2,3,4-Tetrahydro-2,2,4,4-tetramethyl-1,3-dioxo-	m. 81-2°.	2,4
C ₁₈ H ₂₀ NO ₂	1,2,3,4-Tetrahydro-2,2,4,4,4a-pentamethyl-1,2-dioxo-	m. 119.5-20.5°.	2
C ₁₉ H ₂₂ NO ₂	1,2,3,4-Tetrahydro-2,2,4,4,4a,8-hexamethyl-1,3-dioxo-	m. 129-30°.	2
C ₂₁ H ₁₉ NO ₈	1,2,3,4-Tetracarboethoxy-	"Stable adduct," red, m. 234°.	5,12
C ₂₁ H ₂₆ NO ₂	2,2,4,4-Tetraethyl-1,2,3,4-tetrahydro-1,3-dioxo-	m. 76-7°.	4
C ₂₅ H ₁₈ N ₂ O ₃		m. 161-2°. Picrate, m. 178-9° d.	8
C ₃₇ H ₂₃ NO ₂		m. 154-5° d. R.I. 3915	1

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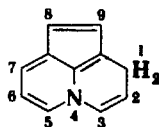
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A-730. Dispiro[fluorene-9,2'-(3')-[1]-benzo[c]quinolizine-4'(4'a),9''-fluorene]. R.I. 3915

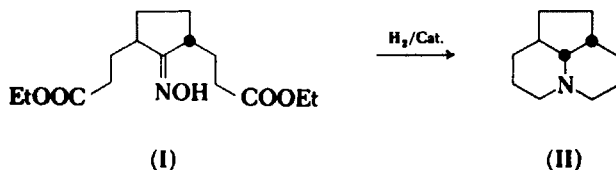


See Section A-729.

A-731. 1H-Cyclopenta[*ij*]quinolizine.



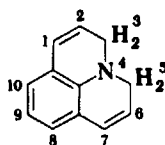
While studying the stereochemistry of a group of related ring systems, Leonard and Middleton¹ prepared compound II ($b_{0.5}$ 56°; n_D^{20} 1.5037; d_4^{20} 0.9671; picrate, m. 211–2°; picrolonate, m. 232–3°) from the *trans*-cyclopentanone oxime derivative I.



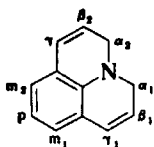
Reference

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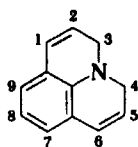
A-732. 3H,5H-Benzo[*ij*]quinolizine
R.I. 1960



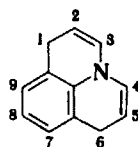
This ring system was assigned, by its discoverer Reissert,¹ the trivial name *julole*, and "numbered" as shown in I. It has also been called *pyrido*[3,2,1-*ij*]*quinoline* and 4,3,5-*pyridoquinoline*. To prevent *julole* being confused with five membered ring systems (the names of which often terminate in *-ole*), the names *juline* (with numbering as in IIa) and *isojuline* (IIb) were recently proposed.^{2,36} The trivial names



(I)

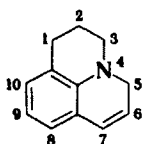


(IIa)

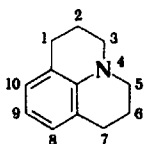


(IIb)

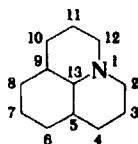
*juloline*¹ and *julolidine*¹ are commonly applied, respectively, to III and IV, although numbering analogous to that of II has been used² for these derivatives. The 1-oxo derivative of IV has been called¹² *tetrahydro(1,8- α , γ -propenyl)-4-quinolone* and the perhydro system V has been named²⁸ 1-azatricyclo[7.3.1.0^{5,13}]*tridecane*.



(III)

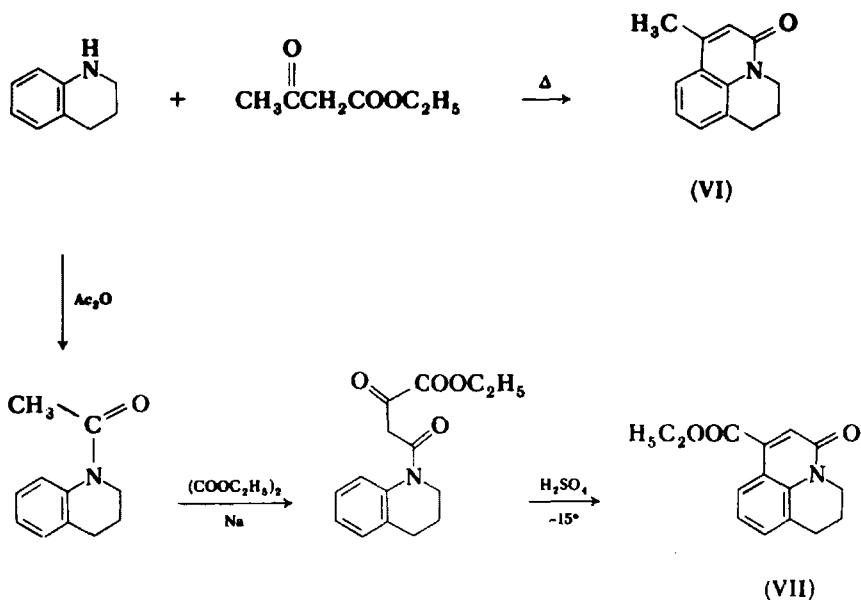


(IV)



(V)

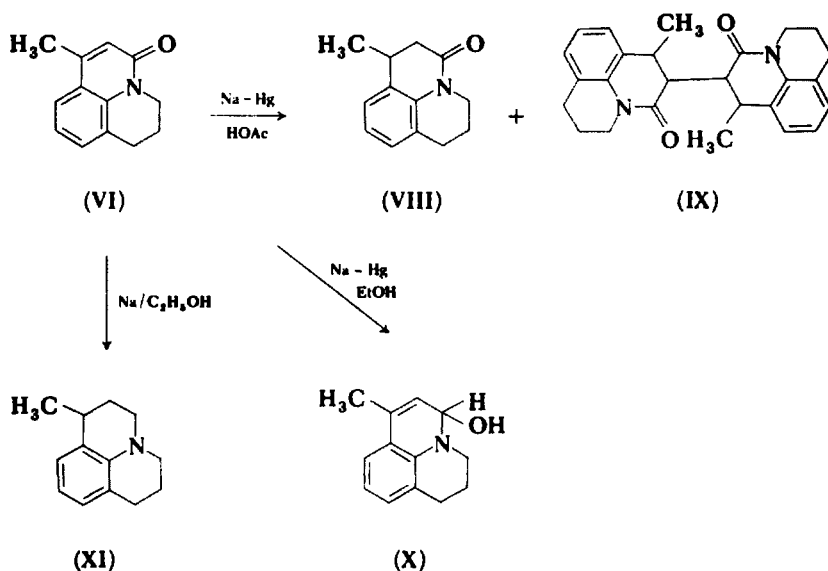
The first examples of this ring system were prepared by Reissert¹ in 1891. Heating 1,2,3,4-tetrahydroquinoline with acetoacetic esters gives,^{1,3-5} at best, about 12% of VI. By employing the modified route shown, Brooker and Heseltine⁶ were able to achieve a yield of about 43% (over-all) of VII. Bromine adds readily to the isolated double bond of VI giving¹ an unstable dibromide, which loses hydrogen bromide to give the 2-bromo derivative of VI. Further bromina-



tion occurs¹ in the benz ring, presumably at position 9, to give the 2,9-dibromo homolog of VI. Nitration of VI gave¹ two isomeric nitro derivatives, presumably the 2- and -9-nitro derivatives of VI. When the 2-position of VI is blocked with an ethyl group, bromination and nitration give⁴ only a single (probably the 9) substitution product. The methyl group of VI can be oxidized to the corresponding aldehyde^{7,8} or acid,⁸ and it may be acylated by oxalic ester to yield the pyruvic ester.⁸ The oxygen in 2-oxojuloline can be replaced by sulfur through the action of phosphorus pentasulfide.⁶

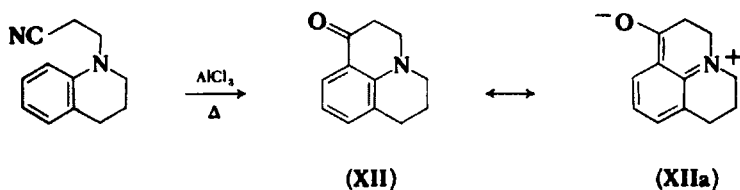
The reduction of VI was studied in some detail by Reissert,³ who found that the action of sodium amalgam in acetic acid gave two products: (A), m. 242°, to which he assigned structure VIII, and (B), a compound $C_{26}H_{28}N_2O_2$, m. 257.5°, which may have structure IX. When VI was reduced with sodium amalgam in ethanol, a product (C, m. 45°), was obtained, and assigned the improbable structure X (although with some misgivings) by Reissert.³ That (C) is actually a racemate of structure VIII was recently demonstrated⁴² when one of the antipodes (m. 70°) was isolated from the degradation of the alkaloid *annotinine*. The structure of Reissert's compound (A) remains obscure, although from the high melting point it would

seem to be dimeric, possibly a form of IX. When VIII was treated³ with bromine, the first product formed was the unstable adduct $C_{13}H_{15}NO \cdot Br_2$, which lost hydrogen bromide to yield a bromo derivative of VIII (probably the 9 isomer), which in turn can form a red dissociable addition product with another mole of bromine. Reissert³ showed that reduction of VI with sodium in ethanol gave methyljulolidine (XI) of unspecified stereochemical configuration.

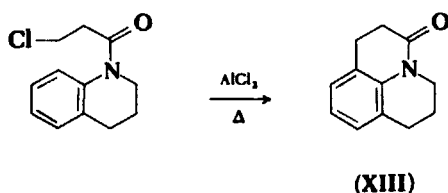


The drastic permanganate oxidation of VI yields,³ chiefly, 2-hydroxylepidine-8-carboxylic acid (XX). Treatment of VI with phosphorus pentachloride produced¹¹ a trimeric purple dye ($C_{39}H_{36}N_3O_3Cl$) named *julol violet*, the nature of which is unknown.

Ring closure of 1-(2-cyanoethyl)-1,2,3,4-tetrahydroquinoline^{2,12} with aluminum chloride, or, in much better yield,² by the action of phosphorus pentoxide upon a xylene solution of the corresponding ethyl ester, leads to XII. This ketone is yellow and forms salts only with strong acids, and these salts dissociate readily. Such properties are perhaps best explained by assuming² that polar forms such as XIIa make a substantial contribution to the resonance hybrid.

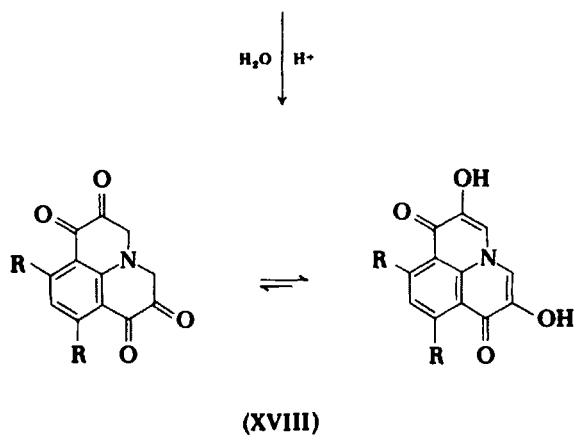
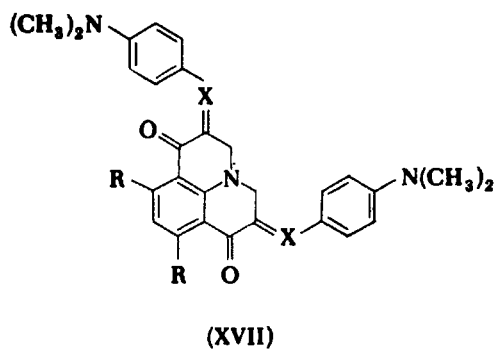
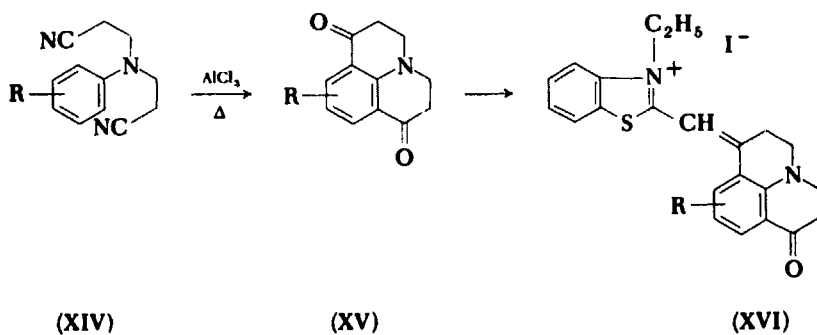


Cyclization of 1-(β-chloropropionyl)-1,2,3,4-tetrahydroquinoline^{9,10} by heating with aluminum chloride affords a good method for the preparation 3-oxojulolidine (XIII).



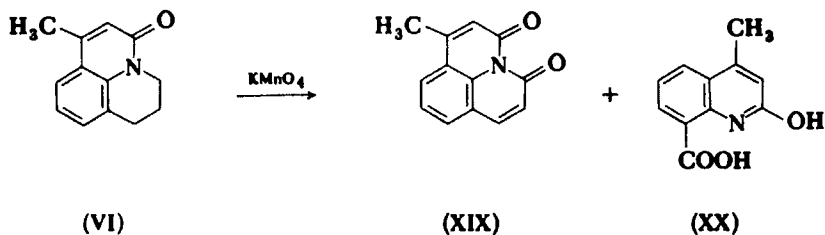
A considerable study has been made by Mann and his co-workers^{2,14,16} of the double cyclization of *N,N*-bis-(2-cyanoethyl)anilines (XIV) to dioxojulolidines (XV). When anilines (XIV, in which R represents H, *m*- or *p*-Cl or *m*-CH₃) are cyclized, yields of diketones (XV) as high as 75% may be attained, but when R = *p*-CH₃ or *p*-OCH₃, the yield of the corresponding XV falls to about 7%. In contrast to the preparation of XII, treatment in xylene with phosphorus pentoxide of the diester corresponding to XIV gave very little XV, although cyclization of the corresponding acid has been claimed.¹³

Compounds of type XV yield carbonyl group derivatives, but do not form stable salts with acids. Nitrosation of XV (R = H) was not successful, although a methyl homolog (XV, R = 8-CH₃) yielded a mononitroso derivative.³⁵ Bromination with *N*-bromosuccinimide, and nitration occurred in the 9-position.⁴⁹ Compound XV, when R = H, failed to condense with the activated methyl groups of lepidine, quinaldine or 2-benzothiazole ethiodides, although this last reagent, under forcing conditions, gave³⁶ a 1:1 condensation product (XVI) with XV (R = 8-CH₃), and both a 1:1 and a 1:2 condensation product could be obtained⁴⁵ from XV (but only when R = H, not CH₃) and malononitrile. Condensation of XV (R = H)³⁵ or its 8,10-dimethyl homolog⁴⁹ with *p*-dimethylamino-

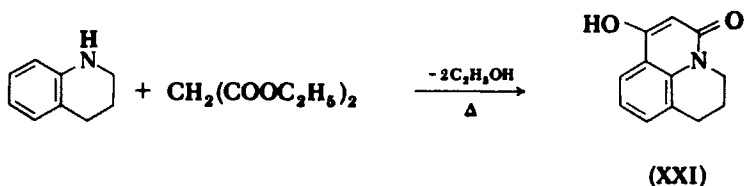


benzaldehyde or with *p*-nitrosodimethylaniline yielded merocyanine dyes of type XVII ($R = H$ or CH_3 , $X = -CH=$ or $-N=$, respectively). Acid hydrolysis of XVII ($X = -N=$) yielded the tetra-ketones XVIII ($R = H$ or CH_3), for which the dienolic structure is suggested by their insolubility and lack of reactivity with *o*-phenylenediamine. With hydrazoic acid, XV yielded⁴⁹ a dilactam (see Section A-897). When XV was subjected to the Fischer indole synthesis, and to the Pfitzinger reaction, the corresponding indolo and quinolo homologs (see Sections A-775 and A-776) were obtained.^{36, 49} Dehydrogenation of XV with palladium charcoal yielded⁴⁹ the $\Delta^{2,3}$ homolog (isojuloline-1,7-dione), which formed stable salts with acids, but only the carbonyl group in the saturated ring reacted with phenylhydrazine or malononitrile.

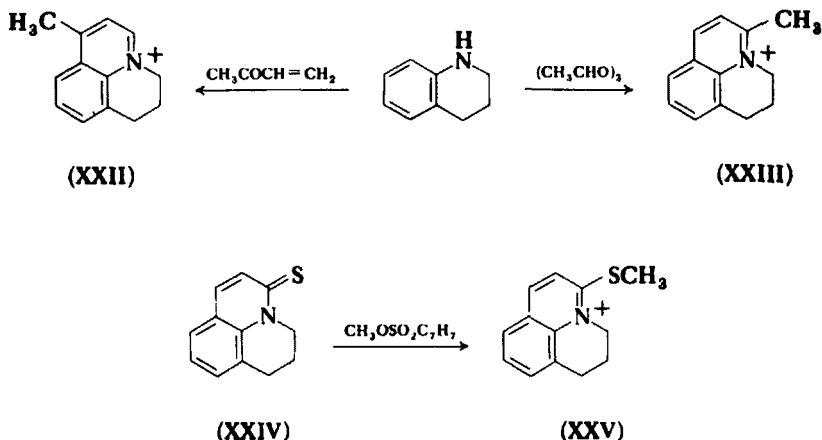
From the oxidation of VI, Reissert³ was able to isolate XIX, and the position of the new carbonyl group was established by evidence that the product did not condense with phenylhydrazine. Also formed, as a result of further oxidation, was XX.



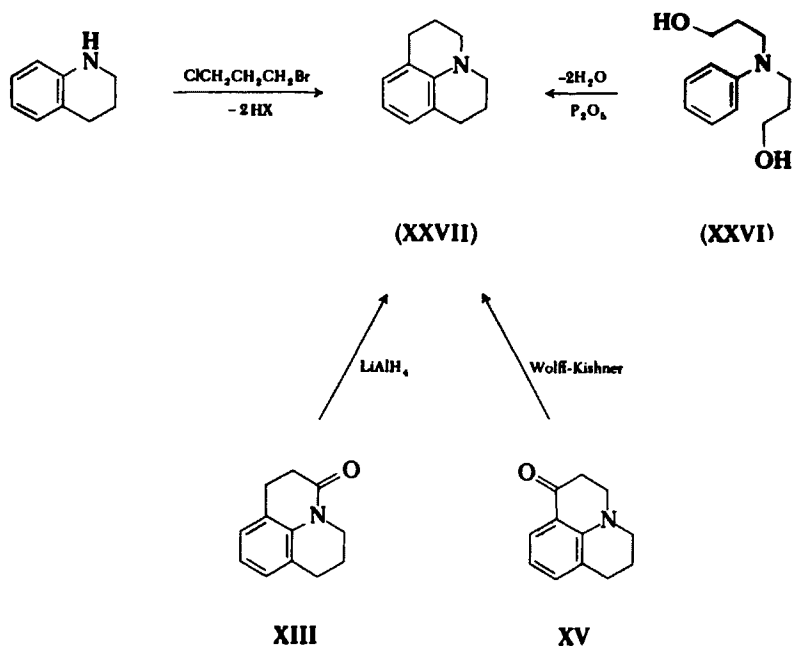
When 1,2,3,4-tetrahydroquinoline was heated with malonic ester, compound XXI was obtained.⁵ The hydroxyl group of XXI can be benzoylated or replaced by chlorine, and treatment of XXI with nitrous acid yields the 2-nitroso derivative. When XXI was refluxed in 50% acetic acid with phenylhydrazine, instead of a phenylhydrazone, an unidentified yellow substance ($C_{12}H_{11}NO_3$, m. 260°)⁵ resulted. A number of azo dyes have been prepared^{31, 47} by coupling diazonium salts into the 2-position of XXI.



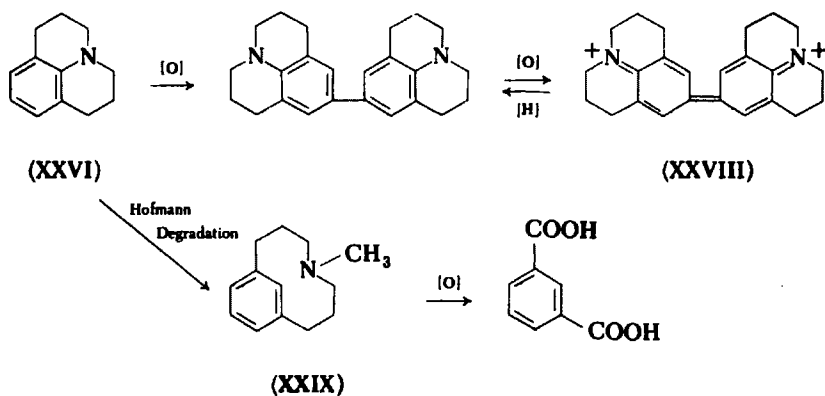
Three methods were devised by Heseltine and Brooker^{6,17,18,37} for the synthesis of quaternary salts of types XII–XXV. Tetrahydroquinoline reacts with methyl vinyl ketone to yield XXII, and with paraldehyde to form the isomeric XXIII. Treatment of XXIV with methyl *p*-toluenesulfonate, followed by sodium iodide, gave XXV.



Julolidine (XXVI) was first prepared by Pinkus,¹⁹ who heated 1,2,3,4-tetrahydroquinoline with trimethylene chlorobromide. Jones and Dunlop³³ employed γ -chloropropyl phenyl ether similarly. The process was subsequently refined^{20,21} so that an 80% yield of XXVI may be achieved. Compound XXVI has also been prepared by the reduction^{9,10} of XIII and of XV,⁴⁹ and by the dehydration²² of XXVII. As might be expected, electrophilic attack (halogenation,²³ nitration¹⁰ and diazonium coupling^{24,40}) occurs at the 9-position of XXVI. Normal Friedel-Crafts acylation of XXVI failed, but formylation and benzoylation by the Vilsmaier-Haack method were successful and gave 9-substituted derivatives. The 9-aldehyde has been condensed with nitromethane, α -picolinium salts²³ and with cyanoacetic ester⁴⁸ to yield vinyl derivatives, and reduced with tin and hydrochloric acid to a product originally thought^{44,50} to contain an anthracene nucleus, but later shown⁵¹ to be a stilbene derivative. Oxidation of this product gave red bis-quaternary salts. Smith and Yu noted²³ the disinclination of 9-bromojulolidine to form a Grignard reagent. A variety of different oxidants convert XXVI, through 9,9'-bijulolidyl, into a "red substance" assigned²³

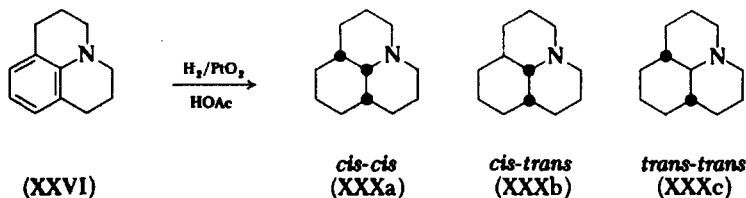


structure XXVIII. The Hofmann degradation of XXVI has been shown²⁰ to yield XXIX, the structure of which in turn was demonstrated by its oxidation²⁵ to isophthalic acid.

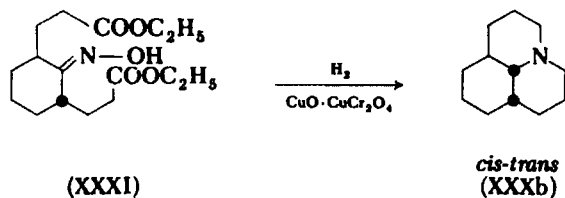


The hydrogenation of XXVI in ethanol, using a Raney nickel catalyst at 200° and 2000 p.s.i., resulted in reduction of the

benzene ring.²⁶ In a more careful study of this reduction, using Adams catalyst, Protiva and Prelog²⁷ isolated two isomeric hexahydrojulolidines, which they suggested were two of the three possible stereochemical modifications of XXX (a-c). By the reductive cycliza-



tion of XXXI, to which they assigned the *trans* configuration shown, Leonard and Middleton²⁸ secured a product identical with the major isomer obtained by Protiva and Prelog.²⁷ Since no change in configuration was expected during the cyclization, it was reasoned that the product must be the *cis-trans* isomer (XXXb). Isomers XXXa

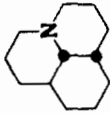
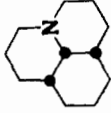


and XXXc are *meso* forms (*ergo* unresolvable), whereas XXXb would be racemic, and capable of resolution. To confirm their configurational assignment, Leonard and Middleton chromatographed their product on a column of D-lactose, and were able to effect a partial, but definite, selective adsorption of the *laevo*-form of XXXb. In view of the *cis* addition of hydrogen to XXVI to give XXXb, it is probable²⁸ that the other isomer concomitantly formed is the *cis-cis* form (XXXa). As expected, no resolution of XXXa, analogous to that of XXXb, could be effected.²⁸

The alkaloid *annotinine* was shown^{41,43,46} to possess the hexahydrojulolidine skeleton.

Derivatives of 3*H*,5*H*-Benzof[*c*,*β*]quinolizine

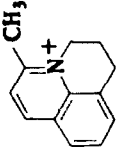
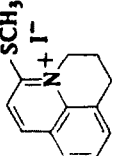
Empirical formula	Substituents or structure	Properties and comments	Refs.
C ₁₂ H ₇ NO ₄	1,2,6,7-Tetrahydro-1,2,6,7-tetraoxo-	Brn., m. ~440°.	35
C ₁₂ H ₉ NO ₂	5,6-Dihydro-1(1 <i>H</i>),7(7 <i>H</i>)-dioxo-	m. 202°. HBr Salt, m. 270° d. Perchlorate, m. 125°; hemiperchlorate, m. 240° d. Methyltoluene- <i>p</i> -sulfonate, m. 180° d. Phenylhydrazine, scarlet, m. 220°.	49
C ₁₂ H ₁₀ ClNO	1-Chloro-6,7-dihydro-3-oxo-	Pink, m. 135°.	5
C ₁₂ H ₁₀ BrNO ₂	9-Bromo-1,2,6,7-tetrahydro-1,7-dioxo-	Golden-yel., m. 208°. Bisphenylhydrazine, yel., m. 270°. 2,6-Dibenzylidene deriv., red, m. 200°.	49
C ₁₂ H ₁₀ ClNO ₂	8-Chloro-1,2,6,7-tetrahydro-1,7-dioxo- 9-Chloro-1,2,6,7-tetrahydro-1,7-dioxo-	Yel., m. 164-5°. Yel., m. 200-1°. Bisphenylhydrazine, yel., m. 283° d.	29 16,49
C ₁₂ H ₁₀ N ₂ O ₃	6,7-Dihydro-1-hydroxy-2-nitroso-3-oxo-	Red, m. 158° d.	5
C ₁₂ H ₁₀ N ₂ O ₄	1,2,6,7-Tetrahydro-9-nitro-1,7-dioxo-	Yel., m. 250°. Bisphenylhydrazine, red, m. 270° d.	49
C ₁₂ H ₁₁ NO	6,7-Dihydro-3-oxo-	m. 102-3°, b ₁ 140-5°.	6,37
C ₁₂ H ₁₁ NS	6,7-Dihydro-3-thiocarbonyl-	m. 152-3°.	6
C ₁₂ H ₁₁ NO ₂	6,7-Dihydro-1-hydroxy-3-oxo- 1,2,6,7-Tetrahydro-1,7-dioxo-	m. >300°, sol. in acids or bases. Yel., m. 145-6°. Bisphenylhydrazine, yel., m. 210-1° (248°). Dioxime, m. 237.5-8.5° d. Dioxime diacetate, yel., m. 192.5° d. Dioxime dibenzoate, m. 175° d. Nitroso deriv., m. 156°.	5 2,13-15, 35,49

$C_{12}H_{11}NO_3$	1,2,6,7-Tetrahydro-9-hydroxy-1,7-dioxo-	Or., m. 258-9° d. Bisphenylhydrazone, <i>yel.</i> , m. 271-2° d. Acetyl deriv., <i>yel.</i> , m. 208.5- 9.5° d. Acetyl deriv. Bisphenylhydra- zone, <i>yel.</i> m. 263° d.	14
$C_{12}H_{12}N_2O_3$	1,2,6,7-Tetrahydro-9-nitro-3-oxo-	m. 155.0-6.5°.	10
$C_{12}H_{13}NO$	1,2,6,7-Tetrahydro-1-oxo-	<i>Yel.</i> , m. 62.5-3.5° (66°), <i>b</i> _{0,9} 143.4°.	2,12
	1,2,6,7-Tetrahydro-3-oxo-	m. 55°, <i>b</i> ₃ 154-7°.	9,10
$C_{12}H_{14}BrN$	9-Bromo-1,2,6,7-tetrahydro-	m. 36.5°, <i>b</i> _{0,15} 135-6.5°.	23
$C_{12}H_{14}N_2O_2$	9-Nitro-	—	23,24
$C_{12}H_{15}N$	1,2,6,7-Tetrahydro- (Julolidine)	m. 40°, <i>b</i> , 105-10°, <i>b</i> _{4,5} 125-7°, <i>b</i> ₁₇ 155- 6°, <i>b</i> ₃₁ 170-3, <i>b</i> ~280°; <i>n</i> _D ²⁵ 1.568; <i>d</i> ₂₀ 1.003. Picrate, m. 174° (173°, 172°, 165°) d. HCl salt, m. 223° (d. 218°). HBr salt, m. 227°. HI salt, d. 219-22°. Me- Chloroplatinate, m. 220° (221°) d. Me- thiodide, m. 186° (d. 181.3°). Styph- nate, m. 172° d. Picrolonate, m. 194°. Sulfate, d. 242°. Monohydrochloride, m. 252° (in sealed, evacuated tube).	9,10,19, 20-23, 26-28 32,33, 49
$C_{12}H_{16}N_2$	9-Amino-1,2,6,7-tetrahydro-		24,30,40
			
$C_{12}H_{21}N$		<i>b</i> ₁₉ 124°; <i>d</i> ₄ ²⁰ 0.9606; <i>n</i> _D ²⁰ 1.50375. Picrate, m. 186-7°. Scyphnate, m. 177°. Picrolo- nate, m. 265-6°. Methiodide, m. 299- 300° d. <i>b</i> _{0,4} 75°; <i>n</i> _D ²⁰ 1.5132. Picrate, m. 222-3°. Picrolonate, m. 245-6° d.	26-28 27,28

(continued)

Derivatives of 3*H*,5*H*-Benzof[*i,j*]quinolizine (*continued*)

Empirical formula	Substituents or structure	Properties and comments	Refs.
C ₁₃ H ₉ NO ₂	1-Methyl-3,5-dioxo-	Yel., m. 245°.	3
C ₁₃ H ₁₁ Br ₂ NO	2,9-Dibromo-6,7-dihydro-1-methyl-3-oxo-	Yel., m. 153°.	1
C ₁₃ H ₁₁ NO ₂	1-Formyl-6,7-dihydro-3-oxo-	m. 149-50°.	7,8
C ₁₃ H ₁₁ NO ₃	1-Carboxy-6,7-dihydro-3-oxo-	m. 230-1° (208-11°). Ethyl ester, m. 147-8°.	6,8,37
C ₁₃ H ₁₂ BrNO	2-Bromo-6,7-dihydro-1-methyl-3-oxo-	m. 178.5°.	1
C ₁₃ H ₁₂ ClNO	1-Chloromethyl-6,7-dihydro-3-oxo-	m. 127-8°.	8
C ₁₃ H ₁₂ N ₂ O ₃	6,7-Dihydro-1-methyl-2 (or 9?)-nitro-3-oxo-	m. 223.8°.	1
	6,7-Dihydro-1-methyl-9 (or 2?)-nitro-3-oxo-	Yel., m. 149°.	1
C ₁₃ H ₁₃ Br ₂ NO	1,2-Dibromo-1,2,6,7-tetrahydro-1-methyl-3-oxo-	Yel., easily loses HBr.	1
C ₁₃ H ₁₃ NO	6,7-Dihydro-1-methyl-3-oxo-	m. 129.8°.	1,3,7,8,11
C ₁₃ H ₁₃ NO ₂	6,7-Dihydro-1-hydroxymethyl-3-oxo-	m. 179-81°.	8
	1,2,6,7-Tetrahydro-8-methyl-1,7-dioxo-	Yel., m. 121-2°. Dioxime, yel., m. 211-2° d. Bisphenylhydrazone, yel., m. 207-8°.	14,16
	1,2,6,7-Tetrahydro-9-methyl-1,7-dioxo-	Yel., m. 151-2°; λ _{max} 228, 305 and 414-20 mμ (ε 32,600, 2,600 and 5,680). Dioxime, yel., m. 218° d. Bisphenylhydrazone, yel., m. 269° d.	14,15
C ₁₃ H ₁₄ BrNO	9-Bromo-1,2,6,7-tetrahydro-1-methyl-6-oxo- (?)	m. 80.5°. Forms red dissociable adduct with Br ₂ , d. ~140°.	3

C ₁₃ H ₁₄ N ⁺					39
			Iodide.		6,18,37
C ₁₃ H ₁₄ INS					6
C ₁₃ H ₁₄ N ₂	9-Cyano-1,2,6,7-tetrahydro-	Golden, m. 119-20°.			23
C ₁₃ H ₁₄ N ₂ S	1,2,6,7-Tetrahydro-9-thiocyano-	m. 93.4°.			23
C ₁₃ H ₁₅ NO	9-Formyl-1,2,3,4-tetrahydro-	m. 83-4°. Oxime, m. 127.8°. <i>p</i> -Nitrophenyl-			23,44,48
	1,2,6,7-Tetrahydro-1-methyl-3-oxo-	hydrazone; blk., m. 254°.			
C ₁₃ H ₁₅ NO ₂	9-Carboxy-1,2,5,7-tetrahydro-	Racemate, m. 45°; <i>d</i> -isomer, m. 70°.			3,42
C ₁₃ H ₁₇ N	1,2,6,7-Tetrahydro-1-methyl-	Yel., m. 240-1°.			23
	1,2,6,7-Tetrahydro-9-methyl-	b. 283-7°. Picrate, yel., d. 130-40°.			3
C ₁₃ H ₁₇ NO	1,2,6,7-Tetrahydro-9-methoxy-	Oil.			19
	1,2,6,7-Tetrahydro-9-hydroxymethyl-	Oil. HCl salt, m. 188° d. Chloroplatinate,			19
C ₁₃ H ₁₈ N ₂	9-Aminomethyl-1,2,6,7-tetrahydro-	m. 209-10°.			
	9-Amino-1,2,6,7-tetrahydro-8-methyl-	m. 50°, unstable. Methiodide, m. 186°.			23
C ₁₄ H ₁₁ NO ₄	1,2,6,7-Tetrahydro-1,2,6,7-tetraoxo-	Unstable. Acetyl deriv., m. 142.5°.			23
C ₁₄ H ₁₂ N ₂ O	1-Cyanomethyl-6,7-dihydro-3-oxo-	DiHCl salt, m. 242-6°.			40
C ₁₄ H ₁₄ N ₂ O ₄	6,7-Dihydro-1-(1-hydroxy-2-nitroethyl)-3-oxo-	Bronze, d. > 330°.			49
		m. 194-6°			8
		m. 189-91° d.			8

(continued)

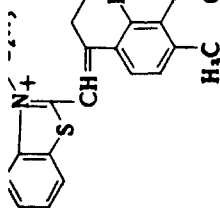
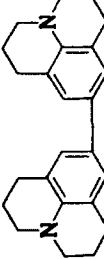
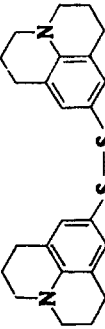
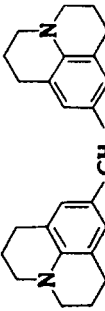
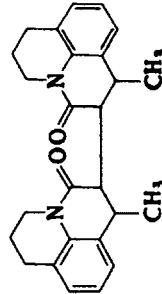
Derivatives of 3*H*,5*H*-Benzof[*i,j*]quinolizine (continued)

Empirical formula	Substituents or structure	Properties and comments	Refs.
C ₁₄ H ₁₅ NO ₂	1,2,6,7-Tetrahydro-8,10-dimethyl-1,7-dioxo-	m. 168-9°. Bisphenylhydrazone, pale yel., m. 230° d. Bis-2,4-dinitrophenylhydrazones, red. Monoxime, pale yel., m. 166° d. Dioxime, pale yel., m. 230°. m. 226°.	45
C ₁₄ H ₁₅ NO ₃	8-Carboxy-1,2,6,7-tetrahydro-1-methyl-3-oxo- 10-Carboxy-1,2,6,7-tetrahydro-1-methyl-3-oxo- 6,7-Dihydro-8-hydroxymethyl-1-methyl-3-oxo- 6,7-Dihydro-10-hydroxymethyl-1-methyl-3-oxo-	d. 205-10°. Methyl ester, m. 88-90°. m. 215°. Oil.	42 42 42 42
C ₁₄ H ₁₅ N ₂ O ₂ C ₁₄ H ₁₅ N C ₁₄ H ₂₀ N ₂	1,2,6,7-Tetrahydro-9-(2-nitrovinyl)-1,2,6,7-Tetrahydro-8,10-dimethyl-9-Amino-1,2,6,7-tetrahydro-8,10-dimethyl-9-(2-Aminoethyl)-1,2,6,7-tetrahydro-	m. 142-3°. Picrate, or.-yel., m. 160°. m. 105°. DiHCl salt, m. 246-8°. Dipicrate, m. 166-7° d.	48 49 40 48
C ₁₅ H ₉ N ₃ O	1(1 <i>H</i>)-Dicyanomethylene-2,3-dihydro-7(7 <i>H</i>)-oxo-	Deep yel., m. 245° d.	49
C ₁₅ H ₁₀ ClN ₃ O	9-Chloro-1-dicyanomethylene-1,2,6,7-tetrahydro-7-oxo-	Dk. red, m. 198°.	45
C ₁₅ H ₁₁ N ₃ O	1-Dicyanomethylene-1,2,6,7-tetrahydro-7-oxo-	Red, m. 178-80°.	45
C ₁₅ H ₁₆ BrNO	9-Bromo-2-ethyl-6,7-dihydro-1-methyl-3-oxo-	m. 140°.	4

$C_{13}H_{16}N_2O_3$	Z-Ethyl-6,7-dihydro-1-methyl-9-nitro-3-oxo-	Yel., m. 168°.	4
$C_{15}H_{16}N_2O_4$	6,7-Dihydro-1-(1-hydroxy-2-nitropropyl)-3-oxo-	m. 167-9°.	8
$C_{16}H_{13}NO$	1-Dicyanomethylene-1,2,6,7-tetrahydro-8-methyl-7-oxo-	Red, m. 180-2°; λ_{max} 469 $m\mu$ (ϵ 12,000).	45
$C_{16}H_{24}N_2O$	 H ₂ NCH(CH ₂)OH <chem>O=C1C=CC2(C=C1)CCC3CCCC3C2</chem>	HCl salt, m. 170-5°.	48
$C_{17}H_{15}NO_2$	1,2,6,7-Tetrahydro-1,7-dioxo-9-phenyl-	Yel., m. 228.5-9.5°. Bisphenylhydrazone, m. 239-40°.	15
$C_{17}H_{17}NO_4$	 CH ₂ COCOOCH ₂ H,	m. 168.0-8.5°. 2,4-Dinitrophenyl hydrazone, m. 129-31°. Oxime, m. 215-8° d. Oxime of corresp. acid, m. 178-82° d.	8
$C_{18}H_{10}ClIN_5$	9-Chloro-1';7-bisdicyanomethylene-1,2,6,7-tetrahydro-	Bra.-purple, m. 210-11°; λ_{max} 523 $m\mu$ (ϵ 15,000).	45
$C_{18}H_{11}N_5$	1,7-Bisdicyanomethylene-1,2,6,7-tetrahydro-	Purple, m. 205°; λ_{max} 512 $m\mu$ (ϵ 9900).	45
$C_{18}H_{17}Cl_2N_3$	1,2,6,7-Tetrahydro-9-(2,5-dichlorophenylazo)-	m. 147-8°.	24
$C_{18}H_{19}N_3O_3S$	9-(4-Sulfophenylazo)-1,2,6,7-tetrahydro-	m. 177-9°.	40
$C_{18}H_{20}N_2O_2$	9-(2-Carboethoxy-2-cyanovinyl)-1,2,6,7-tetrahydro-	m. 190-1°.	48

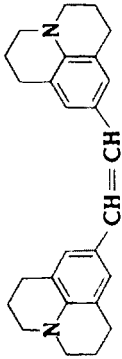
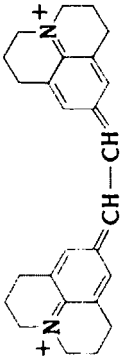
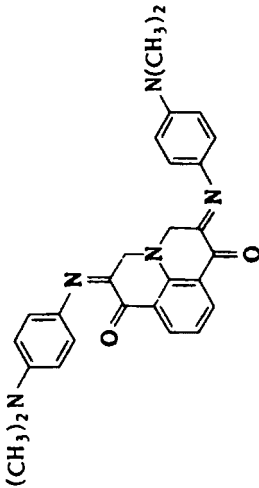
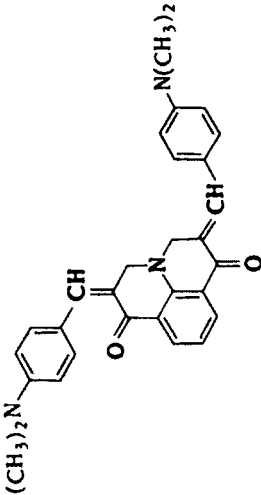
(*continued*)

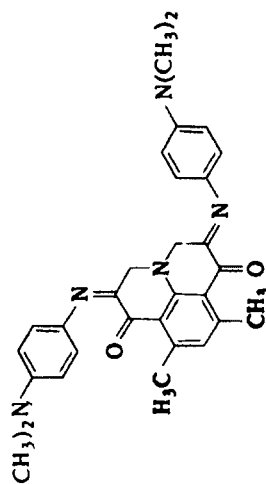
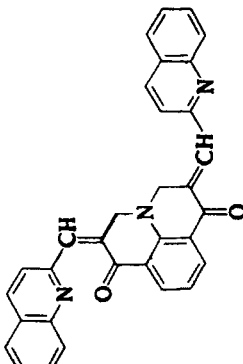
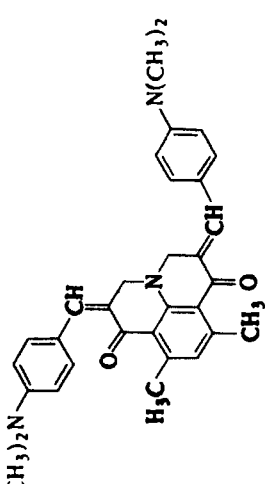
(continued)

$C_{23}H_{15}N_2OS$		Iodide, brn.-red, m. 288°; λ_{max} 523 m μ (ϵ 122,000).	35
$C_{24}H_{15}N_5$	1,7-Bisdicyanomethylene-1,2,6,7-tetrahydro-9-phenyl-	Dk. purple, m. 233°; λ_{max} 529 m μ (ϵ 7000).	45
$C_{24}H_{20}N_2$		m. 207-8° (205-6°); di-HCl salt, m. > 300°; dipicrolonate, m. 193-4°.	23,32
$C_{24}H_{20}N_2S_2$		Yel., m. 185-6° d.	23
$C_{25}H_{30}N_2$		Oil. Dimethiodide, m. 288°.	20
$C_{26}H_{28}N_2O_2$		m. 257.5°.	3

(continued)

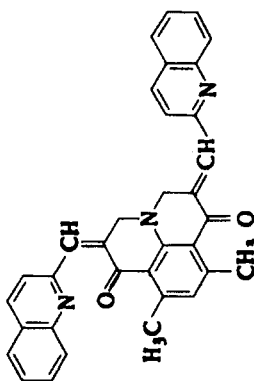
Derivatives of 3*H*,5*H*-Benzol*i*,flquinolizine (*continued*)

Empirical formula	Substituents or structure	Properties and comments	Refs.
$C_{26}H_{30}N_2$		m. 226-8°.	44,50,51
		Chloride, λ_{max} 516 m μ .	44,50,51
$C_{28}H_{27}N_3O_2$		Bl.-purple, m. 277° d., λ_{max} 582 m μ (ϵ 13,000).	35
$C_{30}H_{29}N_3O_2$		Or., m. 247-8°, λ_{max} 409 m μ (ϵ 44,000).	35

$C_{30}H_{31}N_5O_2$		Dk. purple, m. 268° d.	49
$C_{32}H_{21}N_3O_2$		Yel., m. 185°.	49
$C_{33}H_{33}N_3O_2$		Yel., m. 245°.	49

(continued)

Derivatives of 3*H*,5*H*-Benzo[*i,j*]quinolizine (continued)

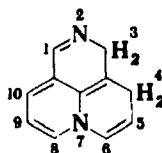
Empirical formula	Substituents or structure	Properties and comments	Refs.
$C_{34}H_{25}N_3O_2$		Yel., m. 225°.	49
$C_{39}H_{36}ClN_3O_3$	"Julole Violet"	Dyes cotton a dirty violet.	11

References

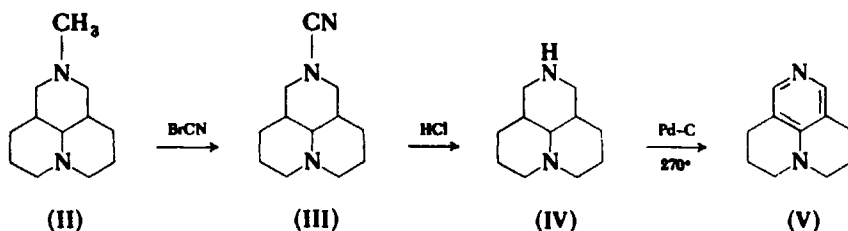
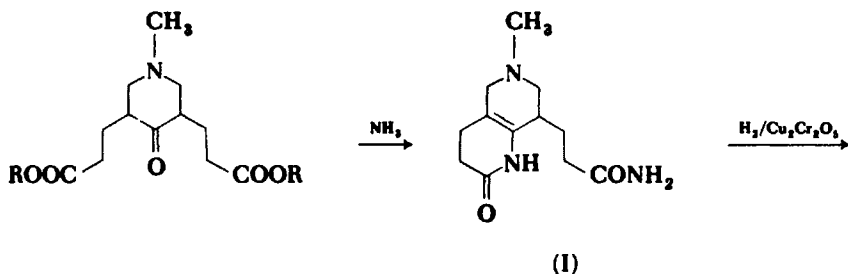
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A-733. 3H,4H-Pyrido[3,4,5-ij]-quinolizine



Ochiai¹ degraded the alkaloid *matrine*^{2,3} to nordehydro- α -matrinidine (V), which was synthesized⁴ as shown. Catalytic hydrogenation of I at high pressures gave II (b_{0.01} 70°, m. 40–2°; mono-

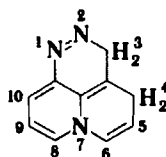


hydrate, m. 74–5°). Demethylation of II gave, via III (m. 51–3°), IV (m. 46–50°; *p*-nitrobenzoyl derivative, m. 116°). Catalytic dehydrogenation of IV yielded V (b_{0.05} 140–160°, m. 62–6°; picrate, m. 222–3°; HBr salt, m. 275°) identical with Ochiai's product.

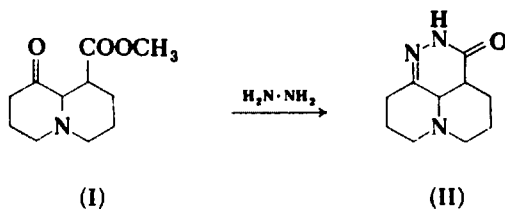
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A-734. 3*H*,4*H*-Pyridazo[*ij*]quinolizine. R.I. 1885

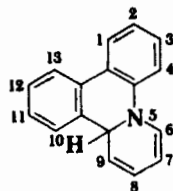


This nucleus has also been named *peri-pyridazopyridocoline*. The sole example (II, m. 137°) was obtained by Clemo, Morgan and Raper¹ from the reaction of I with hydrazine.

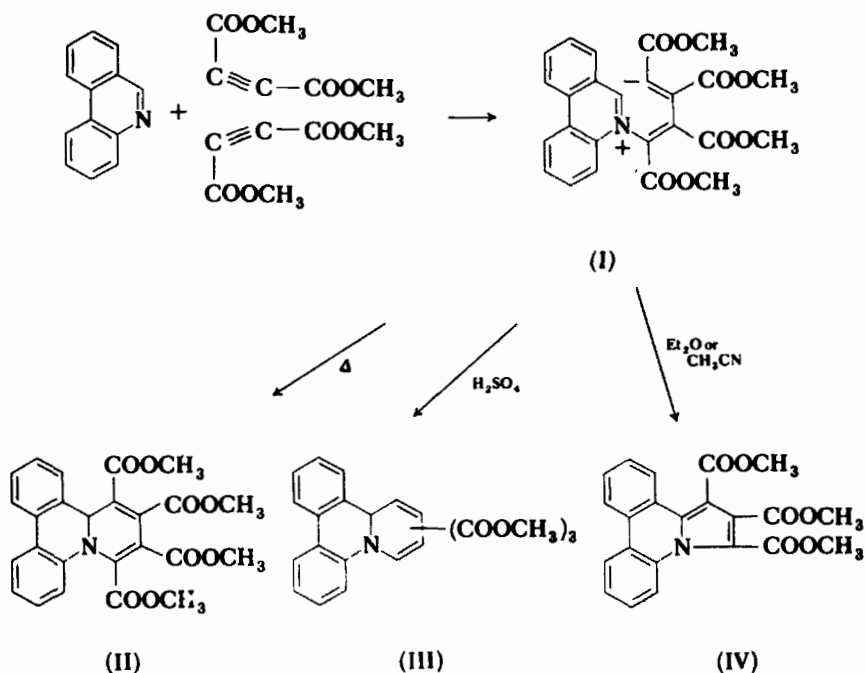


Reference

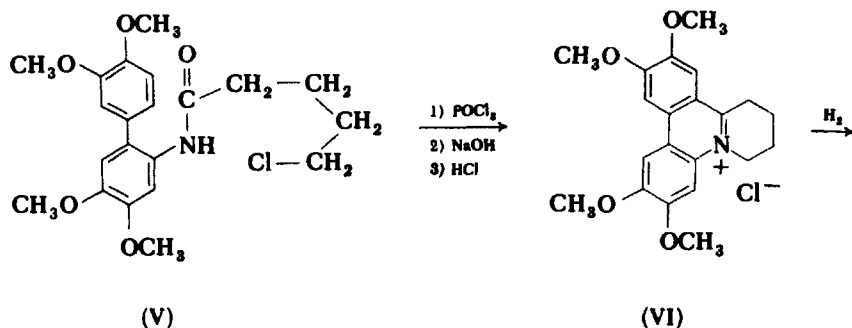
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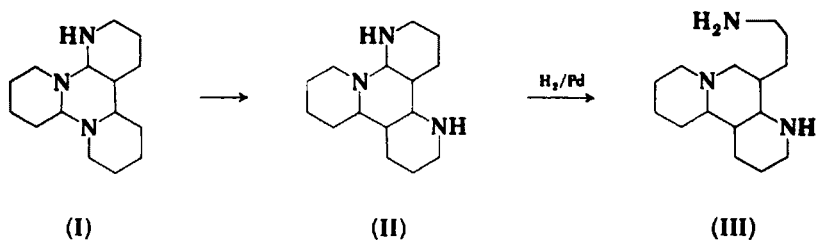
A-735. 9aH-Pyrido[1,2-f]phenanthridine

Only two syntheses of this ring system have been described. By permitting phenanthridine to condense with acetylene dicarboxylic ester, Diels and Thiele¹ obtained the "labile adduct" I, which when heated in quinoline, gave the "stable adduct" II (red, dichroic, m. 245°d.). Treatment of I with sulfuric acid produced III (light orange, m. 184°), while ether or acetonitrile converted I into IV (see Section A-216).



Sugasawa and Ohki² obtained VI by treating V with POCl_3 to form the ω -chlorobutylphenanthridine intermediate, which cyclized when heated in toluene. Compound VI (yellow, d. 223–4°; picrate, yellow, d. 220–1°; iodide, d. 228–30°) was reduced to VII (m. 156°; picrate, d. 212°; methiodide, d. 202–3°).

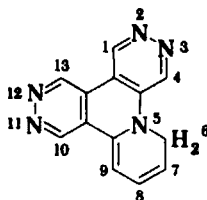




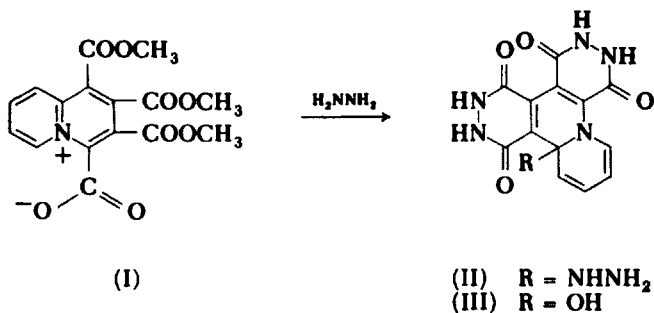
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A-737. 6H-Dipyridazo[4,5-a,4',5'-c]-quinolizine. R.I. 2639



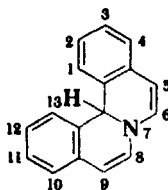
Diels and Alder¹ obtained compound II (golden, m. > 350°) by treating I (see Section A-721) with hydrazine. Heating II with hydrochloric acid produced III.



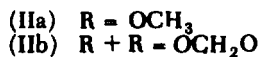
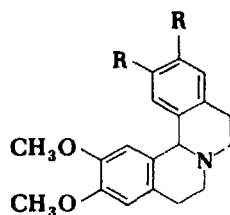
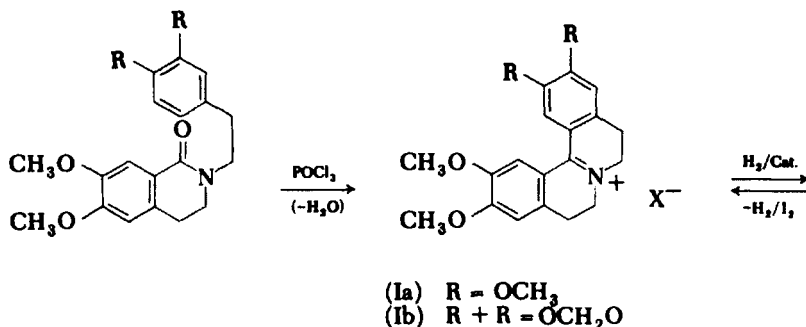
Reference

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A-738. 13*b*H-Dibenzo[*a,h*]quinolizine.
R.I. 2710M, 2710R

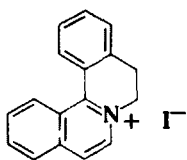


Several compounds containing this ring system were prepared by Sugawara and Kakemi.¹⁻³ Compound Ia ($R = \text{OCH}_3$, $X = \text{I}^-$, yellow, m. 195°) is reduced to IIa ($R = \text{OCH}_3$, m. 116° ; HCl salt, m. $236-7^\circ$; HI salt, m. 207°), which has also been named as a

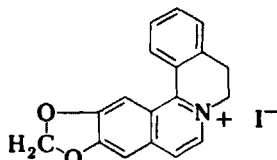


tetramethoxy - 3,4,5,6 - tetrahydro[1'.2':1.2; 1''.2'':7.8 - Dibenzoquinolizine]. The closely related salt Ib ($R + R = \text{OCH}_2\text{O}$; $X = \text{I}^-$, yellow, m. $188-9^\circ$; $X = \text{Cl}^-$, yellow, m. 150°) and IIb ($R + R = \text{OCH}_2\text{O}$ m. $101-2^\circ$; HCl salt, m. $219-220^\circ$; HI salt, m. 209° .d.; MeI, m. $199-200^\circ$; picrate, d. $176-7^\circ$) have been named as derivatives of 14*b*H-benzo[*a*][1,3]benzodioxolo[5,6-*h*]quinolizine, assigned Ring Index Numbers 3051R and

3051M. By analogous methods, compounds III (m. 155° anhydr., or 120°)⁵ (d. $116-7^{\circ}$)⁴ and IV (d. $178-9^{\circ}$)⁴ were obtained. Catalytic reduction of III gave⁵ the corresponding tetrahydrodibenzoquinolizine (oil; HCl salt, m. 207° ; picrolonate, yellow, m. 169°).

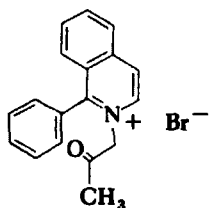


(III)

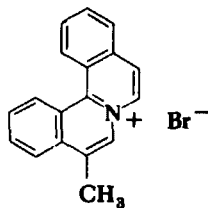


(IV)

The attempted⁶ cyclodehydration of V to VI was unsuccessful, and the failure was attributed to inability of the system to attain coplanarity because of interference between the hydrogen atom in the



(V)



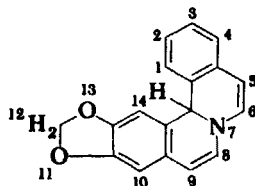
(VI)

8-position of the quinoline ring and those in the *ortho* positions of the phenyl ring.

References

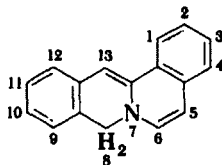
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- A-739. 14*b*H-Benzo[*a*][1,3]-benzodioxolo[5,6-*h*]quinolizine.**
R.I.3051M

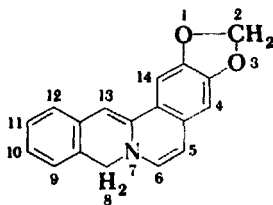


SeeSectionA-738.

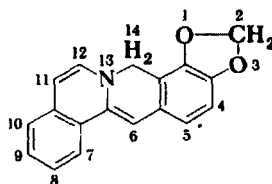
- A-740. 8*H*-Dibenzo[*a,g*]quinolizine.**
R.I. 2703 and 2704



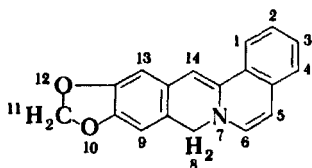
Other closely related systems which may be grouped under this heading are 8*H*-benzo[*g*][1,3]benzodioxolo[5,6-*a*]quinolizine (I, *R.I.* 3051), 14*H*,-[1,3]dioxolo[*h*]isoquinolo[2,1-*b*]isoquinoline (II, *R.I.* 3052), 8*H*-benzo[*a*][1,3]benzodioxolo[5,6-*g*]quinolizine (III, *R.I.* 3050) and 4*H*-[1,3]dioxolo[*g*]-1,3-dioxolo[7,8]isoquinolo[3,2-*a*]-isoquinoline (IV, *R.I.* 3467).



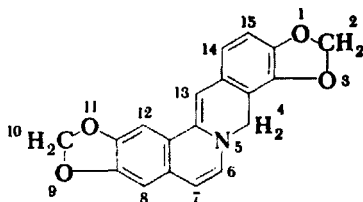
(I)



(II)



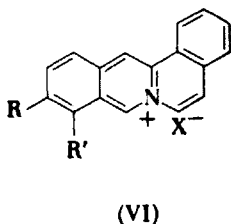
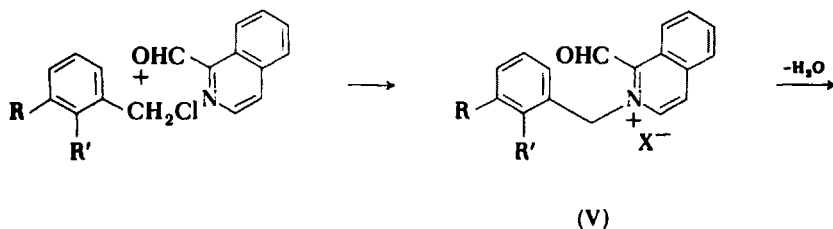
(III)



(IV)

Numerous alkaloids, such as *berberine*, *palmatine*, *corydaline*, *coptisine*, etc., having a wide distribution throughout many genera of the Papaveraceae, Berberidaceae, Anonaceae, Menispermaceae, Rutaceae and Ranunculaceae, are known to contain these nuclei. An extensive literature concerning these alkaloids has accumulated, and apparently these nuclei have been studied almost exclusively in connection with alkaloid research. In view of these facts, and because of the existence of excellent recent reviews^{1,2} of these alkaloids, no further discussion of them will be given.

Recently, by cyclizing benzylisoquinolinium salts of type V, Bradsher and Jones³ prepared dibenzo[*a,g*]quinolizinium compounds of structure VI ($R = R' = H$, $X = Br$, yellow, m. 257–8°, $X = ClO_4$,



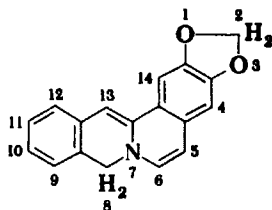
reddish, m. 234–5°, $X = \text{picrate}$, m. 277°; $R = OCH_3$, $R' = H$, $X = Br$, yellow, m. 235°d., $X = ClO_4$, yellow, m. 276°d., $X = \text{picrate}$, m. 283°d.; $R = R' = OCH_3$, $X = ClO_4$, orange-brown, m. 265–7°, $X = \text{picrate}$, m. 212°; $R + R' = OCH_2O$, $X = Cl$, red, m. 309°, $X = ClO_4$, red, m. 318–20°, $X = \text{picrate}$, m. 274–5°). The ultraviolet spectra of these salts were reported.

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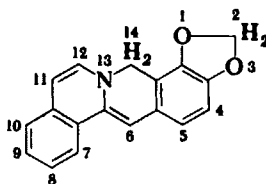
2. Henry, *The Plant Alkaloids*, 4th Ed., The Blakiston Co., Philadelphia, 1949, pp. 297-306; 333-46, etc.
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A-741. 8H-Benzo[g][1,3]benzodioxolo-[5,6-a]quinolizine. R.I. 3051



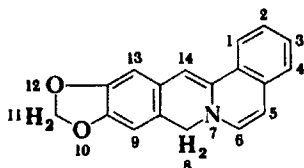
and

A-742. 14H-[1,3]Dioxolo[h]isoquinolo-[2,1-b]isoquinoline. R.I. 3052



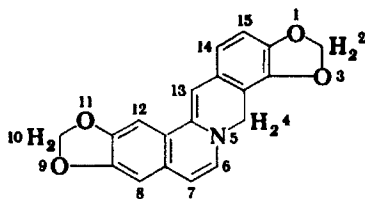
and

A-743. 8H-Benzo[a][1,3]benzodioxolo-[5,6-g]quinolizine. R.I. 3050



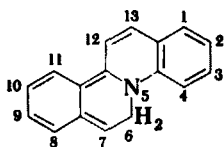
and

A-744. 4H-[1,3]Dioxolo[g]-1,3-dioxolo-[7,8]isoquino[3,2-a]isoquinoline. R.I. 3467

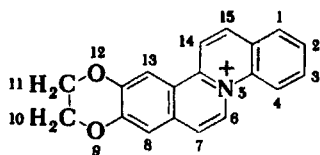


See Section A-740.

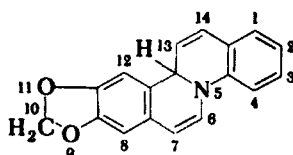
A-745. 6H-Dibenzo[*a,f*]quinolizine.
R.I. 2708-9



This ring system has also been named *5,8,9,14-dibenzopyridocoline*. Other closely related nuclei which will be considered under this heading are *benzo[*a*]-*p*-dioxino[4,5]benzo[*f*]quinolizinium* (I, *R.I.* 3264) and *12bH-benzo[*f*][1,3]benzodioxolo[5,6-*a*]quinolizine* (II, *R.I.* 3050M and 3050R).

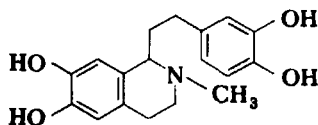


(I)

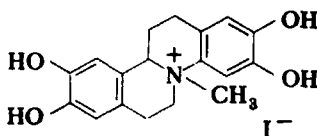


(II)

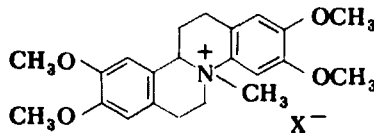
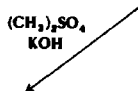
The first synthesis of this nucleus was accomplished by Sugasawa and Yoshikawa^{1,2} who treated *dl*-homolaudanoline (III) with mild oxidizing agents (chloranil¹ or aniline hydrochloride²) in acetic acid solution, and obtained IV (yel.-brn., m. 253-4°). Compound



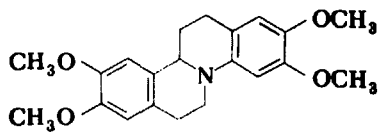
(III)



(IV)

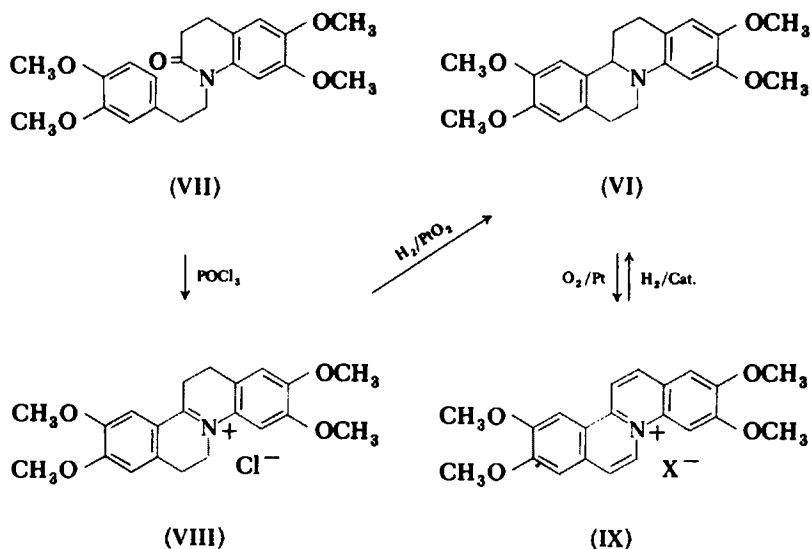


(V)



(VI)

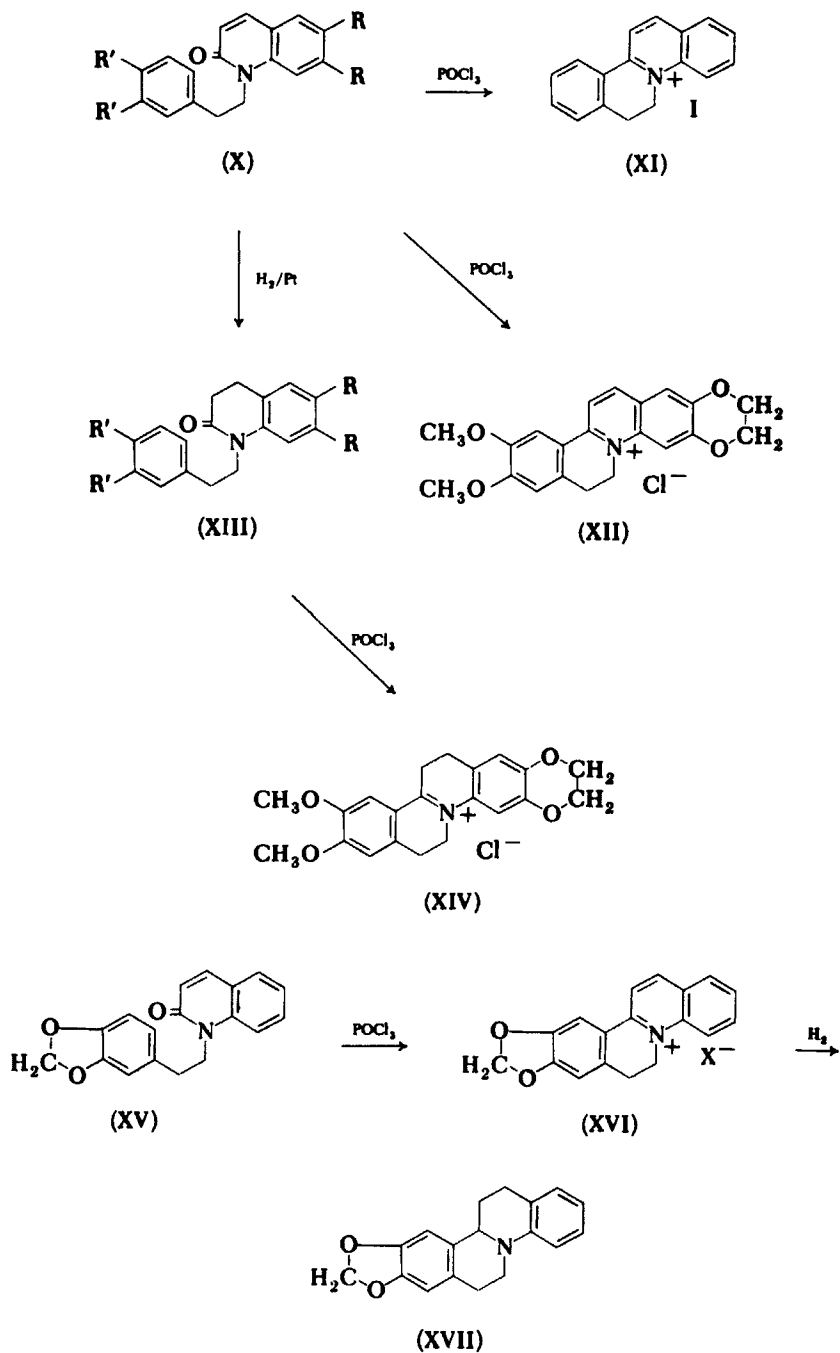
IV was methylated to V ($X = \text{Cl}$, yel. m. 216° ³ or d. $204-5^\circ$ ^{1,2}; $X = \text{I}$, yel. d. $237-8^\circ$) and this ($X = \text{Cl}$) was pyrolyzed to VI (m. $153.5-4.5^\circ$; hydrochloride, d. $236-7^\circ$).^{1,2,4-6} An alternative preparation of VI has been accomplished from VII, via VIII (yel., d. 228°).⁴⁻⁶ Treatment of an alcoholic solution of VI, in the presence of platinum black, with air (oxygen) gave IX ($X = \text{Cl}$, d. $231-2^\circ$; $X = \text{I}$, d. $279-80^\circ$),⁴⁻⁶ catalytic reduction of which yielded VI.



Sugasawa was unable to cyclize X ($R = R' = \text{H}$) to XI, but recently Akahoshi⁸ has reported the preparation of XI (d. $185-6^\circ$) in this manner. When $R' = \text{OCH}_3$ and $R + R' = \text{OCH}_2\text{CH}_2\text{O}-$, compound X was reported⁷ to yield XII (yel., m. $267-8^\circ$). Catalytic reduction of X to XIII followed by cyclization gave XIV (yel., d. $229-30^\circ$)⁷, but preparation of the dihydro analog of XI from XIII ($R = R' = \text{H}$) failed.⁷

Cyclodehydration of XV has been stated⁸⁻¹⁰ to yield XVI ($X = \text{I}$, yel., m. 254° d.), which was reduced to XVII (hydrochloride, m. 227°). This type of ring closure is a variation of the Bischler-Napieralski reaction, which has recently been reviewed.¹¹

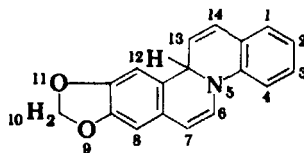
Compound V ($X = \text{Cl}$) has been reported³ to resemble curare in pharmacodynamic action.



References

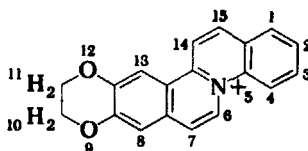
1. Sugasawa and Yoshikawa, *J. Chem. Soc.*, **1933**, 1583.
2. Sugasawa and Yoshikawa, *J. Pharm. Soc. Japan*, **54**, 305 (1934); *Chem. Abstracts*, **29**, 169 (1935).
3. Usizima, *Japan. J. Med. Sci. IV Pharmacol.*, **11**, No. 2/3; *Proc. Japan. Pharmacol. Soc.*, **12**, 221 (1938); *Chem. Abstracts*, **34**, 7426 (1940).
4. Sugasawa and Kakemi, *Proc. Imp. Acad. (Tokyo)*, **14**, 214 (1938); *Chem. Zentr.*, **II**, 3929 (1939); *Chem. Abstracts*, **32**, 8421 (1938).
5. Sugasawa and Kakemi, *Ber.*, **71**, 1860 (1938).
6. Kakemi, *J. Pharm. Soc. Japan*, **60**, 2 (1940); *Chem. Abstracts*, **34**, 3747 (1940).
7. Sugasawa, *J. Pharm. Soc. Japan*, **57**, 1023 (English translation p. 296) (1937); *Chem. Zentr.*, **II**, 1409 (1938); *Chem. Abstracts*, **32**, 3402 (1938).
8. Akahoshi, *J. Pharm. Soc. Japan*, **72**, 1277 (1952); *Chem. Abstracts*, **47**, 10540 (1953).
9. Sugasawa and Sugimoto, *Proc. Imp. Acad. (Tokyo)*, **15**, 49 (1939); *Chem. Zentr.*, **II**, 3088 (1939); *Chem. Abstracts*, **33**, 5401 (1939).
10. Sugasawa and Sugimoto, *Ber.*, **72**, 977 (1939).
11. Whaley and Govindachari in Adams *et al.*, *Organic Reactions*, J. Wiley and Sons, Inc., New York, 1951, Vol. VI, pp. 74ff.

A-746. 12*bH*-Benzo[*f*][1,3]benzodioxolo[5,6-*a*]quinolizine. R.I. 3050M



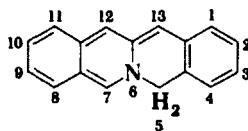
and

A-747. Benzo[*a*]-*p*-Dioxino[4,5]benzo[*f*]quinolizinium. R.I. 3264



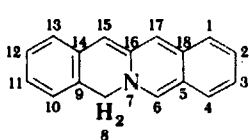
See Section A-745.

A-748. 5*H*-Dibenzo[*b,g*]quinolizine. R.I. 2697

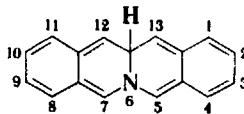


For this nucleus the trivial name *paraberine* and the numbering system shown in I have also been proposed.¹ The tautomeric 12*aH*-

dibenzo[b,g]quinolizine (II, *R.I.* 2697H) has been called *1',6'-2,3,1'',6,7-dibenzopyridocoline* and *1'.6':2.3; 1''.6'':6.7-dibenzoquinolizine*.

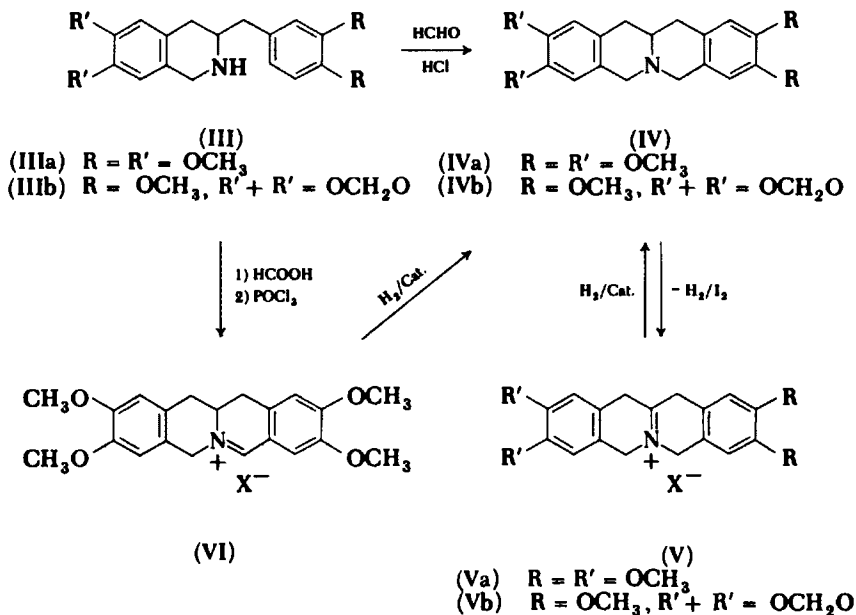


(I)



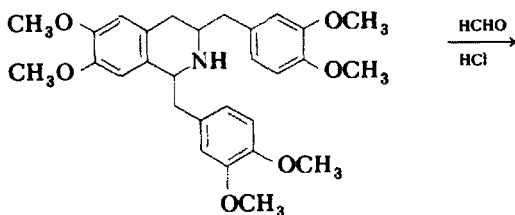
(II)

Treatment of III with formaldehyde and hydrochloric acid yielded IV (IVa, m. 283–4°d.; HCl salt, yel., m. 272°d.; methiodide, lt. yel., d. 266°)^{2,3,4,8} (IVb, m. 221–2°; HCl salt, m. 236–8°; picrate, yel., m. 199–201°d.; methiodide, m. 268°; methochloride, m. 260°d.),¹ and oxidation of IV with iodine afforded V (Va, X = I, yel., m. 255–6°; Vb, X = I, lt. yel., m. 255–6°; X = Cl, yel., m. 120°). The double bond thus introduced was originally¹ placed at either the 12-12a or 12a-13 positions, but the structure (V) shown is probably³ correct for the salts. Formylation of IIIa followed by cyclodehydration yielded³ VI (X = Cl⁻, d. 272°; X = I⁻, yel., m. 190–2°), which was reduced to IVa. Compound IVa was also pre-

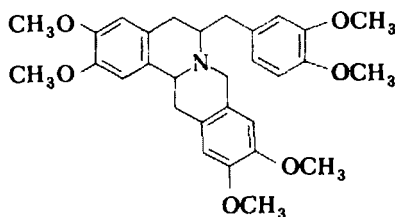


pared⁸ by treating diveratylmethylaniline with formaldehyde in acid solution.

When VII was treated with formaldehyde and hydrochloric acid a crude product was obtained, which may be a mixture of VIII and IX, but from which only IX (lt. yel., m. 172°)³ was isolated in pure condition. The structure of IX was demonstrated by its synthesis from X via XI (X = I⁻, yel., d. 183–4°).³

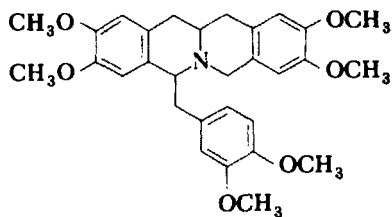


(VII)

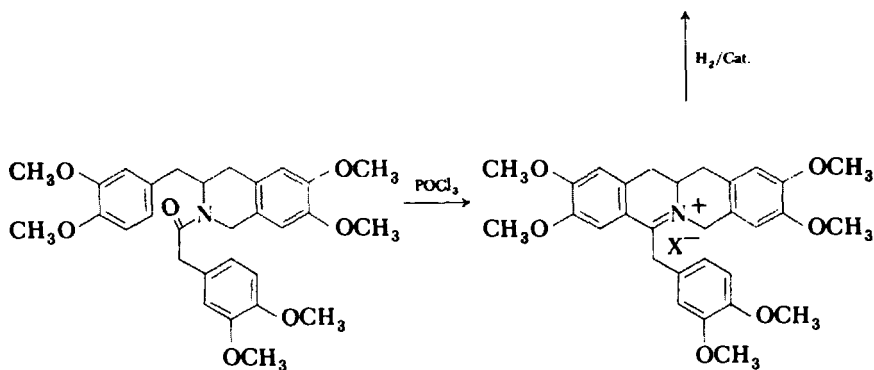


(VIII)

and/or



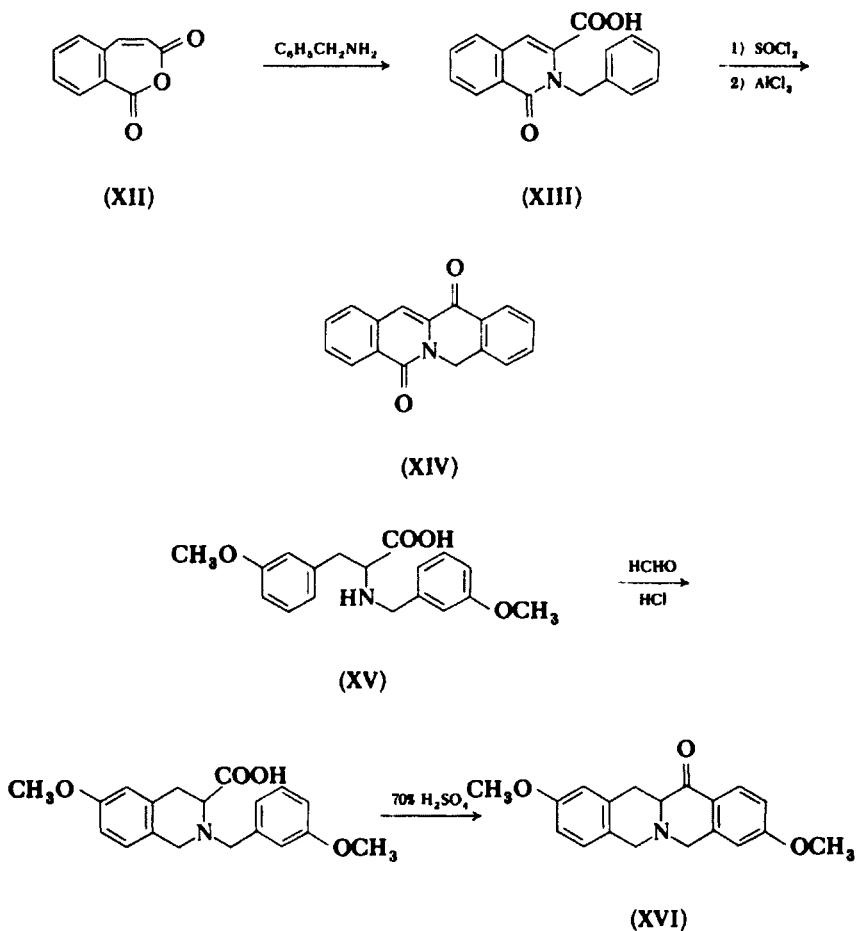
(IX)



(X)

(XI)

The reaction⁵ of XII with benzylamine yielded XIII, which was cyclized to XIV (m. 189°; oxime, m. 360°). A closely related compound XVI (semicarbazone, m. 250–2°d.) was obtained⁶ from XV.



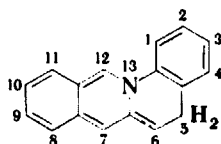
The Pictet-Spengler synthesis, by which many of the dibenzo-*b*,*g*-quinolizines were made, has been reviewed.⁷

References

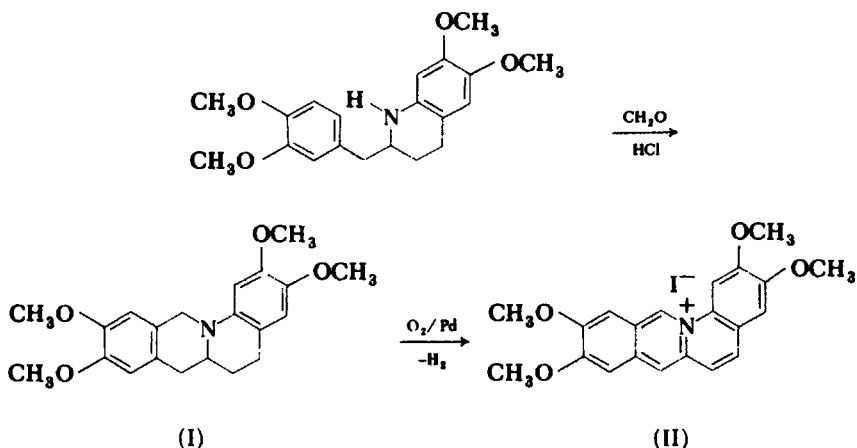
1. Campbell, Haworth and Perkin, *J. Chem. Soc.*, **1926**, 32.
2. Sugawara, Kakemi and Kazumi, *Proc. Imp. Acad. (Tokyo)*, **15**, 223 (1939); *Chem. Abstracts*, **33**, 8617 (1939).
3. Sugawara, Kakemi and Kazumi, *Ber.*, **73**, 782 (1940).

4. Sugasawa and Kakemi, *J. Pharm. Soc. Japan*, **60**, 11 (1940); *Chem. Abstracts*, **34**, 3748 (1940).
5. Chakravarti and Ganapati, *J. Annamalai Univ.*, **3**, 208 (1934); *Chem. Zentr.*, **I**, 1713 (1935); *Chem. Abstracts*, **29**, 1094 (1935).
6. Chakravarti and Rao, *J. Chem. Soc.*, **1938**, 172.
7. Whaley and Govindachari in Adams *et al.*, *Organic Reactions*, J. Wiley and Sons, Inc., New York, 1951, Vol. VI, p. 151.
8. Sugasawa and Tachikawa, *Pharm. Bull. (Japan)*, **2**, 297 (1954); *Chem. Abstracts*, **50**, 1017 (1956).

A-749. 5H-Dibenzo[*b,f*]quinolizine

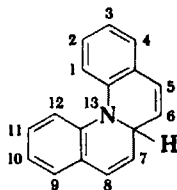


In the course of his studies on the dibenzoquinolizines, Sugasawa¹ prepared compound I (HCl salt d. 80°). When a solution of the hydrochloride of I in ethanol was treated with air in the presence of a palladium catalyst, and the resulting hydrochloride was converted into the iodide, an orange-red material, m. 235°¹ (227–8°)² thought to be II was obtained.

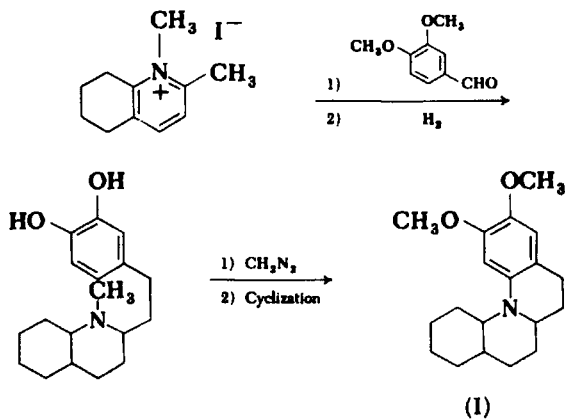


References

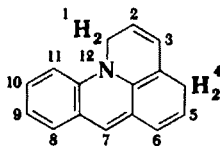
1. Sugasawa, Kodama and Inagaki, *Ber.*, **74**, 455 (1941).
2. Sugasawa, Kodama and Inagaki, *Proc. Imp. Acad. (Tokyo)*, **16**, 473 (1940); *Chem. Abstracts*, **35**, 1789 (1941).

A-750. 6aH-Dibenzo[c,f]quinolizine

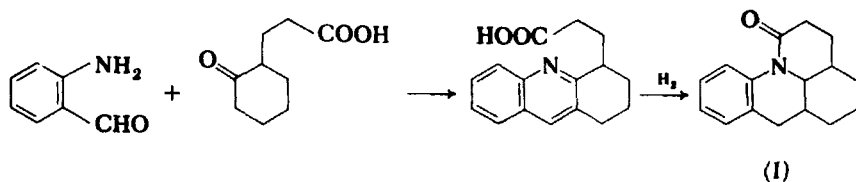
Partly to investigate the hypothesis¹ that derivatives of this nucleus were much less stable than those of the other dibenzoquinolizines, compound I (yellow oil) was prepared as shown by Sugasawa and Sugimoto.²

*References*

1. Sugasawa, Kodama and Inagaki, *Ber.*, **74**, 455 (1941).
2. Sugasawa and Sugimoto, *J. Pharm. Soc. Japan*, **63**, 127 (1943); *Chem. Abstracts*, **45**, 5169 (1951).

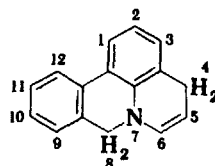
**A-751. 1H,4H-Pyrid[3,2,1-de]acridine.
R.I. 2712**

The sole example of this nucleus (which might also be called *dibenzo[c,ij]quinolizine*) is the lactam I, prepared by Lions.¹ No physical properties were disclosed for I beyond stating that it gave a positive Otto reaction (the red color produced by strychnine and many other compounds when a little potassium bichromate is added to their solutions in 60% sulfuric acid).

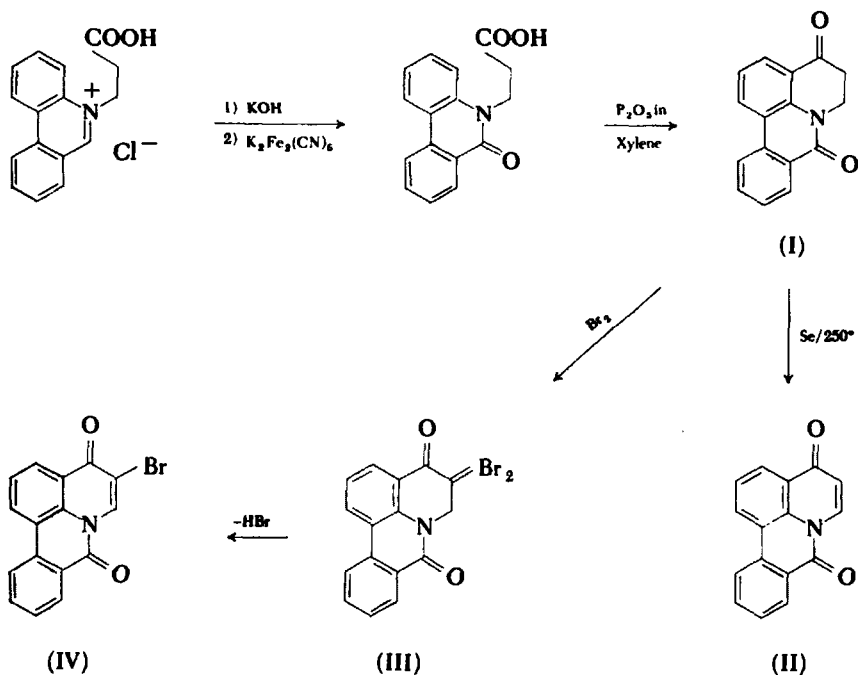


Reference

1. Lions, J. *Proc. Roy. Soc. N.S. Wales*, **71**, 192 (1938); *Chem. Zentr.*, **II**, 1958 (1938); *Chem. Abstracts*, **32**, 5843 (1938).

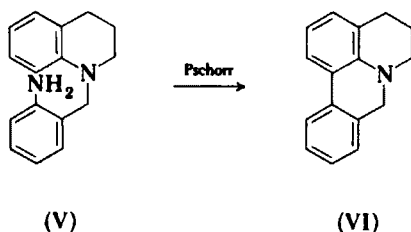
A-752. 4*H*,7*H*-Dibenzo[*b*,*ij*]quinolizine

As an outgrowth of one facet of his work on the structures of *Höchst Yellows I* and *R* and related dyes (see Section A-210 and A-260), deDriesbach¹ prepared compound I (m. 238°, benzal derivative, m. 221°). Dehydrogenation of I with selenium at 250° for



several days gave II (m. 269°), which does not react with phenylhydrazine and is stable to hot caustic solutions. Treatment of I in chloroform solution with bromine gave III (brown, m. 274°), which, when warmed with pyridine, lost hydrogen bromide to yield IV (m. 277°).

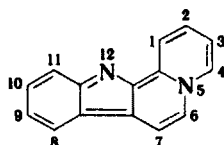
The Pschorr reaction was used² to prepare VI (oil, HClO_4 salt, m. 275°) from V.



References

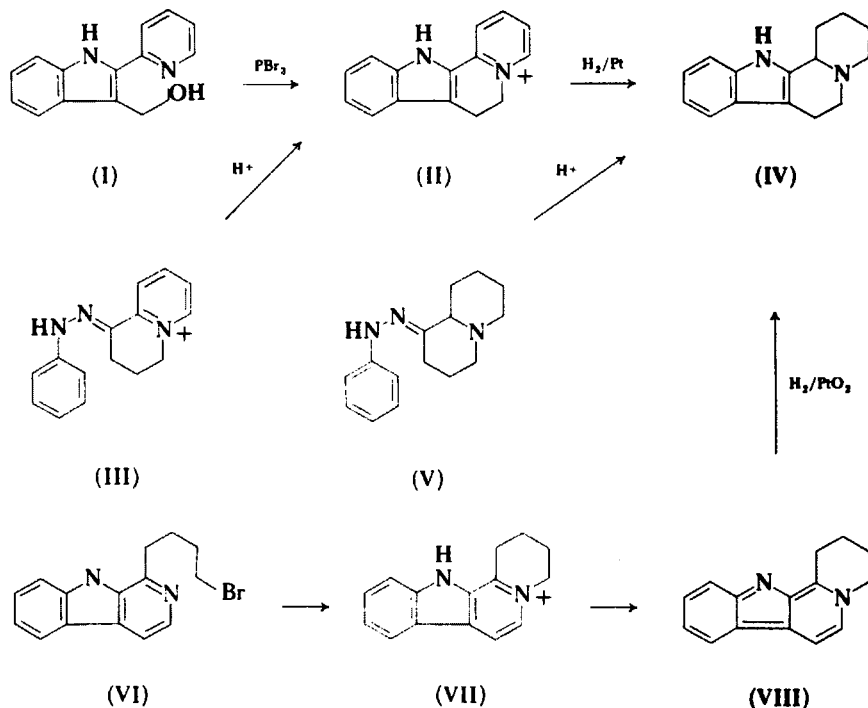
1. deDiesbach and Aeschbach, *Helv. Chim. Acta*, **28**, 1392 (1945).
2. Patel and Patel, *Indian J. Pharm.*, **18**, 334 (1956); *Chem. Abstracts*, **51**, 11351 (1957).

A-753. Indolo[2,3-a]quinolizine. R.I. 2420

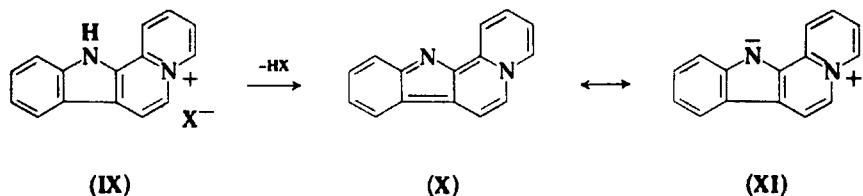


Interest in this nucleus derives chiefly from its presence as rings A, B, C and D of the *yohimbine* alkaloids and their relatives (e.g., *serpentine*, *alstonine*, *ajmaline*, etc.). These alkaloids have recently been reviewed,¹⁻³ and as most of the work upon this ring system is directed towards their synthesis, no complete listing of products has been attempted here, and only a few representative references and compounds are discussed.

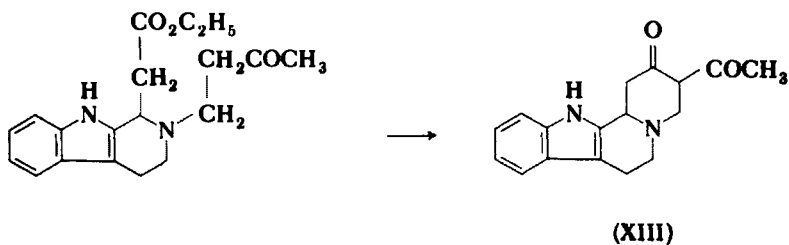
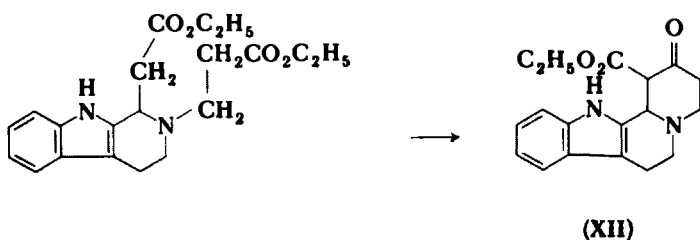
Cyclization of I yielded⁴ II, which was also obtained^{5,6} by the Fischer indole reaction from III. Reduction of II produced⁴ IV, which was also prepared⁷ by the Fischer indole reaction upon V. The conversion of VI into VII followed by treatment with base yielded⁸ the yellow product VIII, which also could be reduced to IV.



Dehydrogenation of II with acidic palladium charcoal⁵ or with tetrachloro-*o*-quinone⁶ produced salts of structure IX, which were converted by the action of base into the prototype of this nucleus, which may be written as X, although some evidence favors a large contribution to the resonance hybrid by the dipolar form XI. The same type of dipolar structure, of course, may participate in the case of compound VIII.



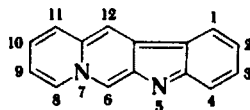
The Dieckmann cyclization has been employed⁹ to prepare the ketones XII and XIII.



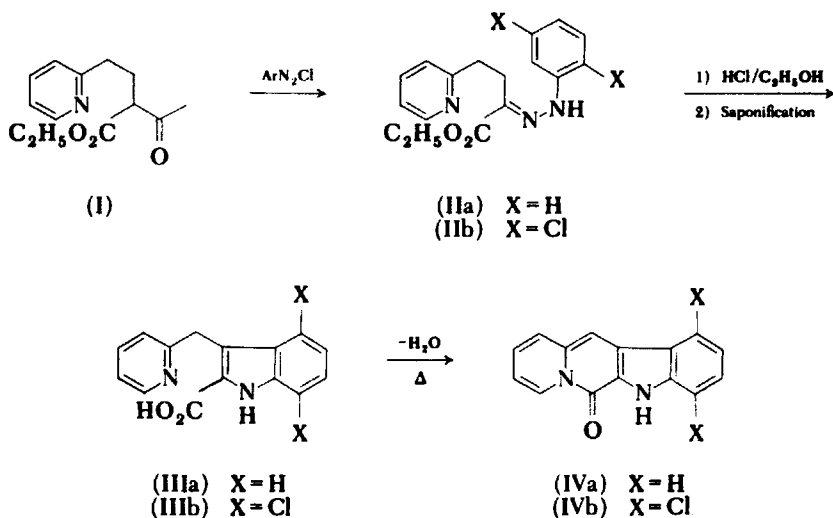
References

1. Manske and Holmes, *The Alkaloids*, Academic Press Inc., New York, 1952, Vol. 2, pp. 424ff.
2. Henry, *The Plant Alkaloids*, 4th Ed., The Blakiston Company, Philadelphia, 1949, pp. 716ff, 762ff.
3. Boekelheide and Prelog, "Indole Alkaloids," in Cook, *Progress in Organic Chemistry*, Vol. 3, Academic Press Inc., New York, 1955, p. 218.
4. Sugawara, Terashima and Kanaoka, *Pharm. Bull. (Japan)*, **4**, 16 (1956); *Chem. Abstracts*, **51**, 3593 (1957).
5. Glover and Jones, *J. Chem. Soc.*, **1956**, 1750.
6. Prasad and Swan, *J. Chem. Soc.*, **1958**, 2024.
7. Reckhow and Tarbell, *J. Am. Chem. Soc.*, **74**, 4960 (1952).
8. Groves and Swan, *J. Chem. Soc.*, **1952**, 650.
9. Prasad and Swan, *J. Chem. Soc.*, **1958**, 2045.

A-754. Indolo[3,2-*b*]quinolizine

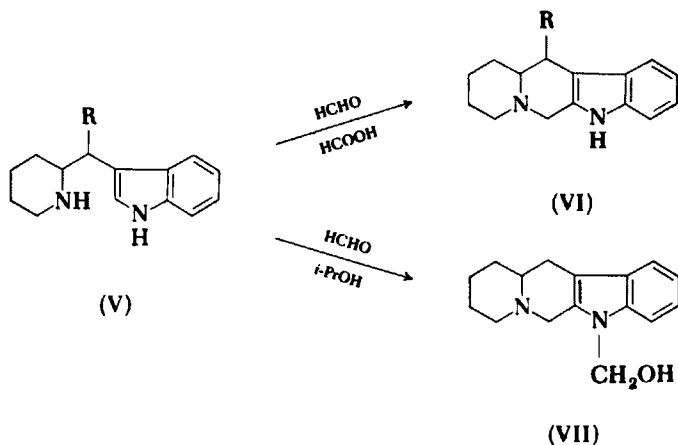


The reaction¹ of I with benzene diazonium chloride and with 2,5-dichlorobenzene diazonium chloride yielded IIa and IIb, which were converted by means of the Fischer indole reaction and saponification, into IIIa and IIIb, respectively. Compound IIIa was dehydrated to IVa (yellow, m. 308°) by heating at 200°/0.1 mm., while



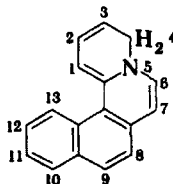
IIIb yielded IVb (yellow, m. 327°) when heated at 150° with zinc chloride. Compound IVa was called ¹ 4-oxoindolo(3':2-2:3)pyridocoline.

Attempts to methylate V by heating with formaldehyde and formic acid (the Clarke-Eschweiler reaction) gave, ² as a result of the Pictet-Spengler ring closure, only VI (R = H, m. 218-9°; HCl salt, m. 236.5-8.5°, methiodide, m. 277°; R = OH, m. 234-6°). Treatment of V (R = H) with formaldehyde in isopropyl alcohol gave VII (m. 180.5°, but resolidifies and then m. 213-4°; HCl salt, m. 218-9°).

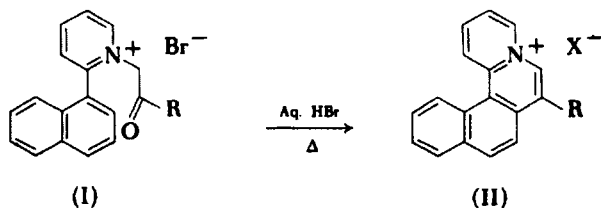


References

1. Clemo and Seaton, *J. Chem. Soc.*, **1954**, 2582.
2. Bader and Oroshnik, *J. Am. Chem. Soc.*, **79**, 5686 (1957).

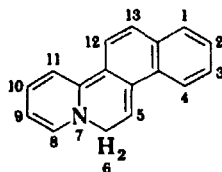
A-755. 4H-Naphtho[1,2-*a*]quinolizine

Bradsher and Beavers prepared naphtho[1,2-*a*]quinolizinium salts of type II ($R = CH_3$, $X = Br$, pale yellow, d. $\sim 347^\circ$; $X = ClO_4$, d. $> 340^\circ$, λ_{max} 226, 265.5, and 355.8 $m\mu$ ($\log \epsilon = 4.57$, 4.21 and 3.97); $X =$ picrate, yellow, m. $253.5-4^\circ d.$; $R = C_6H_5$, $X = Br$, yellow-brown (yellow fluorescence under ultraviolet light or in solutions), m. $274-6^\circ d.$; $X = ClO_4$, orange-yellow, m. $267-8^\circ d.$, λ_{max} 261, 289, 338.5, 355 and 401 $m\mu$ ($\log \epsilon = 4.50$, 4.39, 3.63, 3.70 and 3.80 respectively); $X =$ picrate, yellow, d. $\sim 227-8^\circ$), by the cyclodehydration of I.

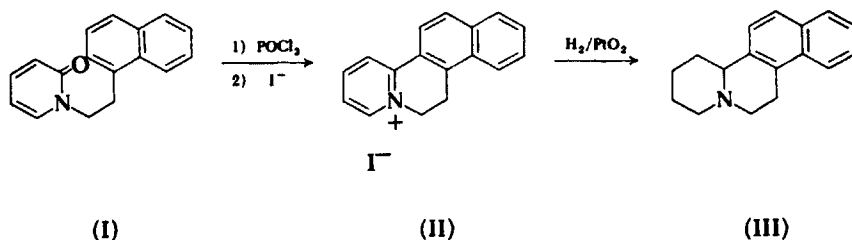


Reference

1. Bradsher and Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).

A-756. 6H-Naphtho[2,1-*a*]quinolizine

By applying Sugawara's benzoquinolizine synthesis to I, Govindachari and Thyagarajan¹ obtained II (m. 177°). Catalytic reduc-

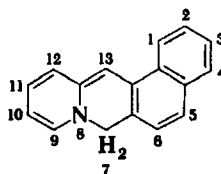


tion of II yielded III (oil; HCl salt, m. 218°; picrate, yel., m. 157°).

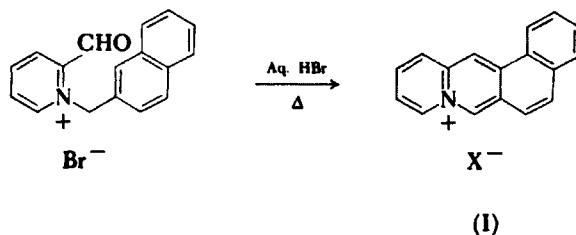
Reference

1. Govindachari and Thyagarajan, *Proc. Indian Acad. Sci.*, **39A**, 232 (1954); *Chem. Abstracts*, **49**, 9653 (1955).

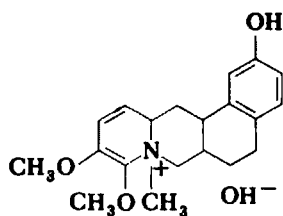
A-757. 7*H*-Naphtho[1,2-*b*]quinolizine



Bradsher and Beavers¹ prepared dehydroquaternary salts of structure I ($X = Br^-$, yellow, m. 302–3°d.; $X = ClO_4^-$, pale yellow, m. 268–70°d., λ_{max} 227.5, 276, 321.5, 364, 384, and 405.5 $m\mu$ ($\log \epsilon = 4.52, 4.57, 4.55, 3.91, 3.91$, and 3.89 respectively); $X =$ picrate, yellow, m. 259–60°d.), which they named *benzo[*j*]acridizinium* salts.



The alkaloid *thalictrine*, isolated from *Thalictrum foliosum* was tentatively assigned² structure II, but little evidence to support this structure was adduced.

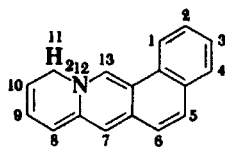


(II)

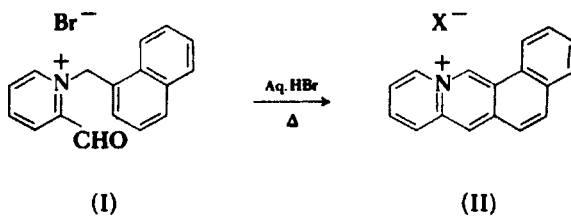
References

1. Bradsher and Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).
2. Vashistha and Siddiqui, *J. Indian Chem. Soc.*, **18**, 641 (1941).

A-758. 11*H*-Naphtho[2,1-*b*]quinolizine



The cyclodehydration of I yielded II ($X = Br^-$, yellow, m. 308–9°d.; $X = ClO_4^-$, golden, m. 291–2°d., λ_{max} 232.5, 274, 305, 317,

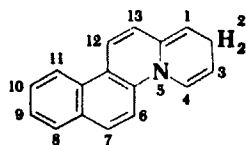


358, 376 and 395 $m\mu$ ($\log \epsilon = 4.54, 4.58, 4.33, 4.39, 3.93, 4.22$ and 4.34 respectively); $X = \text{picrate}$, yellow, m. 232°d.), which was named *benzo[h]acridizinium*.

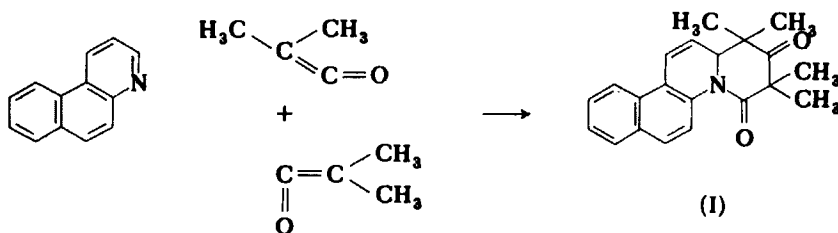
Reference

1. Bradsher and Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).

A-759. 2H-Naphtho[1,2-c]quinolizine
R.I. 2707



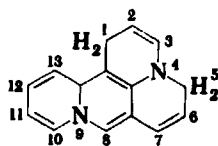
While exploring the reactions of ketenes, Staudinger¹ obtained compound I (m. 163°).



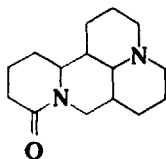
Reference

1. Staudinger, Klever and Kober, *Ann.*, **374**, 1 (1910).

A-760. 1H,5H-Quinolizo[1,8-ab]-quinolizine



A group of natural (from *Sophora* species) and synthetic alkaloids, *matrine* and its derivatives, are the only reported examples of this ring system. The chemistry of these alkaloids has been discussed by Leonard¹ and only a few recent references²⁻⁷ will be added. It has been suggested that matrine has structure I.

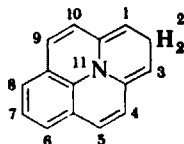


(I)

References

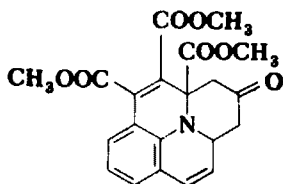
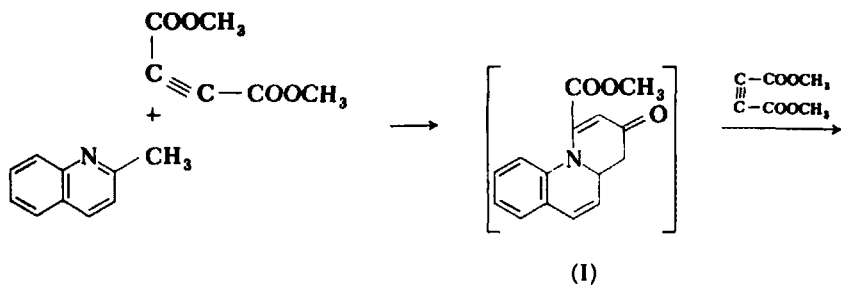
1. Manske and Holmes, *The Alkaloids*, Academic Press, New York, 1953, Vol. 3, pp. 178ff.
2. Ochiai, Haginiwa and Okuda, *J. Pharm. Soc. Japan*, **71**, 1279 (1951); *Chem. Abstracts*, **46**, 5604 (1952).
3. Ochiai, Okuda and Minato, *J. Pharm. Soc. Japan*, **72**, 781 (1952); *Chem. Abstracts*, **48**, 2724 (1954).
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5. Henry, *The Plant Alkaloids*, 4th Ed., The Blakiston Co., Philadelphia, 1949, p. 147.
6. Platonova and Kusovov, *J. Gen. Chem. (U.S.S.R.)*, **26**, 283 (1956).
7. Tsuda, Sacki, Imura, Okuda, Sato and Mishima, *J. Org. Chem.*, **21**, 1481 (1956).

A-761. 2H-Quino[2,1,8-def]quinolizine.
R.I. 2693



The 3aH form was given R.I. No. 2594.

One of the products obtained¹ from the reaction of quinaldine and acetylene dicarboxylic ester is II (d. 179°, hydrochloride, m. 215°d.), thought to be formed via the (not isolated) intermediate I.



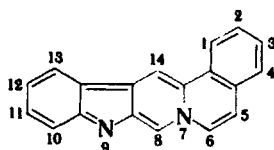
(II)

Treatment of II with diazomethane yields the enol methyl ether (m. 173°) and bromination of II occurs at position 1, giving an α -bromo-ketone.

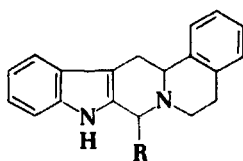
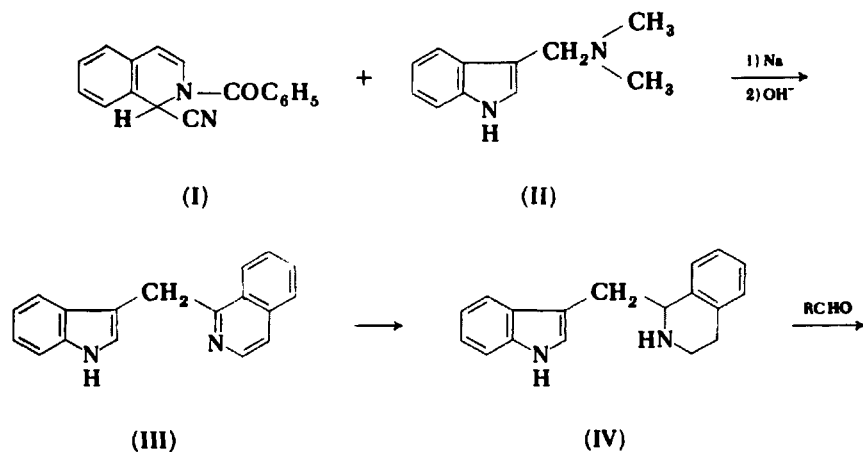
Reference

1. Diels and Kech, *Ann.*, **519**, 140 (1935).

A-762. Benz[*h*]indolo[2,3-*b*]quinolizine



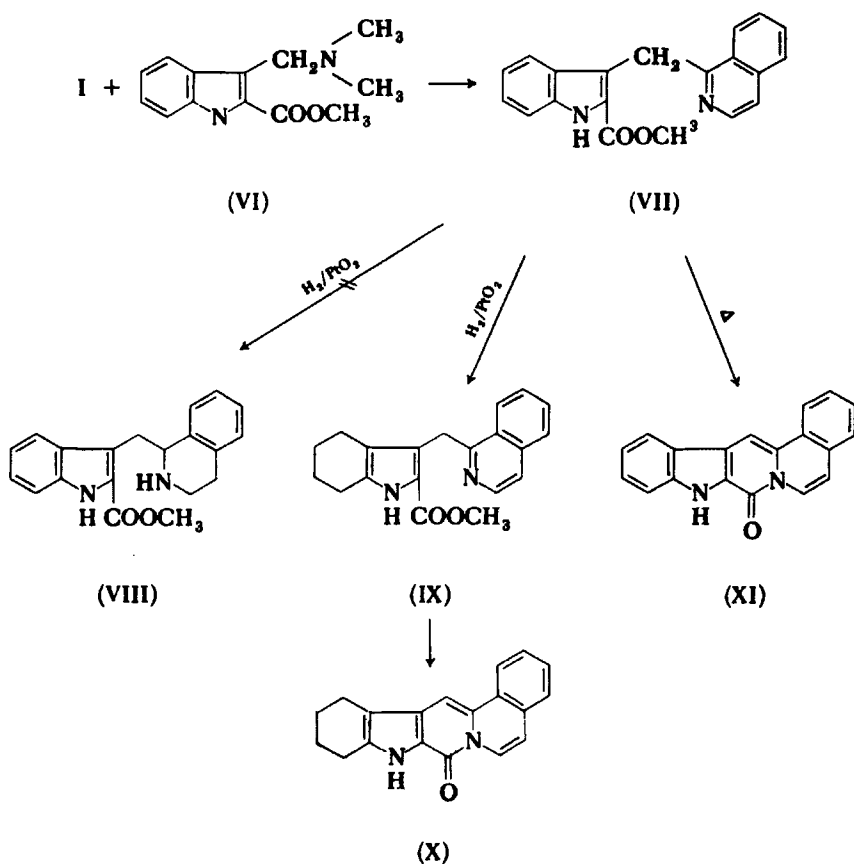
By alkylating Reissert's compound (I) with gramine (II), compound III has been obtained.¹ Reduction of III with sodium and butanol² (but not by hydrogenation over platinum oxide)^{1,2} gave the tetrahydro compound IV, which readily reacted² with formalde-



- (Va) R = H
(Vb) R = CH₃

hyde to yield Va (HCl salt, m. 280–2°; picrate, yellow, m. 225°; methiodide, m. 242–3°; methochloride, m. 238–9°). The reaction of IV with an excess of formaldehyde gave the *N*-hydroxymethyl derivative of Va (m. 169–70°; HCl salt, 250–2°; methiodide, m. 205–6°), which in turn was converted into the corresponding *N*-ethoxymethyl compound (HCl salt, m. 244–6°d.). When IV was condensed with acetaldehyde in place of formaldehyde, compound Vb was obtained (m. 249–50°).

An analogous condensation of I with VI yielded VII, which was expected to give VIII after hydrogenation using Adams catalyst. However, a tetrahydro compound other than VIII was obtained, probably³ compound IX. When IX was heated in tetralin, lactamization occurred, yielding a product (yellow, m. 310–2°) thought

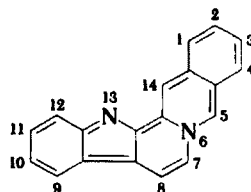


to be X. Similar treatment of VII gave XI (yellow, m. 248–50°), the structure of which was demonstrated by its reduction to Va.

References

1. Boekelheide and Ainsworth, *J. Am. Chem. Soc.*, **72**, 2134 (1950).
2. Boekelheide and Liu, *J. Am. Chem. Soc.*, **74**, 4920 (1952).
3. Schwarz and Schlittler, *Helv. Chim. Acta*, **34**, 629 (1951).

A-763. Benz[*g*]indolo[2,3-*a*]quinolizine. R.I. 3066

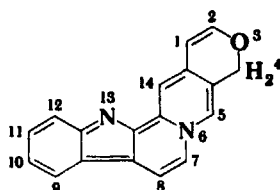


Investigations of this ring system have been quite numerous, as it is the nucleus of several interesting groups of alkaloids, such as *gelsemine*, *rauwolscine*, *reserpine* and the *yohimbe* alkaloids. Since these subjects have recently been discussed by Marion,¹ by Boekelheide and Prelog,⁸ and by Saxton,¹⁰ and since the chemistry of this ring system is confined to the study of these various alkaloids, no further review of the subject is appropriate here.

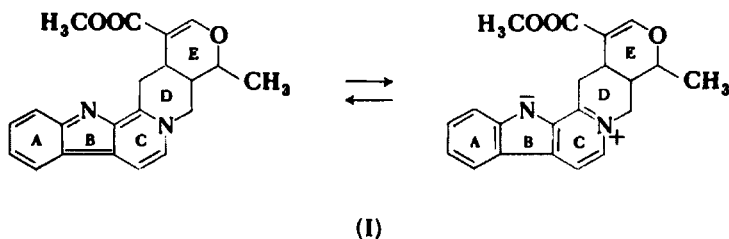
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2. Chatterjee and Bose, *Experientia*, **10**, 246 (1954).
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4. Henry, *The Plant Alkaloids*, 4th Ed., The Blakiston Company, Philadelphia, 1949, pp. 520ff, 737, 763.
5. Potts and Robinson, *J. Chem. Soc.*, **1955**, 2675.
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7. Logemann, Almirante, Caprio and Meli, *Chem. Ber.*, **88**, 1952 (1955).
8. Boekelheide and Prelog, "Indole Alkaloids" in Cook, *Progress in Organic Chemistry*, Vol. 3, Academic Press, New York, 1955, p. 218.
9. Elderfield and McCurdy, *J. Org. Chem.*, **21**, 295 (1956).
10. Saxton, "The Indole Alkaloids," *Quart. Rev.*, **10**, 108 (1956).
11. Van Tamlen, Shamma and Aldrich, *J. Am. Chem. Soc.*, **78**, 4628 (1956).
12. Glover and Jones, *J. Chem. Soc.*, **1958**, 1750.
13. Swan, *J. Chem. Soc.*, **1958**, 2038.

A-764. 4*H*-Indolo[2,3-*a*]pyrano[3,4-*g*]-quinolizine



The representation of this ring system is, so far, confined to two groups of alkaloids: *alstonine* and its congeners, isolated from *Alstonia constricta*. F. Muell., an Apocyanaceae of Southwest Asia, and the *serpentine* bases found in *Rauwolfia serpentina* Benth., also a member of the Apocyanaceae, found in India. Recent investigations suggest^{4,5} structure I for alstonine, while serpentine is thought⁵ to



differ only by absence of the double bond in ring E, and reserpinine is probably⁷ 11-methoxytetrahydroalstonine.

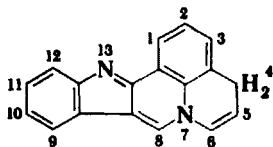
Some of the more recent papers and reviews^{8, 13, 18, 20, 21, 23, 24} are cited below, and reference should be made to them for details concerning the chemistry of these alkaloids, and for a more complete bibliography.

References

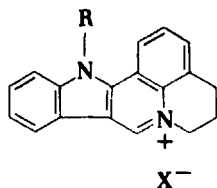
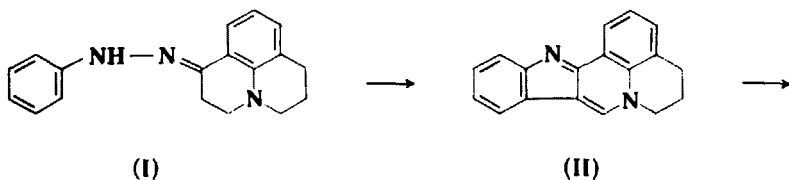
1. Schlittler and Schwarz, *Helv. Chim. Acta*, **33**, 1463 (1950).
2. Elderfield and Gray, *J. Org. Chem.*, **16**, 506 (1951).
3. Schwarz and Schlittler, *Helv. Chim. Acta*, **34**, 629 (1951).
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5. Bader and Schwarz, *Helv. Chim. Acta*, **35**, 1594 (1952).
6. Bader, *Helv. Chim. Acta*, **36**, 215 (1953).
7. Weisenborn, Moore and Diassi, *Chem. and Ind.*, **1954**, 375.
8. Manske and Holmes, *The Alkaloids*, Academic Press Inc., New York, 1952, Vol. 2, pp. 451ff.
9. Hofmann, *Helv. Chim. Acta*, **37**, 849 (1954).
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11. Janot, Goutarel and Massonneau, *Compt. rend.*, **234**, 850 (1952).

12. Schlittler and Hohl, *Helv. Chim. Acta*, **35**, 29 (1952).
13. Schlittler, Schneider and Plummer, *Angew. Chem.*, **66**, 386 (1954).
14. Haack, Popelak, Spingler, Kaiser and Kroneberg, *Naturwiss.*, **41**, 214 (1954).
15. Goutarel, Janot, LeHir, Corrodi and Prelog, *Helv. Chim. Acta*, **37**, 1805 (1954).
16. Schlittler, Huber, Bader and Zahnd, *Helv. Chim. Acta*, **37**, 1912 (1954).
17. Robinson and Thomas, *J. Chem. Soc.*, **1954**, 3479.
18. Henry, *The Plant Alkaloids*, 4th Ed., The Blakiston Co., Philadelphia, 1949, pg. 716ff.
19. Goutarel, LeHir and Janot, *Bull. soc. chim. France*, **1954**, 1481.
20. Boekelheide and Prelog, "Indole Alkaloids" in Cook, *Progress in Organic Chemistry*, Vol. 3, Academic Press, New York, 1955, p. 218.
21. Saxton, "The Indole Alkaloids," *Quart. Rev.*, **10**, 108 (1956).
22. Djerassi, Fishman, Gorman, Kutney and Pakrashi, *J. Am. Chem. Soc.*, **79**, 1217 (1957).
23. Chatterjee, Pakrashi and Werner in Zechmeister, *Fortschritte der Chemie Organischer Naturstoffe*, Springer Verlag, Vienna, Vol. XIII, 1956.
24. Woodson, Youngken, Schlittler and Schneider, *Rauwolfia*, Little, Brown & Co., Boston, 1957.

A-765. 4*H*-Benz[*ij*]indolo[2,3-*b*]-quinolizine



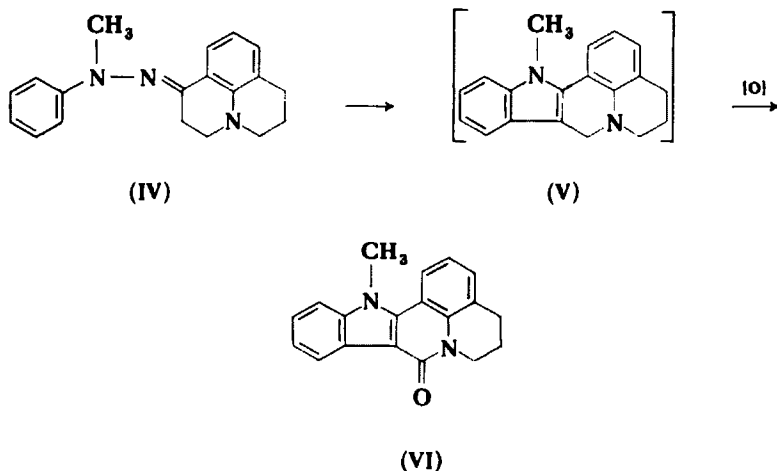
Treatment of the phenylhydrazone of 1-oxojulolidine (I) with dilute sulfuric acid, or with aqueous-ethanolic hydrogen chloride



(III)

yielded a yellow crystalline product (m. $198-9^\circ$) to which the ψ -indole structure II was assigned.¹ Compound II was readily converted into a colorless hydrochloride, m. 448° (in an evacuated sealed capillary tube) and methiodide, m. 364° (in an evacuated sealed capillary tube), thought to possess structure III (R = H and CH₃ respectively).

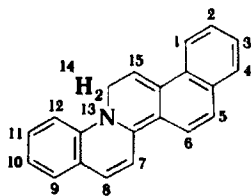
An analogous reaction with the methylphenylhydrazone of 1-oxo-julolidine (IV) gave VI (m. $211.0-1.5^\circ$; picrate, orange, m. $170.0-0.5^\circ$), as the only isolated product, presumably because of the facile oxidation of the intermediate V. By contrast, II was shown to be resistant to oxidation. Compound VI was named *3-keto-1-methyl-indolo(2':3'-1:2)juloline*.



Reference

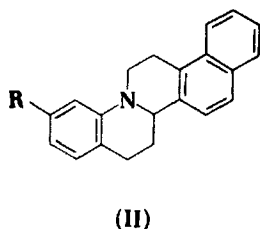
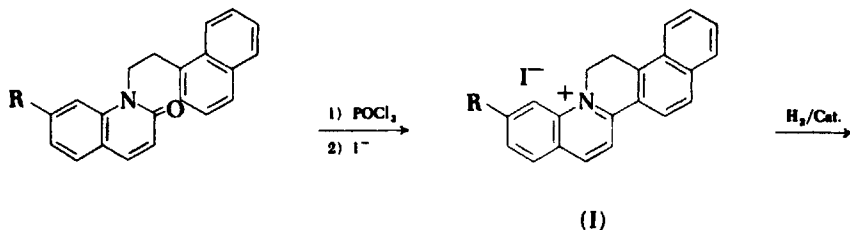
1. Mann and Smith, *J. Chem. Soc.*, **1951**, 1898.

A-766. 14*H*-Benzo[*f*]naphtho[2,1-*a*]-quinolizine



The name *naphtho-1',2',1,2-benzo-5,6-quinolizine* has been used.

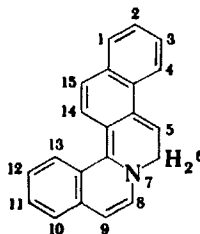
While investigating the scope of Sugasawa's benzoquinolizine synthesis, Govindachari and Thyagarajan¹ obtained I (Ia, R = H, yel. m. 193°; Ib, R = CH₃, yel., m. 180°). Catalytic reduction of I gave II (IIa, R = H, m. 117°; picrate, yel., m. 77°; IIb, R = CH₃, m. 131°; picrate, yel., m. 145°).



Reference

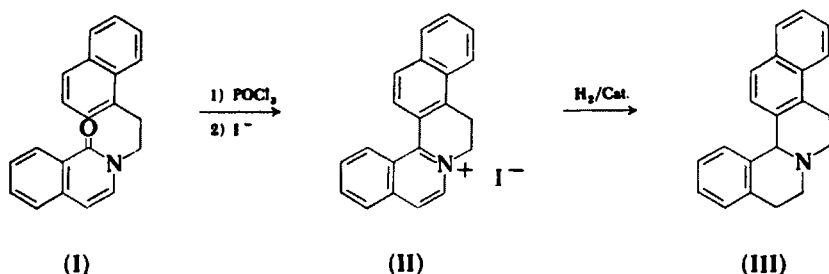
1. Govindachari and Thyagarajan, *Proc. Indian Acad. Sci.*, **39A**, 232 (1954); *Chem. Abstracts*, **49**, 9543 (1955).

A-767. 6H-Benzo[*a*]naphtho[1,2-*h*]-quinolizine



This nucleus has been called *naphtho-1',2',1,2-benzo-7,8-quinolizine*.

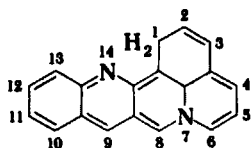
Cyclodehydration of I is reported¹ to yield II (yel., m. 192°), which can be reduced to III (m. 98°; picrate, yel., m. 209°; picrolonate, yel., m. 190°).



Reference

1. Govindachari and Thyagarajan, *Proc. Indian Acad. Sci.*, **39A**, 232 (1954); *Chem. Abstracts*, **49**, 9653 (1955).

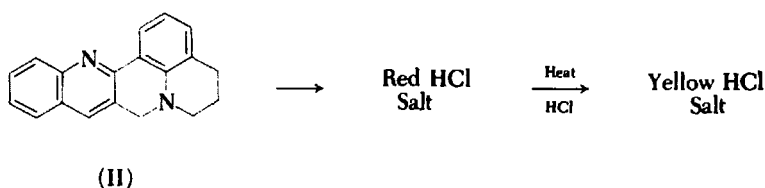
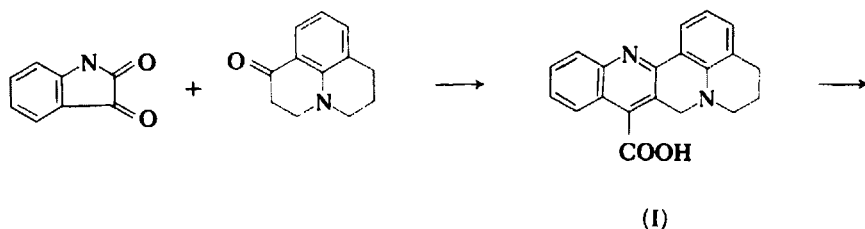
A-768. 1*H*-Benzo[*ij*]quino[2,3-*b*]-quinolizine



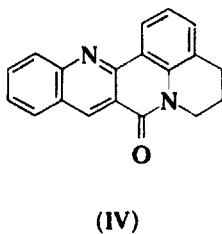
This nucleus has also been called ¹quinolino(2':3'-1:2)juloline.

By subjecting 1-oxojulolidine to the Pfitzinger reaction, Mann and Smith¹ obtained compound I (maroon, m. 177.5–9.0°), which was decarboxylated when heated in vacuo, to give II (yel. m. 150°). The base II yields a monomethiodide, m. 173.5°d. (in an evacuated, sealed capillary tube); a monometho-*p*-toluenesulfonate, lemon-yellow, m. 207° (in an evacuated, sealed capillary tube), and by reaction in cold acetone solution with dilute hydrochloric acid, a red monohydrochloride, melting, after a series of color changes, at 390°.

When the red hydrochloride salt of II was heated, or when II was boiled with dilute hydrochloric acid, a new yellow hydrochloride, m. 388°, was obtained. Treatment of this yellow salt with caustic gave a new orange base, m. 190° (in an evacuated, sealed capillary tube), to which structure III was given. Compound III was reconverted into II when heated in vacuo at 200°. In addition to the yellow hydrochloride, m. 388°, III forms a yellow mono-*p*-toluenesulfonate salt, which sinters and darkens at 237° and melts at 253–60°; a yellow monometho-*p*-toluenesulfonate, m. 171.0–1.5° (in an evacuated, sealed capillary tube), and a yellow methiodide, m. 220°d. (in an evacuated, sealed capillary tube).

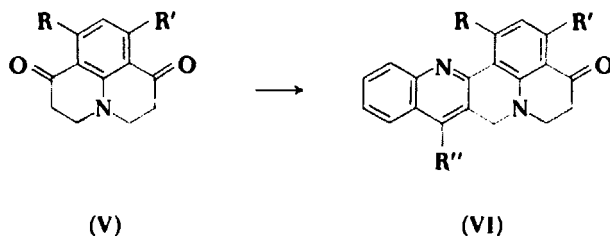


Air-oxidation of either II or III afforded the same product, IV (cream-colored, m. 177°), which gave a yellow *p*-toluenesulfonate salt, m. 203°.



Although V ($R = R' = H$) reacted with two equivalents of isatin to produce the diquinolo compound (see Section A-776), the 8-methyl

homolog (V, $R = H$, $R' = CH_3$) reacted only once to form VI ($R = H$, $R' = CH_3$, $R'' = COOH$, deep purple, m. $215^\circ d.$), and dimethyldioxojulolidine (V, $R = R' = CH_3$) failed to react at all with isatin.² Apparently the steric effect of the methyl group(s) is

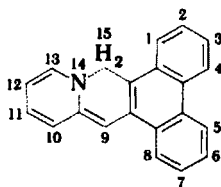


responsible for this behavior. Thermal decarboxylation of VI ($R = H$, $R' = CH_3$, $R'' = COOH$) yielded VI ($R = R'' = H$, $R' = CH_3$, yellow, m. 185°).

References

1. Mann and Smith, *J. Chem. Soc.*, **1951**, 1898.
2. Ittyerah and Mann, *J. Chem. Soc.*, **1958**, 467.

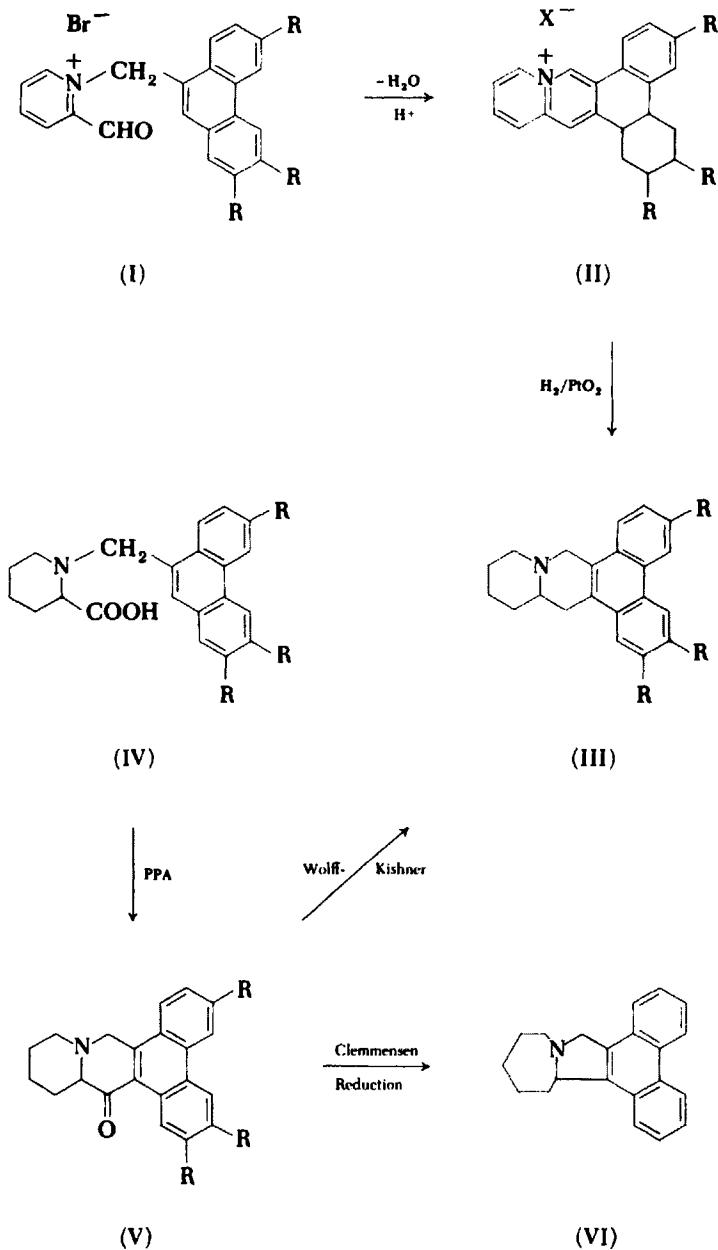
A-769. 15*H*-Phenanthra[9,10-*b*]-quinolizine



The interest in this ring system derives from its presence in the highly toxic alkaloid *cryptopleurine*, which has the action of a vesicant mitotic poison, and is isolated from *Cryptocaria pleurosperma*, an Australian Lauraceae. A summary of the pertinent references to this alkaloid is given in reference 1. X-ray diffraction studies suggested structure III ($R = OCH_3$) for cryptopleurine, and recent independent syntheses^{1,2} by two slightly different routes confirm this structure.

Cyclization of I ($R = OCH_3$, obtained from the bromomethylphenanthrene and picolinic aldehyde) with polyphosphoric acid gave¹ II ($R = OCH_3$) and this salt was reduced directly to cryptopleurine [III, $R = OCH_3$, m. $199-200^\circ$ ($197-8^\circ$)]. Alternatively,

IV ($R = \text{OCH}_3$) was cyclized² by hot polyphosphoric acid to V ($R = \text{OCH}_3$, yellow, m. $154.5\text{--}5.0^\circ$), which was reduced to III.



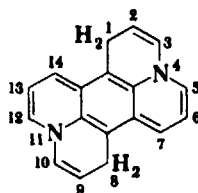
The unsubstituted compound II ($R = H$, $X = Br$, yellow, d. $\sim 328^\circ$; $X = ClO_4^-$, d. $\sim 327^\circ$; $X = \text{picrate}$, m. 336° d.) was obtained³ by treatment of I ($R = H$) with aqueous hydrobromic acid. The name *dibenzo[h,i]acridizinium* was given to these salts by Bradsher and Beavers.³ Cyclization² of IV ($R = H$) with polyphosphoric acid gave V ($R = H$, yellow, m. $168-9^\circ$), which was reduced, as before, to III ($R = H$, m. $169-70^\circ$). The Clemmensen reduction of V gave² the rearranged product VI.

The ultraviolet spectra of several of these products were recorded.^{1,2,3}

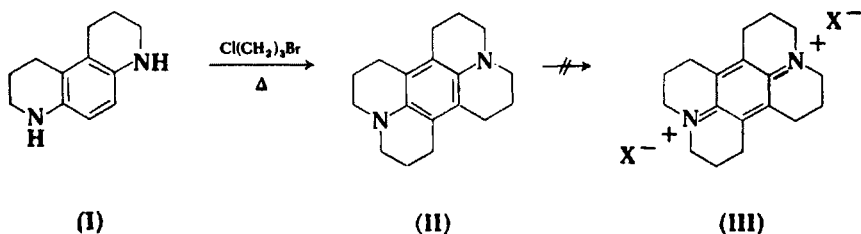
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1. Bradsher and Berger, *J. Am. Chem. Soc.*, **79**, 3287 (1957); **80**, 930 (1958).
2. Marchini and Belleau, *Can. J. Chem.*, **36**, 581 (1958).
3. Bradsher and Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).

A-770. 1*H*,8*H*-Benzo[*ij*,*i'**j'*]diquinolizine



By refluxing tetrahydro-1,8-phenanthroline (I) with trimethylene chlorobromide, Smith and Yu¹ obtained II (m. $190-1^\circ$; picrate, yel., m. 125° , but it is converted by recrystallization from ether or ethanol into black needles, m. $205-10^\circ$), which they named *1,2,3,3a,4,5,6,7,8,9,9a,10,11,12-tetradecahydro-3a,9a-diazaperylene*.

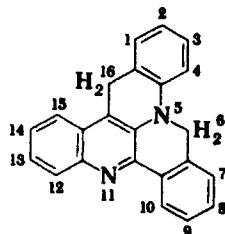


The failure to form the diimmonium salt III from II has been recorded.²

References

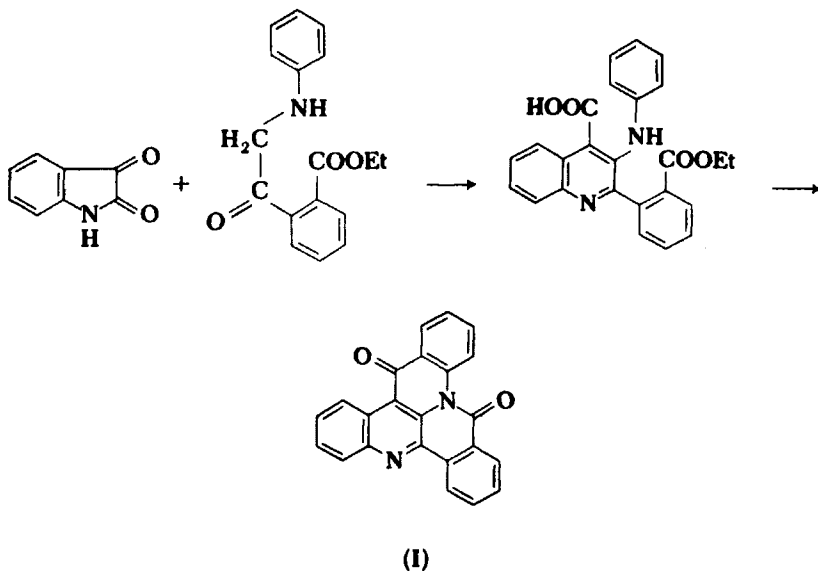
1. Smith and Yu, *J. Am. Chem. Soc.*, **74**, 1096 (1952).
2. Hünig and Richters, *Chem. Ber.*, **91**, 442 (1958).

A-771. 6H,16H-Benzo[c]quino[3,2,1-mn]-[1]azacridine. R.I. 3610



Chemical Abstracts (Index, Vols. 31-40) indexes this nucleus under the name *benzo[c]quino[2,3,4-mn][2]azacridine*.

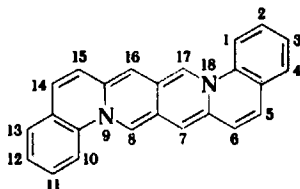
This nucleus has at various times been claimed to be present in the dyes *Höchst Yellow R*, *Höchst Yellow U*, and *Ciba Yellow 3G* (see Sections A-210, A-259 and A-260). The currently favored structures, however, lack this nucleus. This was shown, in part, by the synthesis¹ of I (m. 297°), and demonstration of its non-identity with *Ciba Yellow 3G*.



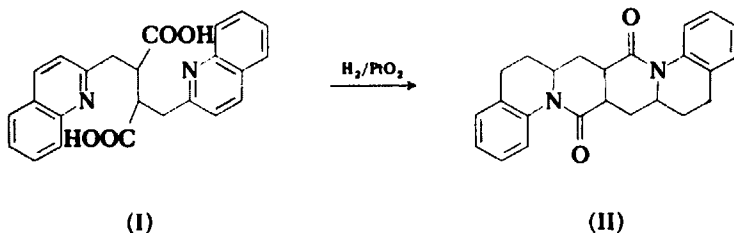
Reference

1. de Diesbach and Klement, *Helv. Chim. Acta*, **24**, 158 (1941).

A-772. 8a,16a-Diazadibenzo[aj]-naphthacene. R.I. 3608



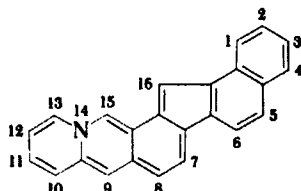
The only example of this nucleus occurs in the work of Kondo and Wantanabe,¹ who obtained the dilactam II (m. 245–7°) from the reduction of I.



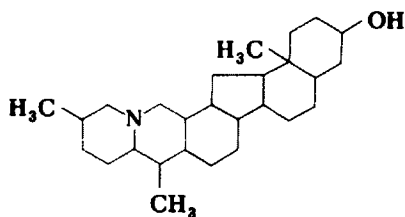
Reference

1. Kondo and Watanabe, *J. Pharm. Soc. Japan*, **54**, 905 (1934); *Chem. Zentr.*, **I**, 1381 (1935); *Chem. Abstracts*, **31**, 104 (1937).

A-773. Benzo[7,8]fluoreno[2,1-b]-quinolizine*



Certain steroidal alkaloids such as *germine*, *cevine* and their congeners, isolated from various *Veraltrum* species, are thought to contain this nucleus. The historical background of this subject has been discussed thoroughly by Prelog and Jeger,¹ and recent work,²⁻¹³ indicates that these alkaloids possess the partial structure I. Steroid



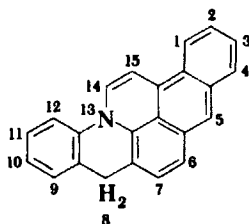
(I)

numbering and nomenclature are customarily used in describing these alkaloids.

References

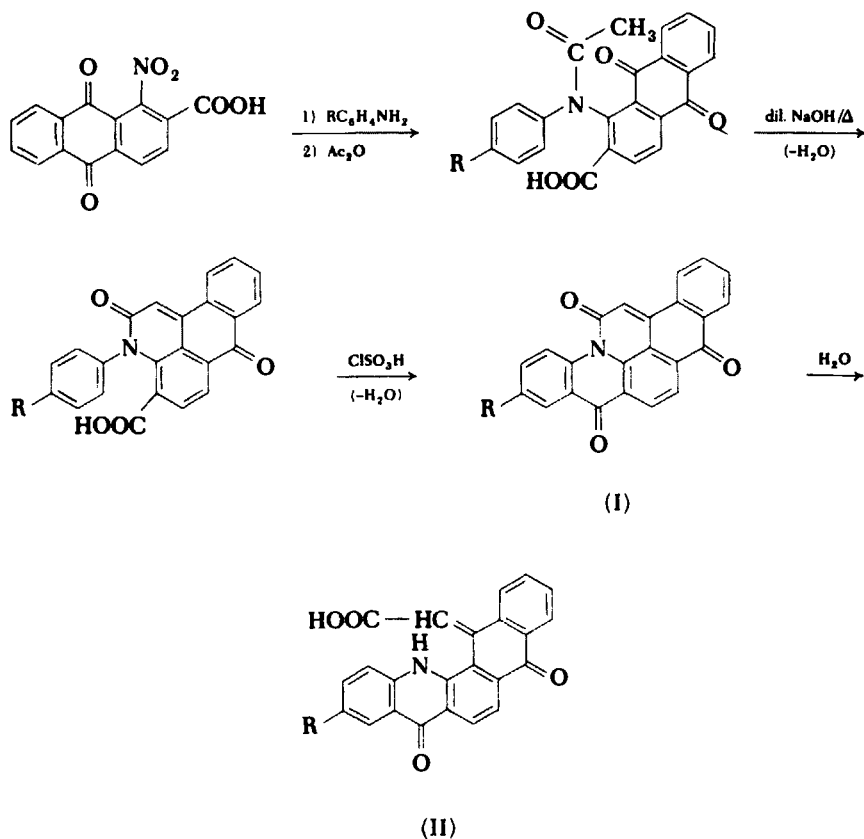
1. Manske and Holmes, *The Alkaloids*, Academic Press Inc., New York, 1953, Vol. 3, pg. 270ff.
2. Jacobs and Pelletier, *J. Org. Chem.*, **18**, 765 (1953).
3. Pelletier and Jacobs, *J. Am. Chem. Soc.*, **76**, 2028 (1954).
4. Kupchan and Lavie, *J. Am. Chem. Soc.*, **76**, 314 (1954).
5. Barton, Jeger, Prelog and Woodward, *Experientia*, **10**, 81 (1954).
6. Kupchan, Fieser, Narayanan, Fieser and Fried, *J. Am. Chem. Soc.*, **76**, 1200 and 5259 (1954).
7. Kupchan, *Abstracts of Papers, Am. Chem. Soc. Meeting*, New York, Sept. 12-17, 1954, p. 35-O.
8. Stoll and Seebeck, *Helv. Chim. Acta*, **37**, 824 (1954).
9. Barton, Brooks and de Mayo, *J. Chem. Soc.*, **1954**, 3950.
10. Kupchan and Lavie, *J. Am. Chem. Soc.*, **77**, 683 (1955).
11. Kupchan, Fieser, Narayanan, Fieser and Fried, *J. Am. Chem. Soc.*, **77**, 5896 (1955).
12. Pelletier and Jacobs, *J. Am. Chem. Soc.*, **78**, 1914 (1956).
13. Boit and Paul, *Chem. Ber.*, **90**, 723 (1957).

A-774. 8*H*-Benz[5,6]isoquin-[8,1,2-*cde*]acridine



Vat dyes containing this ring system have been prepared by Lukin and Aronovich,^{1,2,3} and have been referred to as *anthrapyridoneacri-*

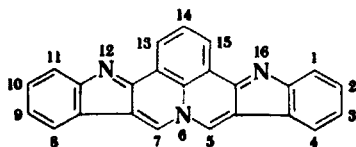
done or 1(*N*)anthrapyridone-1'1''-phenylene-2,2''-ketones. Compound I ($R = H$) is a yellow dye, $m. > 300^\circ$, giving a violet vat, and having (in 94% H_2SO_4 solution) absorption maxima at 270 and 330 $m\mu$; when $R = CH_3$, λ_{max} 280 and 340 $m\mu$. In alkaline media, and especially in the presence of reducing agents, scission of the pyridone ring occurs to yield II.



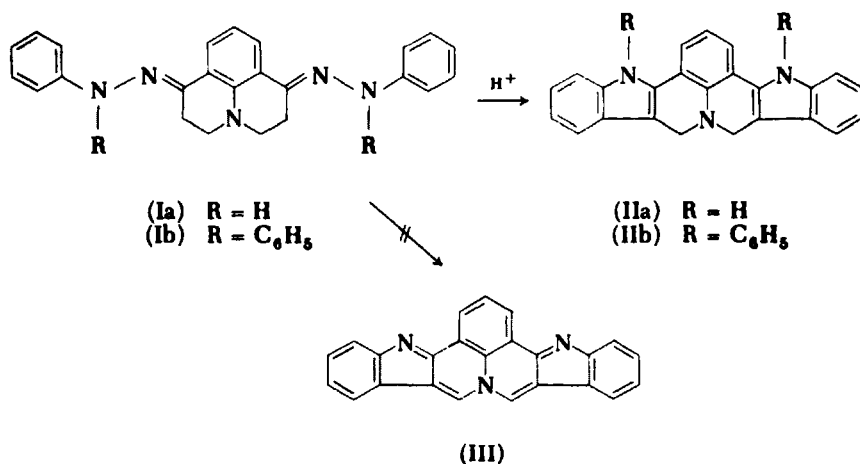
References

1. Lukin and Aronovich, *J. Gen. Chem. (U.S.S.R.)*, **9**, 1774 (1939); *Chem. Abstracts*, **34**, 3749 (1940); *British Chem. Abstracts*, **A11**, 192 (1940).
2. Lukin and Aronovich, *J. Gen. Chem. (U.S.S.R.)*, **19**, 358 (1949); *Chem. Abstracts*, **44**, 1079 (1950).
3. Lukin, Aronovich and Brin, *J. Gen. Chem. (U.S.S.R.)*, **20**, 2219 (English translation 2305) (1950); *Chem. Abstracts*, **45**, 7124 (1951).

**A-775. Benz[*ij*]diindolo-
[2,3-*b*, 3',2'-*g*]quinolizine**



Braunholtz and Mann¹ found that subjection of the bisphenylhydrazone of 1,6-dioxojulolidine (Ia, R = H) to conditions of the Fisher indole synthesis (hot alcoholic hydrogen chloride), yielded compound IIa (yellow, decomposes rapidly in light and air; HCl salt, orange m. 346°d.; HI salt, orange, m. >400°; picrate, orange, m. 253°d., and thiocyanate, orange, m. 318°d.), which they named *di-indolo(2':3'-1:2)(3'':2''-5:6)juline*. In a similar manner from Ib (R = C₆H₅), compound IIb (yellow-brown, amorphous, m. 170°d.;

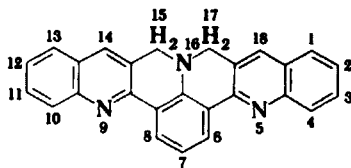


HCl salt, orange, m. 260°d.) was obtained. In view of the dehydrogenation which accompanied the indolization of 1-oxojulolidine phenylhydrazone (see Section A-765), the formation, in the present case, of III might have been expected, but was not encountered.

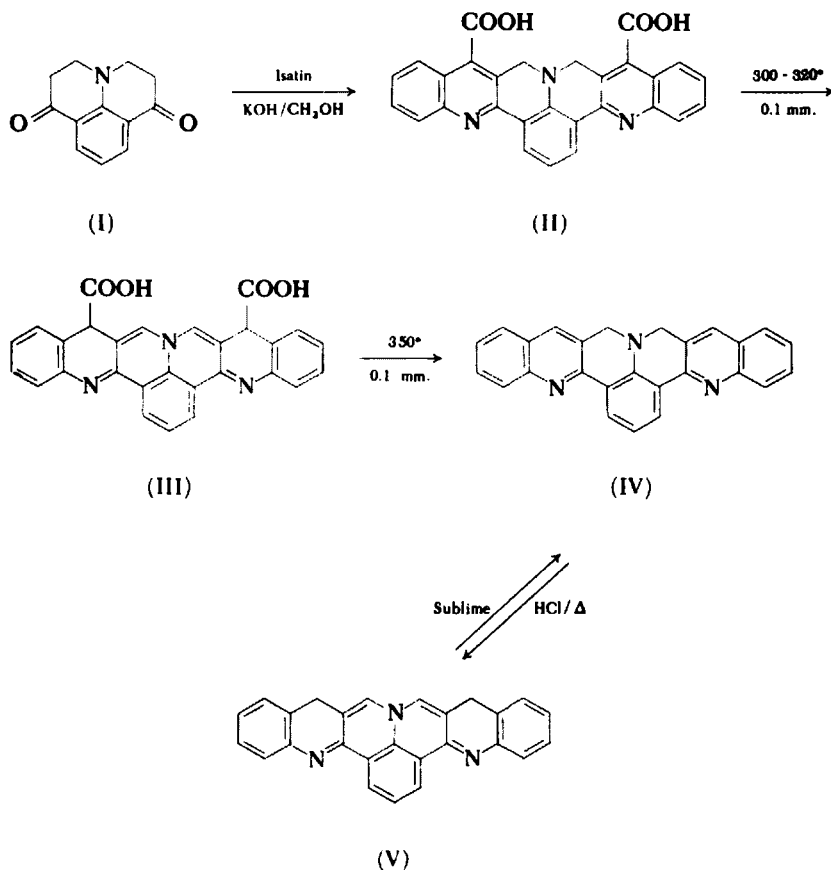
Reference

1. Braunholtz and Mann, *J. Chem. Soc.*, **1955**, 393.

**A-776. 15H,17H-Benzo[*ij*]diquino-
[2,3-*b*, 3',2'-*g*]quinolizine**



The condensation of 1,6-dioxojulolidine (I) with isatin in methanolic caustic (a Pfitzinger reaction) yielded compound II (purple, m. 363°d.), which Braunholtz and Mann¹ named *diquino-lino-(2':3'-1:2)(3'':2''-5:6)juline-4':4''-dicarboxylic acid*. Alkaline solutions of II are orange, whereas II dissolves in hydrochloric acid yielding a blackish-purple solution.

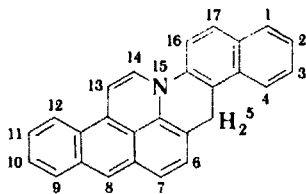


Compound II underwent decarboxylation and rearrangement when heated, giving an unusual series of products, the structures of which were assigned¹ by observing their properties and spectra. When II was heated in vacuo at 300–20°, an allylic rearrangement occurred to yield III (orange, m. 363°). Further heating in vacuo at 350° gave IV (orange, m. 319.5°), which was converted by refluxing hydrochloric acid into V (red, m. 319°). Vacuum sublimation of V reconverted it into IV. See Section A-775.

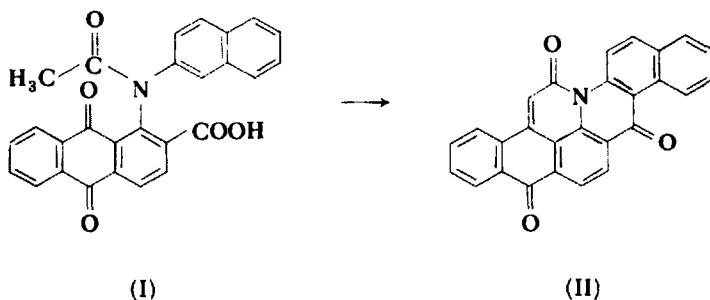
Reference

1. Braunholtz and Mann, *J. Chem. Soc.*, **1955**, 393.

A-777. 5*H*-Benzo[*a*]benz[5,6]isoquin-[2,1,8-*fgh*]acridine



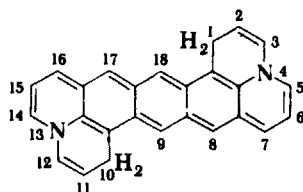
A dye having structure II (weak $\lambda_{\max}$ at $\sim 500 \text{ m}\mu$ in 94% H_2SO_4) and giving a blue vat was prepared by Lukin and Aronovich^{1,2} from I. See Section A-774.



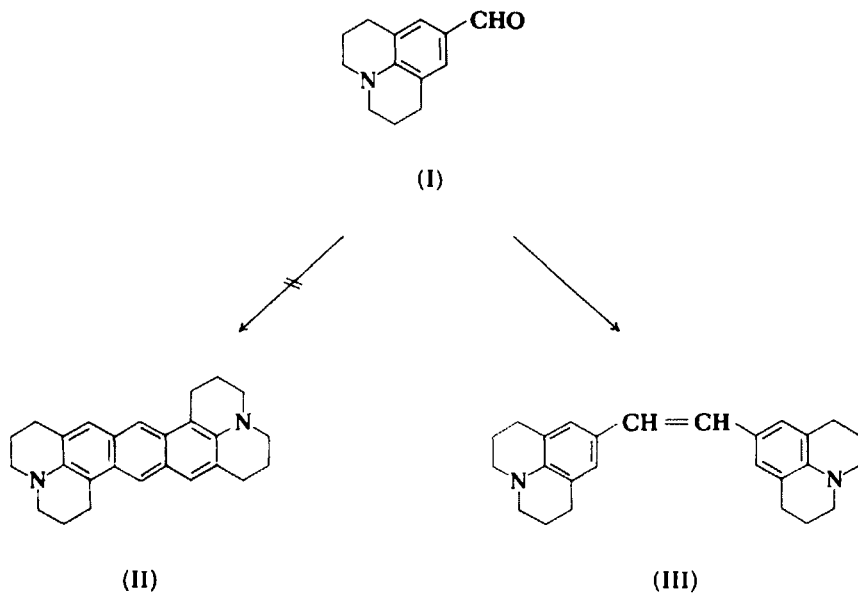
References

1. Lukin and Aronovich, *J. Gen. Chem. (USSR)*, **19**, 358 (1949); *Chem. Abstracts*, **44**, 1079 (1950).
2. Lukin, Aronovich and Brin, *J. Gen. Chem. (USSR)*, **20**, 2219 (English translation, 2305) (1950); *Chem. Abstracts*, **45**, 7124 (1951).

**A-778. 1*H*,10*H*-Anthra[1,2,3-*ij*, 5,6,7-*i'j'*]-
diquinolizine***



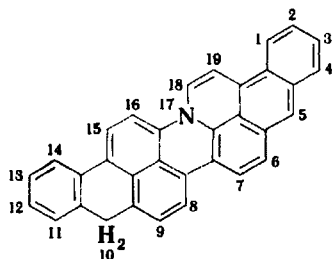
Reduction of I by tin and hydrochloric acid yielded a product first thought^{1,2} to be II, but later found³ to have structure III. See Section A-732.



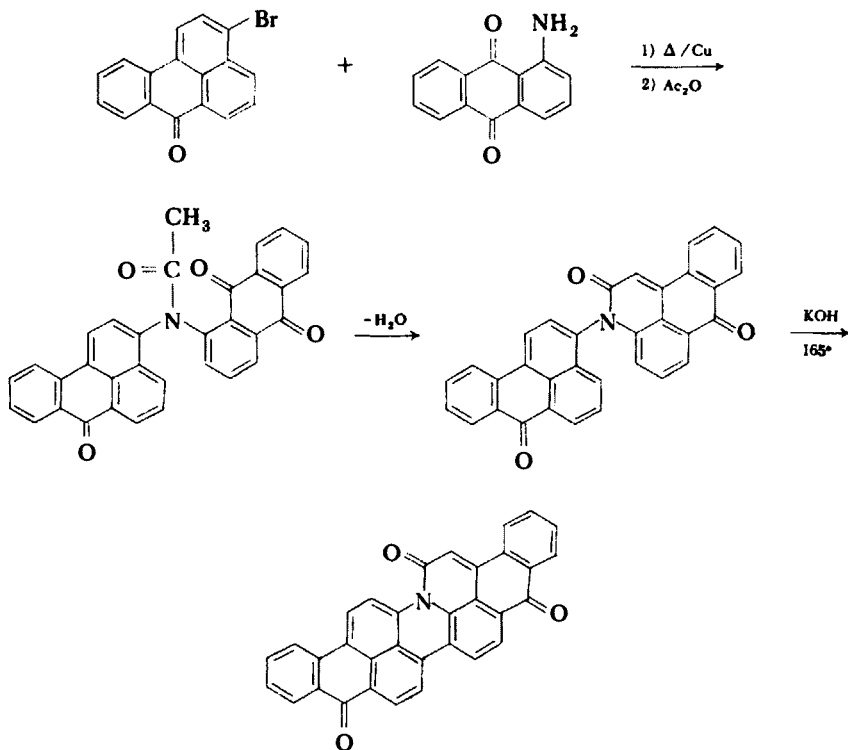
References

1. Stewart, *Chem. and Ind.*, **1956**, 579.
2. Stewart, *J. Chem. Soc.*, **1957**, 1026.
3. Stewart, *Chem. and Ind.*, **1957**, 761.

A-779. 10H-Anthra[2,1,9-*mna*]benz-[5,6]isoquin[2,1,8-*fgh*]acridine*



A dye thought to contain this nucleus, and to possess structure I, was reported by Baumann.¹ The product crystallized from quinoline in blue needles, gave a red solution in sulfuric acid, was very difficult to vat and possessed poor affinity for cotton.



(I)

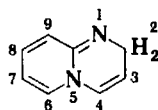
Reference

1. Baumann, *I.G. Farbenindustrie, A.G.*, 32 *Wissenschaftlicher Austausch der Gruppe IX*, Ludwigshafen, Nov. 9, 1934; *PB Report No. 70339*, frames 11046-8; *PB Report No. 25632*, frame 337.

CHAPTER XII

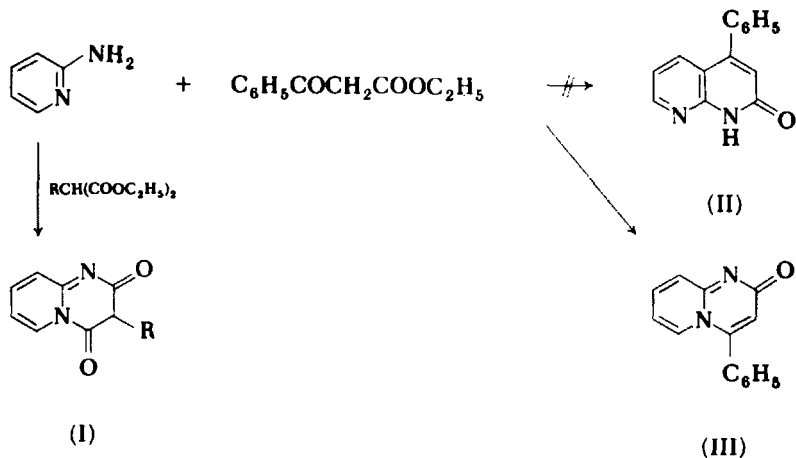
Fused 6/6 Ring Systems with One Extra Heteroatom

A-780. 2*H*-Pyrido[1,2-*a*]pyrimidine.
R.I. 970

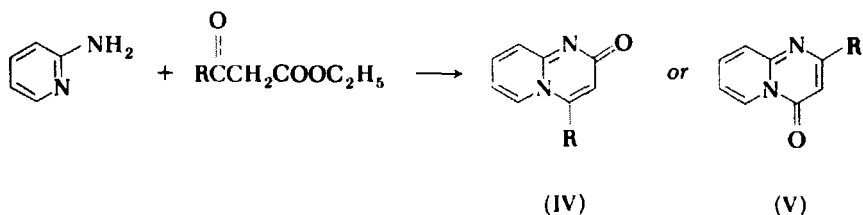


A variety of ill-chosen and confusing names have been bequeathed to derivatives of this ring system. They have been called *1,5,2-pyridopyrimidines* and *homopyrimidazoles*; the 2-oxo derivatives have been called *1,2-divinylene-4-pyrimidones*, *2,10-dihydro-2-keto-1,10-diazanaphthalenes* and *2-keto-1,4a-diazanaphthalenes*, while a 4-oxo-derivative was named *4-keto-2,3-divinylenedihydropyrimidine*, and the 2,4-diketo compound was called *malonyl- α -pyridine*. The 2,3,4-trihydro compounds are found described as both *1,2-divinylene-1,4,5,6-tetrahydropyrimidines* and *1,2-(dihydropyridino-1',2')-5,6-dihydropyrimidines*, while the completely hydrogenated nucleus was called *cyclotetramethylene-1,2-hexahydropyrimidine*.

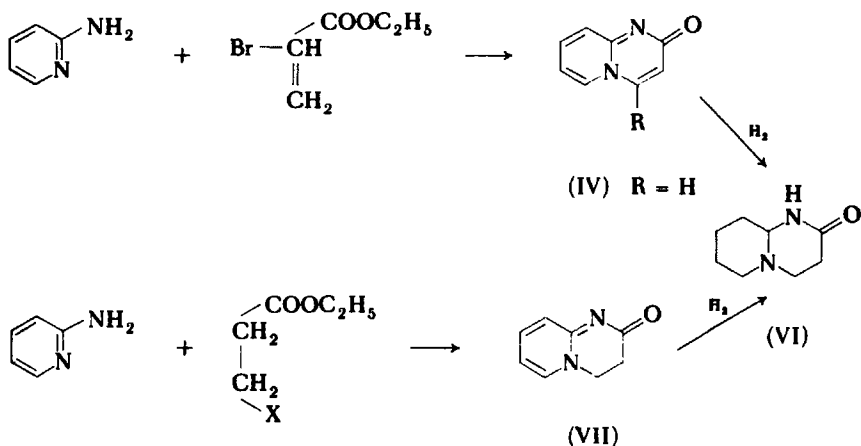
During his extensive investigations upon the reactions of 2-amino-pyridine, Tschitschibabin¹ found that it reacted with malonic esters at 165–95° to yield a bicyclic system of structure I. Actually, the first pyrido[1,2-*a*]pyridine derivative was obtained by Palazzo and Tamburini² who, applying the Knorr quinoline synthesis to 2-amino-pyridine and benzoylacetic ester, obtained a product to which they assigned structure II. This was shown to be incorrect by Seide,³ who proposed structure III for the reaction product. An analogous condensation was conducted with acetoacetic ester by Crippa and Scevola,⁴ and similar reactions were studied by others.^{5–11} It is evident that such a reaction, a priori, could yield two possible products (IV and V), although invariably a single product resulted. Without sub-



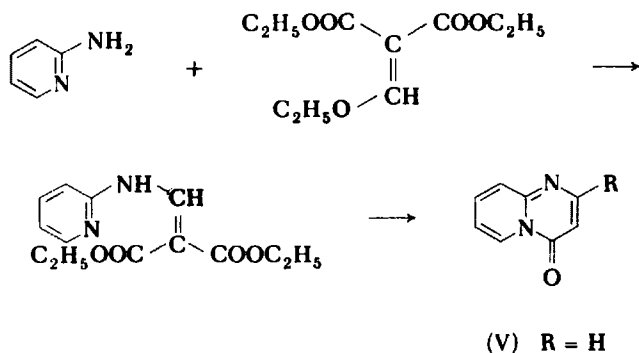
stantial evidence, structure IV was generally favored by the earlier workers. However, in 1951 Antaki and Petrow¹² showed that V ($R = CH_3$) could be obtained from (a) 2-aminopyridine and acetoacetic ester, (b) 2-aminopyridine and β -aminocrotonic ester, and (c) 2-bromopyridine and β -aminocrotonic ester. This work provided good evidence in favor of structure V for the product of such reactions.



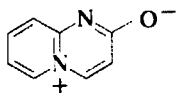
Further confirmation of structure V was given by Adams and Pachter,¹³ who prepared pure samples of IV and V ($R = H$), measured the ultraviolet absorption spectra and compared them with the spectra of the products obtained by the earlier workers. An authentic specimen of compound IV ($R = H$) was obtained by these authors^{13, 14} by reacting 2-aminopyridine with α -bromoacrylic ester. The identity of the product as a 2-oxo derivative was demonstrated by converting it into the octahydro compound VI, which proved to be identical with the product obtained by the reduction of VII. Compound VII has been prepared by the reaction of 2-aminopyridine with β -halopropionic acids¹⁴ or esters,^{14, 15} with ethyl acrylate¹⁴ or



with β -propiolactone.^{15,36} It was also obtained by the reaction of sulfanilamide with ethyl β -bromopropionate.¹⁶ The proof of the identity of VII depends on the demonstration of preferential attack by alkylating agents upon the ring nitrogen of 2-aminopyridine.¹⁷⁻¹⁹ A noteworthy exception to these generalizations is 2-amino-5-bromopyridine, which is reported³⁶ to react with β -bromopropionic acid or propiolactone to yield a 4-oxo derivative (such as V) instead of the customary 2-oxo compound. Compound V ($R = \text{H}$)



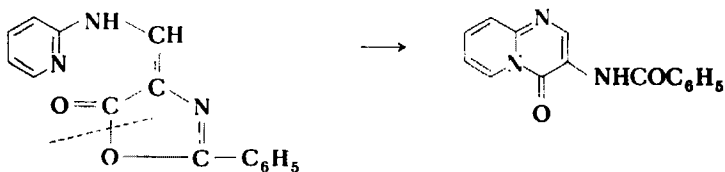
was obtained from 2-aminopyridine and ethoxymethylenemalononic ester. The ultraviolet absorption spectra of IV and V ($R = \text{H}$) are quite dissimilar, as are their physical properties; compound IV ($R = \text{H}$) is higher melting and more soluble in polar solvents than V ($R = \text{H}$) suggesting¹³ a large contribution to the resonance hybrid by dipolar structures such as VIII.



(VIII)

Another method for the preparation of pyrido[1,2-*a*]pyrimidones is the cyclization by sulfuric acid of 2-acylacetamidopyridines.^{5,9,10,12} The demonstrable structure of these intermediates led originally to the conclusion that the pyridopyrimidones produced possessed structure IV. However, it has recently been shown^{12,13,34} that the cyclization is accompanied by a rearrangement, and that products of structure V are formed.

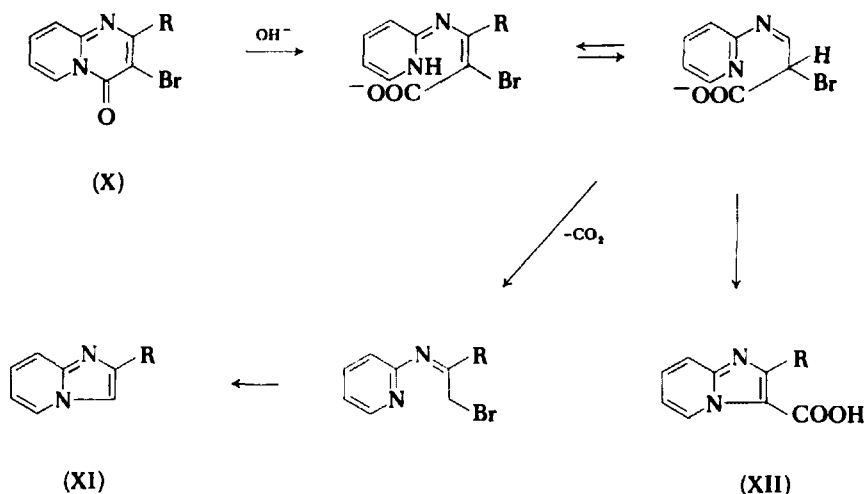
A novel synthesis of the pyrido[1,2-*a*]pyrimid-4-one nucleus from 2-phenyl-4-(α -pyridylamino)-methylene-5-oxazolone (IX), has been reported.²⁵



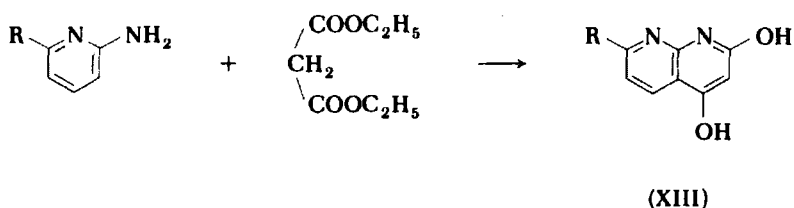
(IX)

Treatment of 2-substituted-3-bromopyrido[1,2-*a*]pyrimid-4-ones (X) with aqueous alkali results in their rearrangement to products XI and XII, possibly via the route shown.³⁴ Under these conditions 3-bromopyrido[1,2-*a*]pyrimid-4-one yields 2-amino pyridine.³⁴

In a recent reinvestigation of the synthesis of compounds of structure I, Lappin, Peterson and Wheeler²⁰ showed that products of that structure are obtained from 2-aminopyridines having methyl groups in the 4 or 5 positions, or with chlorine or bromine in the 5 position. However, 2-aminopyridines with a methyl, amino, acetamino or ethoxy group in the 6 position gave, instead, 2,4-dihydroxy-1,8-naphthyridines (XIII). Also, methyl 2-aminonicotinate has been found²³ to yield 6-carbomethoxy-2,4-dihydro-1,8-naphthyridine. Various explanations have been advanced for the behavior of the 6-substituted-2-aminopyridines in this and related reac-

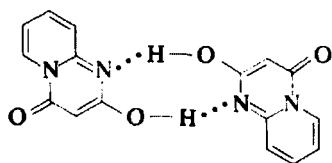


tions,^{8,13,20,23,24,39} and apparently steric factors are largely responsible. It has been shown⁷ that 5-nitro-2-aminopyridine does not react at all with malonic ester, and that 5-halo and 3,5-dihalo-2-aminopyridines give only noncyclic products. The claim,⁶ that 3,5-dibromo-2-aminopyridine reacts with acetoacetic ester to give a cyclic product, has been refuted.¹³



It was known that disubstituted malonic esters¹ and even disubstituted malonyl chlorides⁴ fail to react with 2-aminopyridines to form cyclic products of type I. This was shown to arise from factors other than steric hinderance.³⁵ On the basis of these facts and, especially, the physical properties of the products, Snyder and Robinson²¹ suggest an *enol-dimer* structure such as XIV.

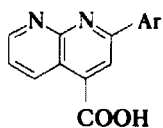
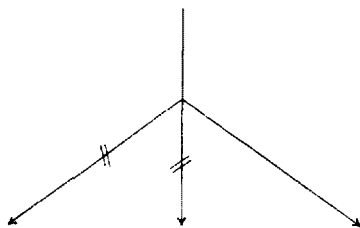
Compounds of types I (or XIV) and V are substituted in the 3 position by halogenation,^{3,13,21,34} nitration^{1,5,11} and diazonium coupling.²¹ The 3-azo derivatives of I (or XIV) are easily decom-



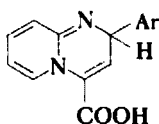
(XIV)

posed under alkaline conditions.²² Replacement of the 2-hydroxyl group in XIV by chlorine is readily accomplished with phosphorus oxychloride, whereas with a mixture of phosphorus oxychloride and pentachloride, the 2,3-dichloro-4-oxo compound results.^{21,43} The chlorine atom in the 2-position of these compounds is readily displaced by nucleophilic reagents.⁴³

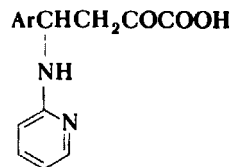
From the reaction of 2-aminopyridine with pyruvic acid and various aromatic aldehydes, Mazza and Migliardi^{26,27} claimed to obtain a group of compounds considered to be 2-aryl-1,8-naphthyridine-4-carboxylic acids (XV). This structure was questioned by Petrow, who suggested²⁸ that the products might have structure XVI. However, an effort to repeat the work of Mazza and Migliardi



(XV)



(XVI)

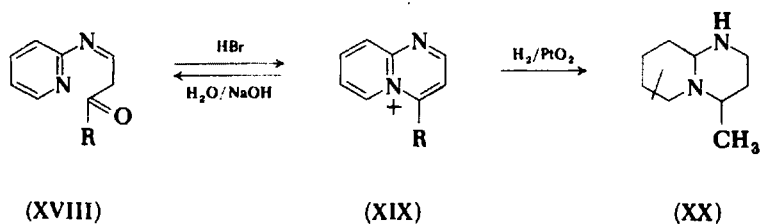


(XVII)

gave only products thought to have structure XVII, and no cyclic products were obtained.²⁹

Partially hydrogenated pyrido[1,2-*a*]pyrimidines have been obtained by condensing 1-chloro-3-bromopropane³⁰ or epichlorhydrin³¹ with 2-aminopyridine. Perhydro³⁰ and 2,4-dioxoperhydro³² derivatives have been prepared by catalytic reduction.

Heating ketones of structure XVIII with aqueous hydrobromic acid and ethanol, is reported⁴² to yield quaternary salts of type XIX. When treated with aqueous caustic, XIX is reconverted into XVIII. Catalytic hydrogenation of XIX ($R = CH_3$) produced XX.



Derivatives of Pyrido[1,2-*a*]pyrimidine

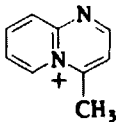
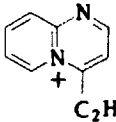
Empirical formula	Substituents	Properties and comments	Refs.
$C_8H_4BrClN_2O$	3-Bromo-3-chloro-4-oxo-	m. 225–8°.	34
$C_8H_4Cl_2N_2O$	2,3-Dichloro-4-oxo-	m. 230° (225.8–6.5°).	21,43
$C_8H_5BrN_2O$	3-Bromo-4-oxo-	m. 133–4°.	34
$C_8H_5BrN_2O_2$	5-Bromo-2-hydroxy-4-oxo-	d. 310°.	20
$C_8H_5ClN_2O$	2-Chloro-4-oxo-	m. 159° (155.2–6.2°).	21,43
$C_8H_5ClN_2O_2$	3-Chloro-2-hydroxy-4-oxo-	m. 310° (d. ~290°).	21,43
	5-Chloro-2-hydroxy-4-oxo-	d. 310°.	20
$C_8H_5N_3O_4$	2-Hydroxy-3-nitro-4-oxo-	Lt. yel., d. 255°.	1,38
$C_8H_6N_2O$	2-Oxo-	m. 249–50°.	13,14
	4-Oxo-	m. 129° (127°).	13,43
$C_8H_6N_2O_2$	2-Hydroxy-4-oxo-	Lt. yel. Begins to d. 285°, and d. 295–8°.	1,21,38, 41
$C_8H_6ClN_3O$	2-Amino-3-chloro-4-oxo-	m. 254°.	43
$C_8H_7BrN_2O$	7-Bromo-3,4-dihydro-4-oxo-	HBr salt, m. 322° d.	36

(continued)

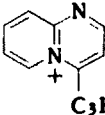
Derivatives of Pyrido[1,2-*a*]pyrimidine (*continued*)

Empirical formula	Substituents	Properties and comments	Refs.
$C_8H_8N_2O$	3,4-Dihydro-2-oxo-	m. 188–90°. HCl salt, m. 295–6° d. (275–6°; 288–9°). HBr salt, m. 303–5° d. (299–300°; 293–4°). HI salt, m. 263–4°. Picrate, m. 224–6° (219–20°; 216–7°).	13–15, 36,39
$C_8H_8N_2O_2$	2,3-Dihydroxy-4 <i>H</i> -	HBr salt, m. 301–3° d.	14
$C_8H_8N_4O$	2-Hydrazino-4(4 <i>H</i>)-oxo-	m. 245°.	43
$C_8H_{10}N_2$	2,3,4-Trihydro-	Yel., hygroscopic, strong base; m. 55–6°, b_{10} 145–55°. HCl salt m. 82–3°. Picrate, m. 172–3°.	30
$C_8H_{10}N_2O$	3-Hydroxy-2,3,4-trihydro-	Oil. HCl salt, m. 190°. Chloroplatinate, yel. m. 215° d.	31
$C_8H_{12}N_2O_2$	2,4-Dioxo-perhydro-	m. 174.0–4.5°.	32
$C_8H_{14}N_2O$	Perhydro-2-oxo-	m. 140–2°. Picrate, m. 149–50°.	14
	Perhydro-4-oxo-	Hygroscopic, m. 61.0–1.8°. Phenyl thiourea deriv., m. 174.5–6.0°.	13,21
$C_8H_{16}N_2$	Perhydro-	b_{10} 85–90°; d. in air and resinifies in acids.	30
$C_9H_6N_2O_3$	3-Carboxy-4-oxo-	m. 265°.	13
$C_9H_7BrN_2O$	3-Bromo-2-methyl-4-oxo-	m. 181.5–2.5°.	34
	7-Bromo-2-methyl-4-oxo- [corrected structure (13)]	m. 169–71° (169–70°).	9,10,13
$C_9H_7ClN_2O$	6-Chloro-2-methyl-4-oxo- [corrected structure (13)]	m. 167–9° (165–6°).	9,10
$C_9H_7IN_2O$	7-Iodo-2-methyl-4-oxo- [corrected structure (13)]	m. 192–3°.	9
$C_9H_7N_3O_3$	2-Methyl-3-nitro-4-oxo- [corrected structure (13)]	Yel. m. 184°, forms no picrate or methiodide.	5

Derivatives of Pyrido[1,2-*a*]pyrimidine (*continued*)

Empirical formula	Substituents	Properties and comments	Refs.
$C_9H_8N_2O$	2-Methyl-4-oxo- [corrected structure (13)]	m. 124–5° (123°; 122°; 120.0–0.5°) b_{3-4} 143–153°. Forms hydrates: 1 H_2O , m. 105–7° (104–5°) and 1.25 H_2O , m. 84°. HCl salt, m. 280–315°. Picrate, m. 184° (177° d.). Chloroplatinate, brn., m. 229° d. Methiodide, or., m. > 280°. Maleic anhydride adduct, m. 135–6°.	4,5,8,12, 13
$C_9H_8N_2O_2$	2-Methoxy-4(4 <i>H</i>)-oxo- 2-Hydroxy-3-methyl-4-oxo- 2-Hydroxy-7-methyl-4-oxo- 2-Hydroxy-8-methyl-4-oxo-	m. 146°. d. 302–3°. d. 300°. d. 270°.	43 1,21,38 20 20
$C_9H_9N_2$		Bromide, d. 204–5°. Perchlorate, d. 226°.	42
$C_9H_{10}N_2O$	3,4-Dihydro-6-methyl-2-oxo- 3,4-Dihydro-7-methyl-2-oxo- 3,4-Dihydro-8-methyl-2-oxo- 3,4-Dihydro-9-methyl-2-oxo-	HI salt, m. 260–3° d. m. 183–5°. HI salt, m. 275–8° d. Picrate, m. 170–1°. HI salt, m. 236–8°. Picrate, m. 169–70°. m. 221°. HI salt, m. 247.0–8.5°. Picrate, m. 166–7°.	39 39 39 39
$C_9H_{17}N_2$	Perhydro-4-methyl-	Picrate, m. 112°.	42
$C_{10}H_{10}N_2O$	2,8-Dimethyl-4-oxo- 2,9-Dimethyl-4-oxo-	m. 137°. Picrate, m. 198°. m. 130°. Picrate, m. 154°.	12 12
$C_{10}H_{10}N_2O_2$	3-Ethyl-2-hydroxy-4-oxo-	d. 260°.	1
$C_{10}H_{11}N_2$		Bromide, m. 210–2°. Perchlorate, m. 169–70°.	42

(continued)

Empirical formula	Substituents	Properties and comments	Refs.
$C_{11}H_9BrN_2O_3$	7-Bromo-3-carbethoxy-4-oxo-	m. 134-5°.	23
$C_{11}H_9ClN_2O_3$	7-Chloro-3-carbethoxy-4-oxo-	m. 132-3°.	23
$C_{11}H_{10}N_2O_3$	3-Carbethoxy-4-oxo-	m. 110-1°.	13
$C_{11}H_{12}N_2O_2$	2-Hydroxy-4-oxo-3-(2-propyl)-	Yel., m. 270°	35
$C_{11}H_{13}N_2$	 Perchlorate, m. 145°.	42	
$C_{11}H_{16}N_2O_3$	3-Carbethoxy-1,6,7,8,9,9a-hexahydro-	m. 211-3°.	13
$C_{12}H_{12}N_2O_3$	3-Carbethoxy-7-methyl-4-oxo-	m. 135-6°.	23
	3-Carbethoxy-8-methyl-4-oxo-	m. 171-2°.	23
$C_{12}H_{14}N_2O_2$	3-(1-Butyl)-2-hydroxy-4-oxo-	Yel., m. 238°.	35
	3-(2-Butyl)-2-hydroxy-4-oxo-	Yel., d. 278°.	35
	2-Hydroxy-3-(2-methylpropyl)-4-oxo-	Yel., m. 237°.	35
$C_{13}H_{14}N_2O_2$	3-Carbethoxy-8-ethoxy-4-oxo-	m. 168-9°.	23
$C_{13}H_{16}N_2O_2$	2-Hydroxy-4-oxo-3-(1-pentyl)-	Yel., m. 224°.	35
	2-Hydroxy-4-oxo-3-(2-pentyl)-	Yel., m. 252°.	35
$C_{14}H_9BrN_2O$	3-Bromo-4-oxo-2-phenyl-	m. 174.5-5.5°.	13
$C_{14}H_9ClN_2O$	3-Chloro-4-oxo-2-phenyl- [corrected structure (13)]	Lt. yel., m. 164°.	3,13
$C_{14}H_9ClN_2O_2$	3-Chloro-4-oxo-2-phenoxy-	m. 148°.	43
$C_{14}H_{10}N_2O$	4-Oxo-2-phenyl-	m. 157° (151°). HCl salt, m. 211-6° d. Picrate, yel. m. 183°. Methiodide, m. 162°.	2,3,13

Derivatives of Pyrido[1,2-a]pyrimidine (*continued*)

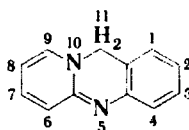
Empirical formula	Substituents	Properties and comments	Refs.
C ₁₄ H ₁₀ N ₂ O ₂	2-Hydroxy-4-oxo-3-phenyl-	Grn.-yel., m. 306-7° (295-7° d.)	35,37,40
C ₁₄ H ₁₀ ClN ₂ O	2-Anilino-3-chloro-4-oxo-	m. 195°.	43
C ₁₄ H ₁₀ ClN ₄ O	2-Chloro-4-oxo-3-phenylazo-	Red, m. 177.0-8.2°.	21
C ₁₄ H ₁₁ N ₄ O ₂	2-Hydroxy-4-oxo-3-phenylazo-	Gold-or., m. 246.0-6.4°.	21,22
C ₁₄ H ₁₆ N ₄ O ₃	2-Methyl-9-(1-methyl-2-pyrrolidyl)-3-nitro-4-oxo-	m. 120-1°.	11
C ₁₄ H ₁₇ N ₃ O	2-Methyl-9-(1-methyl-2-pyrrolidyl)-4-oxo-	m. 112°. HCl salt, d. 244-7°. Picrate, m. 209°. Methiodide, d. 238-40°.	11
C ₁₄ H ₁₈ N ₂ O ₂	3-(1-Hexyl)-2-hydroxy-4-oxo-	Yel., m. 207°.	35
C ₁₅ H ₁₀ N ₄ O ₅ S	2-Hydroxy-4-oxo-3-(4-sulfophenylazo)-	m. 248° d.	21
C ₁₅ H ₁₁ N ₃ O ₂	3-Benzoylamino-4-oxo-	m. 168°.	25
C ₁₅ H ₁₁ N ₄ O ₄	3-(4-Carboxyphenylazo)-2-hydroxy-4-oxo-	Or., m. 261.2-2.0° d.	21
C ₁₅ H ₁₂ N ₂ O ₂	3-Benzyl-2-hydroxy-4-oxo-	Yel., d. <310°.	35
C ₁₆ H ₁₂ N ₄ O ₄	3-(4-Carbomethoxyphenylazo)-2-hydroxy-4-oxo-	Gold-brn., m. 252° d.	21
C ₁₆ H ₁₄ N ₂ O ₂	2-Hydroxy-3-(2-phenylethyl)-4-oxo-	Yel., m. 245°.	35
C ₁₆ H ₁₄ N ₂ O ₃	2-Hydroxy-3-(4-methoxybenzyl)-4-oxo-	Yel., m. 290°.	35
C ₁₇ H ₁₄ N ₄ O ₄	3-(4-Carbomethoxyphenylazo)-2-hydroxy-4-oxo-	Red-or., m. 249° d.	21
C ₁₉ H ₁₈ N ₂ O ₂	2-Hydroxy-3-(6-tetralylmethyl)-4-oxo-	Yel., m. 276°.	35
C ₂₁ H ₂₄ N ₂ O ₂	2,3,4-Trihydro-3-(1-phenylcyclohexanecarboxy)-	m. 186-8°.	33

References

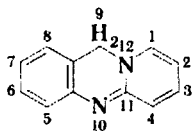
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A-781. 11H-Pyrido[1,2-b]quinazoline.
R.I. 1890

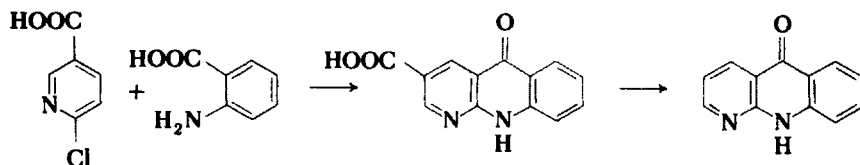


Derivatives of this nucleus have been referred to as *piperidino-1':2':3:2-(3,4-dihydroquinazoline)*, numbered as shown in I, and as *2,3-dihydrobenzquinazolines*.



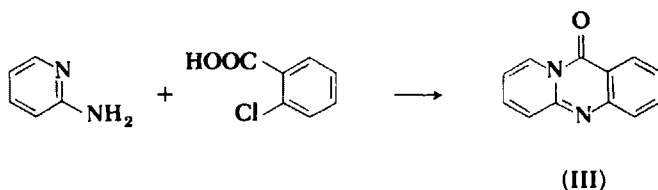
(I)

In 1895 Reissert, from the reaction of 6-chloronicotinic acid with anthranilic acid followed by decarboxylation, obtained¹ a product to which he assigned structure II and the name *pyracridone*. Seide²



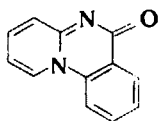
(II)

obtained the same compound from the reaction of *o*-chlorobenzoic acid with 2-aminopyridine, and considered that the correct structure was III. He pointed out that Reissert's inability to obtain an oxygen-



free substance (e.g. by reacting II with POCl_3 , etc.) was to be expected from a compound of structure III, but not from structure II. It was also shown by Bose and Sen,³ that a substance with the same properties as the compound described by Reissert and Seide, was obtained from 2-chloropyridine and anthranilic acid.

This reaction product was also studied by R  th and Binz,⁴ who confirmed the various properties and derivatives previously described. It should be noted that, despite disagreement concerning structure, the various authors are in uniform accord as to the properties of the product obtained. In spite of this, R  th and Binz postulated that their product and Reissert's, had structure II, whereas Seide's product they assigned structure IV. The basis for this postu-

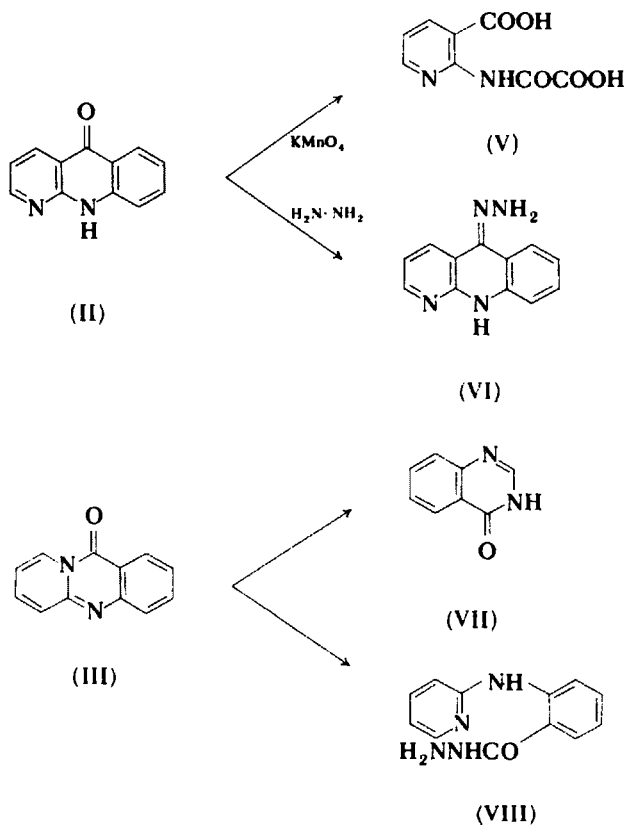


(IV)

late was the belief that they had isolated V and VI from the degradation of their product.

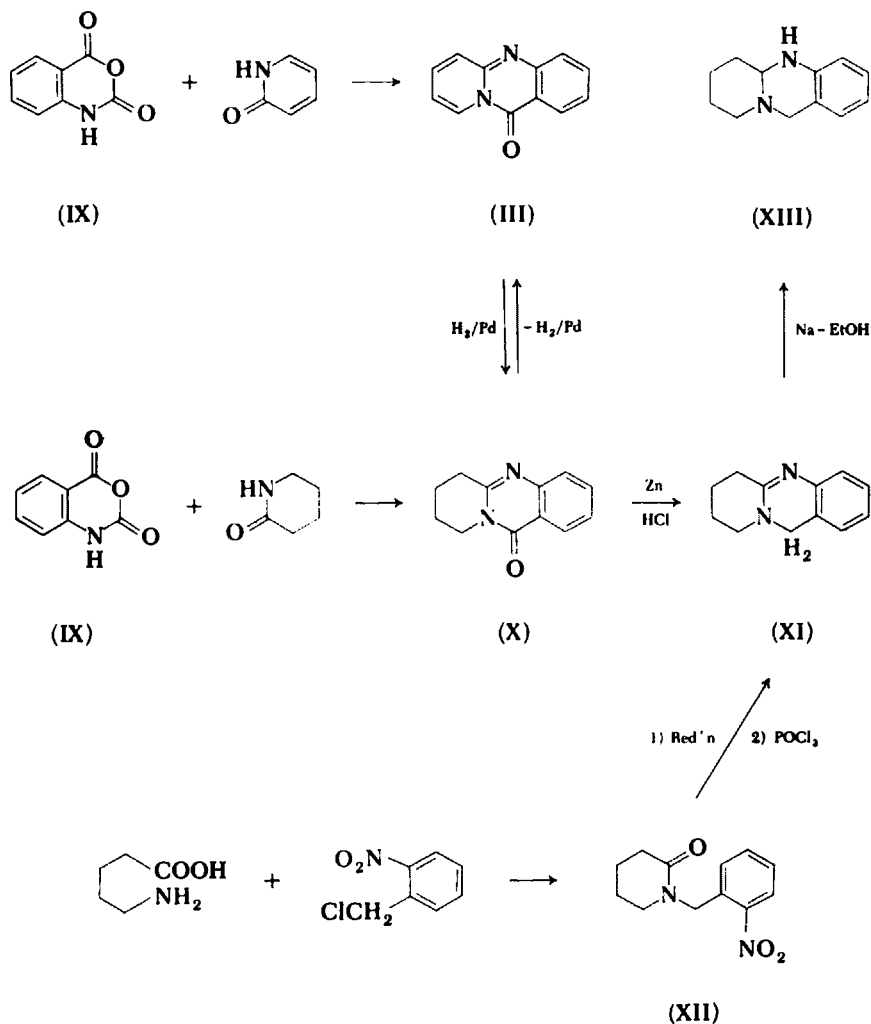
The subject was finally settled by Seide and Tschelinzew,⁵ who showed that all of the products of the previous workers were identical and correctly represented by structure III. They also showed that the degradation products thought⁴ to be V and VI were actually VII and VIII. Further support for structure III was adduced by Sp  th,^{6,7} who prepared the compound during his investigations upon the *peganine* alkaloids (v.i.). Alkaline hydrolysis of III yielded¹⁹ 2-(2-pyridylamino)-benzoic acid.

It is of interest that 2,6-diaminopyridine reacts with o-chlorobenzoic acid to yield, apparently, an amino derivative of II. Con-

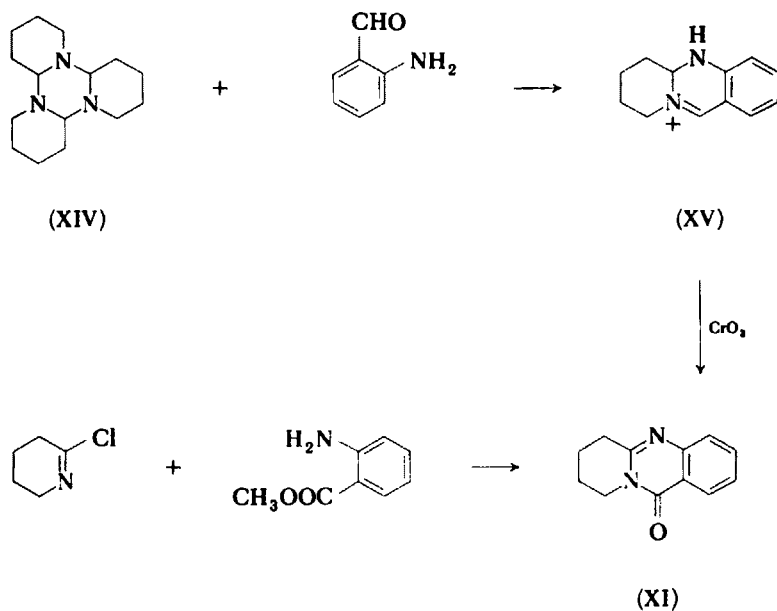


vincing evidence is offered by Kabachnik¹⁴ in favor of the pyracridone structure for this product. This appears to be another example of the anomalous cyclizations undergone by 2-aminopyridines having (electron releasing) substituents in the 6-position (see Section A-780), and other suitable 6-substituted-2-aminopyridines might similarly be expected to yield derivatives of II.

As mentioned earlier, Späth obtained⁷ III from the condensation of IX with α -pyridone. Catalytic reduction of III yielded⁷ X, which was again dehydrogenated to III when heated briefly at 210°. Reduction of X with zinc and hydrochloric acid in acetic acid yielded⁶ XI, which was also obtained⁶ from XII by reduction of the nitro group followed by dehydration with phosphorus oxychloride. Sodium and alcohol reduced XI still further to XIII.



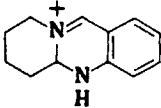
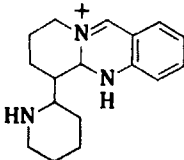
As part of his elegant studies of reactions under "physiological conditions," Schöpf found^{8,9,20} that tripiperidine (e.g. XIV) split in buffered solutions and condensed with *o*-aminobenzaldehyde to yield salts of XV. Oxidation of these salts with chromic acid yielded XI identical with that prepared by Späth from X or XII. Recently, XI was also obtained¹⁸ from the reaction of anthranilic ester with 2-chloro- Δ^1 -piperidine.



While several substitution products of III have been prepared, the location of the substituent is known definitely in only a single case: the 8-nitro derivative of III was obtained from the condensation of anthranilic acid with 2-chloro-5-nitropyridine^{10,17} (or of *o*-chlorobenzoic acid with 2-amino-5-nitropyridine¹⁷). Treatment of III with bromine in acetic acid affords² a monobromoderivative, while heating III with phosphorus pentachloride and phosphorus oxychloride at 180–90° for six hours produced² a trichloro derivative. A mono- and a dinitro derivative were obtained by R  th and Binz, who, however, formulated their products as pyracridones (II). Nonetheless, it is evident that their mononitro-III is not the 8-nitro compound. It seems probable that electrophilic attack upon III would occur first at positions 2 and 4, and upon this basis, several of these substitution products have been assigned structures in the accompanying table.

The amines obtained by reducing nitrated III are claimed¹³ to have bactericidal activity against staphylococci and streptococci.

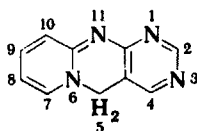
11H-Pyrido[1,2-b]quinazolines

Empirical formula	Substituents or structure	Properties and comments	Refs.
$C_{12}H_3Br_3N_4O_5$	α,α,α -Tribromo-2,4-dinitro-11-oxo-	Yel. m. 220°. Loses Br on solution.	4
$C_{12}H_4Br_2N_4O_5$	α,α -Dibromo-2,4-dinitro-11-oxo-	Yel., m. 200°.	4
$C_{12}H_5Cl_3N_2O$	α,α,α -Trichloro-11-oxo-	m. 328°.	2
$C_{12}H_5BrN_4O_5$	α -Bromo-2,4-dinitro-11-oxo-	Yel., m. 185°.	4
$C_{12}H_6N_4O_5$	2,4-Dinitro-11-oxo-	Yel., m. 282°.	4,13
$C_{12}H_7BrN_2O$	2-(or 4-)-Bromo-11-oxo-	Yel., m. 162°. Br shown by oxid'n. to be in benz ring.	2
$C_{12}H_7N_3O_3$	2-(or 4-)-Nitro-11-oxo-	Yel.-grn., m. 252°.	4,13
	8-Nitro-11-oxo-	Gold-yel., m. 197.5-8.5°.	10,17
$C_{12}H_8N_2O$	11-oxo-	Pale yel., m. 213-4° (210°, 211°). HCl salt, m. 293°, bl. fluorescence in soln. Picrate, yel., m. 238° d. Aurichloride, m. 236°. Chloroplatinate, or., m. 248°. Pheniodide, brn. m. 365°. Methiodide, or.	1-5,7, 13,15
$C_{12}H_9N_3O$	2-(or 4-)-Amino-11-oxo-	Dk. yel., m. 267°.	4,13
$C_{12}H_{10}N_4O$	2,4-Diamino-11-oxo-	Lt. yel., m. 297°.	4,13
$C_{12}H_{12}N_2O$	6,7,8,9-Tetrahydro-11-oxo-	m. 99-100°. Picrate, m. 184-6°.	6-8
	6,7,8,9,10,11-Hexahydro-	m. 82-3°.	6
$C_{12}H_{14}N_2$		Picrate exists in 2 interconvertible forms, red, m. 171-2° and m. 173-5°. Chloride.	8,9,11, 12,20, 21
$C_{12}H_{16}N_2$	5,5a,6,7,8,9,10,11-Octahydro-	m. 71-2°.	6
$C_{17}H_{24}N_3$		Dipicrate, or., 180-2° (175-8°).	8,16

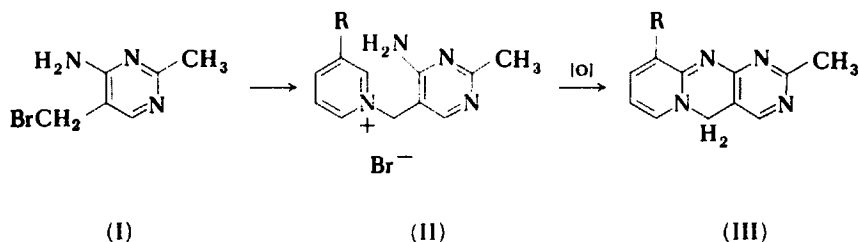
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11. Sch  pf, Bl  dern, Klein and Seitz, *Chem. Ber.*, **83**, 372 (1950).
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15. Tschitschibabin, Ger. Pat. 451,733; *Fr  dl.*, **15**, 335 (1928).
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17. Carboni and Segnini, *Gazz. chim. ital.*, **85**, 1210 (1955).
18. Stephen and Stephen, *J. Chem. Soc.*, **1956**, 4694.
19. Carboni, *Atti soc. toscana sci. nat. (Pisa) Ser. A*, **62**, 261 (1955); *Chem. Abstracts*, **50**, 16767 (1956).
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21. Hasse and Maisack, *Biochem. Z.*, **327**, 296 (1955); *Chem. Abstracts*, **50**, 7162 (1956).

**A-782. 5H-Pyrido[1,2-a]pyrimido-
[4,5-d]pyrimidine**



Compound I reacts with pyridine,^{1,2} quinoline,² nicotinamide,³ and similar tertiary cyclic bases² to yield analogs (such as II) of vitamin B₁ (thiamine). These derivatives also result under certain conditions² in the enzymatic scission of thiamine. Just as thiamine is oxidized by alkaline ferricyanide solution to the strongly fluorescent *thiochrome*, these derivatives (such as II) as oxidized to fluorescent compounds such as III. Compound III (R = H, m. 243°) has been called *pyrichrome* or *pyrichromine*. Compound III (R = CH₃) forms

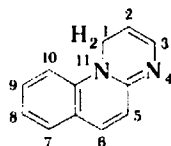


yellow needles, m. 190–200°. ² and gives a picrate, ^{2,5} m. 197.5–9°. The 9-carboxylic acid (III, R = COOH, m. 334.5°) ⁶ and its thiochrome ester ⁴ have been prepared, as has the amide (III, R = CONH₂, m. 273.4°). ^{3,6} See Section A-508.

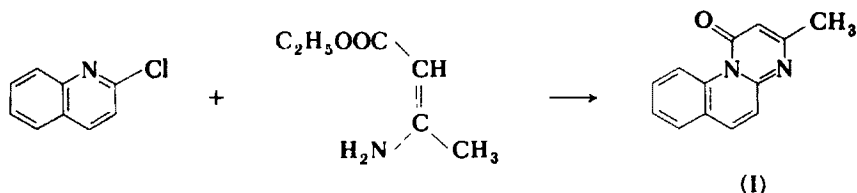
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6. Matsukawa and Yurugi, *J. Vitaminol. (Japan)*, **1**, 27 (1954); *Chem. Abstracts*, **50**, 1010 (1956).

A-783. 1H-Pyrimido[1,2-a]quinoline



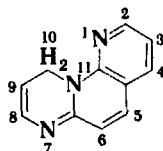
By treating 2-chloroquinoline with ethyl β -aminocrotonate, Antaki and Petrow ¹ obtained compound I (pale yellow, m. 131°; picrate, yellow, m. 207°). An effort to prepare I from 2-aminoquinoline and ethyl β -aminocrotonate gave only *s*-di-(2-quinolyl)-urea. Compound I was called ¹ 4:12-dihydro-4-keto-2-methyl-1:12-diazaphenanthrene.



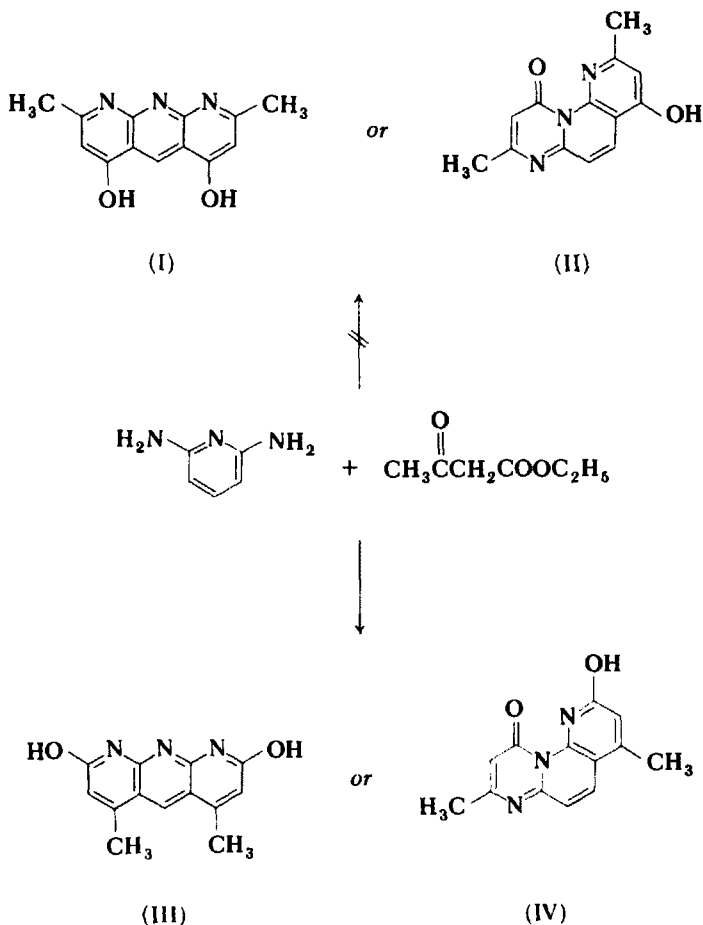
Reference

1. Antaki and Petrow, *J. Chem. Soc.*, **1951**, 551.

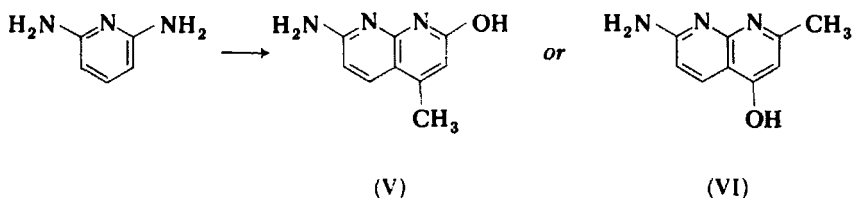
A-784. 10H-Pyrimido[1,2-*a*][1,8]-naphthyridine



By reacting 2,6-diaminopyridine with two moles of acetoacetic ester, Hauser and Weiss¹ obtained a product (m. 230–1°) thought to have either structure I or II. Since Seide² has shown that with



one mole of acetoacetic ester, the product formed has structure V not VI, structures I and II would seem less probable than III or, particularly, IV.

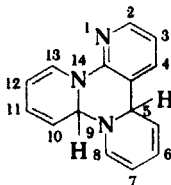


A differentiation between structures III and IV should not be difficult since III contains two, and IV has only one replaceable (e.g. by treatment with phosphorus pentachloride) hydroxyl groups. The infrared and ultraviolet spectra of the related pyrido[1,2-*a*]pyrimidones (see Section A-780) are available and should be of assistance in solving this problem.

References

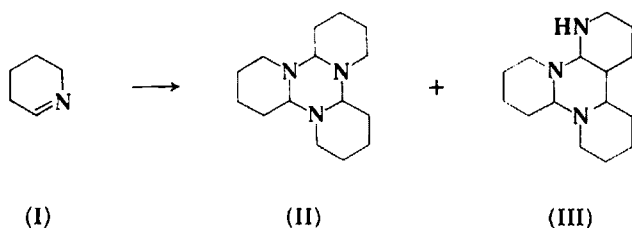
1. Hauser and Weiss, *J. Org. Chem.*, **14**, 353 (1949).
2. Seide, *Ber.*, **59**, 2465 (1926).

A-785. *4bH,9aH*-Tripyrido-
[1,2-*a*, 1',2'-*c*, 3'',2''-*e*]-
pyrimidine



From the electrolytic reduction of nitrosopiperidine, Ahrens^{1,2} obtained a product which he named *dipiperideine*. This same substance was obtained by Ivashchenko and Kirsanov³ from the alkaline hydrolysis of 2-acetamido-1-acetyl piperidine, and assigned by them structure II (see Section A-839).

While investigating the preparation of Δ^1 -piperidine (I), from 1-chloropiperidine, Schöpf and his co-workers⁴⁻⁹ obtained this same compound, gave it the name *isotripiperideine*, and showed that it had structure III. In addition to III, two other trimers of I (α - and β -tripiperideines) were obtained, and these represent stereoisomeric forms of II (see Section A-839). Furthermore, II, when treated^{6,10}

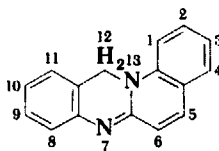


with aqueous alkali, is converted into III. Compound III is a crystalline solid, m. $97-8^{\circ}$, b_{12} $186-90^{\circ}$; it is decomposed by acids, and dissociates into I and tetrahydroanabasine when heated. The cinnamoyl derivative of III (m. $156-7^{\circ}$) has been converted¹¹ into the alkaloid *orensine* (*dl*-adenocarpine).

References

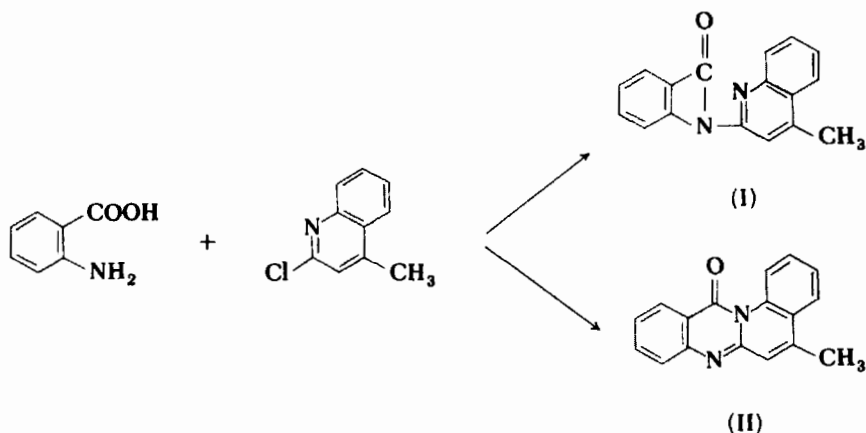
1. Ahrens, *Ber.*, **30**, 533 (1897).
2. Ahrens, *Ber.*, **31**, 2272 (1898).
3. Ivashchenko and Kirsanov, *Bull. soc. chim. France*, [5]3, 2289 (1937)
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5. Schöpf, Arm and Krimm, *Chem. Ber.*, **84**, 690 (1951).
6. Schöpf, Arm and Braun, *Chem. Ber.*, **85**, 937 (1952).
7. Schöpf, Arm, Benz and Krimm, *Naturwissenschaften*, **38**, 186 (1951).
8. Schöpf and Braun, *Naturwissenschaften*, **36**, 377 (1949).
9. Schöpf, Braun and Otte, *Chem. Ber.*, **86**, 918 (1953).
10. Schöpf and Otte, *Chem. Ber.*, **89**, 335 (1956).
11. Schöpf and Kreibich, *Naturwissenschaften*, **41**, 335 (1954).

A-786. 12H-Quino[2,1-b]quinazoline. R.I. 2658

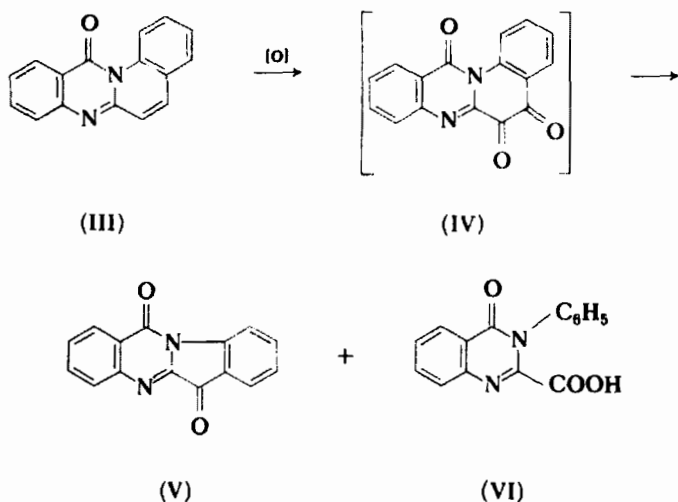


This nucleus has also been called *benzquinazocoline*.

In 1892, Ephraim¹ reported that the reaction of 2-chlorolepidine with anthranilic acid yielded a product to which, because of its solubility in alkalis, he assigned the anthranil structure I. While studying the reaction of anthranilic acid with various haloquinolines and pyridines, Bose and Sen² repeated the preparation of Ephraim's product and proposed structure II by analogy with their preparation of III from anthranilic acid and 2-chloroquinoline.



Apparently unaware of the work of Bose and Sen, Backeberg³ reinvestigated the reaction of anthranilic acid with 2-chlorolepidine, and reaffirmed the accuracy of structure I despite several obvious objections.⁵ However, Seide and Tschelinzew⁴ were able to demonstrate the degradation of III to V and VI (via the intermediate



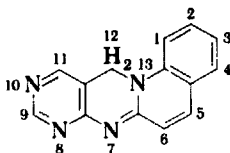
IV), products which could not be obtained from an anthranil structure (such as I). Homologs of II have similarly been prepared.^{2,6}

Quino[2,1-*b*]quinazol-12-ones

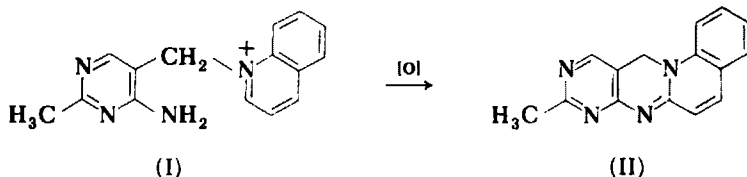
Empirical formula	Substituents	Properties and derivatives	Refs.
C ₁₆ H ₁₀ N ₂ O	Unsubstituted	Lt. yel., m. 170°. HCl salt, forms monohydrate. Picrate, m. 203°. Chloroplatinate, brn., darkens at 275°, d. 327°. Chromate, d. >170°. Methiodide, brn., m. 122° d.	2-4
C ₁₇ H ₁₂ N ₂ O	5-Methyl-	m. 217° (213°). HCl salt m. 222° d. Picrate, m. 223°. Chloroplatinate.	1-3,6
C ₁₈ H ₁₄ N ₂ O	1,5-Dimethyl-	m. 170°.	6
	2,5-Dimethyl-	m. 194.5° (150°).	2,6
	3,5-Dimethyl-	m. 199°.	6
C ₁₈ H ₁₄ N ₂ O ₂	2-Methoxy-5-methyl-	m. 230°.	6
C ₁₉ H ₁₆ N ₂ O ₂	2-Ethoxy-5-methyl-	m. 193°.	6

References

1. Ephraim, *Ber.*, **25**, 2710 (1892).
2. Bose and Sen, *J. Chem. Soc.*, **1931**, 2840.
3. Backeberg, *J. Chem. Soc.*, **1933**, 390.
4. Seide and Tschelinzew, *J. Gen. Chem. (U.S.S.R.)*, **7**, 2318 (1937); *Chem. Zentr.*, **I**, 601 (1938); *Chem. Abstracts*, **32**, 572 (1938).
5. Bose, *Current Sci.*, **2**, 430 (1934); *Chem. Zentr.*, **II**, 2229 (1934).
6. Stephen and Stephen, *J. Chem. Soc.*, **1956**, 4173.

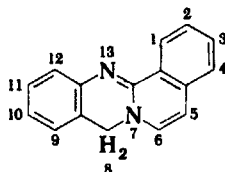
A-787. 12*H*-Benzo[*h*]pyrichromine

Oxidation of I with potassium ferricyanide or with iodine yielded ¹ II, which was not described further. See Section A-782.

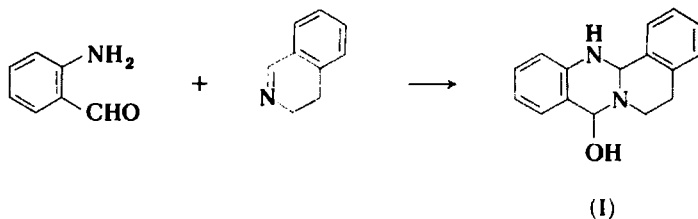


Reference

1. Matsukawa and Yurugi, *J. Vitaminol.* (Japan), **1**, 27 (1954); *Chem. Abstracts*, **50**, 1010 (1956).

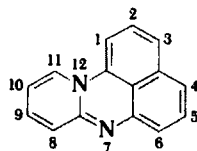
A-788. 8*H*-Isoquino[1,2-*b*]quinazoline

The only recorded representative of this nucleus is compound I (perchlorate, m. 235°) obtained as shown by Schöpf and Steuer.¹



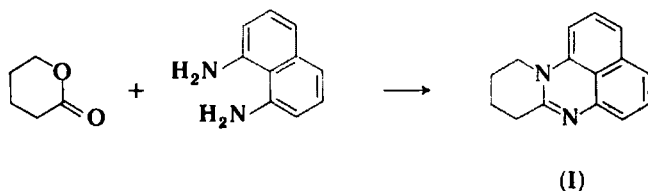
Reference

1. Schöpf and Steuer, *Ann.*, **558**, 124 (1947).

A-789. Benzo[*de*]pyrido[*b*]quinazoline*

The name *pyrido[a]perimidine* might also be used.

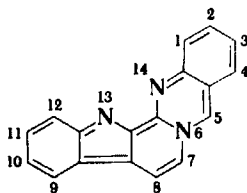
Fusion of 1,8-naphthylenediamine with δ -valerolactone afforded¹ a good yield of compound I (yellow, m. 148–9.5°; picrate, m. 234.3–5.0°).



Reference

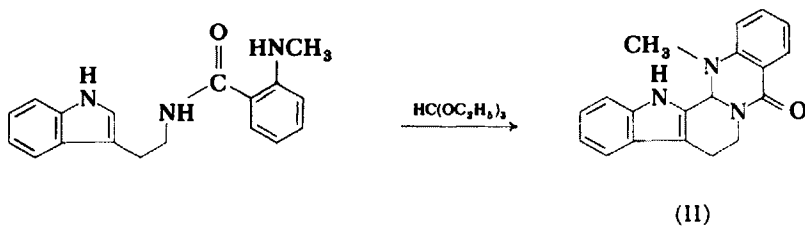
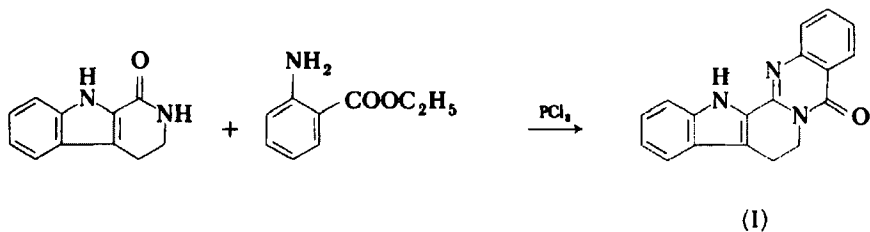
1. Mosby, *J. Org. Chem.*, **24**, 419 (1959).

**A-790. Indolo[2,3-*c*]quinazo-
[3,2-*a*]pyridine**



The 5,13-dihydro derivative was given *R.I.* 3061.

The only representatives known of this ring system are the alkaloids *rutecarpine* (I) and *evodiamine* (II) isolated from *Evodia rutecarpa* Hook. f. and Thoms, and a few of their synthetic derivatives.



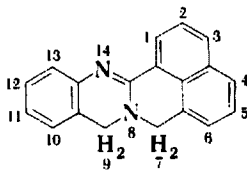
The chemistry of these alkaloids has been discussed *in extenso* by Marion,¹ and will not be repeated here.

Both rutecarpine and evodiamine have been synthesized, the simplest routes being those shown.

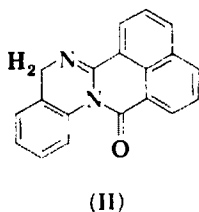
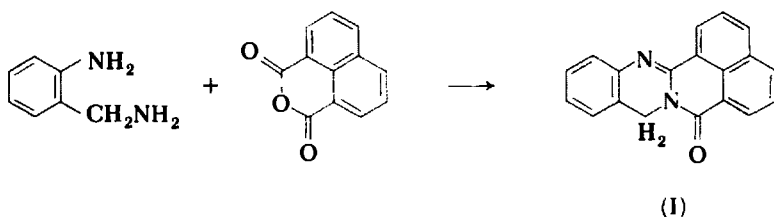
References

1. Marion, in Manske and Holmes, *The Alkaloids*, Academic Press Inc., New York, 1952, Vol. 2, p. 402.
2. Henry, *The Plant Alkaloids*, 4th Ed., The Blakiston Co., Philadelphia, 1949, p. 498ff.

**A-791. 7*H*,9*H*-Benz[4,5]isoquino-
[1,2-*b*]quinazoline**



The condensation of naphthalic anhydride with *o*-aminobenzylamine has been shown¹ to yield I (yellow-orange, m. 211–2°) instead of the alternatively possible II. Compound I, which also results from

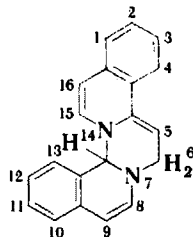


the condensation of *o*-aminobenzylamine with 8-formyl-1-naphthoic acid, has been named¹ 7-oxo-7*H*:9*H*-8:14-diazabenz[de]naphthacene.

Reference

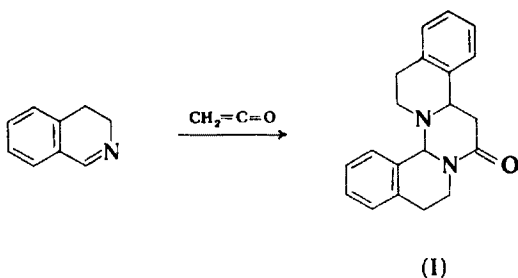
1. Stephenson, *J. Chem. Soc.*, 1954, 2354.

**A-792. 6*H*,13*bH*-Pyrimido[2,1-*a*, 4,3-*a'*]-
diisoquinoline***



The addition of ketenes to a cyclic $>C=N-$ linkage generally occurs in a 1:1 or a 2:1 ratio. However, by passing ketene into

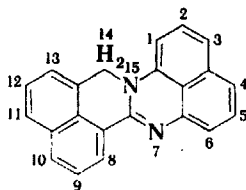
an ethereal solution of 3,4-dihydroisoquinoline, Thesing and Hofmann¹ obtained the 1:2 adduct I (m. 216°) in 75% yield



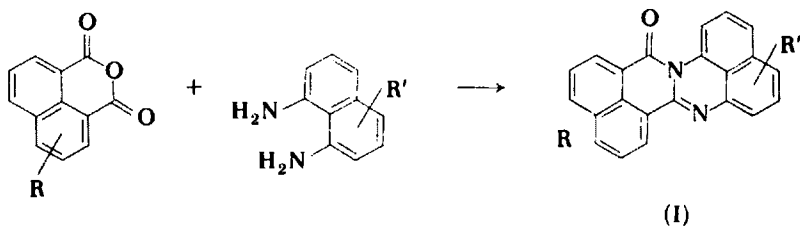
Reference

1. Thesing and Hofmann, *Chem. Ber.*, **90**, 229 (1957).

A-793. Naphthaloperine. R.I. 3587



The trivial name proposed for this nucleus by Sachs¹ has evidently been adopted by *Chemical Abstracts*. The parent compound is unknown, but a variety of naphthaloperinones (I) have been prepared^{1,2,3,5,6} by condensing naphthalic anhydrides with 1,8-naph-



thylenediamines. The use of substituted naphthalic acids (or 1,8-naphthylenediamines) could obviously lead to the formation of two or more isomeric substituted naphthaloperinones. Usually, however, only a single isomer has been reported, although identification of the isomer formed has not been accomplished.

The reaction of 1,8-naphthaldehydic acid with 1,8-naphthylene-diamine failed⁴ to give I ($R = R' = H$).

Naphthaloperinone (I, $R = R' = H$) has been dinitrated and dibrominated to give,¹ presumably, the 3,4-disubstituted derivatives. Prolonged refluxing of I with alcoholic potassium hydroxide opens the pyridone ring.

Several naphthaloperinones have been claimed^{3,5,6} as dyes for superpolyamide resins, and for polyester fibers.⁷

Naphthaloperinones

Empirical formula	Substituents	Properties	Refs.
$C_{22}H_{10}Br_2N_2O$	3,4-Dibromo-	Red, m. 261°.	1
$C_{22}H_{10}N_4O_5$	3,4-Dinitro-	Red, d. 300–10°.	1
	2,5-Dinitro-	—	5
$C_{22}H_{11}BrN_2O$	3-(or 4)-Bromo-	m. 286°. H_2SO_4 solution grn.	2
	10-(or 11)-Bromo-	m. 238–40°. Color in H_2SO_4 , vt., or brn. after 1/2 hr.	3,5,6
$C_{22}H_{11}ClN_2O$	3-(or 4)-Chloro-	m. 276°. H_2SO_4 solution grn.	2
$C_{22}H_{11}BrN_2O_2$	10-(or 11)-Bromo-9-(or 12)-hydroxy-	m. 270°. Color in H_2SO_4 , red, or orange after 1/2 hr.	3,5,6
$C_{22}H_{11}N_3O_3$	9-(or 12)-Nitro-	m. 274°. Color in H_2SO_4 , bl.-vt., or red after 1/2 hr.	3,5,6
	10-(or 11)-Nitro-	m. 292–4°. Color in H_2SO_4 , vt., or red-claret after 1/2 hr.	3,5,6
$C_{22}H_{11}N_3O_4$	9-(or 12)-Hydroxy-	m. > 320°. Color in H_2SO_4 , grn. or blk.-brn. after 1/2 hr.	3,5,6
$C_{22}H_{12}N_2O$	Unsubstituted	Dk. red, m. 253°. H_2SO_4 solution cherry-red.	1,3,5
$C_{22}H_{12}N_2O_2$	9-(or 12)-Hydroxy-	m. 280°. Color in H_2SO_4 , red-brn., unchanged after 1/2 hr. grn.	3,5,6
$C_{22}H_{14}N_4O$	3,4-Diamino-	Blue-vt., d. > 300°.	1
$C_{23}H_{14}N_2O_2$	9-(or 12)-Methoxy-	m. 205°. Color in H_2SO_4 , red-brn., or or. after 1/2 hr.	3,6
$C_{24}H_{12}N_2O_5$	10,11-Dicarboxy-	m. > 350°. Color in H_2SO_4 ,	3
$C_{24}H_{14}N_2O_2$	10-(or 11)-Acetyl-	m. 207°. Color in H_2SO_4 , blk.-bl., or red-brn. after 1/2 hr.	3,6

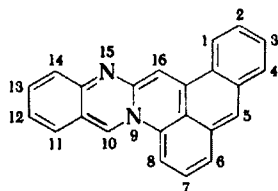
Naphthaloperinones (*continued*)

Empirical formula	Substituents	Properties	Refs.
C ₂₄ H ₁₄ N ₂ O ₃	9-(or 12)-Acetoxy-	m. 320-5°. Color in H ₂ SO ₄ , red-vt., or brn.-or. after 1/2 hr.	3,6
C ₂₄ H ₁₅ N ₃ O ₂	9-(or 12)-Acetylamino-	m. 310°. Color in H ₂ SO ₄ , vt., or brn.-purple after 1/2 hr.	3,6
	10-(or 11)-Acetyl-amino-	m. > 330°. Color in H ₂ SO ₄ , vt., or brn.-purple after 1/2 hr.	3,5,6
C ₂₉ H ₁₆ N ₂ O ₂	10-(or 11)-Benzoyl-	m. 210-5°. Color in H ₂ SO ₄ , vt., or red-brn. after 1/2 hr.	3,6
C ₃₀ H ₁₅ N ₃ O ₃	N-Phenyl-10,11-dicarboximide-	Blue.	3
C ₃₀ H ₁₅ N ₃ O ₄	N-(2-Hydroxyphenyl)-10,11-dicarboximide-	Blue.	3
C ₃₀ H ₁₆ N ₂ O ₄	10-(or 11)-(2-Carboxybenzoyl)-	m. > 300°. Color in H ₂ SO ₄ , blk.-vt., or brn.-vt. after 1/2 hr.	3,6

References

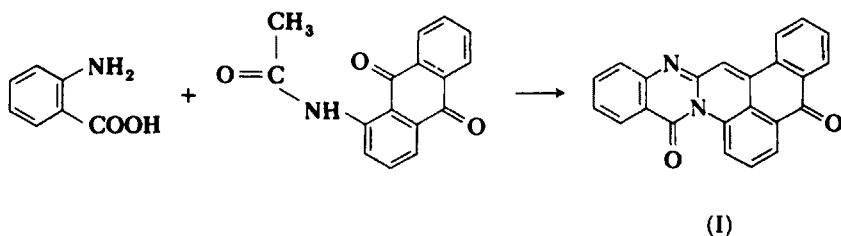
1. Sachs, *Ann.*, **365**, 53 (1909).
2. Hodgson and Hathway, *J. Chem. Soc.*, **1945**, 543.
3. Jones, Brit. Pat. 730,692; Fr. Pat. 1,075,110.
4. Stephenson, *J. Chem. Soc.*, **1952**, 5024.
5. LeThierry d'Ennequin, *Teintex*, **20**, 879 (1955).
6. Robin, Fr. Pat. 1,108,109.
7. Sandoz, Fr. Pat. 1,155,008.

A-794. Dibenzo[*f*,*ij*]quinazo[3,2-*b*]-isoquinoline. R.I. 3586



Dyes containing this nucleus were patented by Lesser and Gad,¹ who obtained them by condensing 1-acetylaminoanthraquinones with anthranilic acids (or 1-aminoanthraquinone with acetylanthran-

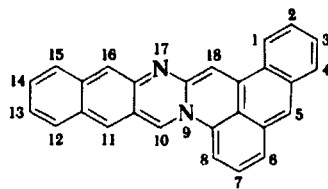
ilic acid) in acetic anhydride in the presence of zinc chloride. Compound I is an orange solid, m. 290°; the 12-bromo derivative of I is orange-yellow, m. over 320°; the 13-chloro-I is orange-red, m. 286–7° and the 13-acetylamino-I is red, m. over 300°



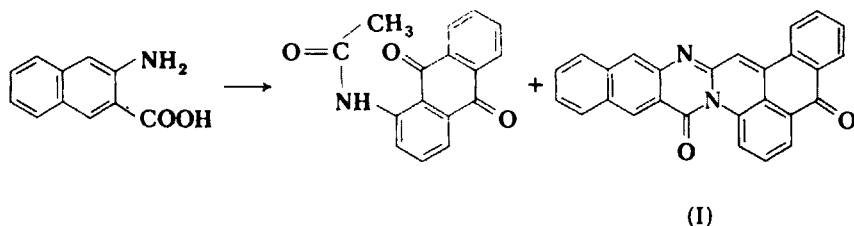
Reference

1. Lesser and Gad, Ger. Pat. 536,448; *Frdl.*, **18**, 1475 (1933).

A-795. Benzo[6,7]quinazolino[3,2-a]-naphtho[1,2,3-de]quinoline*



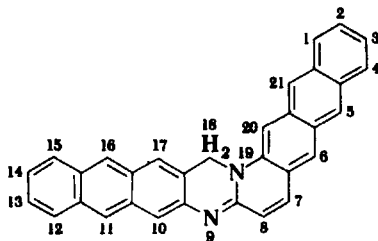
A dye (I) having this ring system was described by Lesser and Gad¹ as orange-red, m. above 310°. It was prepared via the route shown.



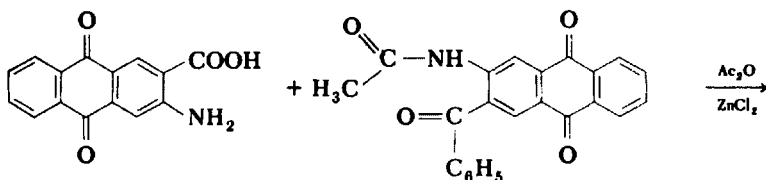
Reference

1. Lesser and Gad, Ger. Pat. 536,448; *Frdl.*, **18**, 1475 (1933).

**A-796. 18*H*-Naphtho[2,3-*g*]naphtho-
[2',3',6,7]quino[2,1-*b*]-
quinazoline***

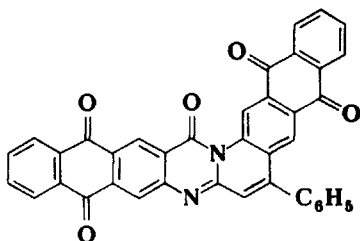


Baumann and Schwechten¹ prepared compound III by the reaction of I with II under acidic dehydrating conditions. The product dyed cotton orange, but showed only fair soda-fastness and poor light-fastness.



(I)

(II)

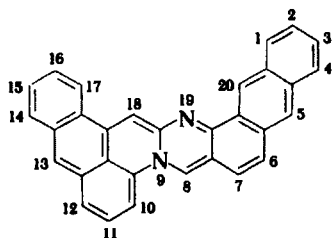


(III)

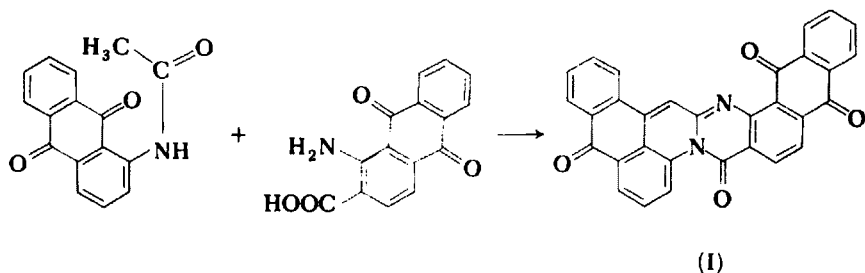
Reference

1. Baumann and Schwechten, *I.G. Farbenindustrie, A.G., 37 Wissenschaftlicher Austausch der Gruppe IX*, Ludwigshafen, March 18 and 19, 1937; *PB Report No. 70339*, frame 11717.

A-797. Dibenz[1,8,5,6]isoquino[3,2-*b*]-naphtho[2,3-*h*]quinazoline*



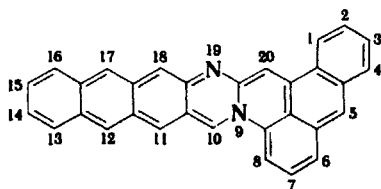
A dye (I) with this nucleus was prepared as shown, by Lesser, Gad and Bruck.¹ The product dyes reddish-yellow from a yellow-brown vat and gives a brown-red solution in sulfuric acid.



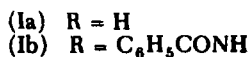
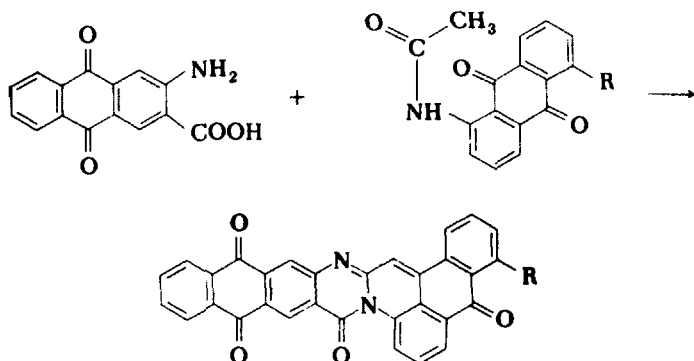
Reference

1. Lesser, Gad and Bruck, Ger. Pat. 561,640; *Frdl.*, **19**, 2166 (1934).

A-798. Naphtho[2,3-*g*]naphtho-[1',2',3',4,5]quino[2,1-*b*]-quinazoline*



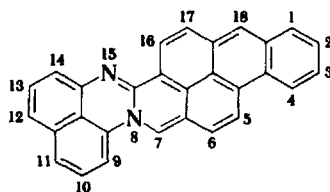
Dyes containing this nucleus were prepared as shown. Compound Ia ($R = H$) dyes orange-yellow from a red vat (sulfuric acid solution is orange-red),¹ while Ib ($R = C_6H_5CONH-$) dyes brown from a red-brown vat (sulfuric acid solution is a brownish bordeaux red).¹ The presence of chlorine or methyl substituents in the 14 or 15 position of Ia gave yellow to brown dyes (yellow to red-brown vats) of indifferent fastness.²



References

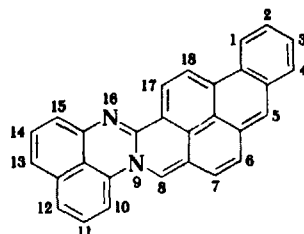
1. Lesser, Gad and Bruck, Ger. Pat., 561,640; *Frdl.*, **19**, 2166 (1934).
2. Braunsdorf, I.G. Farbenindustrie, A.G., 39 Wissenschaftlicher Austausch der Gruppe IX, Mainkur, Feb. 21/2, 1938; P. B. Report No. 70338, frame 10403ff.

A-799. Naphtho[3,2,1-*no*]naphthalopерine*



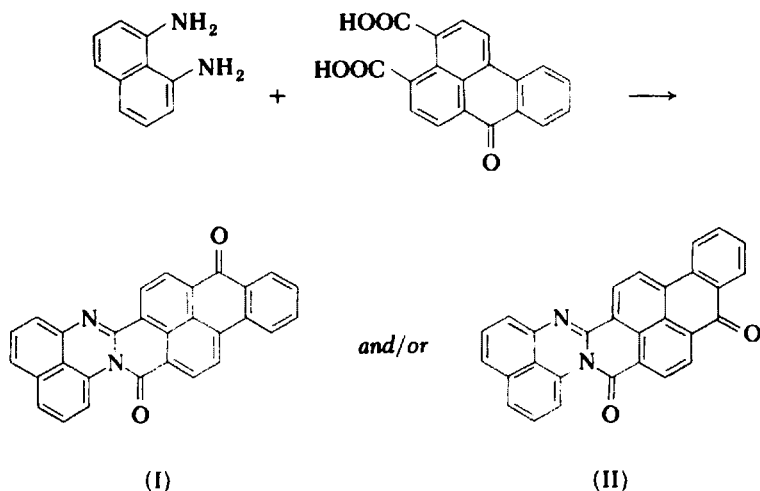
and/or

A-800. Naphtho[1,2,3-*no*]naphthalopерine*



A product, consisting of the oxo derivative of one or both (I and II) of these nuclei has been mentioned.^{1,2}

It was obtained from the condensation of benzanthrone-3,4-dicarboxylic acid with 1,8-naphthylenediamine, melts above 330°, gives

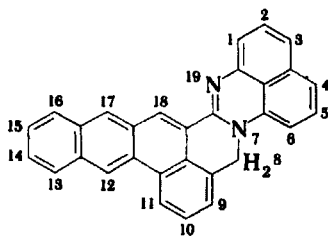


a brown color in sulfuric acid, and dyes cotton a blue-green-grey from a purple vat.³

References

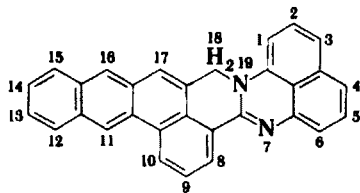
1. Jones, Brit. Pat. 730,692; Fr. Pat. 1,075,110.
2. Robin, Fr. Pat. 1,108,109.
3. Mosby, unpublished observations.

A-801. 8H-Naphtho[2,3-*m*]naphthaloperine*



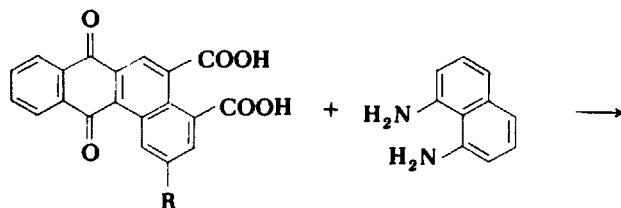
and/or

A-802. 18H-Naphtho[2,3-*p*]naphthaloperine*

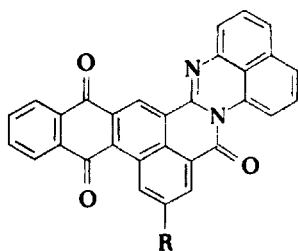


The condensation of benz[*a*]anthraquinone-4,5-dicarboxylic acids (I) with 1,8-naphthylenediamine is reported^{1,2} to yield products

thought to be mixtures of II and III. Four such products were described, in which the nature of the R group, melting point and color

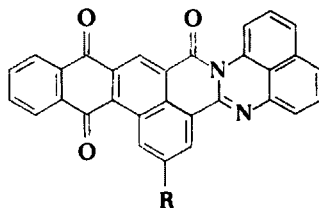


(I)



(II)

and/or



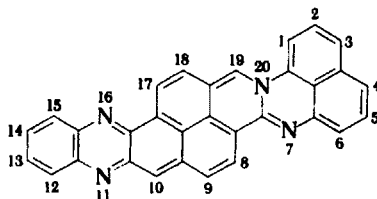
(III)

in sulfuric acid are, respectively, as follows: H, 266°, green; OH, 310–5°, olive-brown; AcO, > 330°, brown; CH₃O, > 330°, brown.

References

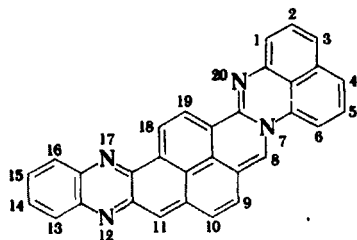
1. Jones, Brit. Pat. 730,692, Fr. Pat. 1,075,110.
2. Robin, Fr. Pat. 1,108,109.

A-803. Phenazino[3,2,1-*no*]-naphthaloperine*

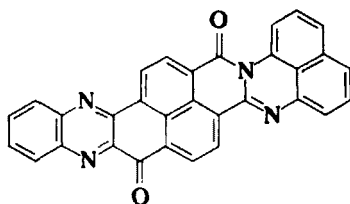


and/or

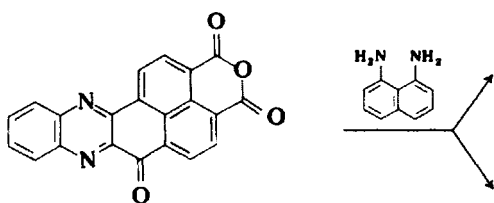
**A-804. Phenazino[1,2,3-*no*]-
naphthaloperine***



A product representing these nuclei, probably a mixture of II and III, was described by Eckert and Sieber¹ as an olive green dye (red vat; yel.-brn. H_2SO_4 solution) formed from I and 1,8-naphthylenediamine.

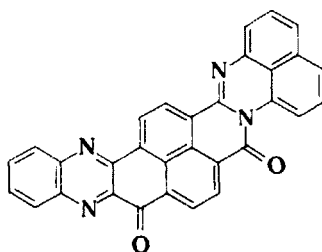


(II)



(I)

and/or

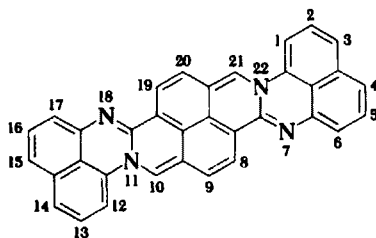


(III)

Reference

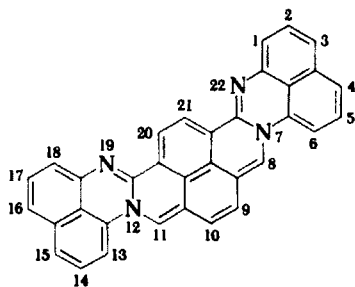
1. Eckert and Sieber, Ger. Pat. 659,095; *Frdl.*, **24**, 973 (1941).

**A-805. Benzo[*lmn*]diperimidino-
[1,2-*c*, 1',2'-*j*][3,8]-
phenanthroline***

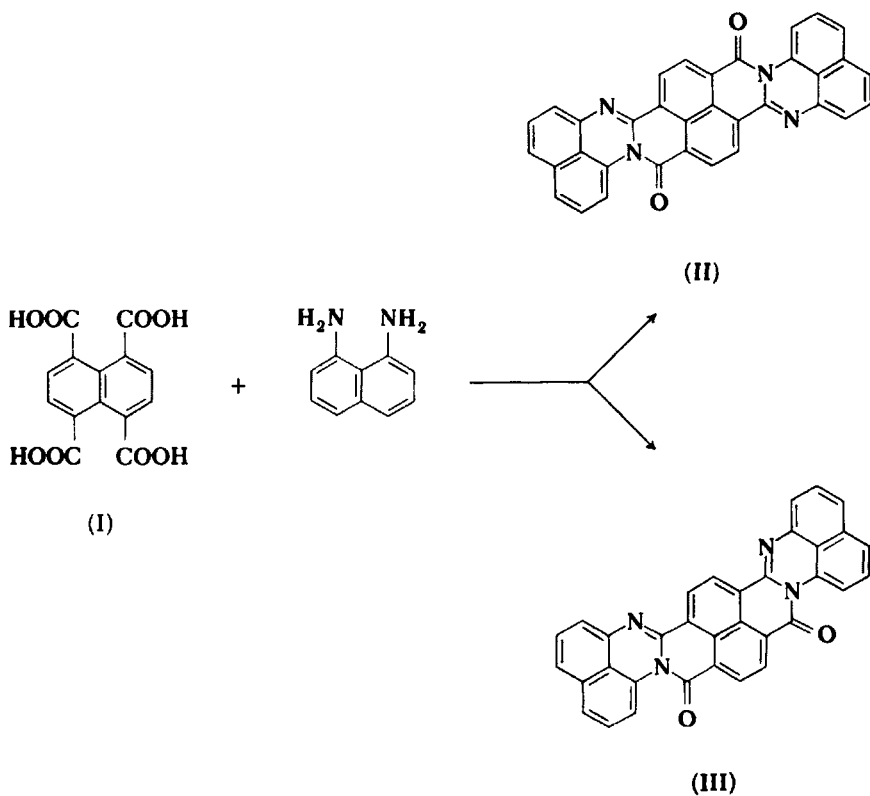


and/or

**A-806. Benzo[*lmn*]diperimidino-
[2,1-*b*, 1',2'-*j*][3,8]-
phenanthroline***



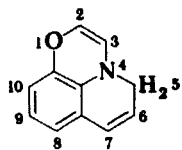
The condensation of 1,4,5,8-naphthylenetetracarboxylic acid (I) with two moles of 1,8-naphthylenediamine yields a product, which might, a priori, be a mixture of II and III. A mixture of analogous isomers results from the condensation of I with *o*-phenylenediamine (see Sections A-324/5) and has been claimed^{1,5,6} to result in the present case. However, paper chromatography (by Klingsberg's method²) fails to disclose³ any inhomogeneity, whereas the imidazole analogs (Sections A-324/5) are readily separated² by this method. The product dyes cotton a rather weak violet from a green vat (the sulfuric acid solution is also green).^{3,5} Chlorination of this dye strengthens the shade and makes it somewhat bluer.³ These products are quite alkali-sensitive (the characteristic vat color is seen only at very low alkali concentrations) presumably as a result of cleavage of the pyridone ring.^{3,5}



References

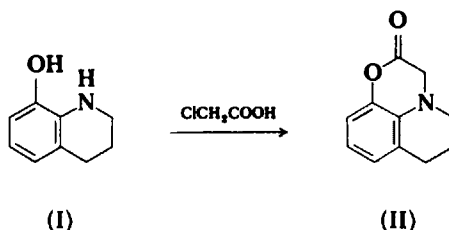
1. Jones, Brit. Pat. 730,692; Fr. Pat. 1,075,110.
2. Klingsberg, *J. Soc. Dyers and Colourists*, **70**, 563 (1954).
3. Mosby, Unpublished observations.
4. d'Ennequin, Dassigny and Robin, *VIIIth International Congress of Pure and Applied Chemistry*, Zurich, 1955, *Handbook*, p. 291.
5. d'Ennequin, *Teintex*, **20**, 879 (1955).
6. Robin, Fr. Pat. 1,108,109.

A-807. 5H-Pyrido[1,2,3-*de*]-1,4-benzoxazine

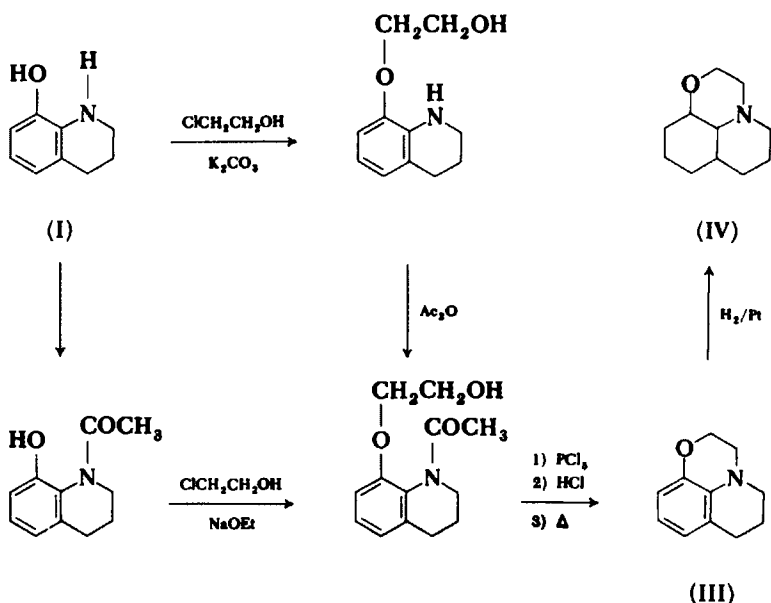


While investigating a series of antipyretics derived from 8-hydroxy-1,2,3,4-tetrahydroquinoline (I), Fischer treated I with chlor-

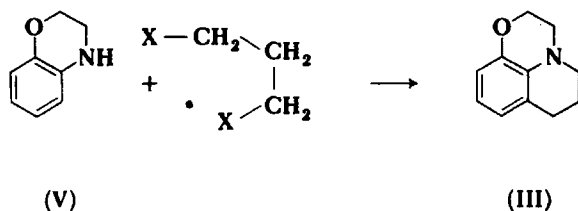
acetic acid and obtained¹ a compound called *Kairocoll* (m. 66°), thought to possess structure II. A similar substance (III, $b_{0.6}$ 86.2–



6.5°; b_6 133–4°; HCl salt, m. 171–2°) was obtained by Isler² from I. Catalytic reduction of III gave IV (b_{12} 122–3°; HCl salt, m. 229–30°; ethiodide, m. 216–7°d.). The preparation of a considerable number of derivatives of III from the reaction of 3,4-dihydro-1,4,2H-



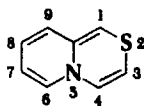
benzoxazines (V) with 1,3-dihaloalkanes and 1,3-dihalo-2-alkanols, etc., was claimed by Dickey and McNally.³ However, as the properties of none of these products were given, they are not enumerated here. It is claimed³ that derivatives of III couple in position 7 with many diazonium salts, to yield orange to red dyes, and with 2,4-dinitro-6-halobenzenediazonium salts to give rubine to green-blue dyes.



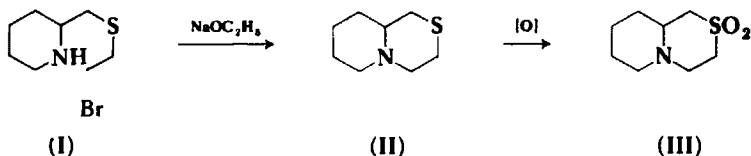
References

1. Fischer, *Ber.*, **16**, 712 (1883).
2. Isler, *Helv. Chim. Acta*, **27**, 1756 (1944).
3. Dickey and McNally, U. S. Pat. 2,448,869.

A-808. Pyrido[2,1-c][1,4]thiazine*



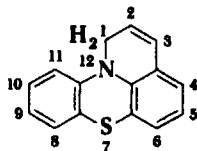
Dehydrohalogenation of I yielded¹ II (b₁₄ 107–8°; picrate, m. 217–20°d.; perchlorate, m. 141–2°; methiodide, m. 280–1°), which could be oxidized to III (m. 165–6°; perchlorate, m. 196–8°) by either peracetic or perphthalic acids.



Reference

1. Rink and Liern, *Naturwissenschaften*, **44**, 559 (1957).

A-809. 1H-Pyrido[3,2,1-jkl]phenothiazine

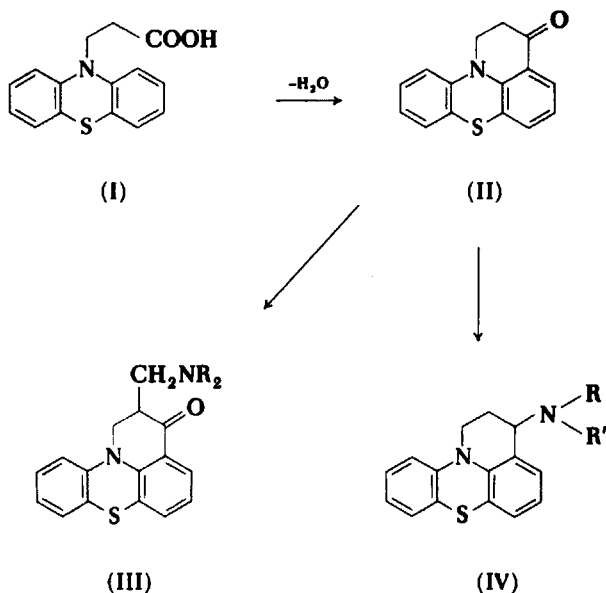


The acid I (obtained from the reaction of acrylonitrile with phenothiazine, followed by hydrolysis of the resulting propionitrile) has been dehydrated^{1-3,11} to II, which was called 5':6'-dihydro-4''-

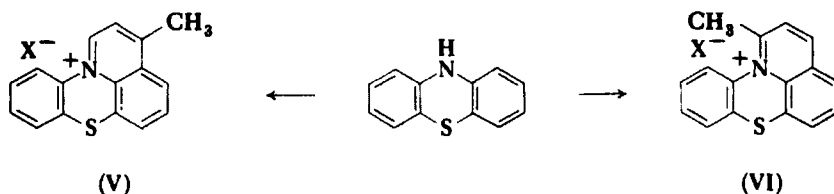
oxopyridino(3':2':1':1:10a:10)phenothiazine. This cyclization occurs with great facility, and the ketone (II) is the usual product of efforts to prepare the acid chloride of I. The 4- and 10-chloro homologs of II were obtained¹¹ similarly. Derivatives of II were investigated^{2,3,10} as anthelmintics.

Reduction of II⁹ and its 10-chloro homolog¹¹ with lithium aluminum hydride or by hydrogenation over Raney nickel catalyst yielded the corresponding carbinols, while hydrogenation of the 4-chloro homolog over Raney nickel in the presence of caustic resulted¹¹ in simultaneous dechlorination.

Compound II underwent the Mannich reaction to yield¹² products of structure III. Upon reaction with formamide or methylformamide, II and its chloro homologs yielded¹² formamides of type IV ($R = \text{CHO}$, $R' = \text{H}$, or CH_3). Hydrolysis gave the corresponding amines (IV, $R = \text{H}$, $R' = \text{H}$ or CH_3), while reduction with lithium aluminum hydride gave the dimethylamino compound (IV, $R = R' = \text{CH}_3$). The melting point reported¹² ($258-60^\circ$) for the primary amine (IV, $R = R' = \text{H}$) prepared in this manner is surprisingly high, and not in accord with the value reported⁹ for the same product obtained by reduction of the oxime of II.



Heseltine and Brooker^{4,5,6} obtained a number of derivatives of this nucleus by treating phenothiazine with methyl vinyl ketone or crotonaldehyde, to yield V and VI, respectively, which were used to prepare cyanine dyes.



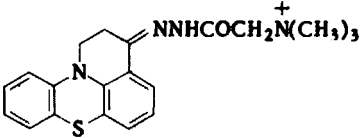
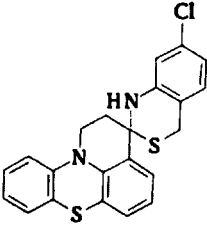
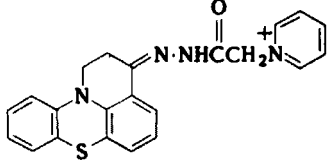
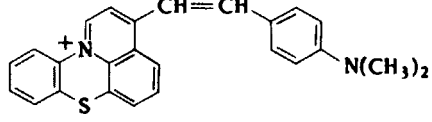
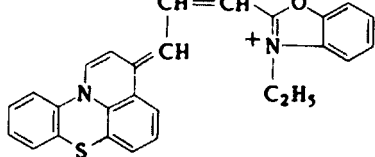
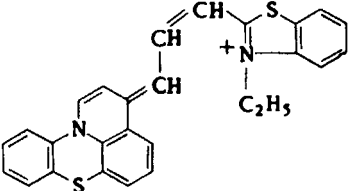
1*H*-Pyrido[3,2,1-*ijkl*]phenothiazines

Empirical formula	Substituents or structure	Properties	Refs.
C ₁₅ H ₁₀ ClNOS	4-Chloro-2,3-dihydro-3-oxo-	Oxime, m. 236-8°.	11
	10-Chloro-2,3-dihydro-3-oxo-	Oxime, m. 228-9°.	11
C ₁₅ H ₁₁ NOS	2,3-Dihydro-3-oxo-	Yel., m. 112-3°.	1,2,8,9,11
		Oxime, m. 206.5-8°.	
		Phenylhydrazo- zone, m. 167°.	
		2,4-DNPH, red, m. 90°. Semi- carbazone, yel., m. 237-8°.	
		Benzylidene deriv., yel., m. 164°.	
C ₁₅ H ₁₁ NO ₄ S ₂	2,3-Dihydro-3-oxo- <i>α</i> -sulfo-	Or., m. > 300°.	9
C ₁₅ H ₁₂ ClNOS	10-Chloro-2,3-dihydro-3-hydroxy-	m. 142-3°.	11
C ₁₅ H ₁₃ NOS	2,3-Dihydro-3-hydroxy-	m. 124.5-5°.	9,11
C ₁₅ H ₁₃ ClN ₂ S	3-Amino-4-chloro-2,3-dihydro-	Picrate, m. 202-3°.	12
		m. 267-8°.	12
		m. 122.5-3° (258-60°?).	9,11
C ₁₅ H ₁₄ N ₂ S	3-Amino-2,3-dihydro-	HCl salt, m. 185-95°.	
		N-Acetyl deriv., m. 172-3° (220-1°?).	

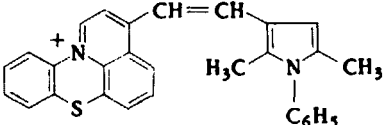
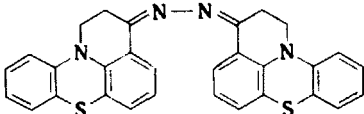
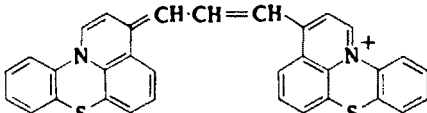
Empirical formula	Substituents or structure	Properties	Refs.
$C_{16}H_{12}NS$		Perchlorate.	6
		Iodide, m. 287-8°.	4,5,7
$C_{16}H_{13}ClN_2OS$	4-Chloro-3-formamido-2,3-dihydro-	m. 199-200°.	12
	10-Chloro-3-formamido-2,3-dihydro-	m. 247-8°.	12
$C_{16}H_{14}N_2OS$	3-Formamido-2,3-dihydro-	m. 199-200°.	12
$C_{16}H_{14}N_6O_2S$		Yel., m. 234-5° d.	3
$C_{16}H_{15}ClN_2S$	10-Chloro-2,3-dihydro-3-methylamino-	Picrate, red, m. 209-10°.	12
$C_{16}H_{16}N_2S$	2,3-Dihydro-3-methylamino-	HCl salt, m. 235-6°. Picrate, red, m. 179-80°.	12
$C_{17}H_{15}N_3OS$		Yel., m. 258-9°.	8
$C_{17}H_{15}ClN_2OS$	4-Chloro-2,3-dihydro-3-methylformamido-	m. 177-8°.	12
	10-Chloro-2,3-dihydro-3-methylformamido-	m. 145-7°.	12
$C_{17}H_{16}N_2OS$	2,3-Dihydro-3-methylformamido-	m. 175-6°.	12
$C_{17}H_{17}ClN_2S$	4-Chloro-2,3-dihydro-3-dimethylamino-	Picrate, m. 180-1° d.	12
	10-Chloro-2,3-dihydro-3-dimethylamino-	Picrate, m. 205-6° d.	12
$C_{17}H_{18}N_2S$	2,3-Dihydro-3-dimethylamino-	Picrate, brn., m. 158-60°.	12
$C_{18}H_{18}N_2OS$	2,3-Dihydro-2-dimethylaminomethyl-3-oxo-	HCl salt, yel., m. 161-2°.	12

(continued)

1*H*-Pyrido[3,2,1-*ijkl*]phenothiazines (*continued*)

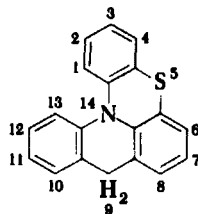
Empirical formula	Substituents or structure	Properties	Refs.
C ₂₀ H ₂₀ N ₂ O ₂ S	2,3-Dihydro-2-(1-morpholinomethyl)-3-oxo-	HCl salt, yel., m. 172-3°.	12
C ₂₀ H ₂₃ ClN ₄ OS		Chloride, yel., m. 200° d.	8
C ₂₁ H ₁₅ ClN ₂ S ₂		Scarlet, m. 206-7°.	3
C ₂₂ H ₁₉ ClN ₄ OS		Chloride, yel., m. 192-4°.	3,8
C ₂₅ H ₂₁ N ₂ S		Iodide, m. 229-30°.	5
C ₂₇ H ₂₁ N ₂ O ₂ S		Iodide, m. 239-41°.	5
C ₂₇ H ₂₁ N ₂ S ₂		Iodide, m. 211-2°.	5

1H-Pyrido[3,2,1-*ijkl*]phenothiazines (*continued*)

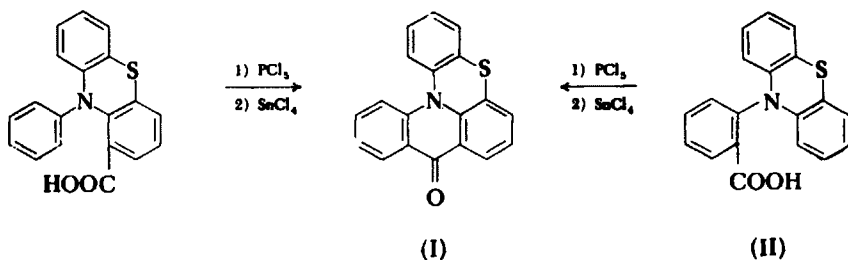
Empirical formula	Substituents or structure	Properties	Refs.
$C_{29}H_{23}N_2S$		Iodide, m. 249–50°.	5
$C_{30}H_{22}N_4S_2$		Or.-yel., m. 299–300° d.	8
$C_{33}H_{21}N_2S_2$		Iodide, m. 277–8°.	5

References

1. Smith, *J. Org. Chem.*, **15**, 1125 (1950).
2. Mackie and Cutler, *J. Chem. Soc.*, **1954**, 2577.
3. Mackie and Misra, *J. Chem. Soc.*, **1955**, 1281.
4. Heseltine and Brooker, U. S. Pat. 2,578,304.
5. Brooker and Heseltine, U. S. Pat. 2,646,430; Brit. Pat. 713,255.
6. Heseltine, U. S. Pats. 2,578,303 and 2,646,433.
7. Heseltine and Brooker, U. S. Pat. 2,636,035.
8. Mackie and Misra, *J. Chem. Soc.*, **1955**, 4025.
9. Godefroi and Wittle, *J. Org. Chem.*, **21**, 1163 (1956).
10. Mackie, Stewart, Cutler and Misra, *Brit. J. Pharmacol.*, **10**, 7 (1955); *Chem. Abstracts*, **49**, 11181 (1955).
11. Fujii, *Yakugaku Zasshi*, **77**, 1065 (1957); *Chem. Abstracts*, **52**, 5417 (1958).
12. Fujii, *Yakugaku Zasshi*, **77**, 1068 (1957); *Chem. Abstracts*, **52**, 5418 (1958).

A-810. 9*H*-Quino[3,2,1-*kl*]phenothiazine

While investigating the metallation of the phenothiazine nucleus, Gilman, Shirley and Van Ess obtained¹ compound I (yellow-green,

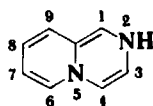


m. 218–9°). The structure was confirmed by an alternate synthesis from II.

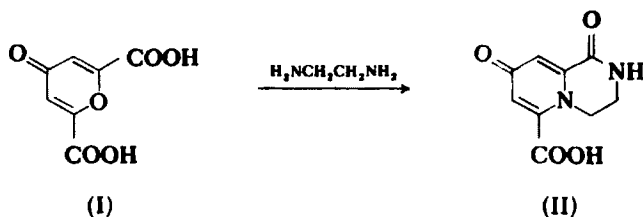
Reference

1. Gilman, Shirley and Van Ess, *J. Am. Chem. Soc.*, **66**, 625 (1944).

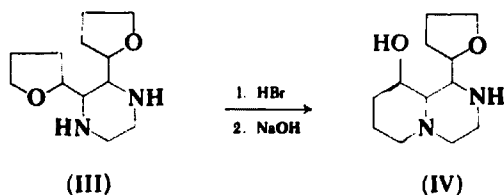
A-811. 2H-Pyrido[1,2-a]pyrazine



By treating chelidonic acid (I) with ethylenediamine, Schwab isolated^{1,2} compound II (m. > 300°; *p*-bromphenacyl derivative dihydrate, m. 172–4°d.). The ultraviolet and infrared spectra of II have been measured.¹

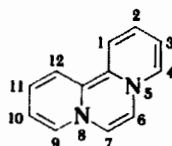


Compound IV ($b_{0.7}$ 143–4°, n_D^{20} 1.5245, dipicrate, m. 240°) was among the products (see Section A-812) isolated³ from the treatment of III with hydrogen bromide followed by caustic.

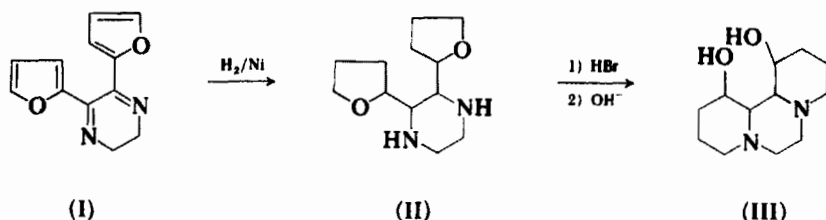


References

1. Schwab, *J. Am. Chem. Soc.*, **76**, 1189 (1954).
2. Schwab, U. S. Pat. 2,740,786.
3. Paul and Buisson, Brit. Pat. 763,990.

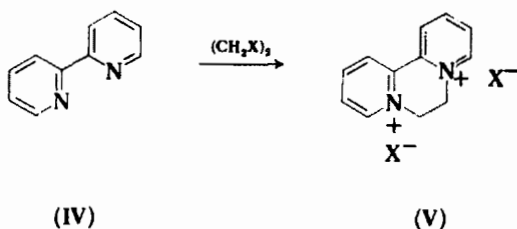
A-812. Dipyrido[1,2-*a*, 2',1'-*c*]pyrazine*

The reaction of furil with ethylenediamine gave I, which was hydrogenated over Raney nickel to II; treatment of this with hydrogen bromide in acetic acid followed by caustic yielded^{1,2} III. The name *bis-(3'-oxypiperidino)-1',2':1,2; 1',2'; 4,3-piperazine* was given to III, which was obtained in two stereoisomeric modifications: *alpha*



(m. 170–1°, b_{1,2} 177–8°; dipicrate, m. 266–8°; bis-diphenylacetate ester, m. 167°, and its dihydrochloride, m. 236–8°; dibenzoate ester, m. 154°, and its monohydrochloride, m. 224–5°) and *beta* (m. 148–9°, b_{0,5} 183–4°; dipicrate, m. 252°; bis-diphenylacetate ester, m. 157° and its dihydrochloride, m. 177–80°; dibenzoate, m. 134°, and its monohydrochloride, m. 153–5°).

Herbicidal compounds⁴ of structure V (X = Cl, m. 320°d.; X = Br, m. 335–40°; X = I, orange, m. 323 d., and X = *p*-toluenesulfonate, m. 235°) have been obtained³ from 2,2'-dipyridyl (IV). Hy-

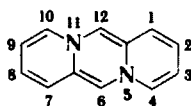


drogenation of V over Raney nickel gave⁴ the perhydro compound ($b_{0.2} 74-6^\circ$).

References

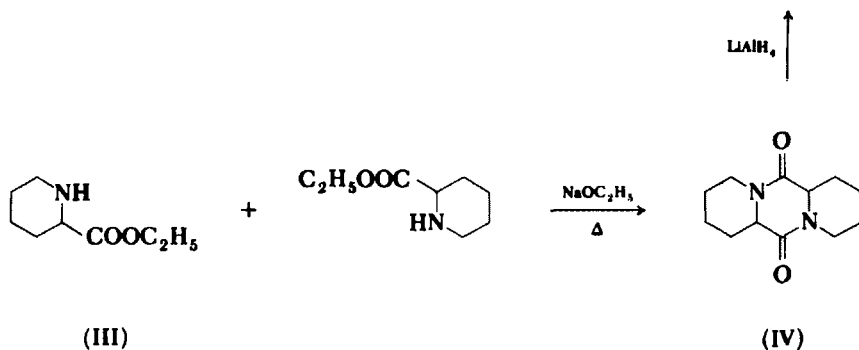
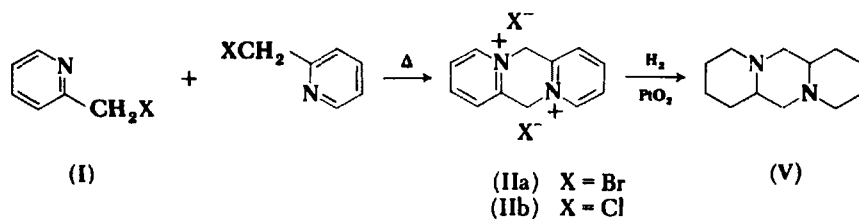
1. Paul, *Bull. soc. chim. France*, **1956**, 838.
2. Paul and Buisson, Ger. Pat. 1,006,422. Brit. Pat. 763,990.
3. Fielden, Homer and Jones, Brit. Pat. 785,732. U. S. Pat. 2,823,987.
4. Brian, Homer, Stubbs and Jones, *Nature*, **181**, 446 (1958).

A-813. Dipyrido[1,2-*a*, 1',2'-*d*]pyrazine



The name *dipyrido[1',2',1,2:1'',2'',4,5]pyrazine* has also been used³ and the trivial name *quinanthridine* has been proposed.²

Heating 2-halomethylpyridines (I) has been shown^{1,3,4} to produce II ($X = \text{Br}$, m. 290°d. ; $X = \text{Cl}$, m. $253-5^\circ$, dihydrate, m. $100-5^\circ$). Compound IIb is also found³ among the products of the reaction of phosphorus oxychloride upon α -picoline-1-oxide, and is undoubtedly formed via I ($X = \text{Cl}$).

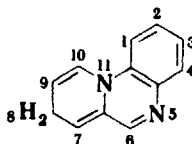


The self-condensation of ethyl pipercolinate (III) yielded² IV (m. 222.5–3.0°), which was reduced to V (m. 95.5–6.0°) by lithium aluminum hydride. The catalytic reduction of IIb also yields³ V (b₁ 95–100°; m. 92–5°; picrate, m. 230°), while the V obtained from the catalytic reduction of IIa is reported¹ to melt at 81° and boil at 170°/30 mm. This latter product may be a different stereoisomeric modification of V, but also may merely be impure.

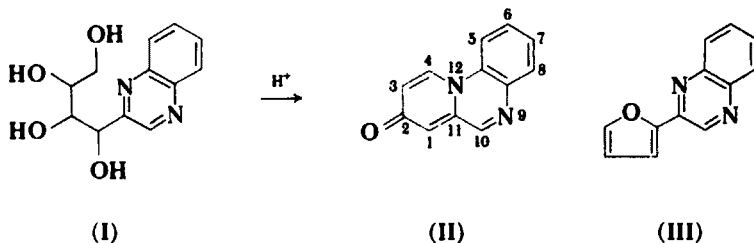
References

1. Šorm and Sedivý, *Collection Czechoslov. Chem. Commun.*, **13**, 289 (1948); *Chem. Obzor.*, **20**, 175 (1945); *Chem. Abstracts*, **43**, 2996 (1949).
2. Winterfeld and Will, *Naturwissenschaften*, **42**, 178 (1955); *Chem. Abstracts*, **50**, 10107 (1956).
3. Kato, *J. Pharm. Soc. Japan*, **75**, 1239 (1955); *Chem. Abstracts*, **50**, 8665 (1956).
4. Boekelheide and Feely, *J. Am. Chem. Soc.*, **80**, 2217 (1958).

A-814. 8H-Pyrido[1,2-a]quinoxaline. R.I. 1895



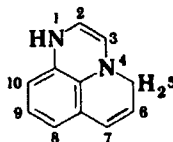
It was found by Griess and Harrow¹ that many hexose sugars condense with *o*-phenylenediamine to yield quinoxalines such as I. This reaction was investigated by Maurer and his co-workers,²⁻⁵ who found that under acidic conditions I is converted into a new product, to which they assigned structure II (with the numbering shown) and the trivial name *glucazidone*. The reactions of this product with a variety of reagents were studied and numerous derivatives were prepared.²⁻⁵ However, Gómez-Sánchez, *et al.*⁶⁻⁸ have recently demonstrated that Maurer's *glucazidone* actually has structure III, which leaves this ring system without representation.



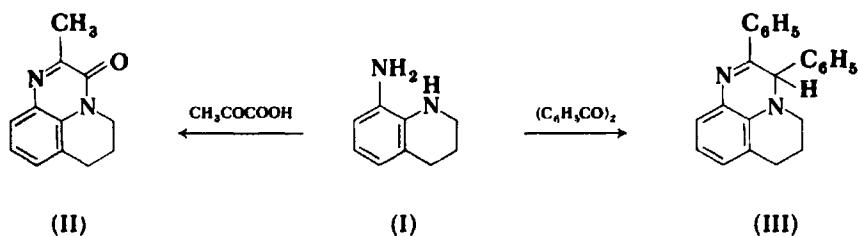
Reference

1. Rupe and Thommen, *Helv. Chim. Acta*, **30**, 920 (1947).

A-816. 1*H*,5*H*-Pyrido[1,2,3-*de*]quinoxaline. R.I. 1896/7



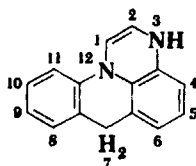
Treatment of 8-amino-1,2,3,4-tetrahydroquinoline (I) with pyruvic acid is reported¹ to yield II (m. 113°). Similarly, the reaction between I and benzil yields an orange product (m. 146°) assigned structure III, which was named 2,3-diphenyl-6,7-dihydroquinolo-1,4-diazine.



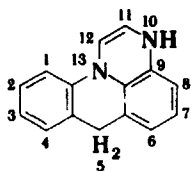
Reference

1. Hazelwood, Hughes and Lions, *J. Proc. Roy. Soc. N.S. Wales*, **71**, 462 (1938); *Chem. Abstracts*, **33**, 610 (1939).

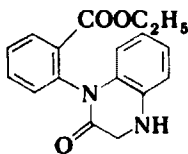
A-817. 3*H*,7*H*-Pyrazino[3,2,1-*de*]-acridine. R.I. 2659



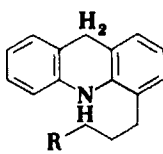
The trivial name *acridoxaline* and the numbering shown in I were given this nucleus by Clemo, Perkin and Robinson.¹ These authors attempted, without success, to prepare derivatives of this nucleus by the cyclization of II and III (R = Cl, OH, etc.). However, IV gave a mixture of V (m. 168°; *N*-nitroso derivative, m. 167°) and VI. Compound VI was saponified with methanolic caustic to VII,



(I)

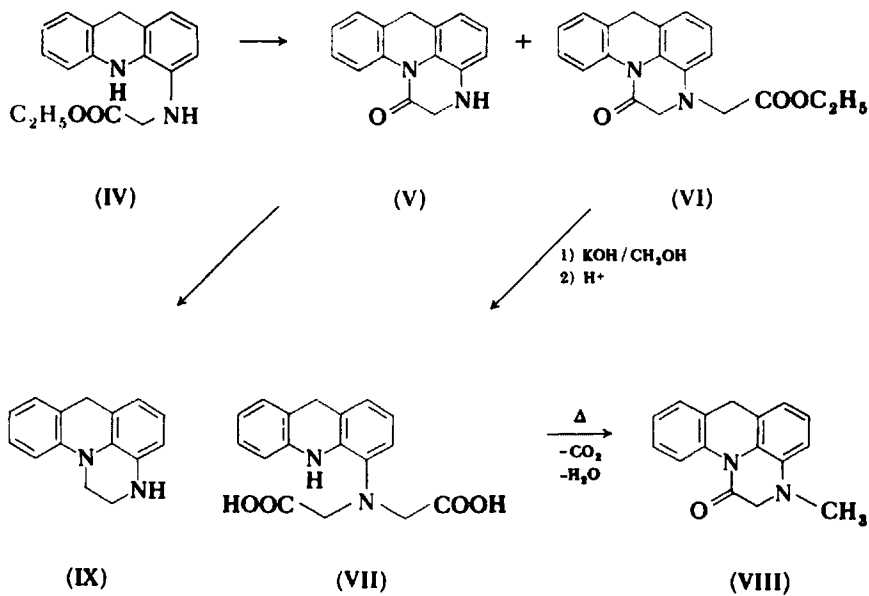


(II)



(III)

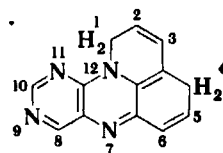
which yielded VIII (m. 131–2°). The carbonyl group of V proved resistant to ordinary reducing agents, but electrolytic reduction yielded a product (acetyl derivative, m. 152°) thought to be IX.



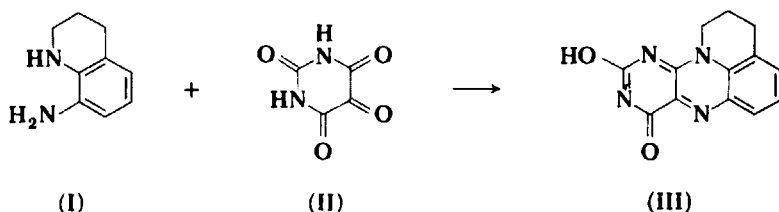
Reference

1. Clemo, Perkin and Robinson, *J. Chem. Soc.*, **125**, 1751 (1924).

A-818. 1*H*,4*H*-Pyrido[1,2,3-*de*]pyrimido-[5,4-*b*]quinoxaline. R.I. 2640



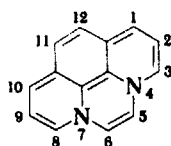
The single example (III) of this nucleus was obtained by the condensation of I with alloxan (II). Compound III melts above 320°, and was named *8,9-trimethylene flavine*.



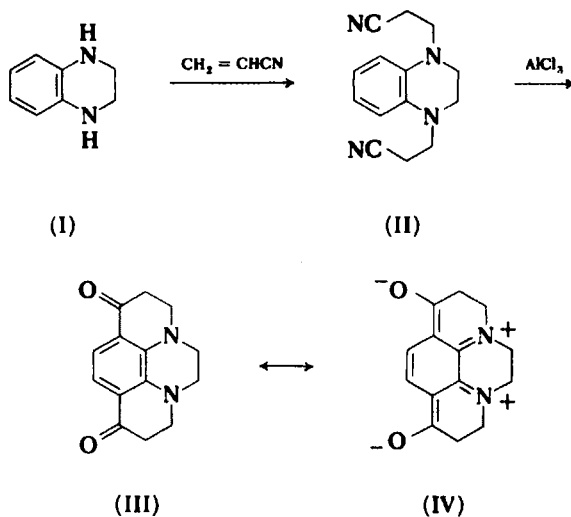
Reference

1. Hazelwood, Hughes and Lions, *J. Proc. Roy. Soc. N.S. Wales*, **71**, 462 (1938); *Chem. Abstracts*, **33**, 610 (1939).

A-819. Pyrazino[*lmn*][1,10]-phenanthroline



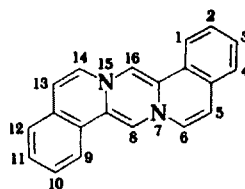
Almond and Mann¹ have obtained compound III by treating 1,2,3,4-tetrahydroquinoxaline (I) with acrylonitrile, and cyclizing the intermediate II by means of aluminum chloride in chlorobenzene. Compound III forms deep red crystals (m. 245–6°; bisphenylhydrazine, golden, m. 242–4°), and is too weakly basic to yield salts, even with strong acids. The color and feeble basicity were explained by Almond and Mann by assuming a large contribution to the resonance hybrid from tetrapolar forms such as IV.



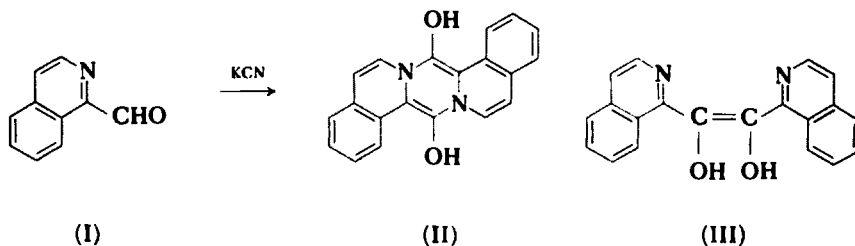
Reference

1. Almond and Mann, *J. Chem. Soc.*, **1951**, 1906.

A-820. Pyrazino[1,2-*a*, 5,4-*a'*]diisoquinoline

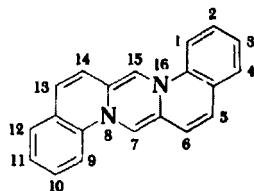


Treatment of isoquinoline-1-aldehyde (I) with potassium cyanide, is reported to yield a product thought¹ to have structure II. This product forms tan needles, m. 163–4° and is thermochromic: an alcoholic solution when heated, passes reversibly from yellow through orange to red. In view of recent findings (see Section A-821), structure III must also be considered.

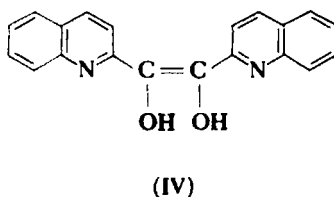
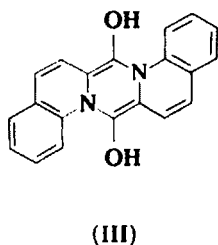
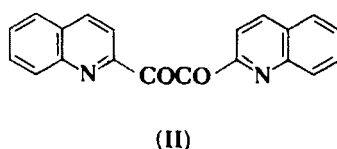
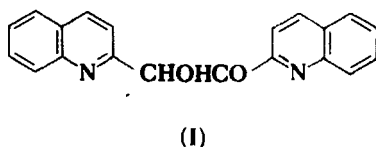


Reference

1. Brown and Hammick, *J. Chem. Soc.*, **1950**, 628.

A-821. Pyrazino[1,2-*a*, 4,5-*a'*]diquinoline

By oxidizing quinaldine with selenium dioxide, or by treating quinaldehyde with solutions of potassium cyanide, there is obtained a product which has variously been assigned structures I,^{1,2} II,³ III^{6,7} and IV.⁴ It is now quite well established^{4,5} that the product does not have structure III.

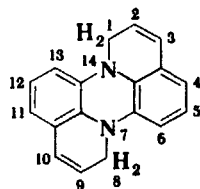


The invalidation of structure III leaves this ring system without representation.

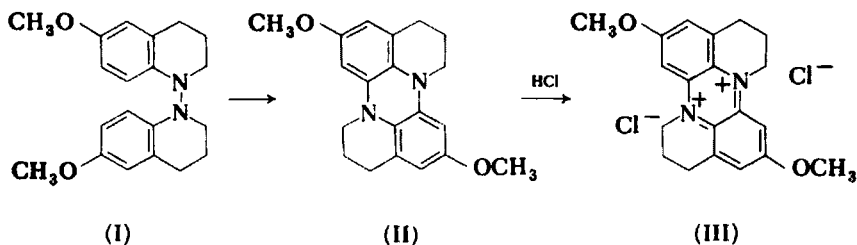
References

1. Henze, *Ber.*, **67**, 753 (1934).
2. Kaplan, *J. Am. Chem. Soc.*, **63**, 2654 (1941).
3. Linsker and Evans, *J. Am. Chem. Soc.*, **68**, 947 (1946).
4. Buehler and Harris, *J. Am. Chem. Soc.*, **72**, 5015 (1950).
5. Davies and Powell, *Nature*, **168**, 386 (1951).
6. Brown and Hammick, *Nature*, **164**, 831 (1949).
7. Brown and Hammick, *J. Chem. Soc.*, **1950**, 628.

**A-822. 1*H*,8*H*-Dipyrido[*de*,*kl*]phenazine.
R.I. 3242**



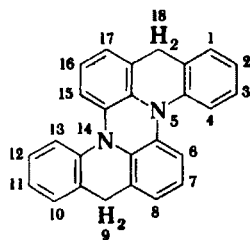
When 1,2,3,4-tetrahydroquinoline is subjected to gentle oxidation, it is converted into 1,1'-bi(1,2,3,4-tetrahydroquinolyl). This in turn undergoes a benzidine rearrangement upon treatment with hydrochloric acid, to yield 6,6'-bi(1,2,3,4-tetrahydroquinolyl). When, however, the 6-position is blocked, as it is, for example, in 6-methoxy-1,2,3,4-tetrahydroquinoline ("thallin"), an alternative reaction occurs. Wieland and Haas¹ showed that the oxidation product (I) of thallin is converted into II (yellow, m. 160°), which yields a red salt of structure III. The trivial name *thalloperazine* was given this nucleus by Wieland and Haas.



Reference

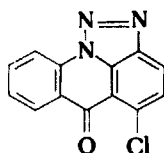
1. Wieland and Haas, *Ber.*, **53**, 1336 (1920).

A-823. 9*H*,18*H*-Diquinolo[3,2,1-*de*, 3',2',1'-*kl*]-phenazine

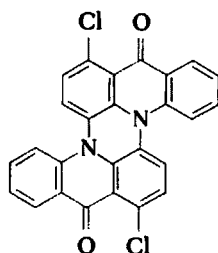


Lehmstedt and Schrader¹ found that when I was heated in the presence of copper salts, nitrogen was lost, and a new product

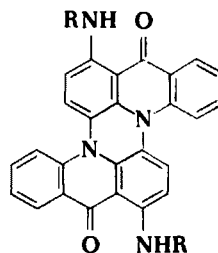
(m. 369–71°), thought to be II, was obtained. Efforts to prepare anthrimides from I by reaction with 1-aminoanthraquinone gave a difficultly vatable brown-black substance, probably III (R = 1-anthraquinonyl). Similar products resulted from the reaction of I with 5- and 8-benzamido-1-aminoanthraquinones.



(I)



(II)

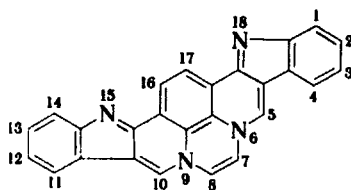


(III)

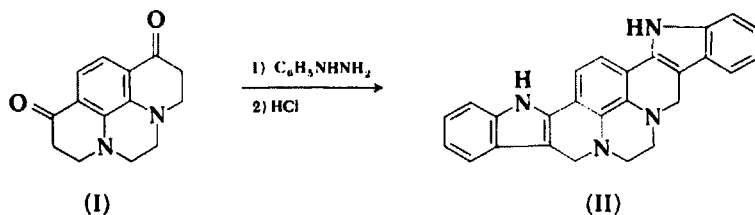
Reference

1. Lehmstedt and Schrader, *Ber.*, **70**, 1526 (1937).

A-824. Diindolo[3,2-c, 2',3'-i]pyrazino-[lmn][1,10]phenanthroline



Treatment of the bisphenylhydrazone of I with ethanolic hydrogen chloride yielded bright yellow crystals of II (m. 438–9°),

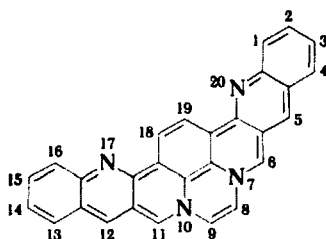


which was named¹ 1:2:2a:3:10:10a-hexahydrodi-indolo(3':2'-4:5)(2''-3''-8:9)-2a:10a-diazapyrene.

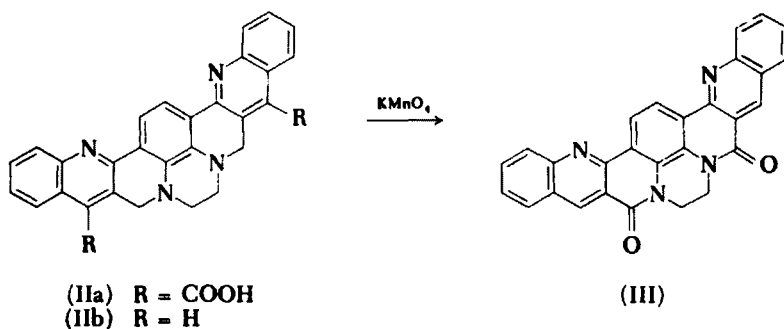
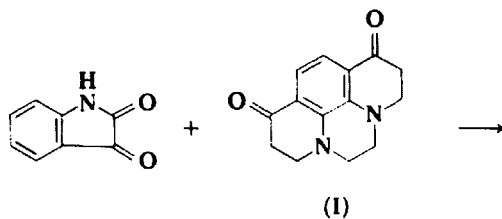
Reference

1. Almond and Mann, *J. Chem. Soc.*, **1951**, 1906.

A-825. Pyrazino[*lmn*]diquino- [3,2-*c*, 2',3'-*i*][1,10]- phenanthroline



Three derivatives of this nucleus have been obtained by Almond and Mann,¹ who subjected compound I to the Pfitzinger reaction.

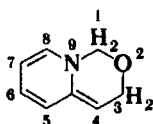


Compound IIa ($R = \text{COOH}$) forms dark green crystals (m. $242-6^\circ$) yielding a red disodium salt, and on heating in vacuo it loses carbon dioxide to give the bright red IIb ($R = \text{H}$, m. $156-8^\circ$). Oxidation of IIb gave the dioxo derivative III (orange, m. $428-30^\circ$). Compound IIb was named¹ *1:2:2a:3:10:10a-hexahydrodiquinolino-(3':2'-4:5)(2'':3''-8:9)-2a:10a-diazapyrene*.

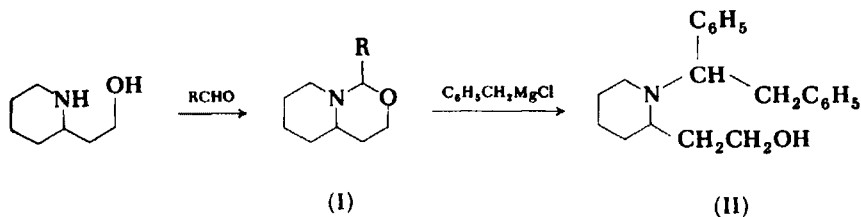
Reference

1. Almond and Mann, *J. Chem. Soc.*, **1951**, 1906.

A-826. 1*H*,3*H*-Pyrid[1,2-*c*]oxazine. R.I. 941



The reaction of 2-(β -hydroxyalkyl)piperidines with aldehydes has been found to yield compounds of structure I. The table lists the examples of this structure which have been described. Certain members of this group exhibit diuretic and antifungal activity.³ Treatment of I ($R = \text{C}_6\text{H}_5$) with benzylmagnesium chloride yields² II. See Sections A-147 and A-884.



Derivatives of Octahydropyrid[1,2-*c*]oxazine

Empirical formula	Substituents	Properties	Refs.
$\text{C}_9\text{H}_{17}\text{NO}$	3-Methyl-	b ₂₈ $108-11^\circ$; picrate, m. $160-1^\circ$.	1
$\text{C}_{10}\text{H}_{17}\text{NO}$	3-Methyl- α -methylene-	b ₂₃ $103-7^\circ$; picrate, m. 190° ; picrolonate, m. 193° .	1
$\text{C}_{14}\text{H}_{19}\text{NO}$	1-Phenyl-	m. $58-9^\circ$.	2
$\text{C}_{14}\text{H}_{25}\text{NO}$	3-Cyclohexyl-	HCl salt, m. $173-5^\circ$.	3

(continued)

Derivatives of Octahydropyrid[1,2-*c*]oxazine (*continued*)

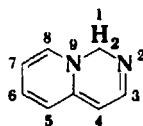
Empirical formula	Substituents	Properties	Refs.
C ₁₅ H ₂₁ NO	4-Methyl-3-phenyl-	HCl salt, m. 188-90 °.	3
C ₁₆ H ₂₁ NO	3-(1-Indanylene)-	HCl salt, m. 290-2 °.	3
C ₁₆ H ₃₁ NO	3,3-Di- <i>i</i> -butyl-	HCl salt, m. 244-5 °.	3
C ₁₇ H ₂₅ NO	3-Phenyl-3- <i>i</i> -propyl-	HCl salt, m. 273-4 °.	3
C ₁₇ H ₂₉ NO	3-(<i>d</i> -Bornylidene)-	HCl salt, m. 246-8 °.	3
	3-(<i>dl</i> -Fenchylidene)-	HCl salt, m. 288-90 °.	3
C ₁₈ H ₃₅ NO	3-Ethyl-3-octyl-	HCl salt, m. 190-2 °.	3
C ₁₉ H ₂₁ NO	3-(1-Acenaphthylidene)-	HCl salt, m. 230-2 °.	3
C ₁₉ H ₂₂ N ₂ O	3-Phenyl-3-(2-pyridyl)-	m. 149-150 °.	3
C ₁₉ H ₂₇ NO	3-Cyclopentyl-3-phenyl	HCl salt, m. 238-40 °.	3
C ₁₉ H ₂₉ NO	3-Pentyl-3-phenyl-	HCl salt, m. 244-6 °.	3
C ₁₉ H ₃₃ NO	3-(2-Cyclohexylcyclohexylidene)-	HCl salt, m. 281-2 °.	3
C ₂₀ H ₂₁ NO	3-(9-Fluorenylidene)-	HCl salt, m. 242-4 °.	3
C ₂₀ H ₂₂ ClNO	3-(<i>p</i> -Chlorophenyl)-3-phenyl-	HCl salt, m. 232-4 °.	3
C ₂₀ H ₂₃ NO	3,3-Diphenyl-	m. 77-9 °; HCl salt, m. 224-6 °.	3
	3,4-Diphenyl-	HCl salt, m. 192-5 °.	3
C ₂₀ H ₂₉ NO	3-Cyclohexyl-3-phenyl-	HCl salt, m. 268-9 °.	3
C ₂₀ H ₂₉ NO ₂	3-(2- <i>p</i> -Anisylcyclohexylidene)-	HCl salt, m. 235-6 °.	3
C ₂₀ H ₃₁ NO	3-Hexyl-3-phenyl-	HCl salt, m. 235-6 °.	3
C ₂₀ H ₃₅ NO	3,3-Dicyclohexyl-	HCl salt, m. 272-3 °.	3
C ₂₀ H ₃₇ NO	3-Cyclohexyl-3-hexyl-	HCl salt, m. 250-1 °.	3
C ₂₀ H ₃₉ NO	3,3-Dihexyl-	HCl salt, m. 229-30 °.	3
C ₂₁ H ₂₄ BrNO ₂	3- <i>p</i> -Anisyl-3- <i>m</i> -bromophenyl-	HCl salt, m. 135-8 °.	3
C ₂₁ H ₂₅ NO	3-Phenyl-3- <i>p</i> -tolyl-	HCl salt, m. 140-1 °.	3
	8-Methyl-3,3-diphenyl-	HCl salt, m. 266-7 °.	3
	1-Methyl-3,3-diphenyl-	HCl salt, m. 139-41 °.	3
C ₂₁ H ₂₉ NO	3-(2-Bicyclo[2,2,1]heptyl)-3-phenyl-	HCl salt, m. 210-2 °.	3
C ₂₁ H ₃₁ NO	3-Cycloheptyl-3-phenyl-	HCl salt, m. 270-2 °.	3
	3-(4-Methylcyclohexyl)-3-phenyl-	HCl salt, m. 273-5 °.	3
C ₂₂ H ₂₇ NO	3,3-Bis(<i>p</i> -tolyl)-	HCl salt, m. 236-8 °.	3
	1-Ethyl-3,3-diphenyl-	HCl salt, m. 162-4 °.	3
C ₂₂ H ₂₇ NO ₂	3-(<i>p</i> -Phenetyl)-3-phenyl-	HCl salt, m. 210-2 °.	3

Derivatives of Octahydropyrid[1,2-*c*]oxazine (*continued*)

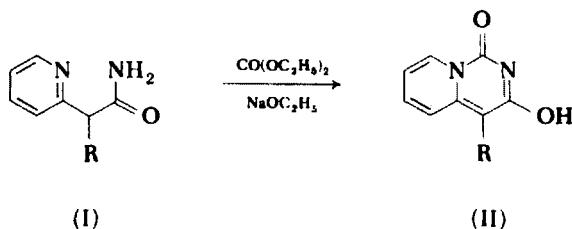
Empirical formula	Substituents	Properties	Refs.
C ₂₂ H ₂₇ NO ₃	3,3-Bis-(<i>p</i> -anisyl)-	HCl salt, m. 218–20 °.	3
C ₂₂ H ₃₅ NO	3-Phenyl-3-undecyl-	HCl salt, m. 212–3 °.	3
C ₂₂ H ₄₃ NO	3,3-Diheptyl-	HCl salt, m. 206–7 °.	3
C ₂₃ H ₃₅ NO	3-(1-Methyl-3- <i>i</i> -propyl-cyclopentyl)-3-phenyl-	HCl salt, m. 191–3 °.	3

References

1. Hess and Eichel, *Ber.*, **50**, 1407 (1917).
2. Goodson and Christopher, *J. Am. Chem. Soc.*, **72**, 358 (1950).
3. Tilford and Van Campen, *J. Am. Chem. Soc.*, **76**, 2431 (1954).

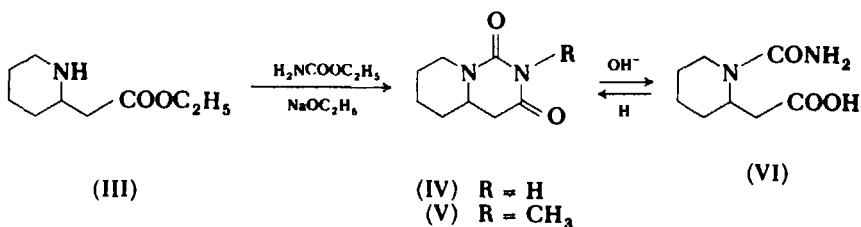
A-827. 1*H*-Pyrido[1,2-*c*]pyrimidine*

Condensation of pyridylacetamides of type I with ethyl carbonate in the presence of sodium ethoxide afforded¹ products of structure II. The yield was good (~85%) when R was a phenyl or substituted phenyl group, but only traces of II were obtained when R = H. Under similar conditions I (R = C₆H₅) reacted with thiophosgene to give the thione analog of II.

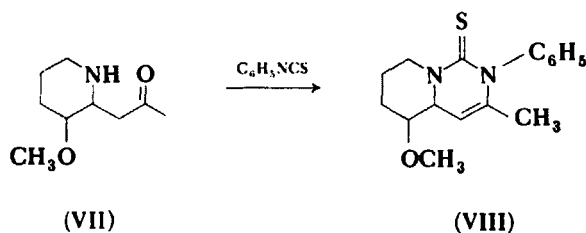


Alkylation of the sodium salt of II (R = C₆H₅) gave 3-substituted derivatives, while the 2-hydroxyl group of II (R = C₆H₅) was replaced with chlorine by treatment with phosphorous oxychloride in dimethylaniline. This chlorine atom, in turn, could be replaced by either an alkoxy, a thiol or a dialkylamino group. The ultraviolet and infrared spectra of most of these compounds were recorded.¹

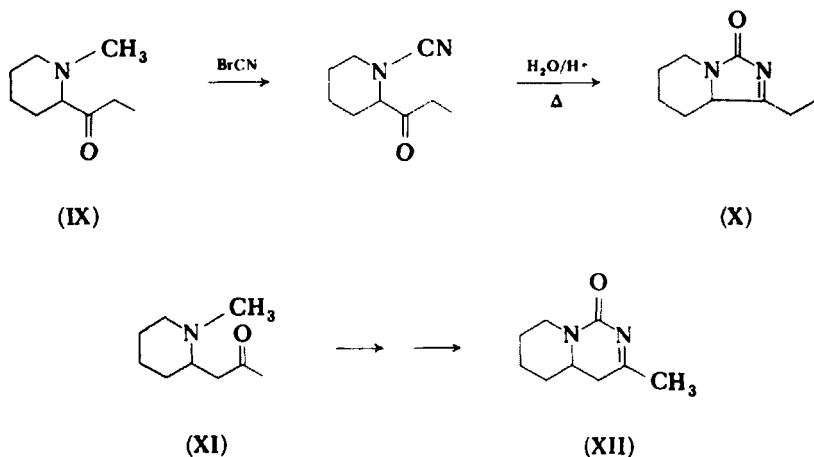
Urethane reacted with III to yield² IV, which could be methylated to V by the action of diazomethane. Alkaline hydrolysis of IV yielded VI, which was reconverted into IV by acid.



Treatment of VII with phenyl isothiocyanate in refluxing ethylene dichloride produced³ VIII.



In 1919, Hess reported⁴ that the reaction of methyl isopelletierine with cyanogen bromide (followed by acid hydrolysis) yielded a product to which he assigned structure X. This structure was predicated upon the erroneous formulation of methyl isopelletierine as IX. Em-



ployment of the correct structure (XI) leads to the conclusion that Hess's product may have been XII.

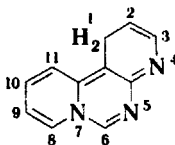
1*H*-Pyrido[1,2-*c*]pyrimidines

Empirical formula	Substituents	Properties	Refs.
C ₈ H ₆ N ₂ O ₂	2,4(3 <i>H</i>)-Dioxo-	m. 200–10°; λ _{max} 290, 302 and 380 mμ (ε = 13,400, 13,900 and 6,900).	1
C ₈ H ₁₂ N ₂ O ₂	1,2,3,6,7,8,9,9 <i>a</i> -Octahydro-2,4-dioxo-	m. 186–8.5°.	2
C ₉ H ₁₄ N ₂ O	1,6,7,8,9,9 <i>a</i> -Hexahydro-2-methyl-4-oxo-	—	4
C ₉ H ₁₄ N ₂ O ₂	1,2,3,6,7,8,9,9 <i>a</i> -Octahydro-3-methyl-2,4-dioxo-	m. 76–8°.	2
C ₁₄ H ₈ Cl ₂ N ₂ O ₂	1-(2,4-Dichlorophenyl)-2,4(3 <i>H</i>)-dioxo-	m. 232°.	1
C ₁₄ H ₉ ClN ₂ O	2-Chloro-4-oxo-1-phenyl-	Yel., m. 286–90°.	1
C ₁₄ H ₉ ClN ₂ O ₂	1-(4-Chlorophenyl)-2,4(3 <i>H</i>)-dioxo-	m. 290°.	1
C ₁₄ H ₁₀ N ₂ OS	1-Phenyl-2(3 <i>H</i>)-oxo-4-thiono-	m. 229–31°. Na salt, yel., m. 247–50°.	1
	1-Phenyl-4-oxo-2(3 <i>H</i>)-thiono-	Or.-red., m. 241–5° d. Na salt, d. 196–212°.	1
C ₁₄ H ₁₀ N ₂ O ₂	1-Phenyl-2,4(3 <i>H</i>)-dioxo-	m. 267–70°.	1
C ₁₅ H ₁₂ N ₂ O ₂	2-Methoxy-1-phenyl-4-oxo-	Yel., m. 240–2°.	1
	3-Methyl-1-phenyl-2,4(3 <i>H</i>)-dioxo-	Yel., m. 199–200°.	1
C ₁₅ H ₁₂ N ₂ O ₃	1-(3-Methoxyphenyl)-2,4(3 <i>H</i>)-dioxo-	m. 256°.	1
C ₁₅ H ₁₂ N ₃ O	2-Dimethylamino-1-phenyl-4-oxo-	Yel., m. 207–8°. HCl salt, m. 206–10°.	1
C ₁₆ H ₁₄ N ₂ O ₂	2-Ethoxy-1-phenyl-4-oxo-	Yel., m. 126–7°.	1
C ₁₆ H ₂₀ N ₂ OS	3,6,7,8,9,9 <i>a</i> -Hexahydro-9-methoxy-2-methyl-3-phenyl-4-thiono-	m. 118–9°.	3
C ₁₈ H ₁₉ N ₃ O ₂	3-Dimethylaminoethyl-1-phenyl-2,4(3 <i>H</i>)-dioxo-	Yel., m. 127–8°. HCl salt, m. 258–9°.	1
C ₁₉ H ₁₉ N ₃ O	2-(1-Piperidino)-1-phenyl-4-oxo-	Yel., m. 177–8°. HCl salt, m. 164–7° d.	1
C ₂₀ H ₂₃ N ₃ O ₂	2-Diethylaminoethyl-1-phenyl-2,4(3 <i>H</i>)-dioxo-	Yel., m. 67–8°. Picrate, m. 143–4°.	1

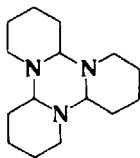
References

1. Hunger and Hoffmann, *Helv. Chim. Acta*, **40**, 1319 (1957).
2. Winterfeld and Göbel, *Chem. Ber.*, **89**, 1642 (1956).
3. Baker and McEvoy, *J. Org. Chem.*, **20**, 136 (1955).
4. Hess, *Ber.*, **52**, 964 (1919).

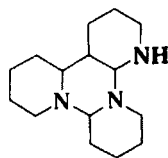
A-828. Dipyrido[1,2-*c*, 3',2'-*e*]-pyrimidine



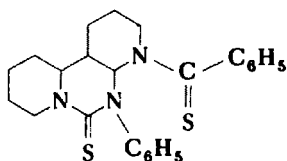
The reaction of α -tripiperidine (I, see Section A-839) or isotripiperidine (II, see Section A-785) with phenyl isothiocyanate, is reported¹ to yield a compound (m. 198–200°d.) thought to possess structure III.



(I)



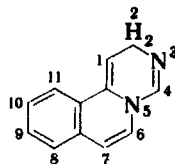
(II)



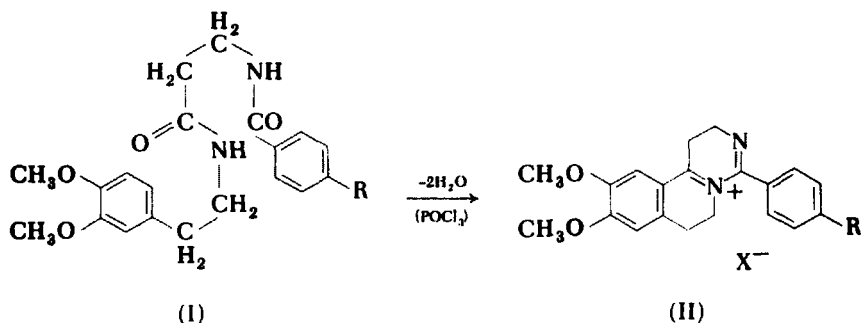
(III)

Reference

1. Schöpf, Komzac, Braun, Jacobi, Bormuth, Bullheimer and Hagel, *Ann.*, **559**, 1 (1947).

A-829. 2H-Pyrimido[4,3-a]isoquinoline

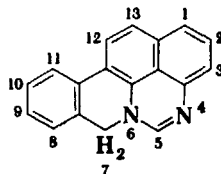
Cyclization of compounds of structure I was reported^{1,2} to yield products possibly having structure II ($R = H$, $X = Cl$, m. 240° ;



$R = H$, $X = \text{picrate}$, m. 223°d. ; $R = \text{NO}_2$, $X = Cl$, m. 245°). However, no proof of these structures is available, and slight variations in the cyclization technique yield unidentified isomeric materials. Further work seems required to demonstrate the precise nature of these products. Several other derivatives of II were reported.

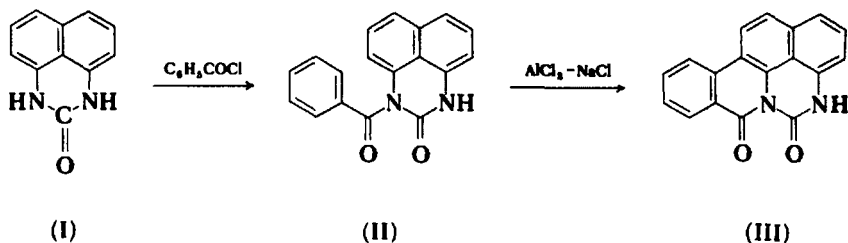
References

1. Kametani and Katagi, *J. Pharm. Soc. Japan*, **75**, 705 (1955); *Chem. Abstracts*, **50**, 3406 (1956).
2. Kametani and Katagi, *Pharm. Bull. (Tokyo)*, **3**, 253 and 259 (1955); *Chem. Abstracts*, **50**, 11343 (1956).

A-830. 7H-Isoquino[2,3,4-cd]perimidine*

Compounds reported to contain this nucleus were described by Mieg and Heidenreich,¹ who obtained them by treating perimidone

(I) with acyl halides, and cyclizing the intermediate II by means of an aluminum chloride melt. Thus I and benzoyl chloride yield III (yellow; dissolves in sulfuric acid giving a yellow solution with a strong green fluorescence). Varying the reaction conditions produced a yellow product (m. 290° unc.; sulfuric acid solution yellowish-red) thought to be "isomeric" with III.

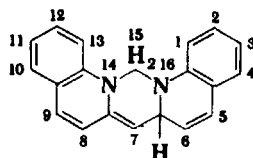


Other examples of this type of compound are mentioned by Mieig and Heidenreich, but no evidence is available to affirm or deny the presence of the nucleus III in these products.

Reference

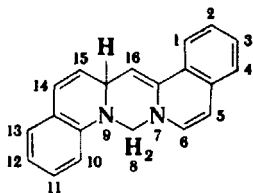
1. Mieig and Heidenreich, Ger. Pat. 511,948; *Frdl.*, **17**, 689 (1932). U. S. Pat. 1,749,955.

A-831. 6aH,15H-Pyrimido[1,6-a, 3,4-a']-diquinoline. R.I. 3239



and

A-832. 8H,15aH-Isoquino[2,1-c]quino-[2,1-f]pyrimidine. R.I. 3241



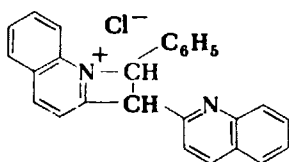
As these nuclei have so much in common both chemically and historically, they will be treated together. They are, respectively, the parent ring systems of the dyes *quinoline red* and *isoquinoline red*, the separate identity of which was long misunderstood, with the

result that the name quinoline red was often given to at least two distinctly different dyes.

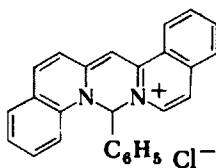
The discovery of these systems is generally credited to E. Jacobsen,^{1,2,3} who heated crude coal tar quinoline with benzotrichloride and obtained a red coloring matter. Variations of the synthesis employing benzal halides³ and various quinoline and quinaldine homologs,^{1-4,12} also yielded red dyes. It soon became evident that the crude quinoline used contained about 20% quinaldine as well as substantial amounts of isoquinoline,⁴ and that pure quinoline, under the same reaction conditions, gave no red dye.^{5,6} Similarly, pure quinaldine alone gave no dye, but when a mixture of quinoline and quinaldine was treated with benzotrichloride, a red dye was obtained.⁶

Professor Hofmann became interested in the structure of these red dyes and demonstrated⁷ that a mixture of quinoline and quinaldine, when heated with benzotrichloride and zinc chloride, yielded the dye quinoline red, while isoquinoline and quinaldine under these conditions yielded the isomeric isoquinoline red. Both dyes have absorption maxima⁷ at about 500 and 540 $m\mu$. Degradative studies by Hofmann⁷ and by Vongerichten and Krantz⁸ showed that sulfide reduction of quinoline red yielded benzyl mercaptan and a base $C_{19}H_{14}N_2$, whereas oxidation with bichromate gave benzaldehyde and a base $C_{14}H_{12}N_2O$, possibly 1-(quinaldoyl)isoquinoline.

On the basis of the available evidence, Krantz proposed structure I for quinoline red, but later⁹ supported the structure II, which was proposed by Vongerichten and Homann¹⁰ for isoquinoline red.

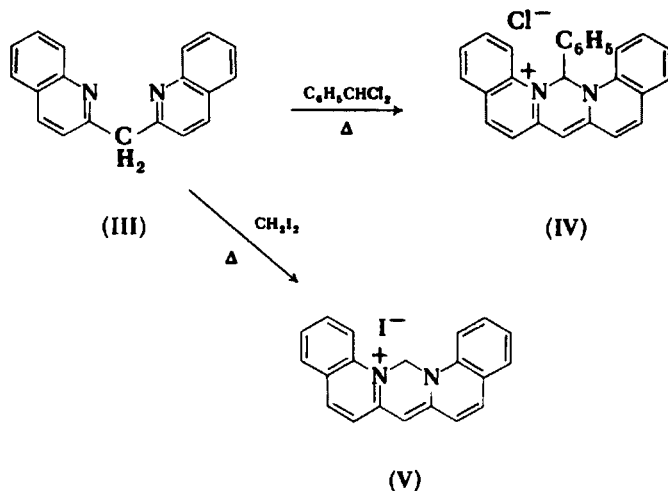


(I)



(II)

That quinoline red has structure IV, exactly analogous to II, was shown by Scheibe and Rossner,¹¹ who synthesized it from 2,2'-di-quinolylmethane (III). Replacing the benzal chloride with methylene iodide yielded V¹³ (red with golden luster, m. $>330^\circ$; $\lambda_{\max}$ 525 and 566.6 $m\mu$), which is similar to IV in fluorescence and color. Quinoline red has absorption maxima at 499 and 536 $m\mu$.¹³



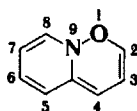
Although these dyes color silk and wool red, the dyeings are not fast to light. The chief interest in these compounds resides in their fluorescence,¹⁴⁻¹⁸ and in their ability to sensitize and render orthochromatic photographic emulsions.¹⁹⁻²¹ Quinoline red has been claimed active against cholera,²² and has been studied in connection with the flotation of quartz.²³

References

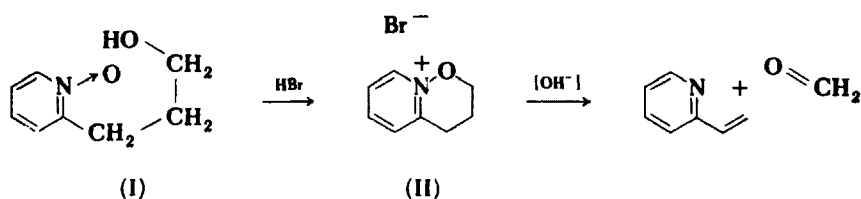
1. Jacobsen, *Ber.*, **15**, 2646 (1882).
2. Jacobsen, Ger. Pat. 19,306; *Frdl.*, **1**, 158 (1888).
3. Jacobsen, Ger. Pat. 23,967; *Frdl.*, **1**, 159 (1888).
4. Aktiengesellschaft für Anilinfabrikation (Agfa), Ger. Pat. 40,420; *Frdl.*, **1**, 160 (1888).
5. Fischer, *Ber.*, **16**, 721 (1883).
6. Jacobsen and Reimer, *Ber.*, **16**, 1082 (1883).
7. Hofmann, *Ber.*, **20**, 4 (1887).
8. Vongerichten and Krantz, *Ber.*, **43**, 128 (1910).
9. Krantz, *Chem. Weekblad.*, **11**, 364 (1914); *Chem. Abstracts*, **10**, 195 (1916).
10. Vongerichten and Homann, *Ber.*, **45**, 3446 (1912).
11. Scheibe and Rossner, *Ber.*, **54**, 786 (1921).
12. Harris and Pope, *J. Chem. Soc.*, **121**, 1029 (1922).
13. Scheibe and Fischer, *Ber.*, **59**, 502 (1926).
14. Duseberg, *Physik. Z.*, **26**, 157 (1924); *Chem. Zentr.*, **I**, 2431 (1925).
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16. Kirchhoff, *Z. Physik.*, **116**, 115 (1940); *Chem. Abstracts*, **35**, 2793 (1941).
17. Feofilov, *Bull. acad. sci. U.R.S.S. Sér. Phys.*, **9**, 317 (1945); *Chem. Abstracts*, **40**, 4296 (1946).
18. Weber and Lokar, *Trans. Faraday Soc.*, **44**, 959 (1948).

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20. Viterbi, *Gazz. chim. ital.*, **56**, 612 (1926); *Chem. Zentr.*, **I**, 679 (1927). *Progresso fot.*, No. 1-2 (1927); *Chem. Zentr.*, **II**, 202 (1927).
21. Lüppe-Cramer, *Z. wiss. Phot.*, **25**, 320 (1928); *Chem. Zentr.*, **II**, 839 (1928).
22. Neufeld, Schiemann and Baumgarten, *Deut. med. Wochschr.*, **46**, 1013 (1920); *Chem. Abstracts*, **15**, 267 (1921).
23. Berl and Vierheller, *Z. angew. Chem.*, **36**, 163 (1923).

A-833. Pyrido[1,2-*c*]-*o*-oxazine*



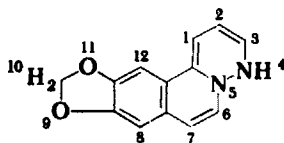
Treatment of I with hydrobromic acid yielded¹ II (m. 151-3°). Hydrogenation over a platinum oxide catalyst afforded 2-(3-hydroxypropyl)piperidine, while the action of aqueous caustic produced 2-vinylpyridine and formaldehyde.



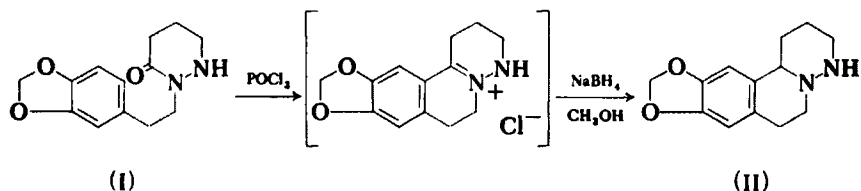
Reference

1. Boekelheide and Feely, *J. Am. Chem. Soc.*, **80**, 2217 (1958).

A-834. 4*H*-[1,3]Dioxolo[*g*]-pyridazino[6,1-*a*]isoquinoline*



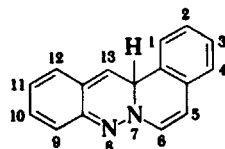
Subjection of I to the Bischler-Napieralski reaction, and reduction of the crude reaction product with sodium borohydride afforded an orange liquid (HCl salt, m. 253°) thought¹ to be II.



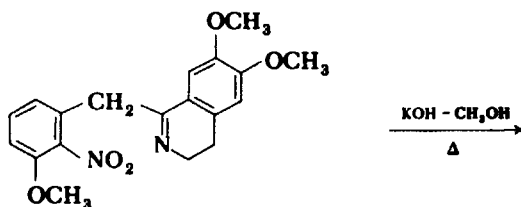
Reference

1. Sugasawa and Kohno, *Pharm. Bull. (Tokyo)*, **4**, 477 (1956); *Chem. Abstracts*, **51**, 13866 (1957).

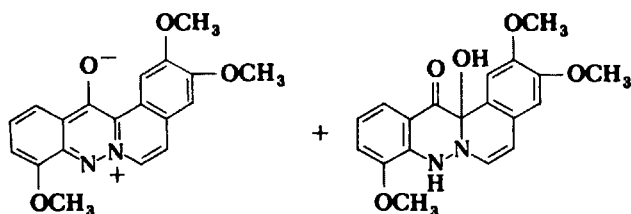
A-835. 13aH-Isoquinolo[2,1-b]cinnoline



While many 1-benzyl-3,4-dihydroisoquinolines are oxidized by hot methanolic potassium hydroxide to the corresponding 1-benzoyl-isoquinolines, it was found by Govindachari and Nagarajan¹ that similar treatment of I yielded another type of product, to which the mesoionic structure II was assigned. A hexacyclic mesoionic system appears unique,² and in this instance, actually, a misnomer, although other possible structures (such as the corresponding quinolyl-benzisoxazole) seemingly were eliminated by examination of the spectra and chemical properties of the compound. The infrared absorption spectrum of the base showed the absence of NH, OH, CO or NO₂ functions, while the spectrum of the hydrochloride



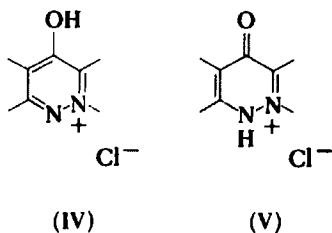
(I)



(II)

(III)

showed no carbonyl absorption, but did show a band at $2.96\ \mu$. This would seem to indicate that the salt has structure IV instead of V. Other examples of the type of structure II were obtained from analogs of I.



Other products were obtained with II in the oxidation of I, among them a compound $C_{19}H_{18}O_5N_2$, which was thought to be III. While the ultraviolet absorption spectra of II and III were different, it was found that III formed hydrochloride and picrate salts (with loss of a mole of water), which were isomeric with those of II, and which may be of type V.

Derivatives of 13aH-Isoquinolo[2,1-b]cinnoline

Empirical formula	Structure	Properties and comments
$C_{16}H_{10}NO_2$		m. $106-7^\circ$; λ_{max} : $245\ m\mu$ (4.31), $275\ m\mu$ (3.68) $370\ m\mu$ (4.23).
$C_{18}H_{12}N_2O_4$		Or., m. 208° ; λ_{max} : $232\ m\mu$ (4.57), $262\ m\mu$ (4.37), $385\ m\mu$ (4.22).
$C_{18}H_{14}N_2O_3$		Yel., m. $184-5^\circ$; λ_{max} : $221\ m\mu$ (4.61), $252\ m\mu$ (4.56), $380\ m\mu$ (4.32). Dihydro deriv. (?) m. 166° .

(continued)

Derivatives of 13aH-Isoquinolo[2,1-b]cinnoline (*continued*)

Empirical formula	Structure	Properties and comments
$C_{19}H_{16}N_2O_4$		Yel., m. 179°; λ_{max} : 225 $m\mu$ (4.61), 262 $m\mu$ (4.39), 385 $m\mu$ (4.21). HCl salt, yel. m. 178° d. Picrate, yel. m. 205° d. Methiodide, yel. m. 178°.
$C_{19}H_{18}N_2O_5$		Yel., m. 117-8°. HCl salt, m. 195° d. Picrate, m. 187° d.
$C_{20}H_{18}N_2O_5$		Yel., m. 150°; λ_{max} : 232 $m\mu$ (4.55), 262 $m\mu$ (4.37), 383 $m\mu$ (4.07).

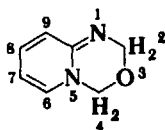
References

- Govindachari and Nagarajan, *J. Chem. Soc.*, **1954**, 3785.
- Baker and Ollis, *Quart. Revs.*, **11**, 15 (1957).

CHAPTER XIII

Fused 6/6 Ring Systems with Two or More Extra Heteroatoms

A-836. 2H,4H-Pyrid[1,2-c][1,3,5]-oxadiazine



The one compound (I) thought to possess this nucleus was described by Lur'e,¹ who obtained it by treating 2-aminopyridine



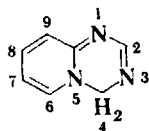
(I)

in moist pyridine with benzoyl chloride. Compound I melts at 89–90° and is decomposed to benzoylaminopyridine by heating in vacuo, or by alcoholic hydrochloric acid.

Reference

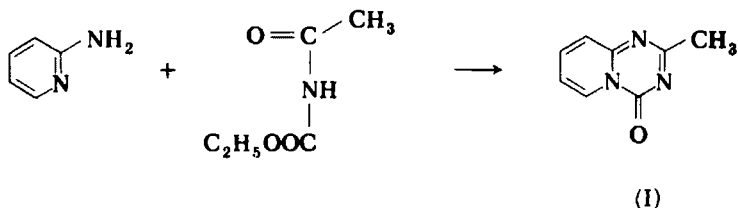
1. Lur'e, *J. Gen. Chem. (U.S.S.R.)*, **20**, 195 (1950); *Chem. Abstracts*, **44**, 5880 (1950).

A-837. 4H-Pyrido-*s*-triazine*



The name *2,4-diazaquinolizine* has been used.

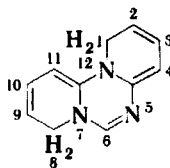
Birr proposed¹ the preparation of I from acetylurethane and 2-aminopyridine, but apparently the synthesis has not been carried out.



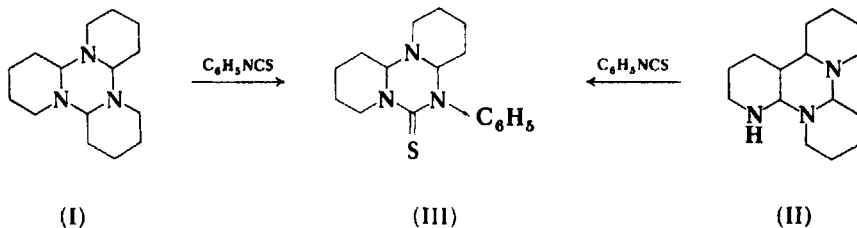
Reference

1. Birr, *Z. wiss. Photo.*, **47**, 2 (1952).

A-838. 1*H*,8*H*-Dipyrido[1,2-*a*,1',2'-*c*]-*s*-triazine



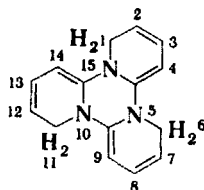
The only reported example (III, m. 143–5°) of this ring system was obtained^{1,2} by the reaction of α - or β -tripiperidineins (I, see Section A-839) or isotripiperidine (II, see Section A-785) with phenyl isothiocyanate. The originally postulated¹ structures of I, II and III have been corrected by Schöpf *et al.*²



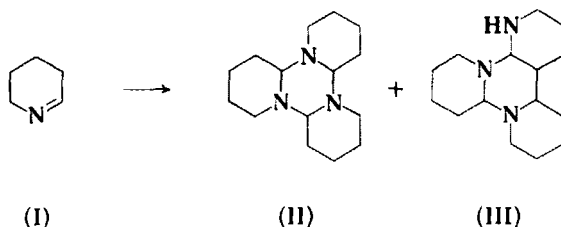
References

1. Lellmann and Schwaderer, *Ber.*, **22**, 1318 (1889).
2. Schöpf, Komzac, Braun, Jacobi, Bormuth, Bullnheimer and Hagel, *Ann.*, **559**, 1 (1947).

**A-839. 1*H*,6*H*,11*H*-Tripyrido-
[1,2-*a*,1',2'-*c*,1'',2''-*e*]-
s-triazine**



The product thought by Ivashchenko and Kirsanov¹ to have structure II was shown by Schöpf *et al.*²⁻⁵ to have structure III (see Section A-785). Both of these products, however, do result from the trimerization of I.^{2,3} Because of the presence of the three CH groups, compound II exists in two stereoisomeric forms: α - and β -tripiperidineines, *m.* 61–2°, *b*_{0.1} 128–30° and *m.* 68–70° (72–4°), *b*₁₂ 184–6°, respectively. Distillation from potassium bisulfate converts the α -form into the β -form. In aqueous solution at pH 9–10, II is rapidly converted into III.⁶



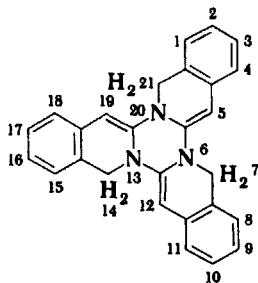
α -Tripiperidineine was first obtained by Lellmann and Schwaderer⁷ from 1-chloropiperidine, and it can also be obtained by the thermal decomposition of phenyldiazopiperidine. Cyclopentyl azide rearranges^{9,10} to II via I. Some further reactions of the two forms of II have been described by Schöpf.^{2,3,5} The enzyme-catalyzed oxidation of both II and III has been studied.⁸

References

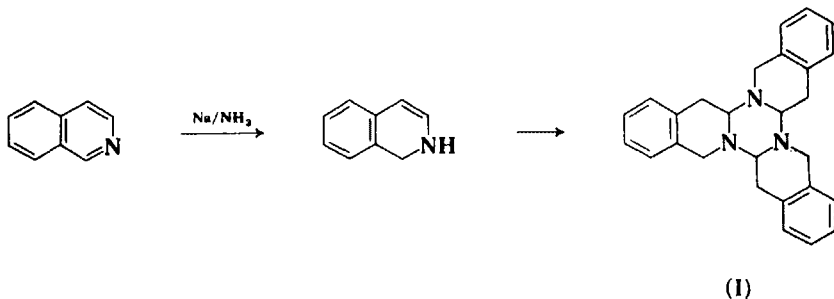
1. Ivashchenko and Kirsanov, *Bull. soc. chim. France*, [5]3, 2289 (1937).
2. Schöpf, Komzac, Braun, Jacobi, Bormuth, Bullheimer and Hagel, *Ann.*, **559**, 1 (1947).
3. Schöpf, Arm and Krimm, *Chem. Ber.*, **84**, 690 (1951).
4. Schöpf, Arm and Braun, *Chem. Ber.*, **85**, 937 (1952).
5. Schöpf, Braun and Otte, *Chem. Ber.*, **86**, 918 (1953).
6. Schöpf and Otte, *Chem. Ber.*, **89**, 335 (1956).
7. Lellmann and Schwaderer, *Ber.*, **22**, 1318 and 1328 (1889).

8. Mann and Smithies, *Biochem. J.*, **61**, 89 (1955).
9. Boyer and Canter, *J. Am. Chem. Soc.*, **77**, 3287 (1955).
10. Boyer, Canter, Hamer and Putney, *J. Am. Chem. Soc.*, **78**, 325 (1956).

A-840. 7H,14H,21H-s-Triazino-tris[2,3,2',3',2'',3'']iso-quinoline*



Reduction of isoquinoline with sodium in liquid ammonia gave 1,2-dihydroisoquinoline, which readily isomerized to 1,4-dihydroquinoline, and this trimerized to I. Compound I was obtained in



two modifications: α , m. 137°, and β , m. 187°. These products are analogous to the piperidine trimers (see Section A-839).

Reference

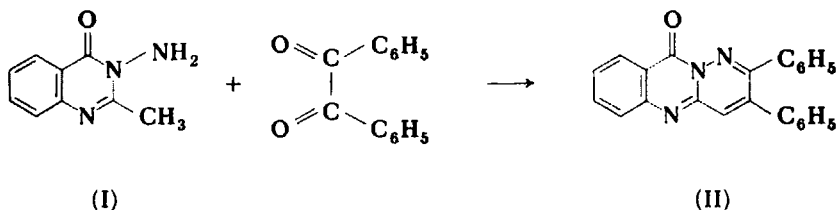
1. Hückel and Graner, *Chem. Ber.*, **90**, 2017 (1957).

**A-841. 10H-Pyridazo[b]quinazoline.
R.I. 1879**



A product (II, yellow, m. $\sim 292^\circ$ d.), thought possibly to have this nucleus, was obtained by Bogert and Beal¹ by treating I with

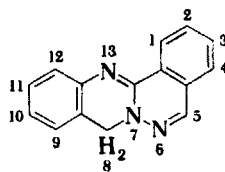
benzil. However, insufficient material was obtained to permit the precise identification of the substance.



Reference

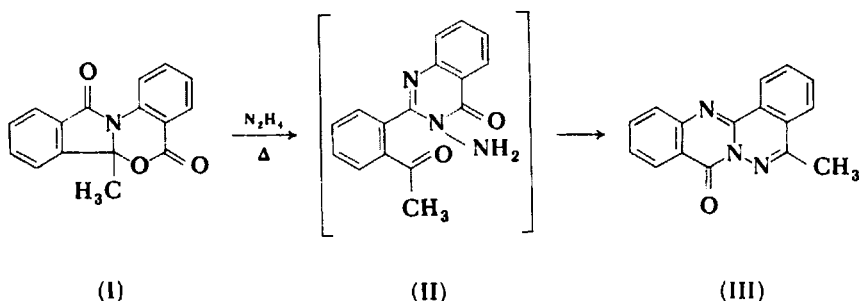
1. Bogert and Beal, *J. Am. Chem. Soc.*, **34**, 516 (1912).

A-842. 8H-Phthalazino[1,2-*b*]quinazoline



This nucleus has also been called *1,2-benzo-4,4a,12-triazaanthracene*.

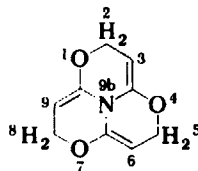
Refluxing an alcoholic solution of I with hydrazine produced a product (m. 263°) thought¹ to have structure III, and presumably formed via II.



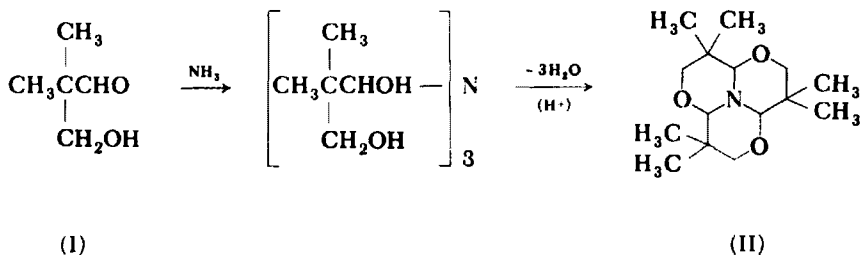
Reference

1. Honzl, *Collection Czechoslov. Chem. Commun.*, **21**, 725 (1956). *Chem. listy*, **49**, 1671 (1955); *Chem. Abstracts*, **50**, 5623 (1956).

A-843. 2H,5H,8H-1,4,7-Trioxa-9b-aza-phenalene*



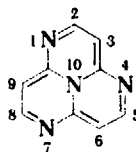
Treatment of 2,2-dimethyl-3-hydroxypropionaldehyde (I) with ammonia followed by dilute acid,¹ or with ammonium acetate and acetic acid,² produced II (m. 186–7°). It forms a perchlorate (m. 250°d.), but not a hydrochloride salt, and it is reduced by neither lithium aluminum hydride nor hydrogen and palladium in ethanol at 100°/80 atm. Compound II was named² *dodecahydro-3:3:6:6:9:9-hexamethyl-1:4:7-trioxa-9b-azaphenalene*.



References

1. Lynn, *J. Am. Chem. Soc.*, **77**, 6067 (1955).
2. Cavalla, *J. Chem. Soc.*, **1956**, 4672

A-844. 1,4,7,9b-Tetrazabenzonaphthene

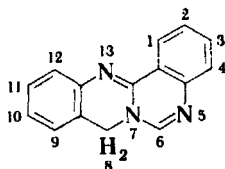


Delépine^{1,2,3} found that three molecules of crotonaldehyde react with ammonia to produce a substance which he called *tricrotonyl-tetramine*, and to which he assigned structure I. The product was obtained in two stereoisomeric forms, one of which formed a hexahydrate melting at about 70°. When heated further, it became anhydrous and then melted at 102°; the picrate melted at 152°. Treatment with nitrous acid gave a trinitroso derivative,² m. 210–40°; sodium hypochlorite converted I into the trichloro compound²

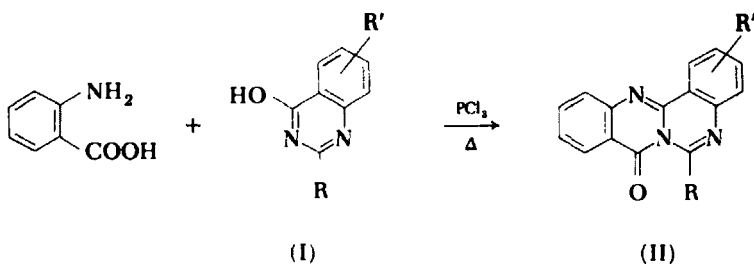
Reference

1. King and King, *J. Chem. Soc.*, **1947**, 726.

A-846. 8*H*-Quinazo[4,3-*b*]quinazoline.
R.I. 2645

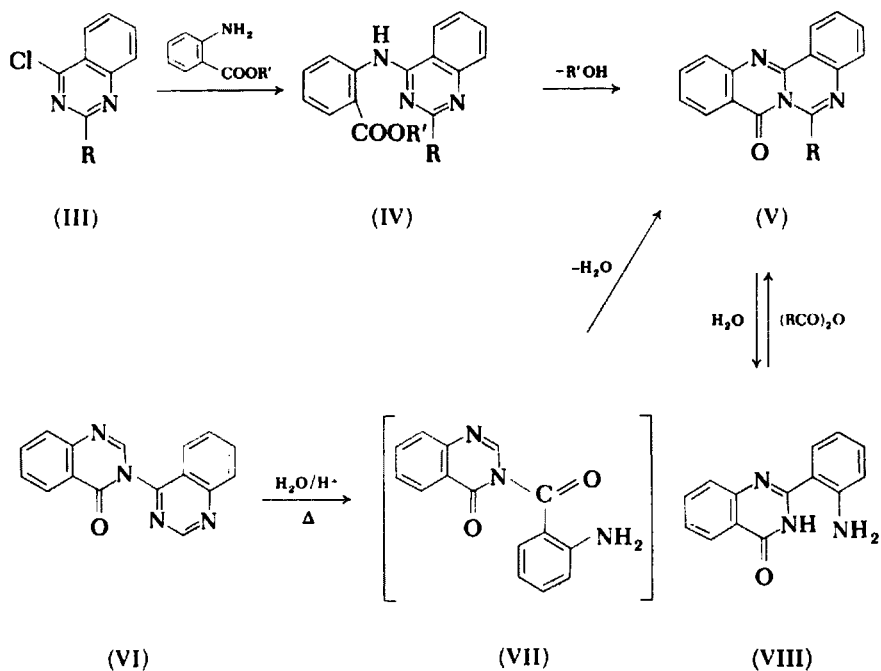


The condensation of 4-hydroxyquinazolines (I) with anthranilic acid was reported¹ to yield II. However, recently one of the products thus prepared (II, R' = H, R = C₆H₅) was shown² to be a



mixture of I (R' = H, R = C₆H₅) with *N*-(2-phenyl-4-quinazoliny)anthranilic acid. This renders questionable the authenticity of the other products (see the table) reported by Aggarwal and Rây.¹

Stephen and Stephen² obtained IV (a, R = H; b, R = CH₃) by the reaction of III (a) with ammonium anthranilate in acetone at 0° or (b) with methyl anthranilate. Cyclization of IVa and IVb to V was effected by heating in acetic anhydride. Compound V (R = H) was also obtained³ by the hydrolysis of VI with dilute hydrochloric acid (presumably via VII) and (R = H, CH₃, C₂H₅, C₆H₅, etc.) by acylation of VIII. Further hydrolysis of V gave VIII.



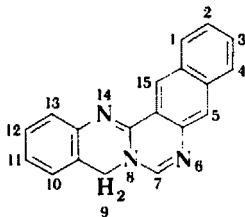
Products of Type II

R	R'	Properties	Refs.
H	H	m. 197°.	2,3
CH ₃	H	m. 177°.	3
CH ₃	3-CH ₃	Yel., m. 285°.	1
CH ₃	4-CH ₃	Yel., m. 250°.	4
C ₂ H ₅	H	m. 250°.	3
CH ₃	2-CH ₃ O	Brn., m. 240°.	1
CH ₃	4-CH ₃ O	Pale yel., m. 260°.	4
C ₆ H ₅	H	m. 292°.	2,3
C ₆ H ₅ CH ₂	H	m. 243-4°.	1
C ₆ H ₅ CH ₂	2-CH ₃	m. 235-6°.	1
C ₆ H ₅ CH ₂	3-CH ₃	m. 213°.	1
C ₆ H ₅ CH ₂	2-CH ₃ O	m. 244°.	1
C ₆ H ₅ CH ₂	4-CH ₃ O	m. 254°.	1

References

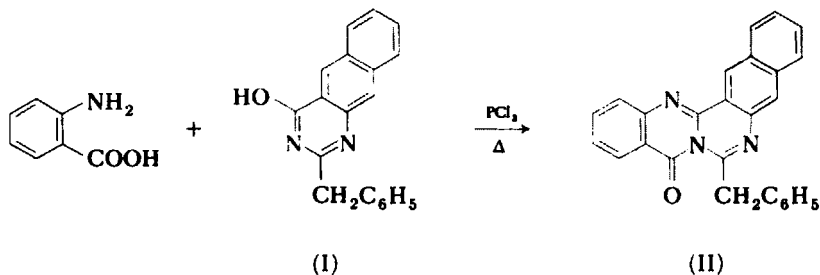
1. Aggarwal and Rây, *J. Indian Chem. Soc.*, **6**, 723 (1929); *Chem. Zentr.*, **I**, 981 (1930); *Chem. Abstracts*, **24**, 1113 (1930).
2. Stephen and Stephen, *J. Chem. Soc.*, **1956**, 4173.
3. Stephen and Stephen, *J. Chem. Soc.*, **1956**, 4178.
4. Indravati, *J. Madras Univ.*, **25B**, 125 (1955); *Chem. Abstracts*, **50**, 11350 (1956).

A-847. 9H-Benzo[g]quinazo[3,2-c]-quinazoline



The name *8H-2,3-benzoquinazo[4,3-b]quinazoline* has been used.

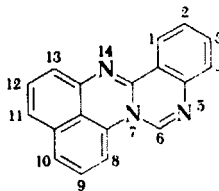
Heating I with anthranilic acid in phosphorus trichloride for five hours yielded ¹ II (m. 276°).



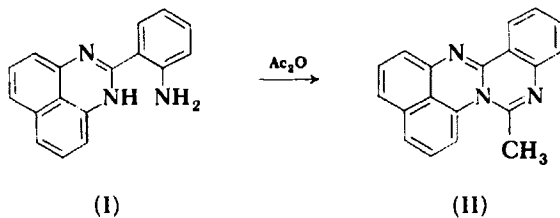
Reference

1. Indravati, *J. Madras Univ.*, **25B**, 125 (1955); *Chem. Abstracts*, **50**, 11350 (1956).

**A-848. Quinazo[3,4-a]perimidine.
R.I. 3235**



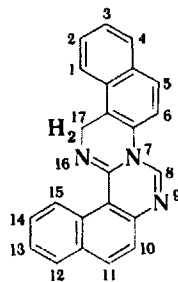
It was found by Sachs and Steiner¹ that II (yellow, m. 139–141°) is produced by the treatment of I with acetic anhydride.



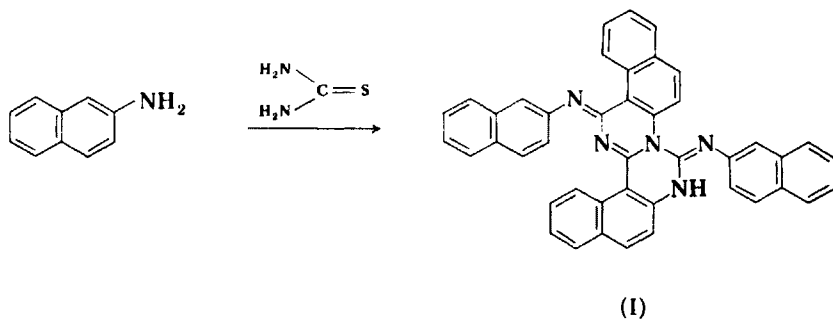
Reference

1. Sachs and Steiner, *Ber.*, **42**, 3674 (1909).

A-849. 17*H*-Naphtho[1,2-*c*]naphtho-[1',2',5,6]pyrimido[1,2-*c*]-pyrimidine. R.I. 3581

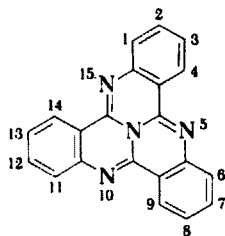


By heating in vacuo at 230–40°, a mixture of thiourea and β -naphthylamine, Dziewonski, Sternbach and Strauchen¹ obtained a yellow product (m. >360°) thought to possess structure I. The nucleus of I was named 5,6,5',6'-dibenzo-1,4,1',2'-tetrahydro-1,2,3',4'-quinazoquinazoline.

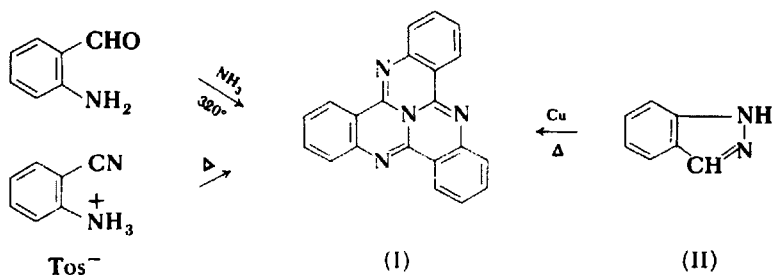


Reference

1. Dziewonski, Sternbach and Strauchen, *Bull. intern. acad. polon. sci., Classe sci. math. nat.*, **A**, 493 (1936); *Roczniki Chem.*, **17**, 1 (1937); *Chem. Zentr.*, **I**, 3961 (1937); *Chem. Abstracts*, **31**, 3053 (1937).

A-850. Tricycloquinazoline. R.I. 3576

By heating *o*-aminobenzaldehyde with compounds (such as ammonium chloride or hydantoin) capable of yielding ammonia, Kozac and Kalmus¹ obtained a product thought to have structure I. This synthesis was recently confirmed by Cooper and Partridge,² who also prepared I (together with other products) by heating *o*-cyanoanilinium *p*-toluenesulfonate. Furthermore, it was also shown² that the product obtained³ by heating indazole (II) with copper powder,



and which had been assigned a linear hexacyclic structure, was, in fact, I. Pyrolysis of various anthranilic acid derivatives (best yield: 20–25%) also produced⁴ I.

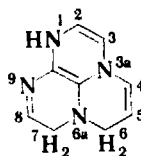
Compound I forms yellow crystals, m. $322\text{--}3^\circ$ ² ($308\text{--}10^\circ$)¹ having the following absorption maxima (in $m\mu$ with values of ϵ_{max} in parentheses): 252 (40,900), 284 (23,500), 296 (32,600), 310 (29,200), 378 (23,800), 400 (23,000), 424 (8200) and 450 (2600). Nitration of I gave¹ a brown trinitro derivative (d. $>360^\circ$) and chlorination yielded¹ trichloro-I (yellow, m. $344\text{--}6^\circ$), which, with nitric acid, gave¹ a trichlorotrinitro-I (dark red, d. 400°). Treatment¹ of I with 60% oleum gave a hexasulfonic acid.

The carcinogenicity of I was examined⁴ and found slight.

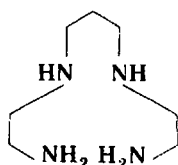
References

1. Kozac and Kalmus, *Bull. intern. acad. polon., Classe sci. math. nat.*, **A**, 532 (1933). *Chem. Zentr.*, **I**, 3595 (1934); *Chem. Abstracts*, **28**, 4424 (1934).
2. Cooper and Partridge, *J. Chem. Soc.*, **1954**, 3429.
3. Jacobson and Huber, *Ber.*, **41**, 660 (1908).
4. Baldwin, Butler, Cooper and Partridge, *Nature*, **181**, 838 (1958).

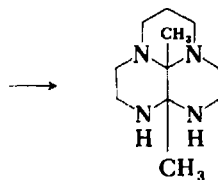
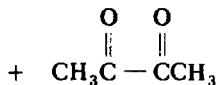
A-851. 1H,6H,7H-1,3a,6a,9-Tetraza-benzonaphthalene



A compound (II) of this nucleus was prepared by Stetter¹ by condensing triethylenetetramine (I) with biacetyl. Compound II (m. 97°) was named *1,8-trimethylene-9,10-dimethylnaphthpiperazine*.



(I)

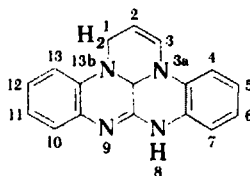


(II)

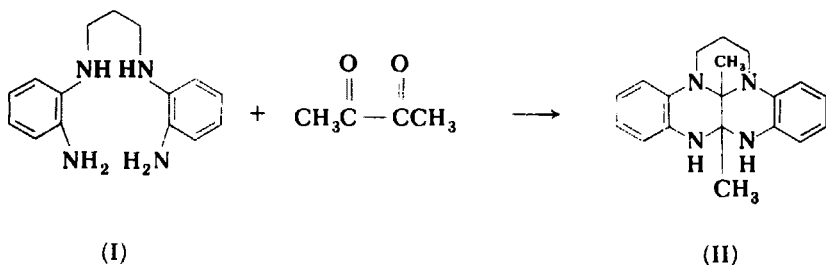
Reference

1. Stetter, *Chem. Ber.*, **86**, 69 (1953).

A-852. 1H,8H-3a,8,9,13b-Tetraza-benzo[fg]naphthacene



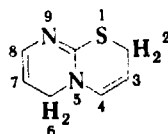
Compound I (obtained from *o*-phenylenediamine and trimethylene bromide) reacts with biacetyl to yield¹ II (m. 182°), which was named *1,8-trimethylene-9,10-dimethyl-2,3,6,7-dibenzonaphthpiperazine*.



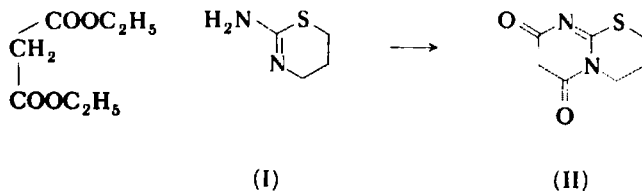
Reference

1. Stetter, *Chem. Ber.*, **86**, 69 (1953).

A-853. 2*H*,6*H*-Pyrimido[2,1-*b*]-*m*-thiazine



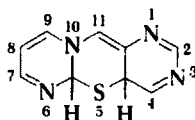
Derivatives of this nucleus have been claimed by Anish^{1,2} to be of value in photography. The reaction of I with malonic ester is reported to yield II, but no details or properties are given for II or the three derivatives reportedly prepared from it.



References

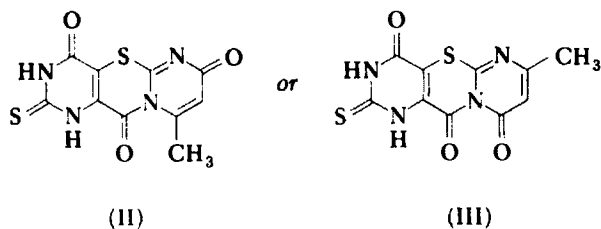
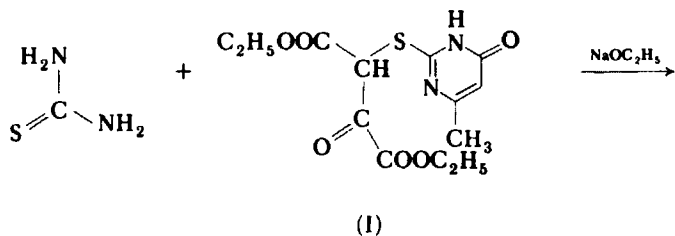
1. Anish, U. S. Pats. 2,464,780, 2,423,218 and 2,482,532.
2. Anish, Brit. Pat. 628,504; *Chem. Abstracts*, **44**, 9286 (1950). Brit. Pat. 637,648.

A-854. 4*aH*,5*aH*-Dipyrimido-[2,1-*b*, 4',5'-*c*]-*m*-thiazine. R.I. 1857



A single compound has been ascribed to this ring system. Johnson and Shepard,¹ by treating I with thiourea, obtained a product

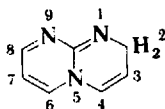
(sinters at 140°, m. 164–5°) thought to possess either structure II or III.



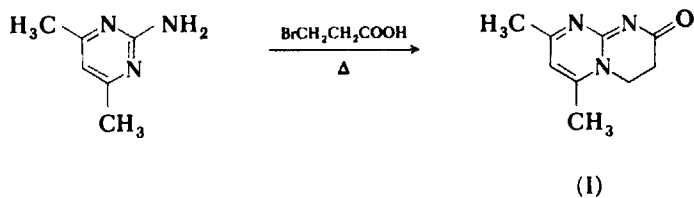
Reference

1. Johnson and Shepard, *Am. Chem. J.*, **46**, 345 (1911).

A-855. 2*H*-Pyrimido[1,2-*a*]pyrimidine

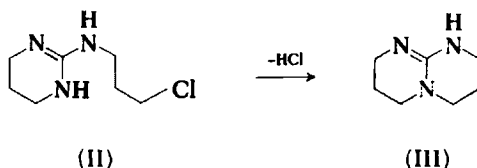


When 2-amino-4,6-dimethylpyrimidine was treated¹ with β -bromopropionic acid, a white product (m. 334–5°d.) of structure I was obtained.



The hexahydro compound III (picrate, m. 220.5–2.0°), which was called Δ^9 -1,5,9-triazabicyclo[4.4.0]decene, was obtained² by de-

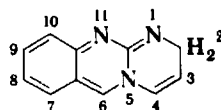
hydrochlorinating II. Nitration of III gave the 1-nitro derivative (nitrate, m. 145.5–6.0°). See Sections A-146 and A-516).



References

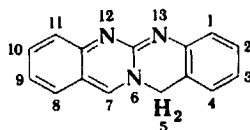
1. Hurd and Hayao, *J. Am. Chem. Soc.*, **77**, 117 (1955).
2. McKay and Kreling, *Can. J. Chem.*, **35**, 1438 (1957).

A-856. 2H-Pyrimido[2,1-b]quinazoline*

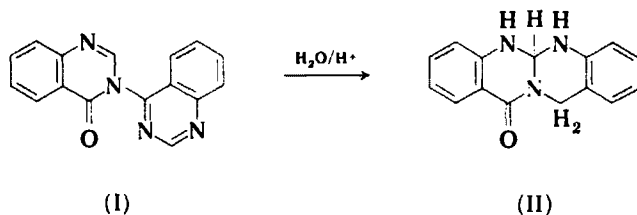


See Section A-845.

A-857. 5H-Quinazo[2,3-b]quinazoline

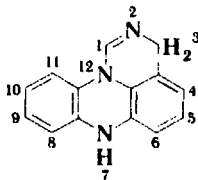


A product (m. 234–6°d.) obtained¹ from the acid hydrolysis of I, and thought possibly to possess structure II, is the only reported example of this ring system. Two other products were recently reported² to be formed from I under these conditions (see Section A-846).

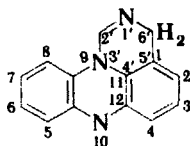


References

1. Culbertson, Willits and Christensen, *J. Am. Chem. Soc.*, **76**, 3533 (1954).
2. Stephen and Stephen, *J. Chem. Soc.*, **1956**, 4178.

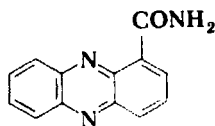
A-858. 3*H*,7*H*-Pyrimido[5,6,1-*de*]-phenazine

This nucleus has been called *pyrimidino*[5',4',3':11,9]*phenazine* and numbered as shown in I. The only reported examples (III) were

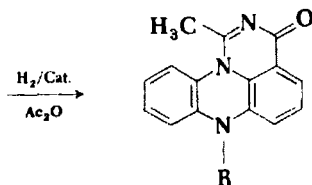


(I)

obtained by Birkofer¹ through the reductive acetylation of phenazine-1-carboxamide (II). Compound IIIa (R = H) is straw yellow, m. 184°, $\lambda_{\max}$ 287.5 m μ and 350 m μ , while IIIb (R = CH₃CO) is yellow m. 199° and has $\lambda_{\max}$ 260–7.5 m μ .



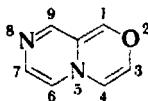
(II)



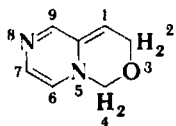
(IIIa) R = H
(IIIb) R = COCH₃

Reference

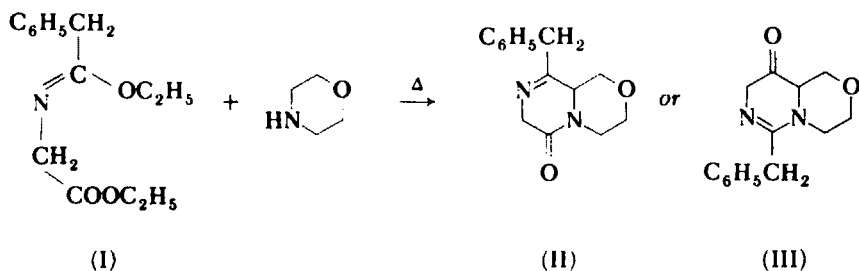
1. Birkofer, *Chem. Ber.*, **85**, 1023 (1952).

A-859. Pyrazin[2,1-*c*][1,4]oxazine

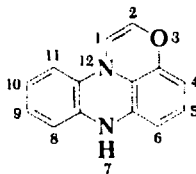
and/or

A-860. 2H,4H-Pyrazin[1,2-c][1,3]-oxazine

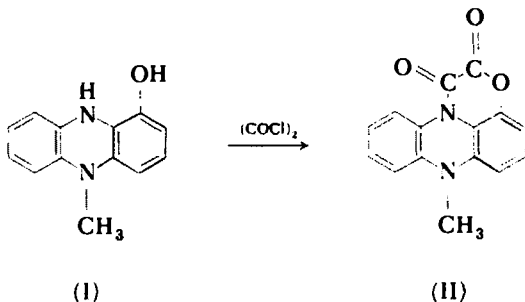
When I was heated with morpholine for thirty minutes at 100°, a product (m. 219°) was obtained, for which either structure II or III was tentatively proposed.¹ The infrared spectrum of this product should provide evidence for a choice between structures II and III.

*Reference*

1. Kjaer, *Acta. Chem. Scand.*, **7**, 1017 (1953).

A-861. 7H-p-Oxazino[de]phenazine

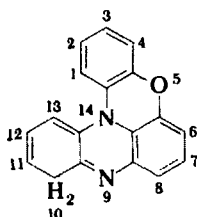
By treating leucopyocyanine (I) with oxalyl chloride, Hillemann¹ obtained compound II (light brown, sinters at 209°, m. 218–22°d.), the only reported example of this nucleus.



Reference

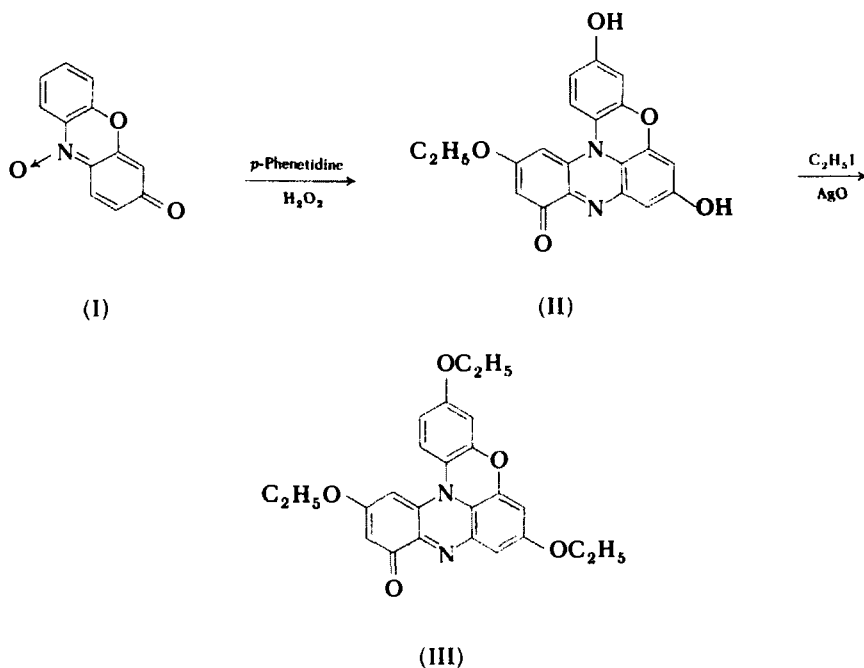
1. Hillemann, *Ber.*, **71**, 46 (1938).

**A-862. 10H-[1,4]Benzoxazino-
[2,3,4-de]phenazine***



Kinzel¹ treated *p*-phenetidine in sulfuric acid solution with hydrogen peroxide, and obtained, in good yield, a light brown crystalline product ($C_{24}H_{22}N_2O_5$), which partly melted, with decomposition, at 280° , and which gave blue or violet salts with mineral acids. The same product (called *p*-phenetidine brown) was obtained from the reaction of 4,4'-diethoxyazobenzene with *p*-phenetidine.

An analogous dye (brown, m. 290°) was prepared² from *p*-anisidine, but *p*-haloanilines and *p*-dialkylaminoanilines did not give similar products. Synthesis of *p*-phenetidine brown was achieved² by

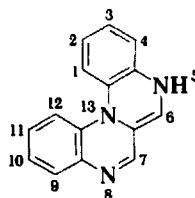


condensing resazarin (I) with *p*-phenetidine to form II, and alkylating this to yield III, thought to represent the structure of the dye.

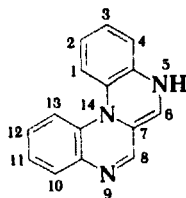
References

1. Kinzel, *Arch. Pharm.*, **229**, 329 (1891); *J. Chem. Soc. (Abstracts)*, **1892**, 158.
2. Pavolini, Gambarin and Manzini, *Ann. Chim. (Rome)*, **40**, 647 (1950); *Chem. Abstracts*, **46**, 4550 (1952).

A-863. 5*H*-Quinoxalo[1,2-*a*]quinoxaline. R.I. 2648

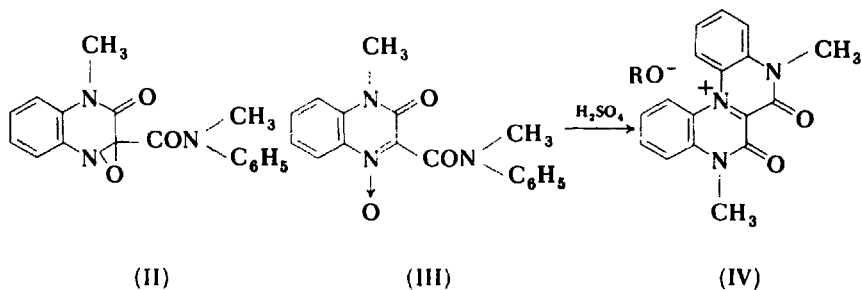


The trivial name *malonaline* has been proposed¹ for this nucleus, together with the numbering shown in I.



(I)

By treating with sulfuric acid, a substance which was written as II (and which may be III), Usherwood and Whiteley¹ obtained a product to which they assigned structure IV ($R = CH_3$, yellow, m. 276–8°; $R = C_2H_5$, yellow, m. 240°), and which was named *6,8-diketo-*

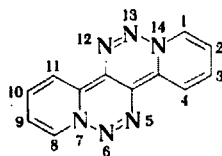


5,9-dimethyl-5,6,8,9-tetrahydromalonalinium alkoxide. Further evidence for the structure would be desirable.

Reference

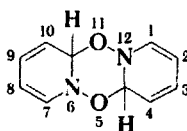
1. Usherwood and Whiteley, *J. Chem. Soc.*, **123**, 1069 (1923)

**A-864. Pyrido[2,1-f]pyrido[2',1',6,1]-
-v-triazino[5,4-d]-v-triazine***

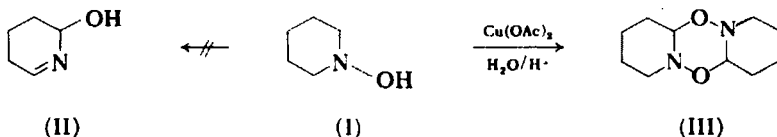


See Section A-535.

**A-865. 4aH,10aH-Dipyrido[1,4,2,5]-
dioxadiazine***



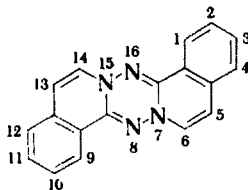
The product (m. 126–7°) first obtained by Wolfenstein¹ from the oxidation of I, and thought by him to be II, was recently reinvestigated² and shown to have structure III. Catalytic hydrogenation reconverts III into I.



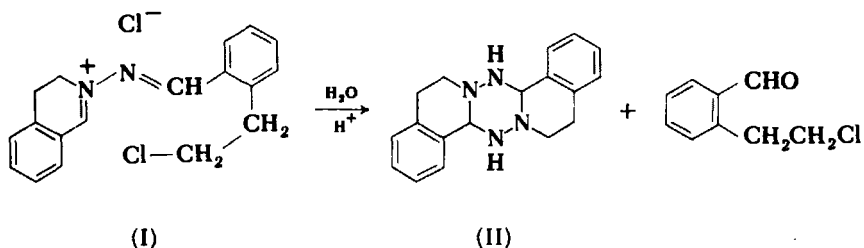
References

1. Wolfenstein, *Ber.*, **25**, 2777 (1892).
2. Thesing and Mayer, *Chem. Ber.*, **89**, 2159 (1956).

**A-866. s-Tetrazino[3,2-a, 6,5-a']diiso-
quinoline***



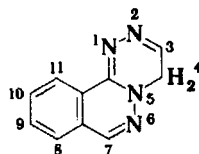
A brief allusion has been made¹ to the presence of a substance assigned structure II amongst the products of the acid hydrolysis of I.



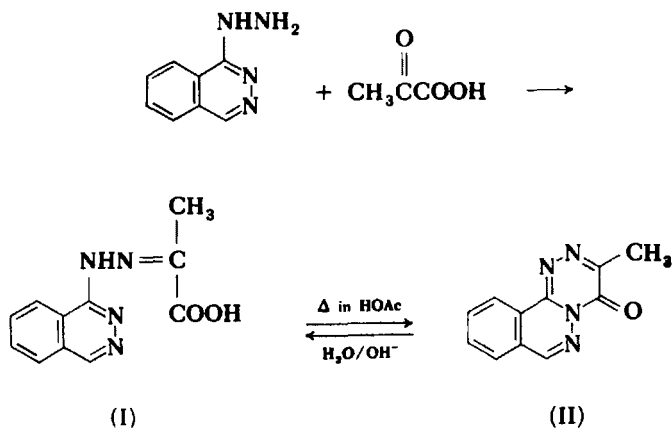
Reference

1. Schmitz, *Angew. Chem.*, **69**, 728 (1957).

A-867. 4*H*-as-Triazino[3,4-*a*]phthalazine



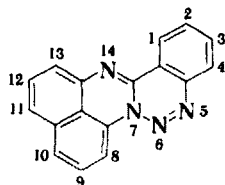
Only one example of this nucleus has been described, compound II (m. 250–2°), which was obtained¹ from the dehydration of I. Basic hydrolysis reconverts II into I.



Reference

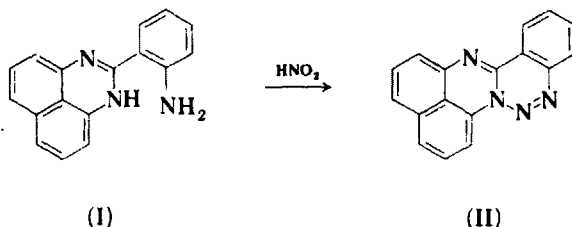
1. Druey and Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).

A-868. [1,2,3]Benzotriazino-
[3,4-*a*]perimidine. R.I. 3187



The name *o*-aminophenylperimidine azoimide was once used.

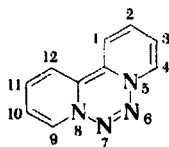
By treating I with nitrous acid, Sachs and Steiner¹ obtained II, a red-brown solid which has no melting point, but which decomposes with sudden vigor at 140°.



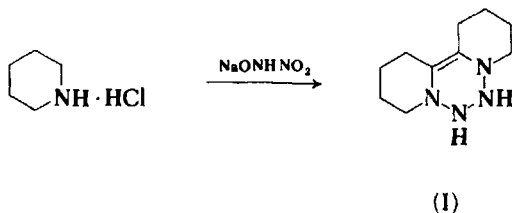
Reference

1. Sachs and Steiner, *Ber.*, **42**, 3674 (1909).

A-869. Dipyrido[1,2-*d*, 2',1'-*f*]-*v*-
tetrazine*



The reaction, in aqueous solution, of piperidine hydrochloride with sodium nitrohydroxamate, yielded,¹ *inter alia*, crystals (m. ~154°) of a product thought to have structure I. This product, which

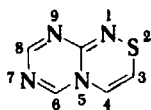


was not obtained in a pure state, gave a dipicrate (m. $\sim 174^\circ$) and a dibenzoyl derivative. Further evidence for the structure assigned would be welcome.

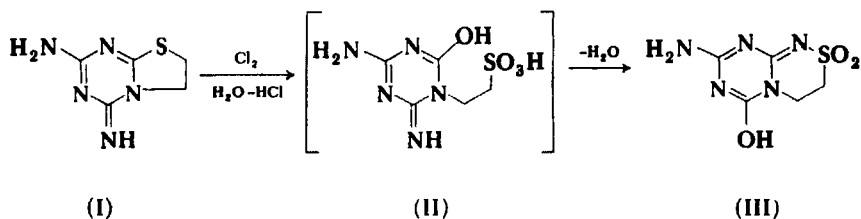
Reference

1. Angeli and Castellana, *Atti reale accad. Lincei*, [5]14, I, 272 (1905); *Chem. Zentr.*, I, 1260 (1905).

A-870. 1,2,4-Thiadiazino[4,3-a]-s-triazine.



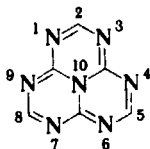
From the reaction of thioammeline with ethylene bromide, Rathke obtained¹ a product, which he thought to be I (see Section A-615). Chlorination of a solution of I in hydrochloric acid produced a new substance, which he considered² to be III, presumably formed via II.



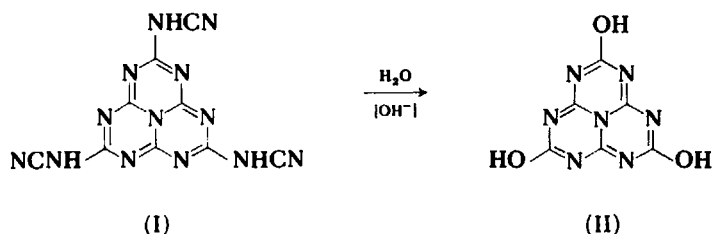
References

1. Rathke, *Ber.*, 20, 1063 (1887).
2. Rathke, *Ber.*, 21, 875 (1888).

A-871. Tri-s-triazine. R.I. 1815



This ring system has recently been shown¹⁻⁵ to be the nucleus of the long-known hydromelonic and cyameluric acids (I and II, respectively). A review of the early work and previously proposed struc-



tures is given by Redmann and Lucas,^{3,4} together with descriptions of the preparation of the products from potassium thiocyanate. Compound I is converted into II by alkaline hydrolysis. The chemistry of cyameluric acid is rather similar to that of cyanuric acid; it is converted into an insoluble, infusible trichloride by phosphorus pentachloride, and with benzyl chloride the trisodium salt gives *N*-tribenzyl cyamelurate (m. 283–4°).

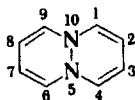
References

1. Pauling and Sturdivant, *Proc. Natl. Acad. Sci.*, **23**, 615 (1937); *Chem. Abstracts*, **32**, 2087 (1938).
2. Pauling, *The Nature of the Chemical Bond*, 2nd Ed., Cornell University Press, Ithaca, N. Y., 1945, p. 224.
3. Redemann and Lucas, *J. Am. Chem. Soc.*, **61**, 3420 (1939).
4. Redemann and Lucas, *J. Am. Chem. Soc.*, **62**, 842 (1940).
5. Maruha, *J. Chem. Soc. Japan*, **71**, 627 (1950); *Chem. Abstracts*, **45**, 9067 (1951).
6. Jacques, *Bull. soc. chim. France*, **1956**, 1315.

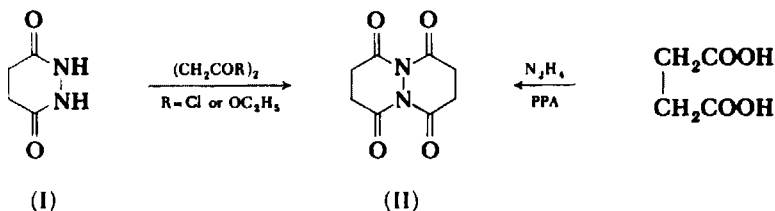
CHAPTER XIV

Fused 6/6 Ring Systems with Two Bridgehead Nitrogen Atoms

A-872. Pyridazo[1,2-*a*]pyridazine

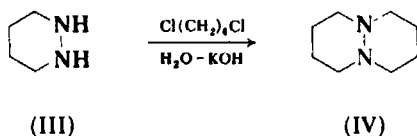


Compound II (m. 308–9°) was prepared¹ by the treatment of I with ethyl succinate, with succinoyl chloride, or, more conveniently in 95% yield,² by simply heating a 2:1 molar ratio of succinic acid and hydrazine in polyphosphoric acid. A somewhat lower yield of II results when succinic acid is heated with hydrazine alone.

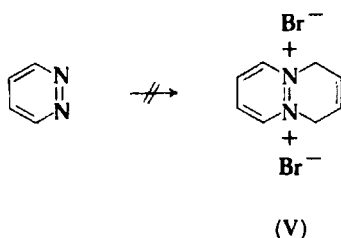


The use of methylsuccinic acid gave² a product (m. 144–5° or 147–9°), which is probably a mixture of the 2,7- and 2,8-dimethyl homologs of II. Phenylsuccinic acid gave² a diphenyl homolog of II (m. 228–9°). Dimethylsuccinic acid gave a 2,3,7,8-tetramethyl compound (m. 238–40° or 242–3°) thought² to be a mixture of stereoisomers.

When piperidazine (III) was refluxed with 1,4-dichlorobutane and aqueous caustic for some time, IV (oil; diperchlorate, m. 229° in a sealed capillary) was formed.³ It was named *10-azaquinolizidine* or *1,2-cyclotetramethylenepiperidazine*.



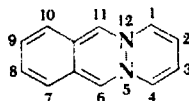
Efforts to obtain V from the reaction of pyridazine with either *cis*- or *trans*-1,4-dibromobutene were not successful.⁴



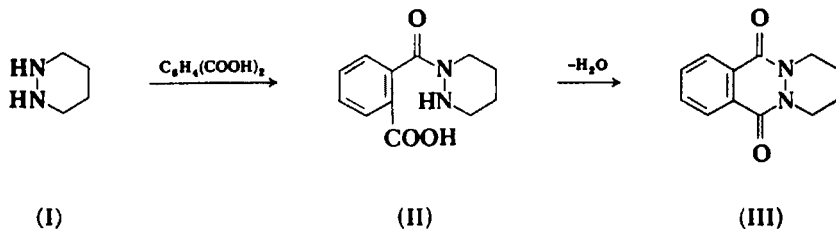
References

1. Feuer, Bachman and White, *J. Am. Chem. Soc.*, **73**, 4716 (1951).
2. Feuer and Wyman, *Chem. & Ind.*, **1956**, 577.
3. Rink and Grabowski, *Naturwissenschaften*, **43**, 326 (1956).
4. Blood and Noller, *J. Org. Chem.*, **22**, 844 (1957).

A-873. Pyridazo[1,2-*b*]phthalazine*



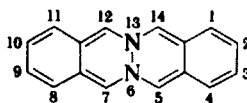
When piperidazine (I) was heated in ethanol with phthalic anhydride for several hours, compound III (m. 158–60°) crystallized.¹ It was named¹ *1,4-dioxo-2,3-cyclotetramethinequinolizidine* or *1,4-dioxo-2,3-cyclotetramethylenetetrahydrophthalazine*. The mother liquors from the preparation of III contained II, which could be dehydrated thermally to III.



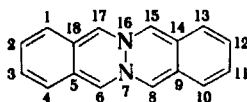
Reference

1. Rink and Grabowski, *Naturwissenschaften*, **43**, 326 (1956).

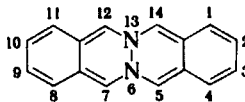
A-874. Phthalazino[2,3-*b*]phthalazine.
R.I. 2644



Compounds having this ring system have been referred to as derivatives of 7:16-diazanaphthacene (numbered as shown in I) and also 6:13-diazanaphthacene (numbered as shown in II).

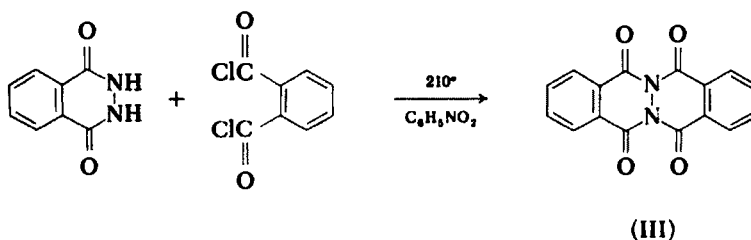


(I)



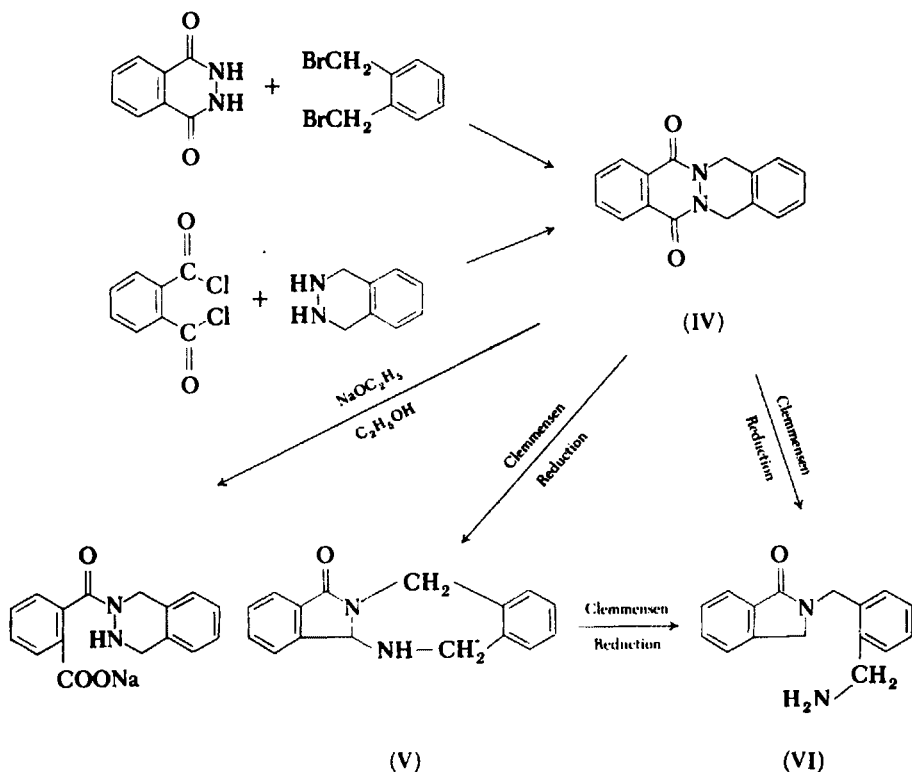
(II)

All of the examples of this nucleus have been described by Hatt and his co-workers.^{1,2,3} The tetraoxo compound III (yellow,



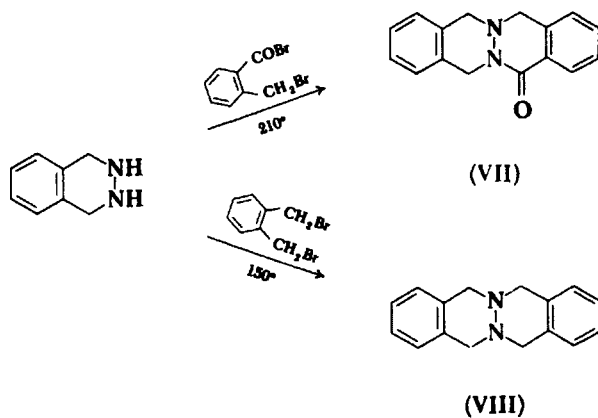
(III)

m. 350–60°) was prepared¹ by heating phthaloyl chloride with phthalazone. Treatment of phthalazone with α,α' -dibromo-*o*-xylene yielded² the dioxo derivative IV (pale yellow, m. 196.5–7.5°), which was also obtained² from 1,2,3,4-tetrahydrophthalazine and phthaloyl chloride. Scission of one of the amide linkages of IV resulted from treatment with sodium ethylate,² whereas the Clemmensen reduction of IV yielded³ either V or VI depending upon the conditions. While 5-nitro- and 6-chlorophthalazones failed to condense² with α,α' -dibromo-*o*-xylene, 4-nitrophthaloyl chloride condensed² with 1,2,3,4-tetrahydrophthalazine to give the 2-nitro analog of IV (yellow, m. 249–50°d.), which was reduced with



stannous chloride to the corresponding amine (m. $185-7^\circ$; benzoyl derivative, m. $260-1^\circ$).

Treatment of 1,2,3,4-tetrahydrophthalazine with α -bromo-*o*-toluyl bromide yielded³ VII (m. $198-9^\circ\text{d.}$), while with α,α' -

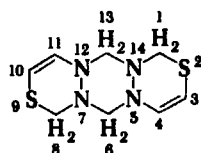


dibromo-*o*-xylene, VIII (m. 132–3°; hydrochloride, m. 248–50°d. and monomethiodide, yellow, m. 221–3°) was formed.³

References

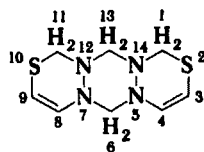
1. Drew and Hatt, *J. Chem. Soc.*, **1937**, 16.
2. Hatt and Stephenson, *J. Chem. Soc.*, **1943**, 658.
3. Hatt and Stephenson, *J. Chem. Soc.*, **1952**, 199.

A-875. 1*H*,6*H*,8*H*,13*H*-Bis[1,3,4]thiadiazino[3,4-*a*, 3',4'-*d*]tetrazine*



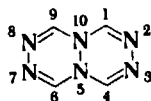
or

A-876. 1*H*,6*H*,11*H*,13*H*-Bis[1,3,4]thiadiazino[3,4-*a*, 4',3'-*d*]tetrazine*



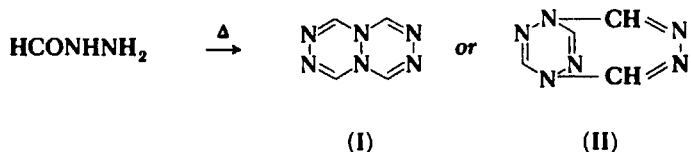
See Section A-35.

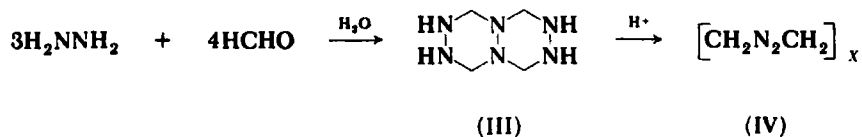
A-877. *s*-Tetrazino[1,2-*a*]-*s*-tetrazine. R.I. 908



By heating formylhydrazine, Pellizzari obtained¹ in about 12% yield a product (m. 263°d.), which he named *diazodimethintetrazoline*. This substance was thought to have either structure I or II. When heated with hydrochloric acid, it decomposed to hydrazine, formic acid and 4-amino-*s*-triazole. Further work is needed to demonstrate the structure of Pellizzari's product.

The reaction of hydrazine with aqueous formaldehyde yielded² a white crystalline product named *tetraformaltrisazine* and assigned structure III. Compound III begins to decompose at about 225°, and





volatilizes without melting; it is readily decomposed by acids, even carbonic acid, to polymeric *formalazine* (IV).

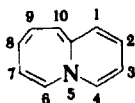
References

1. Pellizzari, *Gazz. chim. ital.*, **39**, I, 520 (1909).
2. Hofmann and Storm, *Ber.*, **45**, 1727 (1912).

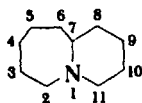
CHAPTER XV

Fused 6/7 and Larger Ring Systems

A-878. Pyrid[1,2-*a*]azepine

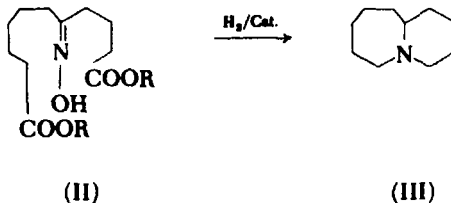


Most of the known examples of this ring system are derivatives of the completely hydrogenated nucleus and have often been named as *1-azabicyclo[5.4.0]hendecanes* and numbered as shown in I.



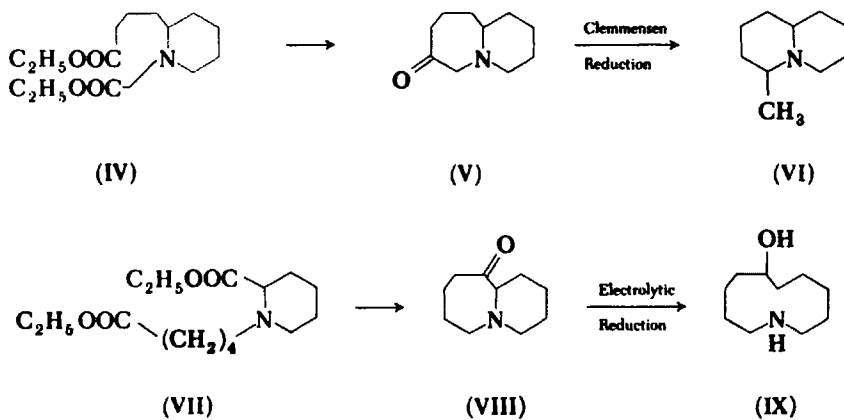
(I)

Leonard and Goode¹ obtained III (b_{16} 90°; n_D^{20} 1.4872; picrate, m. 161–2°; picrolonate, m. 213°; HBr salt, m. 249–50°;⁶ methiodide,⁶ m. 246°) by the hydrogenation of II over a copper chromite

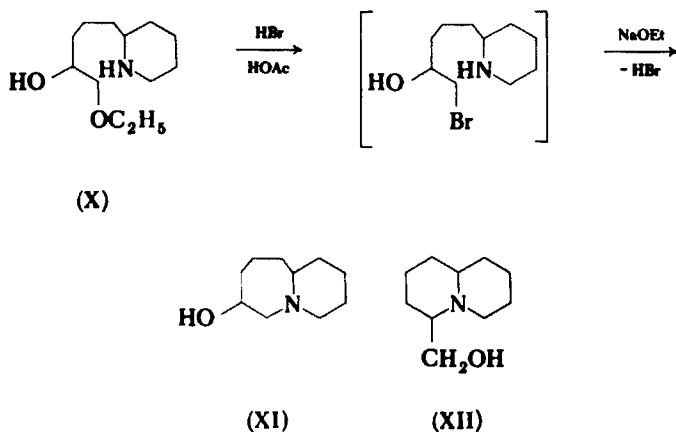


catalyst at 265° and 350 atmospheres. Two keto derivatives, V (b_{18} 130–2°; picrate, m. 157–8°; picrolonate, m. 203–4°)² and VIII (b_{21} 124–5°; picrate, m. 193.0–3.5°; picrolonate, m. 188°)³ were obtained by Leonard, *et al.*^{2,3} from the cyclization of IV and

VII, respectively. Neither of these ketones was reduced directly to III, although, presumably, the Wolff-Kishner reduction of either would yield III. The Clemmensen reduction of V yielded 4-methylquinolizidine (VI), while the electrolytic reduction of VIII resulted in scission of the 5-10a bond giving an undecacyclic amino alcohol (IX).

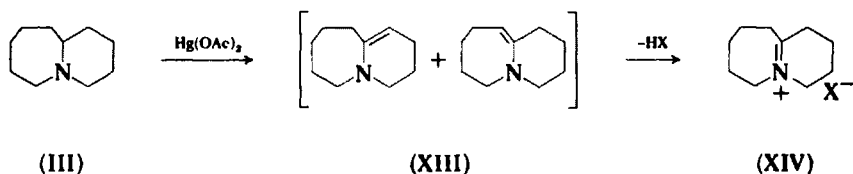


By treating X in acetic acid solution with hydrogen bromide, and heating the resulting product with sodium ethoxide in ethanol, Winterfeld and Müller⁴ obtained a product (b_{3.5} 112-6°; no crystalline salts) thought to be XI. The properties of this product do not permit an unequivocal assignment of structure XI, but the product is

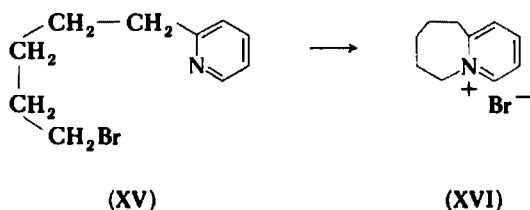


evidently different from the seemingly more likely structure XII (4-lupinidine), which also was synthesized.

Dehydrogenation of III with mercuric acetate yielded⁵ a mixture of the Δ^6 - and Δ^7 -dehydro compounds (XIII, b_{18} 103°; n_D^{20} 1.5167), which was converted into a single perchlorate salt (m. 175–6°) of structure XIV.



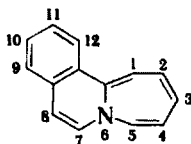
Heating XV in benzene solution produced⁶ XVI (hemihydrate, m. 58–9°), which was hydrogenated over platinum oxide to III.



References

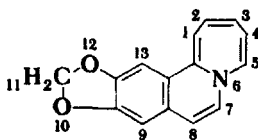
1. Leonard and Goode, *J. Am. Chem. Soc.*, **72**, 5404 (1950).
2. Leonard and Nicolaides, *J. Am. Chem. Soc.*, **73**, 5210 (1951).
3. Leonard, Swann and Mottus, *J. Am. Chem. Soc.*, **74**, 6251 (1952).
4. Winterfeld and Müller, *Ann.*, **581**, 77 (1953).
5. Leonard, Middleton, Thomas and Choudhury, *J. Org. Chem.*, **21**, 344 (1956).
6. Morikawa, *J. Pharm. Soc. Japan*, **75**, 593 (1955); *Chem. Abstracts*, **50**, 5656 (1956).

A-879. Azep[2,1-a]isoquinoline

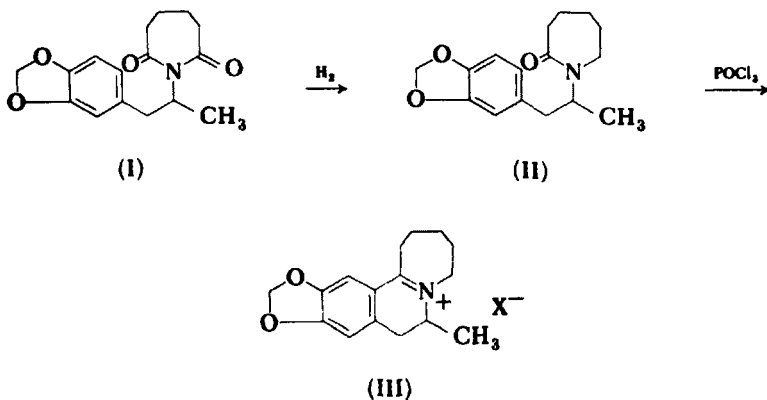


and

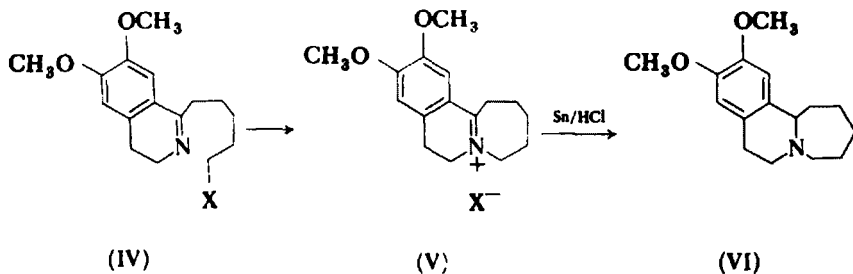
A-880. Azepo[a][1,3]dioxolo[g]-isoquinoline. R.I. 2576M



Sugasawa, Skaurai and Sugimoto¹ obtained III (iodide, m. 238–9°) by the cyclization of II, which was in turn obtained by the electrolytic reduction of I.

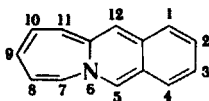


While searching for amoebicidal compounds related to emetine, Osbond² prepared V ($\text{X} = \text{OH}^-$, m. 211–4°; $\text{X} = \text{Br}^-$, m. 215–7°; $\text{X} = \text{PkO}^-$, m. 150–1°) by cyclization of IV. Reduction of V with tin and hydrochloric acid yielded VI (HBr salt, m. 220–2°).



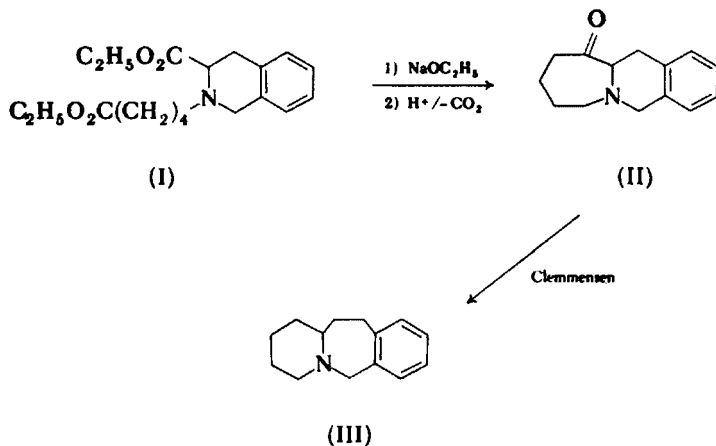
References

1. Sugasawa, Sakurai and Sugimoto, *Proc. Imp. Acad. (Tokyo)*, **15**, 82 (1939); *Chem. Zentr.*, **II**, 3574 (1939); *Chem. Abstracts*, **33**, 6318 (1939).
2. Osbond, *J. Chem. Soc.*, **1951**, 3464.

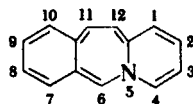
A-881. Azep[1,2-*b*]isoquinoline

Partially hydrogenated derivatives of this nucleus may also be called *benzo[*i*]-1-azabicyclo[5.4.0]hendecanes*.

A single example is known: compound II (light yellow, m. 94–5°), which was obtained by Leonard, Swann and Fuller¹ from the Dieckmann cyclization of I. The electrolytic or Clemmensen reduction of II yielded the rearranged product III (see Section A-882).

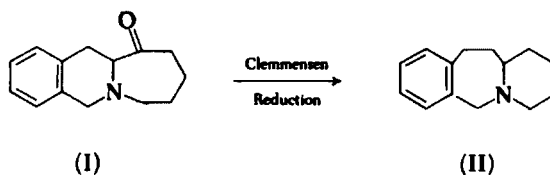
*Reference*

1. Leonard, Swann and Fuller, *J. Am. Chem. Soc.*, **76**, 3193 (1954).

A-882. Benz[*e*]pyrid[*a*]azepine*

The 1,2,3,4,6,11,12,12*a*-octahydro derivative has been named *benzo[*c*]-1-azabicyclo[5.4.0]hendecane*.

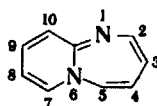
By the Clemmensen reduction of I (see Section A-881) Leonard, Swann and Fuller¹ obtained II (*b*_{0.3} 120°, *n*_D²⁰ 1.5580, picrate, m. 194–5°), which also was one of the products of the electrolytic reduction of I.



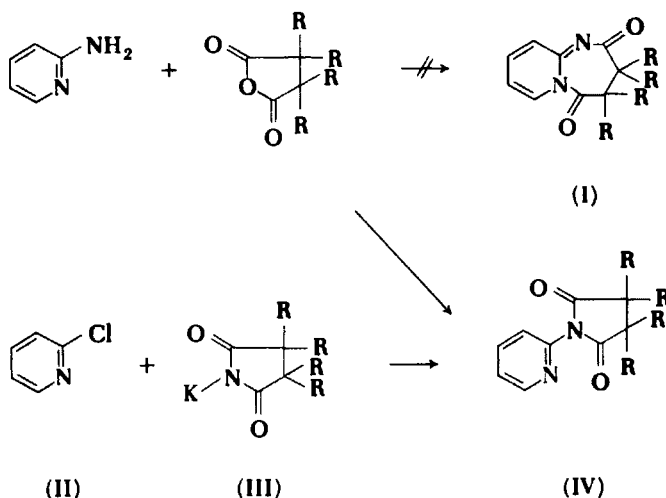
Reference

1. Leonard, Swann and Fuller, *J. Am. Chem. Soc.*, **76**, 3193 (1954).

A-883. Pyrido[1,2-*a*][1,3]diazepine. R.I. 1063

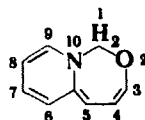


The products obtained by Ott and Hess¹ from the reaction of 2-aminopyridine with tetralkylsuccinic anhydrides, at first thought to have structure I, are known¹ now (because of their synthesis from II and III) to have structure IV.

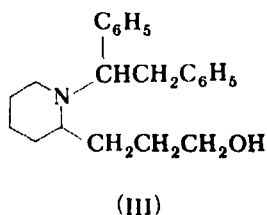
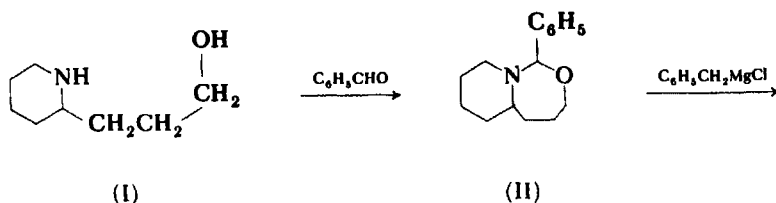


Reference

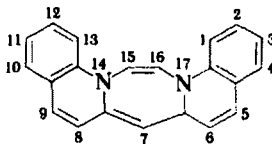
1. Ott and Hess, *Arch. Pharm.*, **276**, 181 (1938); *Chem. Zentr.*, **I**, 4323 (1938); *Chem. Abstracts*, **32**, 5916 (1938).

A-884. 1*H*-Pyrid[1,2-*c*][1,3]oxazepine

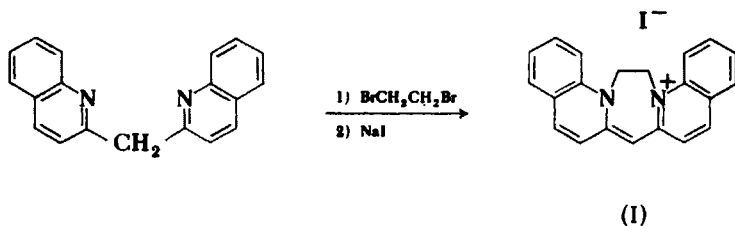
A single example, II ($b_{0.04}$ 93°; n_D^{25} 1.5433), is known of this ring system. It was obtained by Goodson and Christopher¹ by the reaction of I with benzaldehyde. Treatment of II with benzylmagnesium chloride yielded¹ III. See Section A-826.

*Reference*

1. Goodson and Christopher, *J. Am. Chem. Soc.*, **72**, 358 (1950).

A-885. Diquino[1,2-*d*, 2',1'-*g*]diazepine

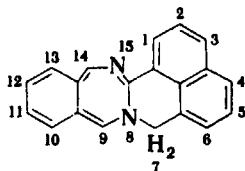
Compound I (orange-red with a green fluorescence, $m. > 330^\circ$, $\lambda_{\max}$ 481.7 and 516.8 $m\mu$) was prepared as shown by Scheibe and Fischer.¹ Recently a modification using ethyleneglycol ditosylate as the alkylating agent was patented by Brooker and Sprague.^{1,2}



References

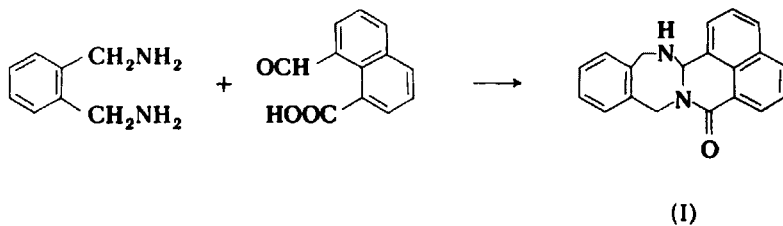
1. Scheibe and Fischer, *Ber.*, **59**, 502 (1926).
2. Brooker and Sprague, U. S. Pat. 2,478,367.
3. Brooker and Sprague, U. S. Pat. 2,541,400; Brit. Pat. 610,064.

A-886. 7H-Benz[4,5]isoquino[2,1-b]-[2,4]benzodiazepine*



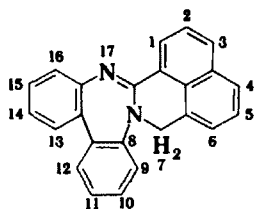
For some reason this nucleus was not named by *Chemical Abstracts*.

A single example (I, m. 195–6°; *N*-acetyl derivative, m. 215.5–6.5°) is known of this nucleus. It was prepared, as shown, by Stephenson.¹



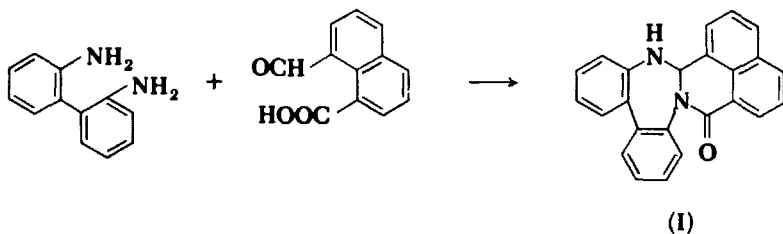
Reference

1. Stephenson, *J. Chem. Soc.*, **1952**, 5024.

A-887. 7H-Benz[4,5]isoquino[2,1-a]-dibenzo[d,f][1,3]diazepine*

For some reason this nucleus was not named by *Chemical Abstracts*.

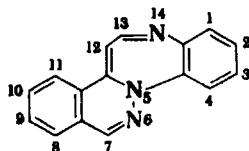
Stephenson¹ reported the preparation of I (yellow, m. 263.5–4.5°; *N*-acetyl derivative, m. 261.0–1.5°; *N*-nitroso derivative, m. 226–7°d.) from the condensation of naphthaldehydic acid with



2,2'-diaminobiphenyl. The product was stable to hot alcoholic sodium ethylate, but was slowly attacked by hot 1:1 hydrochloric acid.

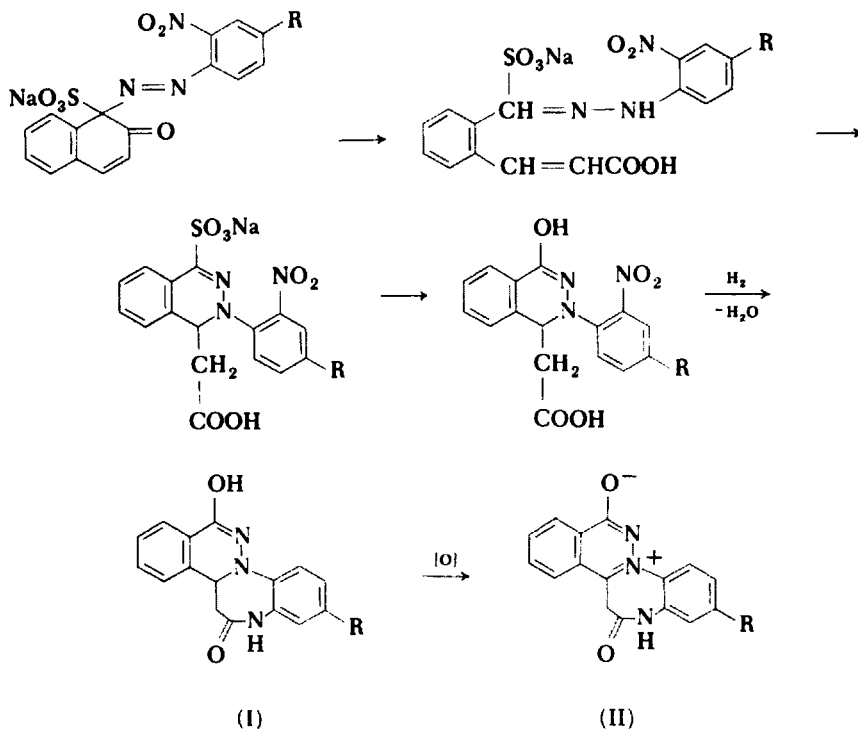
Reference

1. Stephenson, *J. Chem. Soc.*, **1952**, 5024.

A-888. Phthalazino[2,1-a][2,5]benzodiazepine. R.I. 2823

Several derivatives of type I ($R = H$, m. 293°; Me , m. 282–4°; Cl , m. 304°; NH_2 , m. 290°; $NHAc$, m. 306°) were prepared by Rowe and co-workers^{1–3} by the route shown. With the exception² of the compound in which $R = CH_3$, the compounds of type I were unstable to acid and reducing agents. Treatment of I ($R = H$ or Cl)

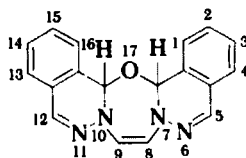
with potassium dichromate in sulfuric acid yielded products formulated¹ as II ($R = H$, m. 302° ; $R = Cl$, m. 314°).



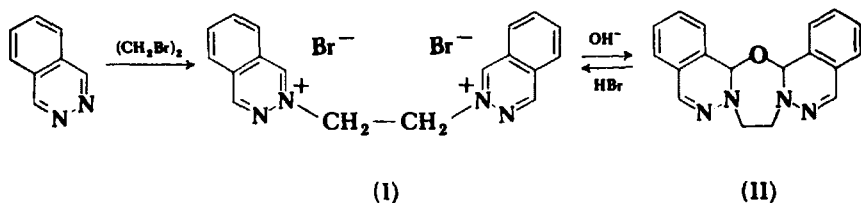
References

1. Rowe, Dovey, Garforth, Levin, Pask and Peters, *J. Chem. Soc.*, **1935**, 1796.
2. Rowe, Haigh and Peters, *J. Chem. Soc.*, **1936**, 1098.
3. Rowe and Osborn, *J. Chem. Soc.*, **1947**, 829.

A-889. 16*b*H,17*a*H-Diphthalazino- [1,2-*b*, 2',1'-*f*][1,3,6]oxdiazepine

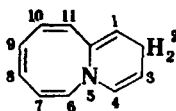


The reaction of phthalazine with ethylene dibromide gave the bisquaternary salt I, which, upon treatment with caustic, yielded¹ II [m. $150-2^\circ$, $\lambda_{\max}$ 234 and 308 $m\mu$ ($\epsilon = 17,750$ and $17,800$)]. Treatment of II with mineral acids reconverted it into salts of type I.

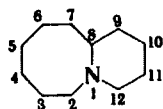


Reference

1. Daeniker and Druey, *Helv. Chim. Acta*, **40**, 918 (1957).

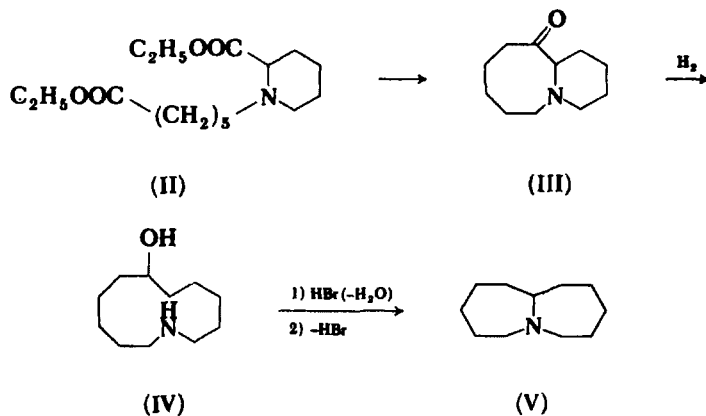
A-890. 2*H*-Pyrid[1,2-*a*]azocine

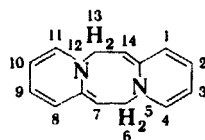
Derivatives of the completely hydrogenated nucleus have also been named as 1-azabicyclo[6.4.0]dodecanes, and numbered as shown in I.



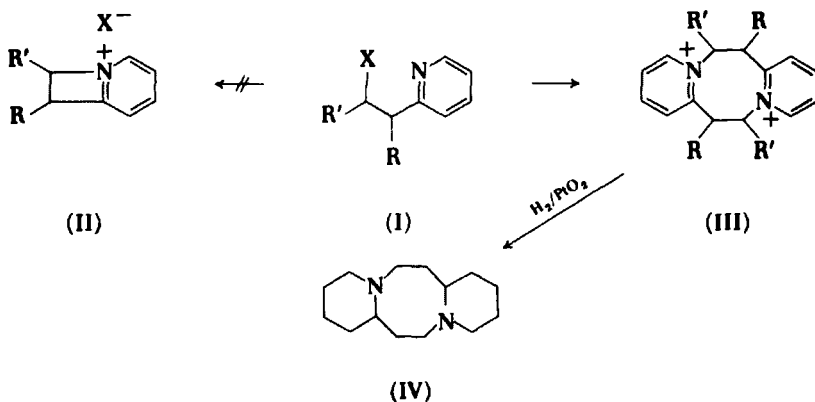
(I)

By the Dieckmann cyclization of II, and decarboxylation of the intermediate keto ester, Leonard, Swann and Mottus¹ obtained III (b_{21} 146–7°; n_D^{20} 1.4992; picrate, m. 156.5–7°; picrolonate, m. 167.5–8.5°). Electrolytic reduction of III resulted in ring scis-



A-893. 6*H*,13*H*-Dipyrido[1,2-*a*,1',2'-*e*]-[1,5]diazocine*

When 2-(2-haloalkyl)-pyridines (I) are allowed to stand, or are heated, they are transformed into crystalline salts, which have been assigned¹⁻⁷ structure II (see Section A-55). However, the product thus obtained from 2-(2-bromomethyl)-pyridine recently was shown⁸ to have structure III, and it seems probable that all of the products assigned structure II are actually of type III. They have been so listed in the table. Catalytic reduction of II yielded⁸ IV ($b_{0.2}$ 105°, n_D^{24} 1.5800; dimethiodide, m. 282–3°d.).



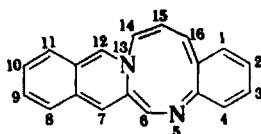
Compounds of Structure III

R	R'	Properties	Refs.
H	H	Chloride, m. 175°. Bromide, m. 238–40° (226–7°, 220–5°). Iodide, m. 230–1° (211–3°). Picrate, m. 179–81°. Bichromate, m. 170–5°d.	1,5–8
CH ₃	H	Chloride. Platinichloride, m. > 260°.	4
H	CH ₃	Chloride, m. 122°. Bromide, m. 162°. Iodide, m. 147°. Platinichloride, m. 188°.	2
H	C ₂ H ₅	Bromide, m. 135–40°. Iodide, m. 153–4°. Platinichloride, m. 212–3°.	3

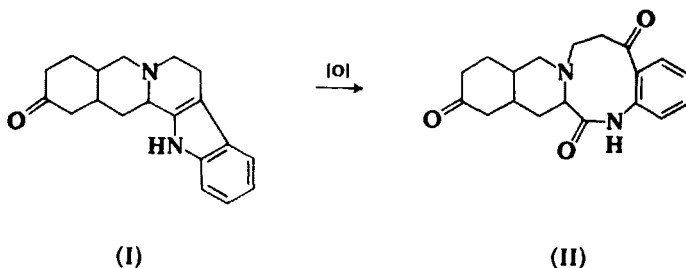
References

1. Löffler, *Ber.*, **37**, 161 (1904).
2. Löffler and Kirschner, *Ber.*, **38**, 3329 (1905).
3. Löffler and Plöcker, *Ber.*, **40**, 1310 (1907).
4. Löffler and Grosse, *Ber.*, **40**, 1325 (1907).
5. Takahashi, Nishigaki and Taniyama, *J. Pharm. Soc. Japan*, **64**, 237 (1944); *Chem. Abstracts*, **45**, 1997 (1951).
6. Ohki and Noike, *J. Pharm. Soc. Japan*, **72**, 490 (1952); *Chem. Abstracts*, **47**, 6419 (1953).
7. Bohlmann, Ottawa, Keller, Nebel and Politt, *Ann.*, **587**, 162 (1954).
8. Boeckelheide and Feely, *J. Am. Chem. Soc.*, **80**, 2217 (1958).

A-894. Benz[*e*]isoquino[2,3-*a*][1,4]-diazonine



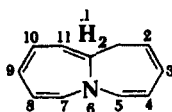
The perbenzoic acid oxidation of yohimbone (I) was shown by Witkop and Fiedler¹ to yield a product (m. 245°) having structure II.



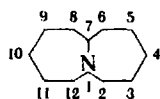
Reference

1. Witkop and Fiedler, *Ann.*, **558**, 91 (1947).

A-895. 1*H*-Azepo[1,2-*a*]azepine

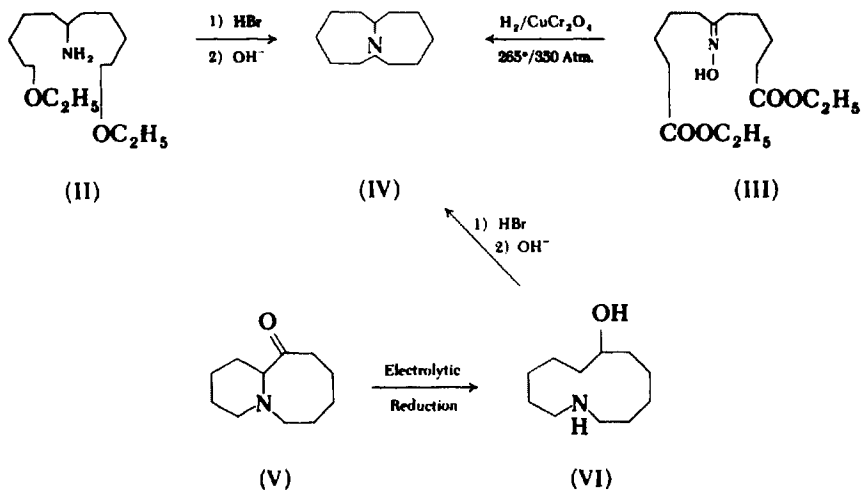


An alternative name encountered for the perhydro derivative is 1-azabicyclo[0.5.5]dodecane, numbered as shown in I.

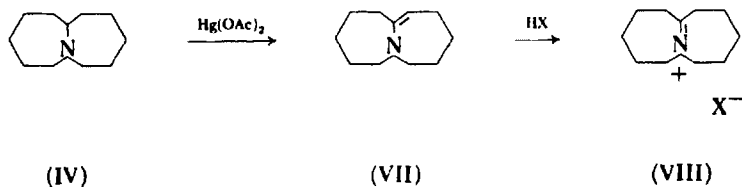


(I)

Until recently, only one compound with this nucleus was known (IV, b_{16} 107–8°¹, b_{18} 111–2°²; n_D^{20} 1.4930;² picrate, m. 141–3°³, 139–40°², 136°¹; picrolonate, m. 186–7°², 181°¹; methiodide, m. 243–4°², 233°¹), but three different syntheses of it have been reported. Prelog and Schönbaum¹ obtained it first by the treatment of II with hydrobromic acid followed by caustic. Then it was prepared by Leonard and Goode² by the catalytic reduction of III, and recently Leonard, Swann and Mottus³ obtained it from VI, which was formed during the electrolytic reduction of V.

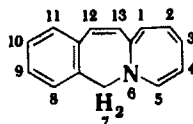


Treatment of IV with mercuric acetate gave⁴ VII (b_{18} 115–7°; n_D^{20} 1.5124) the salts of which (e.g. the perchlorate, m. 226°) have structure VIII.

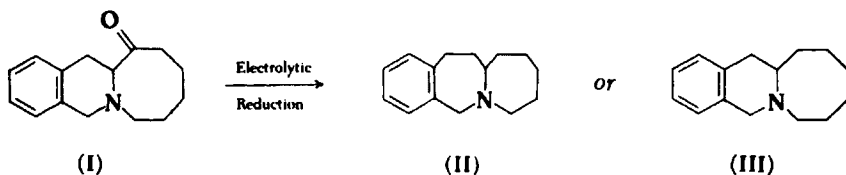


References

1. Prelog and Schönbaum, *Ann.*, **545**, 256 (1940).
2. Leonard and Goode, *J. Am. Chem. Soc.*, **72**, 5404 (1950).
3. Leonard, Swann and Mottus, *J. Am. Chem. Soc.*, **74**, 6251 (1952).
4. Leonard, Middleton, Thomas and Choudhury, *J. Org. Chem.*, **21**, 344 (1956).

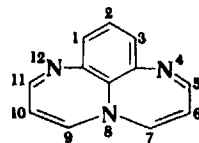
A-896. 7H-Azepo[a]benz[e]azepine

The electrolytic reduction of I (see Section A-891) has been reported¹ to yield a product ($b_{0.7}$ 120–30°; n_D^{20} 1.5508; picrate, m. 165°), which could be either II or III (named *benzo[c]-1-azabicyclo[5.5.0]dodecane* and *benzo[j]-1-azabicyclo[6.4.0]dodecane*, respectively).

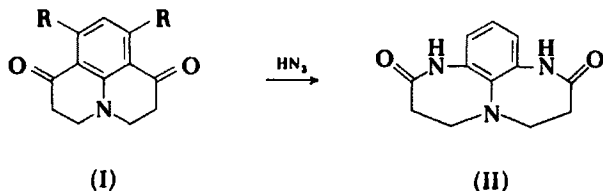


Reference

1. Leonard, Swann and Fuller, *J. Am. Chem. Soc.*, **76**, 3193 (1954).

A-897. [1,4]Diazepino[1,2,3-ef][1,5]-benzodiazepine*

Treatment of I ($R = H$) with hydrazoic acid yielded¹ a dilactam, probably II (m. 356°d.). The methyl homolog (I , $R = CH_3$)

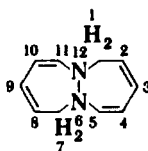


failed to yield a lactam under these conditions, presumably because of hinderance of the carbonyl functions by the methyl groups.

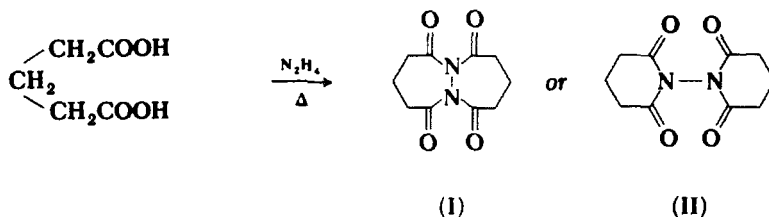
Reference

1. Ittyerah and Mann, *J. Chem. Soc.*, **1958**, 467.

A-898. *1H,7H*-[1,2]Diazepo[1,2-*a*]-[1,2]-diazepine



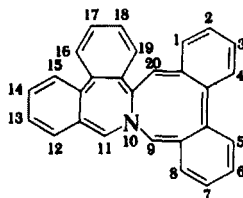
The reaction of glutaric acid with hydrazine yields¹ a product which could be either I or II.



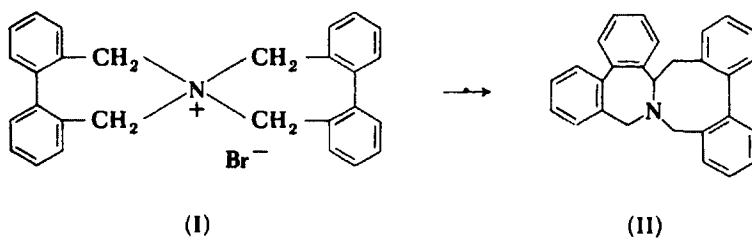
Reference

1. Feuer and Wyman, *Chem. and Ind.*, **1956**, 577.

A-899. Dibenzo[*d,f*]dibenz[3,4,5,6]-azepino[1,2-*a*]azocine



Treatment of I with either silver oxide or with phenyl lithium afforded¹ a 78% yield of II (*b*_{0.1} 260–4°, *m.* 176–7°; methiodide, *m.* 249–50° unless put into the heating bath at 250°, when *m.* 260–2°). Compound II was named *1-aza-3,4,5,6,9,10,11,12-tetrabenzo-bicyclo[6.5.0]tridecatetraene(3,5,9,11)*.

*Reference*

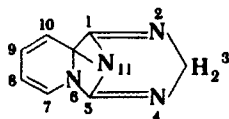
1. Wittig, Koenig and Clauss, *Ann.*, **593**, 1 (1955).

B. BRIDGED RING SYSTEMS

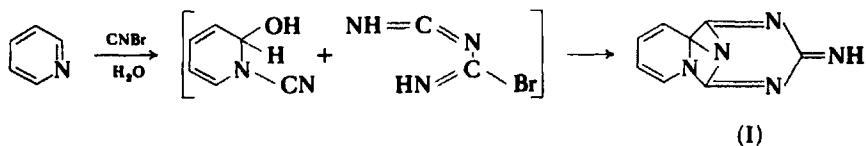
CHAPTER XVI

Bridged 3/4 through 5/6 Ring Systems

B-1. 1,5,10a(3H)-Nitrilopyrido[1,2-e]-[1,3,5]triazepine. R.I. 2183



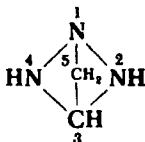
Treatment of pyridine in ethanolic ether with cyanogen bromide yielded, *inter alia*, a product $C_8H_5N_5$, which was assigned¹ the highly improbable structure I. A reinvestigation of this product obviously is necessary.



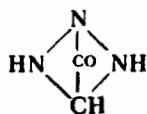
Reference

1. Shimidzu, *J. Pharm. Soc. Japan*, No. 538, 1043 (1926); *Chem. Abstracts*, **21**, 2694 (1927).

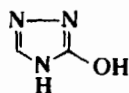
B-2. 1,2,4-Triazabicyclo[1.1.1]pentane. R.I. 488



A product obtained by Diels and Behncke¹ from the reaction of azodicarboxylic ester with malonic ester, and assigned structure I, was shown by Stollé² to be II. See Section B-7.



(I)

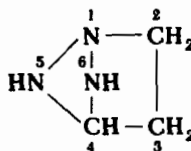


(II)

References

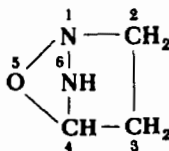
1. Diels and Behncke, *Ber.*, **57**, 653 (1924).
2. Stollé, *Ber.*, **57**, 1558 (1924).

- B-3. 1,5,6-Triazabicyclo[2.1.1]hexane. R.I. 506**



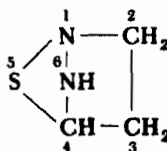
and

- B-4. 5-Oxa-1,6-diazabicyclo[2.1.1]-hexane. R.I. 499**



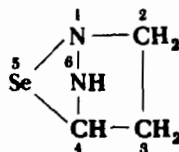
and

- B-5. 5-Thia-1,6-diazabicyclo[2.1.1]-hexane. R.I. 501**

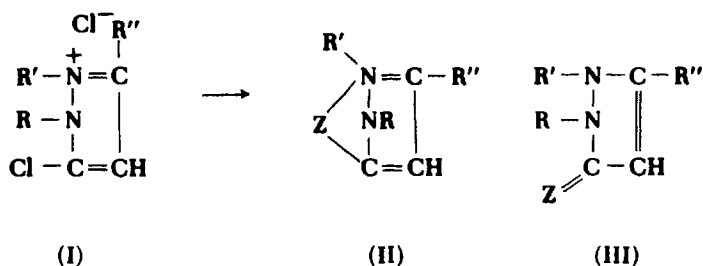


and

- B-6. 5-Selena-1,6-diazabicyclo[2.1.1]-hexane. R.I. 502**



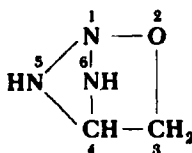
The reaction of pyrazolium salts of type I with ammonia (or primary amines) or potassium hydroxide or sulfhydrate or selenhydrate yielded ¹⁻⁴ products which were formulated as II, but for which structure III is more acceptable (Z = NR, O, S, or Se, respectively).



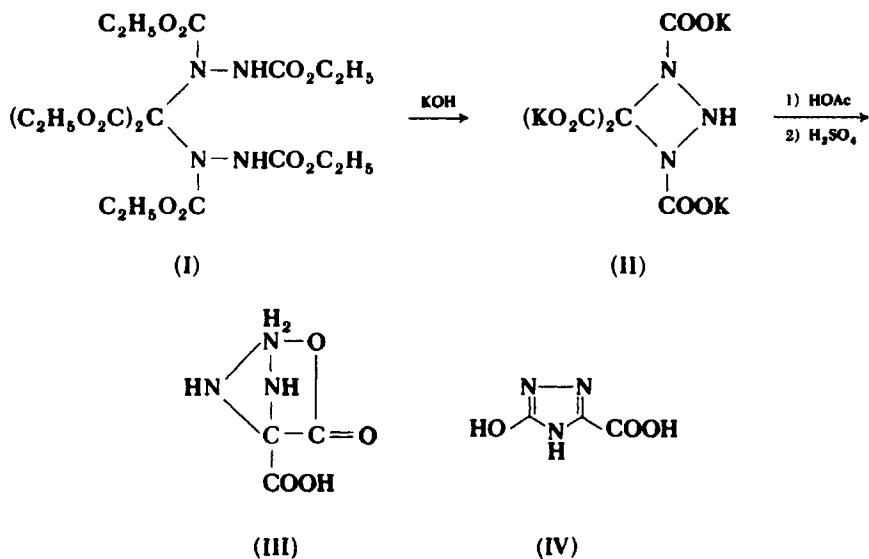
References

1. Michaelis, *Ann.*, **320**, 1 (1901).
2. Michaelis and Hepner, *Ber.*, **36**, 3271 (1903).
3. Stolz, *Ber.*, **36**, 3279 (1903).
4. Michaelis, *Ann.*, **339**, 117 (1905).

B-7. 2-Oxa-1,5,6-triazabicyclo[2.1.1]-hexane. R.I. 504



The reaction of malonic ester with azodicarboxylic ester was reported¹ to yield I, which was converted by alcoholic potash into II.

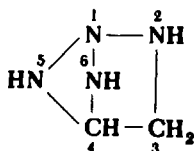


Treatment of II with acetic acid followed by sulfuric acid was thought to give III. However, Stollé² demonstrated that the product actually has structure IV. See Section B-2.

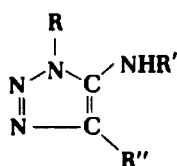
References

1. Diels and Behncke, *Ber.*, **57**, 653 (1924).
2. Stollé, *Ber.*, **57**, 1558 (1924).

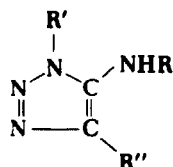
B-8. 1,2,5,6-Tetrazabicyclo[2.1.1]-hexane. R.I. 505



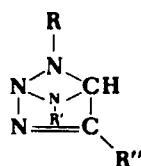
Dimroth^{1,2} found that aminotriazoles of type I were isomerized thermally to products, which he considered to have structure II. Dutt^{3,4} felt obliged to suggest the alternative structure III, but this was discredited by Dimroth and Michaelis.⁵



(I)



(II)

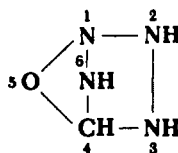


(III)

References

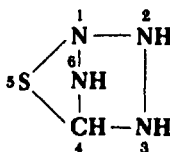
1. Dimroth, *Ber.*, **35**, 4041 (1902).
2. Dimroth, *Ann.*, **364**, 183 (1909).
3. Dutt, *J. Chem. Soc.*, **123**, 265 (1923).
4. Carnelley and Dutt, *J. Chem. Soc.*, **125**, 2476 (1924).
5. Dimroth and Michaelis, *Ann.*, **459**, 39 (1927).

B-9. 5-Oxa-1,2,3,6-tetrazabicyclo-[2.1.1]hexane. R.I. 498



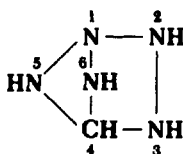
and

- B-10. 5-Thia-1,2,3,6-tetrazabicyclo[2.1.1]hexane. R.I. 500**

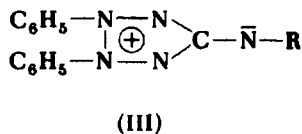
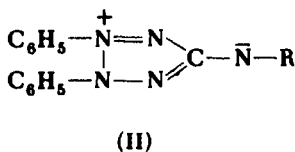
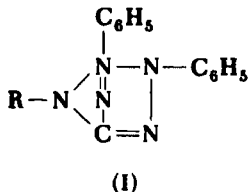


See Section A-11.

- B-11. 1,2,3,5,6-Pentazabicyclo[2.1.1]-hexane. R.I. 503**



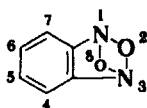
The tetrazolium betaines (obtained by oxidation of the corresponding formazans) originally assigned¹ structure I ($R = \text{NO}$ or COC_6H_5), should at least be written as II, and there is good reason to consider representing them by a mesoionic structure such as III. See Section A-11.



Reference

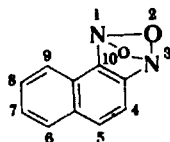
1. Bamberger, Padova and Ormerod, *Ann.*, **446**, 260 (1926).

- B-12. Benzofuroxan. R.I. 1257**

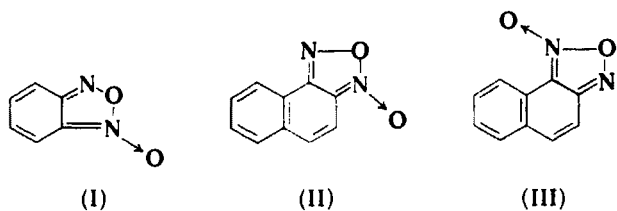


and

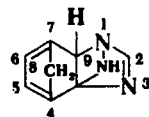
- B-13. 1,3-Epoxy-naphtho[1,2]furan. R.I. 2209**



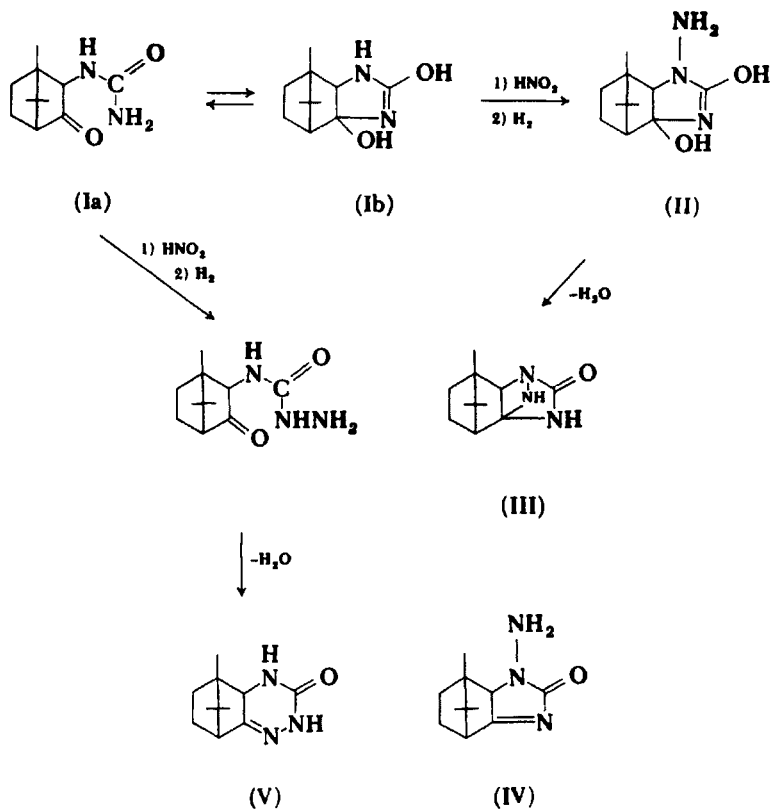
These ring systems are now known to have, respectively, structures I and II or III. See Section A-23.



B-14. 1,3a(7aH)-Imino-4,7-methano-benzimidazole. R.I. 2204



Treatment of camphoryl- ψ -carbamide (I) with nitrous acid, and reduction of the resulting nitroso derivative gave¹ an amine thought to have structure II (camphoryl- ψ -semicarbazide). Treat-

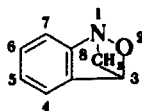


ment of II with hydrochloric acid gave¹ an anhydride assigned structure III. However, structure IV (or a tautomer) would seem to present an alternative possibility, as would structure V, which might be formed from Ia via the reactions shown.

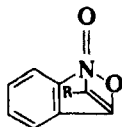
Reference

1. Forster and Fietz, *J. Chem. Soc.*, **87**, 722 (1905).

B-15. 1,3-Methano-2,1-benzisoxazole*



Structure I was considered and rejected¹ for the *iso*-isatogens (see Section A-17).

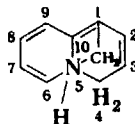


(I)

Reference

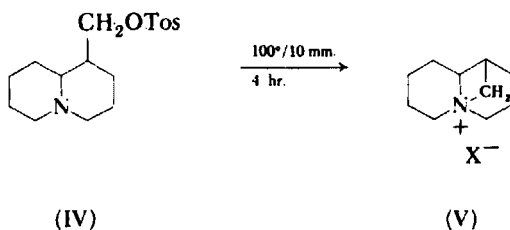
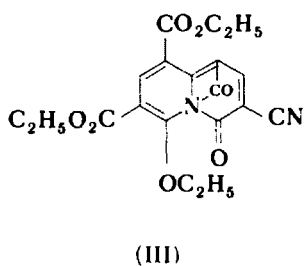
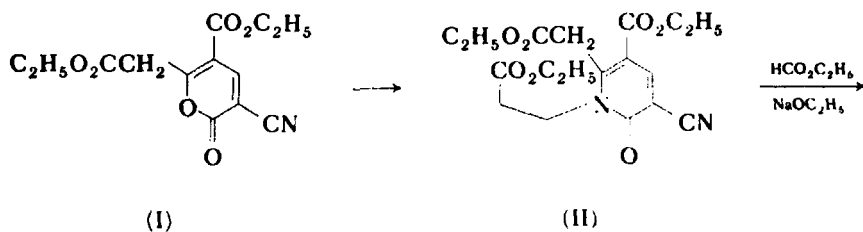
1. Ruggli and Bolliger, *Helv. Chim. Acta*, **4**, 626 (1921).

B-16. 1,5(5)-Methano-4*H*-quinolizine R.I. 1263



The reaction of I (prepared by the condensation of β -keto-glutaric ester with ethoxymethylenecyanoacetic ester) with ethyl β -aminopropionate afforded¹ II, which was treated with formic ester to obtain a product assigned¹ the quite impossible structure III.

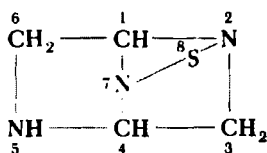
An authentic example of this ring system, V (X = *p*-toluene-sulfonate, m. 135–6°; X = picrate, m. 207–8°d.), was prepared² from IV.



References

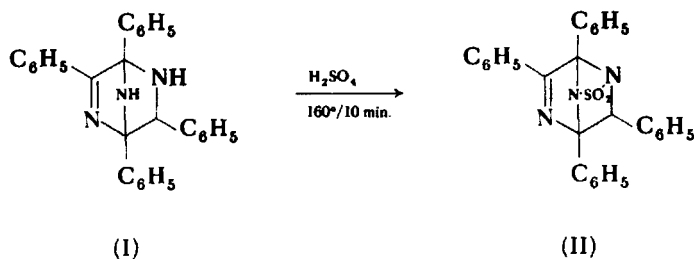
1. Mitra, J. *Indian Chem. Soc.*, **15**, 455 (1938); *Chem. Abstracts*, **33**, 607 (1939).
2. Galinovský and Nesvadba, *Monatsh.*, **85**, 1300 (1954); *Chem. Abstracts*, **50**, 348 (1956).

B-17. 8-Thia-2,5,7-triazatricyclo-[2.2.1.1^{2,7}]octane. R.I. 1243



By condensing benzil with hydrazine, Van Alphen¹ obtained a substance which he considered to be I. Upon treatment with sulfuric acid, I yielded a solid which decomposed without melting

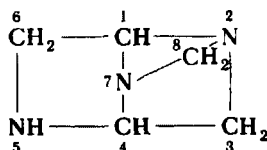
above 280°, and which was difficultly soluble in boiling water giving a neutral solution. Thus the product was assigned structure II. Further evidence for these structures would seem desirable.



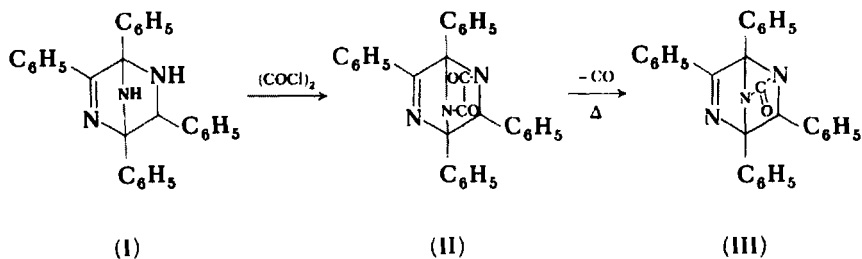
Reference

1. Van Alphen, *Rec. Trav. Chim.*, **52**, 478 (1933).

B-18. 2,5,7-Triazatricyclo-[2.2.1.1^{2,7}]octane. R.I. 1245



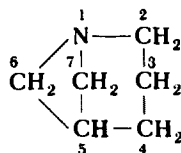
Van Alphen¹ described the formation from benzil and hydrazine of a product thought to be I. This, on treatment with oxalyl chloride yielded a product to which he assigned structure II (see Section B-32). On heating II, carbon monoxide was lost, and a new substance (m. about 335°) was formed. He considered this product to have structure III, and named it Δ^2 -5:7-carbonylo-1:3:4:6-tetraphenyltrimidine. Further study of these structures would seem to be indicated.



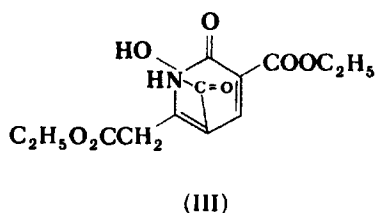
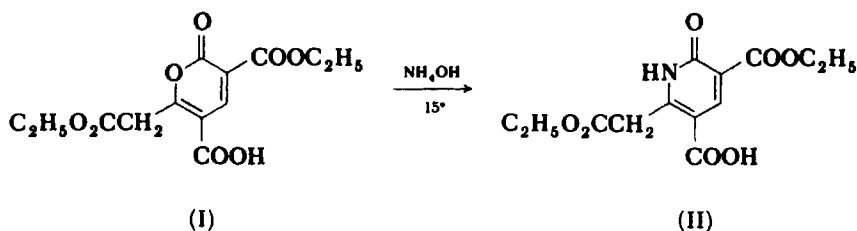
Reference

1. Van Alphen, *Rec. Trav. Chim.*, **52**, 478 (1933).

B-19. 1-Azabicyclo[3.3.1]heptane.
R.I. 550



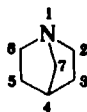
When I (produced from the condensation of β -ketoglutaric ester with ethoxymethylenemalonic ester) was treated with ammonium hydroxide, the acid II was formed.¹ This was transformed into a product for which the most unlikely structure III was proposed.¹



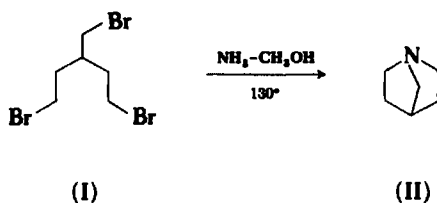
Reference

1. Mitra, *J. Indian Chem. Soc.*, **15**, 455 (1938); *Chem. Abstracts*, **33**, 607 (1939).

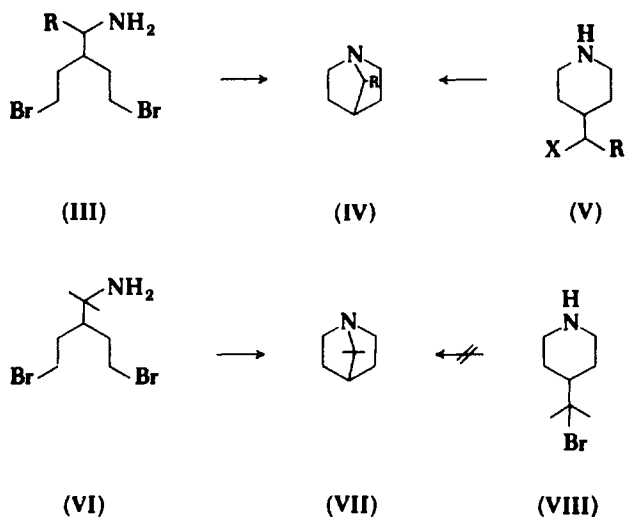
B-20. 1-Azabicyclo[2.2.1]heptane.
R.I. 636



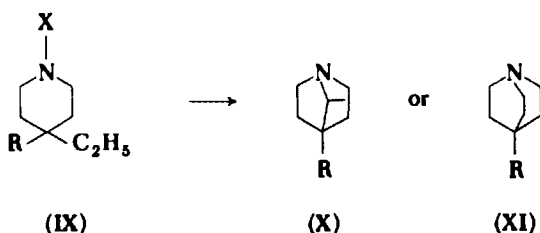
The prototype II, and also the first known example of this class of compounds, was obtained by Prelog¹ from the treatment of the



tribromide I with methanolic ammonia. Several alkyl derivatives of II were obtained via this reaction,^{2,3} but it was soon found⁴⁻⁶ that the cyclization of dibromoamines such as III gave higher yields. In one case, however, the cyclization of III (when $R = C_2H_5$) evidently gave⁶ either a mixture or a product different from that obtained by cyclization of the corresponding tribromoalkane. Also, steric factors may play an important role in these cyclizations, since VI is reported⁶ to cyclize to VII in 43% yield, while it was not found possible⁷ to cyclize VIII. However, the cyclization of compounds such as V generally provides an excellent method for the preparation⁸⁻¹¹ of compounds of type IV.

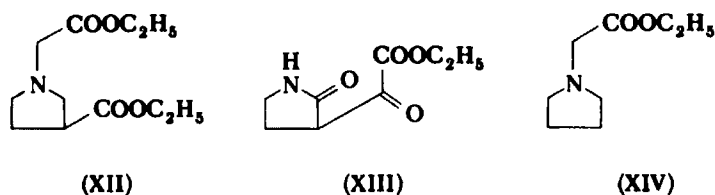


Compounds such as X were recently claimed¹² to be formed in the Löffler-Freytag reaction (the cyclodehydrohalogenation of certain secondary *N*-haloalkylamines). Treatment of IX ($R = H$, $X = Cl$) in sulfuric acid with¹³ or without¹⁴ ultraviolet radiation yielded a product at first^{13,14} considered to be quinuclidine (XI,

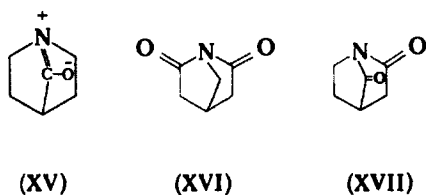


R = H), but which, after reinvestigation, is now thought¹² to have structure X (R = H). Similarly, IX (R = CH₃) is claimed¹² to yield X (R = CH₃). The yield of the bicyclic base obtained in these cyclizations is not large, but the Löffler-Freytag reaction has the attraction of utilizing the comparatively readily available 4-alkyl-piperidines.

Efforts to obtain 1-azabicyclo[2.2.1]heptanone derivatives by the cyclization of compounds XII–XIV were reported¹¹ unsuccessful.



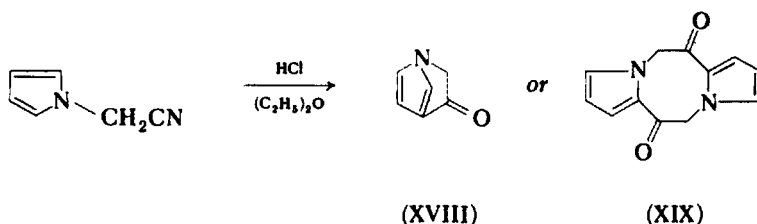
The failure of isonipecotic acid to lactamize has been explained by Lukeš¹⁵ upon the basis that resonance forms such as XV with a bridgehead double bond are incapable of existence (Bredt's rule). Similarly β-(nitromethyl)-glutaric ester and 2-nitroethylsuccinic ester failed¹⁶ to yield 1-azabicyclo[2.2.1]heptane, since their cyclization upon reduction would presumably proceed through "forbidden" intermediates such as XVI and XVII. The application of Bredt's rule to structures of these and related types has been reviewed by Fawcett.¹⁷



Attempts to dehydrogenate II by treatment with palladium-charcoal or selenium at 350° were reported¹⁸ to yield 4-picoline. The Hofmann degradation of X (R = CH₃) yielded^{12,20} 4-ethyl-1-methylpiperidine.

1-Azabicyclo[2.2.1]heptane (II) is a waxy solid with a pyridine-like odor. Its hydrochloride is claimed¹⁹ to lower the blood pressure of cats and rabbits.

Treatment of an ethereal solution of 1-pyrrolylacetonitrile with hydrogen chloride yielded²¹ a product (m. 307–8°; semicarbazone, m. 273°) having the empirical formula (C₆H₅NO)_n. The molecular weight could not be determined, but structures XVIII and XIX were suggested. Of the two, XIX is obviously preferable.



Derivatives of 1-Azabicyclo[2,2,1]heptane

Empirical formula	Substituents	Properties	Refs.
C ₆ H ₁₁ N	Unsubstituted	m. 78–9° (71°); b ₇₅ 130° (b. 120–1°). Picrate, m. 285° cor. (274° unc., 274° d., 270° d.). Picrolonate, m. 255°. Methiodide, m. 320° d. Aurichloride, m. 280° d.	1,3,4,8,10, 11,18,19
C ₇ H ₁₃ N	7-Methyl-	b ₁₁ 43°; b. 135–7°. Hydrochloride, m. 275° d. Picrate, m. 290–3° (292°). Picrolonate, m. 226.5° (225–6°). Methiodide, m. 325–6°. Methobromide, m. 304–5°. Methopicrate, m. 333–5° d. Chloroplatinate, m. 231° d. (227.5°).	2,6,12,20
C ₈ H ₁₅ N	2,6-Dimethyl-	b. 154–6°; d ₁₅ ¹⁵ 0.890; n _D ¹⁵ 1.54942. Picrate, m. 246°. Chloroplatinate, d. before m.	3,5

(continued)

Derivatives of 1-Azabicyclo[2,2,1]heptane (*continued*)

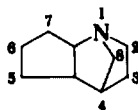
Empirical formula	Substituents	Properties	Refs.
C ₈ H ₁₅ N (Cont'd.)	4,7-Dimethyl-	b ₇₄₈ 153–4°. Picrate, m. 290–8° d. Methiodide, m. 333°. Methopicate, m. 300–1°.	12
	7,7-Dimethyl-	Hydrochloride, m. 299–300° d. Picrate, 6,7 chars > 290° without m. Chloroplatinate, m. 233–4° d.	
	7-Ethyl-	b. 162–3° (160°). Hydrochloride, m. 239–40°. Picrate, m. 198–9° (268–9°, 254°?). Picrolonate, m. 233.0–3.5° (two ?, m. 205–6° and 231–2°) Styphnate, m. 170°. Methiodide, m. 271° d. Chloroplatinate, m. 242° d. (215.5°).	2,3,6
C ₉ H ₁₇ N	3-Propyl-	Oil. Picrate, m. 129–30°. Picrolonate, m. 204–5°.	9

References

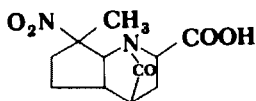
1. Prelog and Cherkovnikov, *Ann.*, **525**, 292 (1936).
2. Prelog, Cherkovnikov and Heimbach, *Collection Czechoslov. Chem. Commun.*, **10**, 399 (1938).
3. Prelog, Ger. Pat. 674,967; *Frdl.*, **25**, 494 (1942).
4. Prelog, Cherkovnikov and Ustricev, *Ann.*, **535**, 37 (1938).
5. Paul and Cottin, *Bull. soc. chim.*, **7**, 626 (1940).
6. Prelog, Heimbach and Režek, *Ann.*, **545**, 231 (1940).
7. Clemo and Hoggarth, *J. Chem. Soc.*, **1941**, 41.
8. Koelsch, *J. Am. Chem. Soc.*, **65**, 2460 (1943).
9. Koelsch, *J. Am. Chem. Soc.*, **68**, 146 (1946).
10. Clemo and Prelog, *J. Chem. Soc.*, **1938**, 400.
11. Clemo and Metcalfe, *J. Chem. Soc.*, **1937**, 1523.
12. Lukeš and Ferles, *Collection Czechoslov. Chem. Commun.*, **20**, 1227 (1955); *Chem. listy*, **49**, 510 (1955).
13. Wawzonek, Nelson and Thelen, *J. Am. Chem. Soc.*, **73**, 2806 (1951).
14. Lukeš and Ferles, *Chem. listy*, **45**, 505 (1951); *Chem. Abstracts*, **47**, 2177 (1953).
15. Lukeš, *Collection Czechoslov. Chem. Commun.*, **10**, 148 (1938).
16. Leonard and Schoemaker, *J. Am. Chem. Soc.*, **71**, 1876 (1949).
17. Fawcett, *Chem. Rev.*, **47**, 219 (1950).
18. Prelog and Balenović, *Ber.*, **74**, 1508 (1941).
19. Stern, *Arch. expl. Path. Pharmacol.*, **197**, 377 (1941); *Chem. Abstracts*, **37**, 5781 (1943).

20. Lukeš, Strouf and Ferles, *Chem. listy*, **51**, 923 (1957); *Chem. Abstracts*, **51**, 14724 (1957).
 21. Ochiai and Ikuma, *J. Pharm. Soc. Japan*, **56**, 379 (1936); *Chem. Zentr.*, **II**, 1938 (1936); *Chem. Abstracts*, **30**, 6363 (1936).

B-21. 1,4-Methano-1-pyrindine.
R.I. 1291



Among the bases present in the kerosine distillate of California petroleum was isolated¹ a fraction analyzing for the formula $C_{16}H_{25}N$. This material, on treatment in a sealed tube at 170° with nitric acid, yielded a mixture of products including one of the formula $C_{11}H_{14}O_5N_2$ (m. $189-90^\circ$), which was assigned² structure I. However, little evidence for this structure was offered, and it seems probable that it is incorrect in view of the "forbidden"³ amide group it contains. See Sections B-20, B-26, B-95, etc.

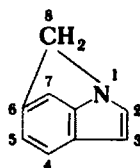


(I)

References

1. Poth, Schultz, King, Thompson, Slagle, Floyd and Bailey, *J. Am. Chem. Soc.*, **52**, 1239 (1930).
2. Thompson and Bailey, *J. Am. Chem. Soc.*, **53**, 1002 (1931).
3. Lukeš, *Collection Czechoslov. Chem. Commun.*, **10**, 148 (1938).

B-22. 1,6-Methanoindole

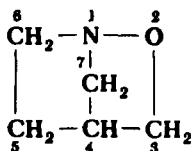


Products containing this ring system have been obtained¹ from the degradation of strychnine.

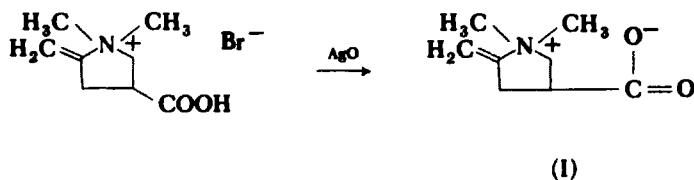
Reference

1. Prelog and Kócor, *Helv. Chim. Acta*, **31**, 237 (1948).

B-23. 2-Ox-1-azabicyclo[2.2.1]-heptane. R.I. 597



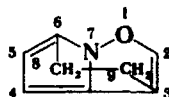
The betaine I was listed by the *Ring Index* as an example of this ring system.



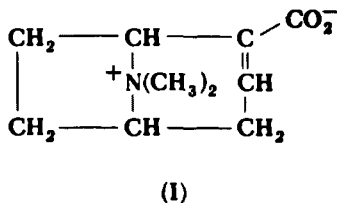
Reference

1. Mannich and Gollasch, *Ann.*, **453**, 177 (1927).

B-24. 3,6-Ethanopyrrolo[1,2-*b*]isoxazole. R.I. 1465



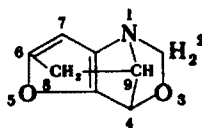
Anhydroecgonine methyl betaine^{1,2} (I) was listed by the *Ring Index* as an example of this nucleus. No true representatives are known.



References

1. Einhorn and Tahara, *Ber.*, **26**, 324 (1893).
2. Einhorn and Willstätter, *Ber.*, **27**, 2439 (1894).

**B-25. 4*H*-6,1,4-(Methanometheno)-
2*H*-furo[3,2-*d*]-*m*-oxazine**

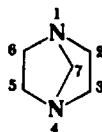


Derivatives of this ring system were obtained^{1,2} during studies upon the stereochemistry of the tropane alkaloids.

References

1. Heusner, *Chem. Ber.*, **87**, 1063 (1954).
2. Fodor, Tóth and Vincze, *J. Chem. Soc.*, **1955**, 3504.

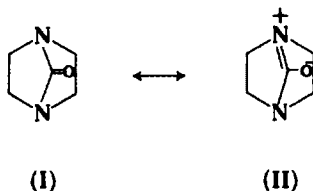
B-26. 1,4-Diazabicyclo[2.2.1]heptane



A number of attempts have been described¹⁻⁴ to prepare derivatives of piperazine having a single carbon atom bridge connecting the two nitrogen atoms. A variety of reagents, such as phosgene, carbon bisulfide, carbon dioxide, ethyl chloroformate, cyanic acid, formaldehyde, etc., were investigated for this purpose, but none of the products obtained had the desired 1,4-diazabicyclo[2.2.1]heptane nucleus.^{5,6}

For example, the reaction product of piperazine with carbon bisulfide^{1-4,7,8,11} (which was called *thioide*⁷) has been assigned several different structures, and is most recently thought¹¹ to be polymeric. The corresponding product from 1-methylpiperazine^{9,10} has been written as the internal salt of 1-methylpiperazine-4-dithiocarbamic acid (see Section B-125).

The failure to prepare structures such as I has been discussed by Lukeš,¹² who pointed out that contributions to the resonance hybrid of the molecule by forms such as II are forbidden



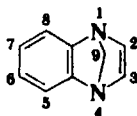
by Bredt's rule. This could explain the failure of most of the previously mentioned synthetic efforts. The condensation of piperazine with formaldehyde, while not excluded on these grounds, appears rather to give a polymeric product.^{5,6,9}

In view of these considerations, it is therefore rather surprising that the only specimen of this nucleus referred to since 1900 is the 7-thio derivative! This compound was mentioned briefly in two surveys^{13,14} of various thiourea derivatives for goitrogenic activity. No indications were given of its properties or preparation, and it is reasonable to suppose that, whatever the material might be, it is probably not 1,4-diazabicyclo[2.2.1]heptane-7-thione.

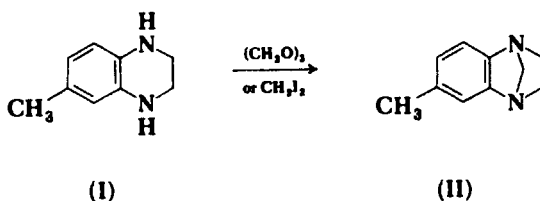
References

1. Schmidt and Wichmann, *Ber.*, **34**, 3237 (1891).
2. Rosdalsky, *J. prakt. Chem.*, **53**, 19 (1896).
3. Feist, *Ber.*, **30**, 1982 (1897).
4. Herz, *Ber.*, **30**, 1584 (1897).
5. Ladenburg, *Ber.*, **30**, 1587 and 3043 (1897).
6. Van Dorp, *Rec. trav. chim.*, **28**, 68 (1909).
7. Charonnat, *Atti X° Congr. intern. chem.*, **3**, 65 (1939); *Chem. Abstracts*, **33**, 9306 (1939).
8. Pavolini and Gambarin, *Ann. chim. Applic.*, **39**, 417 (1939).
9. Morren, Denayer and Linz, *Bull. soc. chim. Belges*, **59**, 223 (1950); *Chem. Abstracts*, **45**, 1601 (1951).
10. Morren, *Ind. chim. belge*, **16**, 475 (1951); *Chem. Abstracts*, **46**, 11211 (1952).
11. Dunderdale and Watkins, *Chem. and Ind.*, **1956**, 174.
12. Lukeš, *Collection Czechoslov. Chem. Commun.*, **10**, 148 (1938).
13. McGinty and Bywater, *J. Pharmacol.*, **84**, 342 (1945).
14. Williams, Kay and Soloman, *Am. J. Med. Sci.*, **213**, 198 (1947).

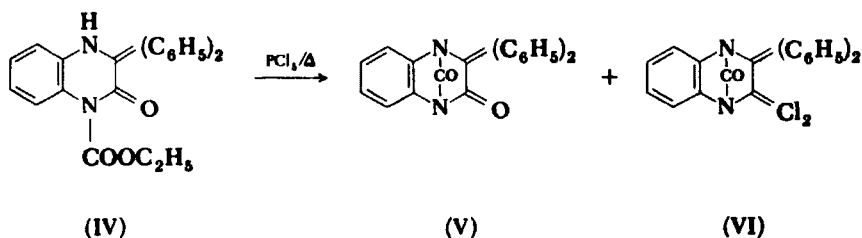
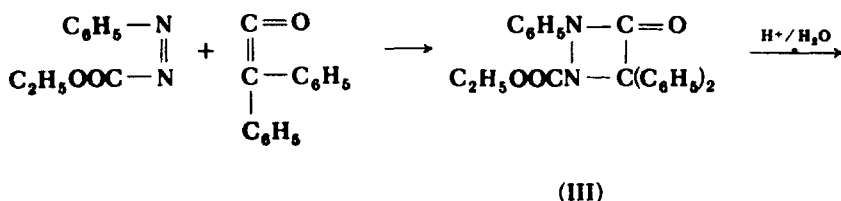
B-27. 1,4-Methanoquinoxaline. R.I. 1368



When I was treated with paraformaldehyde or with methylene iodide, the bridged compound II (m. 150°d.; monomethiodide, m. 118–20°d.; dimethiodide, m. 101°d.) resulted.¹



Ingold and Weaver² treated phenylazocarboxylic ester with diphenylketene and obtained III, which, when heated with aqueous acid, rearranged to a substance considered to be IV. When IV was heated with phosphorus pentachloride, two products thought to have structures V (m. 335°) and VI (m. 246°) were formed.

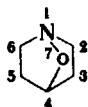


These structures, if correct, are quite unusual, the more so since bicyclic amides having a bridgehead nitrogen are, reportedly, very uncommon.^{3,4}

References

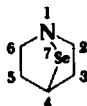
1. Moore and Doubleday, *J. Chem. Soc.*, **119**, 1170 (1921).
2. Ingold and Weaver, *J. Chem. Soc.*, **127**, 378 (1925).
3. Lukeš, *Collection Czechoslov. Chem. Commun.*, **10**, 148 (1938).
4. Fawcett, *Chem. Rev.*, **47**, 258 (1950).

B-28. 7-Oxa-1-azabicyclo[2.2.1]-heptane*



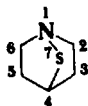
and

B-29. 7-Selena-1-azabicyclo[2.2.1]-heptane*

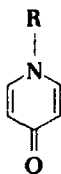


and

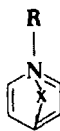
B-30. 7-Thia-1-azabicyclo[2.2.1]-heptane*



The 1-alkyl-4-pyridones (I) and their sulfur and selenium homologs were once written¹ as II (X = O, Se or S).



(I)

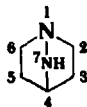


(II)

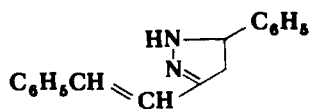
Reference

1. Michaelis and Hölken, *Ann.*, **331**, 245 (1904).

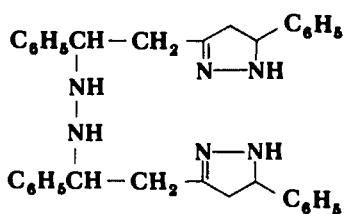
B-31. 1,7-Diazabicyclo[2.2.1]heptane.
R.I. 609



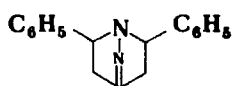
By heating either I or II, Kishner¹ obtained a product (m. 97.5°; b_{10} 255°; b_{737} 424°; hydrochloride, m. 202–4°), which he considered to have structure III. Further investigation of this unlikely structure would seem indicated, if for no other reason than its obvious violation of Bredt's rule.



(I)



(II)

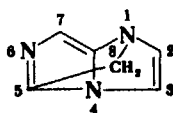


(III)

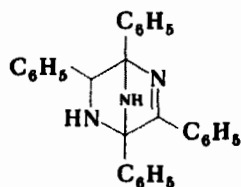
Reference

1. Kishner, J. *Russ. Phys. Chem. Soc.*, **47**, 1819 (1915); *Chem. Zentr.*, **II**, 319 (1916).

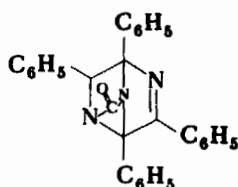
B-32. 1,5-Methano-1H-imidaz[3,4-a]-imidazole. R.I. 1353



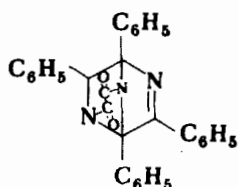
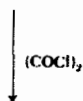
But a single example of this nucleus and of, in turn, its parent nucleus 1H-imidaz[3,4-a]imidazole (see Section A-145), has been claimed. From the reaction of benzil with hydrazine, Van Alphen¹ obtained a product considered to be I. Treatment of I with oxalyl chloride yielded a product thought to be IIa (which can be redrawn as IIb). When heated, II lost carbon monoxide to yield III (see Section B-18). Further evidence for all of these structures would be welcome.



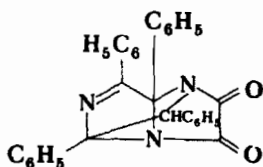
(I)



(III)



(IIa)

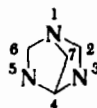


(IIb)

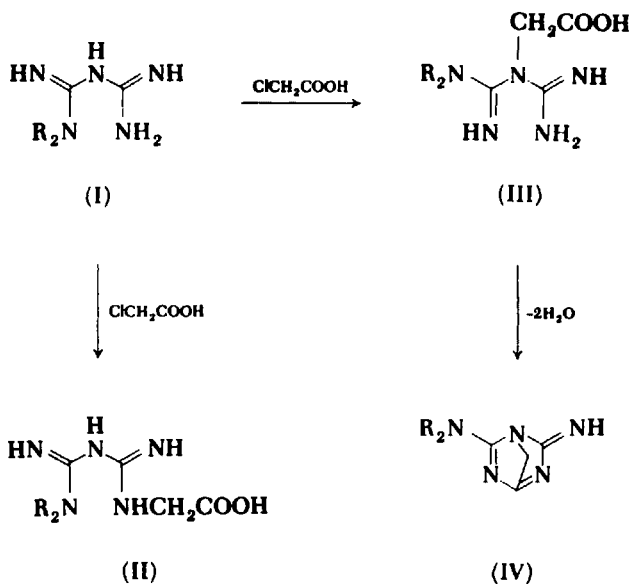
Reference

1. Van Alphen, *Rec. Trav. Chim.*, **52**, 478 (1933).

B-33. 1,3,5-Triazabicyclo[2.2.1]heptane*



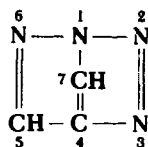
While studying the reactions of biguanide (I, $\text{R} = \text{H}$) and its dimethyl derivative (I, $\text{R} = \text{CH}_3$), Slotta and Tschesche¹ obtained, in addition to the expected product II, a byproduct considered to have structure IV, ($\text{R} = \text{H}$, hydrochloride, m. 215°d. ; $\text{R} = \text{CH}_3$, hydrochloride, m. 176°d.). These by-products, presumably formed via the intermediate III, violate Bredt's rule.



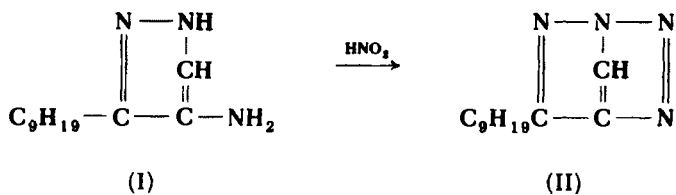
Reference

1. Slotta and Tschesche, *Ber.*, **62**, 1390 (1929).

B-34. 1,2,3,6-Tetrazabicyclo[2.2.1]-hepta-2,4-(7),5-triene



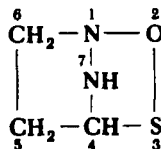
Diazotization of I yielded¹ a product (m. > 80°d.) for which the improbable structure II was proposed.



Reference

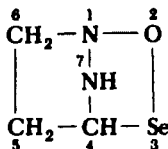
1. Kosuge, Okeda, Aburatani, Ito and Kosada, *J. Pharm. Soc. Japan*, **74**, 1086 (1954); *Chem. Abstracts*, **49**, 11628 (1955).

- B-35. 2-Oxa-3-thia-1,7-diazabicyclo-
[2.2.1]heptane. R.I. 570**



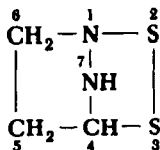
and

- B-36. 2-Oxa-3-selena-1,7-diazabicyclo-
[2.2.1]heptane. R.I. 571**

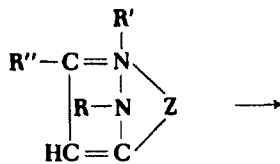


and

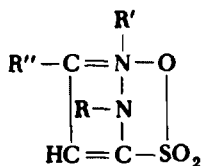
- B-37. 2,3-Dithia-1,7-diazobicyclo-
[2.2.1]heptane. R.I. 572**



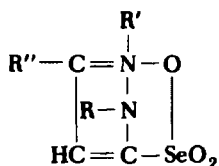
By treating products which were thought to be I (Z = O, S) with sulfurous acid (or when Z = Se, with aqueous chlorine),



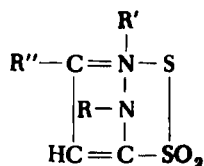
(I)



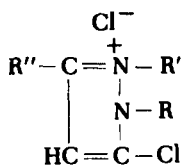
(II)



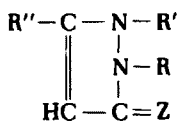
(III)



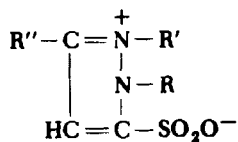
(IV)



(V)



(VI)



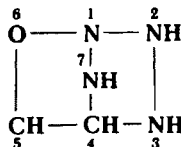
(VII)

compounds assigned structures II, III and IV were obtained.¹ Compound II also was prepared² by treating V with sodium sulfite. However, the precursors (I) are now known (see Sections B-3/6) to have structure VI, and these products have, undoubtedly, a zwitterionic structure (e.g., VII).

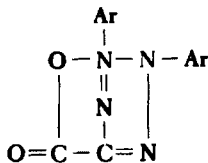
References

1. Michaelis, *Ann.*, **320**, 1 (1901).
2. Michaelis, *Ann.*, **331**, 197 (1904).
3. Michaelis, *Ann.*, **338**, 18 (1905).
4. Michaelis, *Ann.*, **378**, 293 (1910).
5. Michaelis and Lackwitz, *Ber.*, **43**, 2106 (1910).

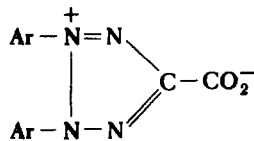
B-38. 6-Oxa-1,2,3,7-tetrazabicyclo-[2.2.1]heptane. R.I. 573



The diaryltetrazoliumcarboxylic acid betaines, for which^{1,2} formula I was once used, are better written as II.



(I)

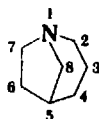


(II)

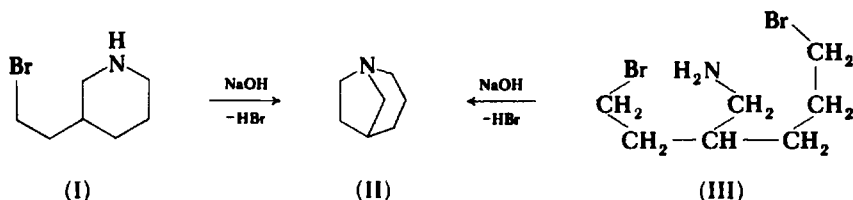
References

1. v. Pechmann and Runge, *Ber.*, **27**, 2920 (1894).
2. v. Pechmann and Wedekind, *Ber.*, **28**, 1688 (1895).

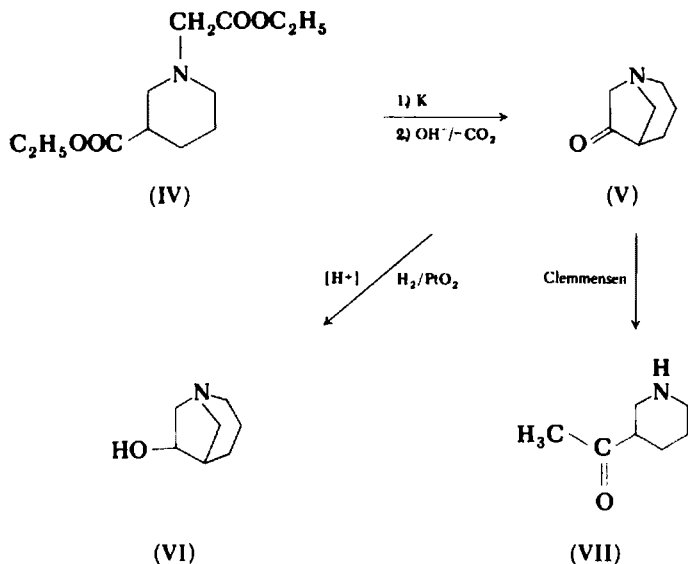
B-39. 1-Azabicyclo[3.2.1]octane.
R.I. 817



The prototype (II) of this ring system has also been called *1,3-ethylenepiperidine*, and was first obtained by Prelog, *et al.*^{1,2} by the cyclodehydrohalogenation of I or III.



Sternbach and Kaiser^{3,4} prepared the ketone V by subjecting IV to a Dieckmann cyclization, using potassium metal in refluxing toluene. This cyclization, using sodium, had previously been reported^{9,10} to fail. While V was readily hydrogenated to VI under acidic conditions using Adams catalyst, the product of a Clemmensen reduction of V was shown,⁵ surprisingly, to be VII. A number of esters of VI were prepared⁶ and investigated⁷ for cholinergic



activity. Efforts⁸ to dehydrogenate II by heating with selenium or with palladium-charcoal failed to give any recognizable products.

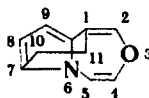
Derivatives of 1-Azabicyclo[3.2.1]octane

Substituents	Properties, derivatives, etc.	Refs.
Unsubstituted	Camphor-like solid, m. 85°, b. 150°. HCl salt, subl. >300°. Picrate, m. 294–5°. Chloroplatinate, or., m. 215.0–5.5°.	1,2
6-oxo-	m. 129–30°. HCl salt, m. 290–2°. Picrate, m. 202.0–3.4° (202–4°).	3,4,5
6-hydroxy-	m. 177–9°. HCl salt, m. >300°. Picrate, m. 224–6°. HCl salt of diphenylacetate ester, m. 191–2°. HCl salt of 9-fluor-enecarboxylate ester, m. 227–32° (212–20°).	4,6,7

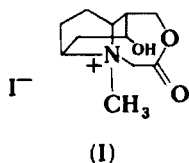
References

1. Prelog, Heimbach and Cerkovnikov, *J. Chem. Soc.*, **1939**, 677.
2. Prelog and Balenović, *Ber.*, **74**, 1510 (1941).
3. Sternbach and Kaiser, *J. Am. Chem. Soc.*, **74**, 2215 (1952).
4. Sternbach, Brit. Pat. 694,067; *Chem. Abstracts*, **48**, 11498 (1954).
5. Leonard, Curry and Sagura, *J. Am. Chem. Soc.*, **75**, 6249 (1953).
6. Sternbach and Kaiser, *J. Am. Chem. Soc.*, **74**, 2219 (1952).
7. Randall, Benson and Stefko, *J. Pharmacol. Exptl. Therap.*, **104**, 284 (1952); *Chem. Abstracts*, **46**, 6739 (1952).
8. Prelog and Balenović, *Ber.*, **74**, 1508 (1941).
9. McElvain and Adams, *J. Am. Chem. Soc.*, **45**, 2738 (1923).
10. Clemo, Ormston and Ramage, *J. Chem. Soc.*, **1931**, 3185.

B-40. 1,7-Ethanopyrrolo[1,2-d][1,4]-oxazepine



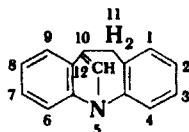
Compound I was prepared¹ during studies upon the stereochemistry of the *tropine* alkaloids.



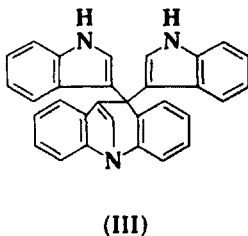
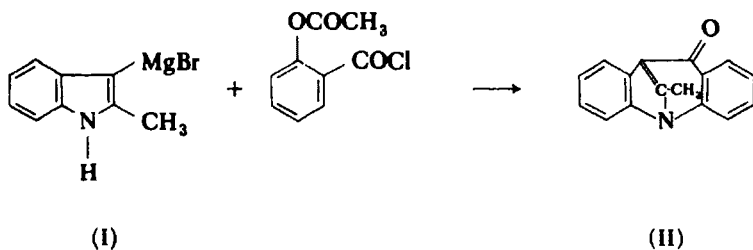
Reference

1. Kovács, Fodor and Halmos, *J. Chem. Soc.*, **1956**, 873.

**B-41. 5,10(11*H*)-Metheno-5-dibenz-
[*b,f*]azepine. R.I. 2441**



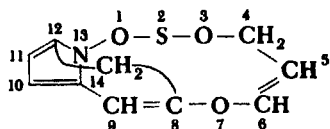
From the reaction of 2-acetoxybenzoyl chloride with one mole of I, Toffoli¹ isolated, together with at least two other substances, a product (yellow, m. 236°; HBr salt, yellow, also m. 236°; picrate, m. 233°) thought to have structure II. When two moles of indole magnesium bromide were used,² a mixture containing III (m. 145–50°; picrate, m. 150–5°d.) resulted. The violation of Bredt's rule by these structures was noted.³



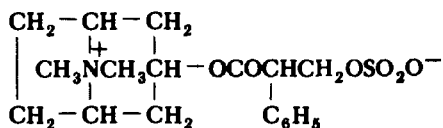
References

1. Toffoli, *Gazz. chim. ital.*, **64**, 364 (1934); *Chem. Abstracts*, **28**, 6437 (1934); *Chem. Zentr.*, **II**, 3253 (1934).
2. Toffoli, *Gazz. chim. ital.*, **65**, 487 (1935); *Chem. Abstracts*, **30**, 455 (1936); *Chem. Zentr.*, **I**, 335 (1936).
3. Fawcett, *Chem. Rev.*, **47**, 264 (1950).

B-42. 8,12-Methano-4*H*-pyrrolo[1,2-*d*]-[1,3,8,2,4]trioxathiazacycloundecine.* R.I. 1797



The zwitterionic compound I^{1,2} was cited by the *Ring Index* as an example of this nucleus.

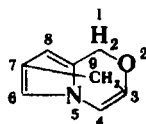


(I)

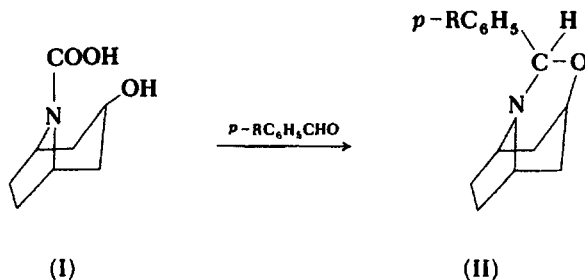
References

1. Willstätter and Hug, *Z. physiol. Chem.*, **79**, 146 (1912); *Chem. Zentr.*, **II**, 840 (1912).
2. Hoffmann-LaRoche & Co., Ger. Pats. 247,456/7; *Frdl.*, **11**, 1023 (1915).

B-43. 3,7-Methano-1*H*-pyrrolo[2,1-*c*]-*p*-oxazine*



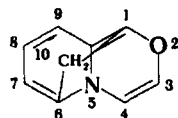
The reaction¹ of nor- ψ -tropine carbamate (I) with aromatic aldehydes yields derivatives (II, R = H, m. 34–6°; R = NO₂, m. 101°), which are stable in vacuo, but are readily hydrolyzed to their components.



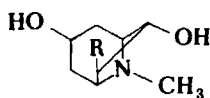
Reference

1. Hardegger and Ott, *Helv. Chim. Acta*, **36**, 1186 (1953).

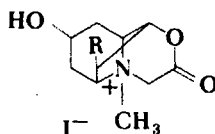
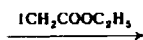
B-44. 1,6-Methanopyrid[2,1-*c*]-*p*-oxazine



Products of type II ($R = H$, m. 259°d.; $R = OH$, also m. 259°d.) prepared¹ from tropane derivatives (I) are the only examples of this ring system.



(I)

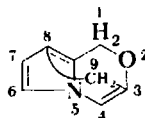


(II)

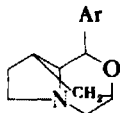
References

1. Fodor, Tóth and Vincze, *Helv. Chim. Acta*, **37**, 907 (1954).
2. Fodor, Tóth and Vincze, *J. Chem. Soc.*, **1955**, 3504.

B-45. 3,7-Methano-1*H*-pyrrolo[1,2-*c*]-*m*-oxazine



A group^{1,2} of tropane derivatives of type I are the only examples of this nucleus.

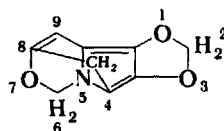


(I)

References

1. Hardegger and Ott, *Helv. Chim. Acta*, **37**, 685 (1954).
2. Kovács, Fodor and Weisz, *Helv. Chim. Acta*, **37**, 892 (1955).

B-46. 4,8-Methano-6H-1,3-dioxolo[3,4]-pyrrolo[1,2-c]-m-oxazine

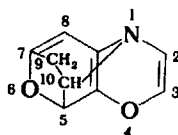


The only example of this ring system was prepared during studies¹ upon the alkaloid *meteloidine*.

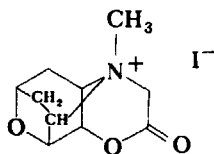
Reference

1. Heusner, *Z. Naturforsch.*, **9b**, 683 (1954); *Chem. Abstracts*, **50**, 15921 (1956).

B-47. 5H-7,1,5-(Methanometheno)-pyrano[3,4-b]-p-oxazine



Synthetic derivatives (such as I)¹ of the tropane alkaloids are the only examples of this nucleus.

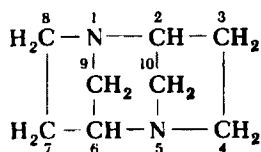


(I)

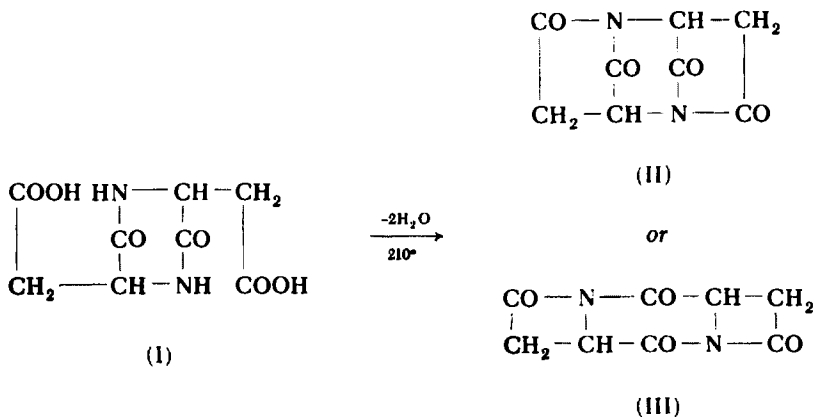
References

1. Fodor, Tóth and Vincze, *Helv. Chim. Acta*, **37**, 907 (1954).
2. Kovács, Weisz, Zoller and Fodor, *Helv. Chim. Acta*, **39**, 99 (1956).

B-48. 1,5-Diazatricyclo[4.2.1.1^{2,5}]-decane. R.I.1396



The action of heat upon ammonium maleate gives a compound (called *fumarimide* in the older literature¹) identified² as a dianhydride of diketopiperazinediacetic acid. This same product was obtained by heating asparagylaspartic acid (I).³⁻⁵ Two structures (II and III) were proposed³ for the dianhydride, and of these, II



seems more acceptable, although it represents a flagrant example of the "forbidden" bridgehead amide⁶ type of molecule. Modern techniques such as the use of X-ray crystallography and infrared spectra should readily elucidate the structure of the dianhydride and affirm or gainsay the accuracy of structure II.

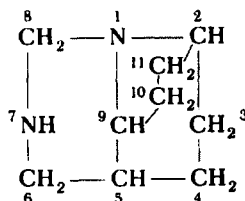
The dianhydride is unchanged by heating to 320°, but is hydrolyzed to the dipeptide I by aqueous barium hydroxide.³

References

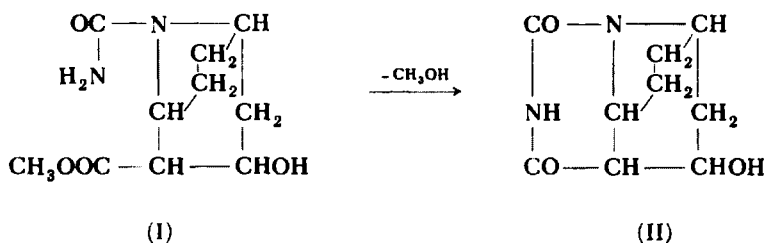
1. Dessaignes, *Jahresber. Fortschr. Chem.*, 375 (1850).
2. Ravenna and Bosinelli, *Atti reale accad. Lincei*, [5]28, II, 137 (1919); *Chem. Abstracts*, 14, 2172 (1920).
3. Ravenna and Bosinelli, *Atti reale accad. Lincei*, [5]28, II, 113 (1919); *Gazz. chim. ital.*, 49, II, 303 (1919); *Chem. Zentr.*, III, 232 (1920); *Chem. Abstracts*, 14, 2172 (1920).
4. Ravenna, *Atti reale accad. Lincei*, [5]30, II, 425 (1921); *Gazz. chim. ital.*, 51, II, 281 (1921); *Chem. Zentr.*, I, 1015 (1922).

5. Ravenna and Bosinelli, *Atti reale accad. Lincei*, [5]**29**, I, 278 (1920); *Gazz. chim. ital.*, **50**, I, 281 (1920); *Chem. Zentr.*, **III**, 830 (1920).
6. Lukeš, *Collection Czechoslov. Chem. Commun.*, **10**, 148 (1938).

B-49. 1,7-Diazatricyclo[3.3.1.2^{2,9}]-undecane



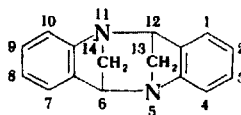
The imide II (m. 198°) was prepared^{1,2} from *N*-carbamyl-*nor*-ecgonine methyl ester (I).



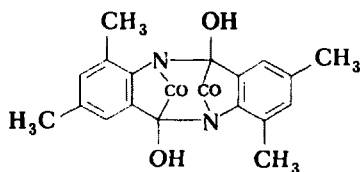
References

1. Kovács, Fodor and Weisz, *Helv. Chim. Acta*, **37**, 892 (1954).
2. Kovács, Fodor and Weisz, *Nature*, **174**, 131 (1954).

B-50. 5,12,6,11-Dimethanodibenzo-[b,f][1,5]diazocine. R.I. 2965



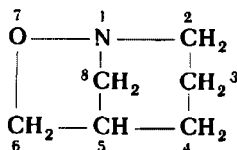
Structure I was, at one time, thought¹ to represent tetramethyl-isatoid (see Section A-46).



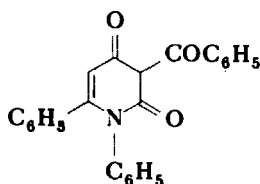
Reference

1. Heller and Lauth, *J. prakt. Chem.*, **112**, 331 (1926).

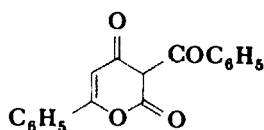
B-51. 7-Ox-1-azabicyclo[3.2.1]-octane. R.I. 727



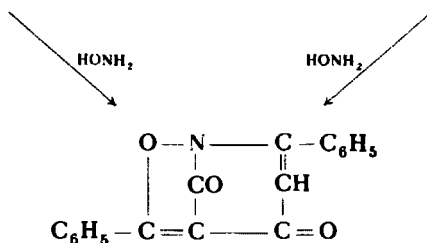
Treatment of either I¹ or II² with hydroxylamine hydrochloride produced the same product, to which Schöttle assigned structure III. More than one objection to this structure is evident, and further work is needed to determine the nature of this product.



(I)

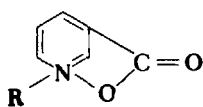


(II)

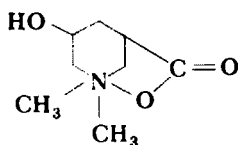


(III)

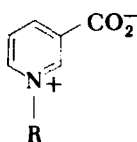
The betaines, which have been written as IV^{3,4} and V,⁵ and their relatives, are, of course, now depicted as VI and VII.



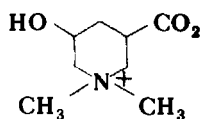
(IV)



(V)



(VI)

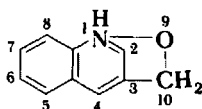


(VII)

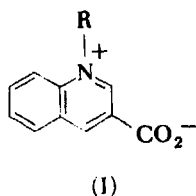
References

1. Schöttle, *J. Russ. Phys. Chem. Soc.*, **47**, 645 (1915); *Chem. Zentr.*, **I**, 929 (1916).
2. Schöttle, *Ber.*, **45**, 2343 (1912).
3. Pollak, *Monatsh.*, **16**, 45 (1895).
4. Wittstätter, *Ber.*, **35**, 584 (1902).
5. Mannich and Sutter, *Ber.*, **58**, 1325 (1925).

B-52. 1(1*H*),3-Epoxymethanoquinoline. R.I. 1518



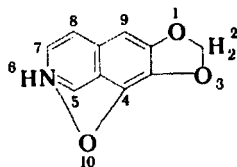
Betaines¹ of type I were considered by the *Ring Index* to represent this nucleus.



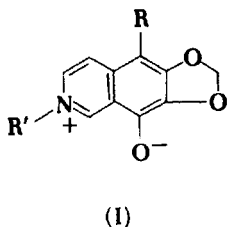
Reference

1. Claus and Steinitz, *Ann.*, **282**, 107 (1894).

B-53. 4,6(6*H*)-Epoxy-1,3-dioxolo[*g*]-isoquinoline. R.I. 2257



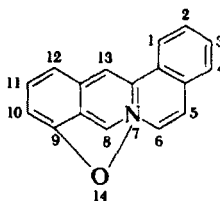
A group of alkaloid derivatives, the "anhydrotarkonines"¹⁻⁵ (I), are the closest approach to examples of this nucleus.



References

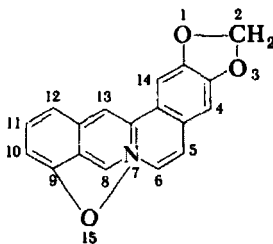
1. Beckett and Wright, *J. Chem. Soc.*, **32**, 525 (1877).
2. Von Gerichten, *Ber.*, **14**, 310 (1881).
3. Von Gerichten, *Ann.*, **210**, 79 (1881).
4. Knorr, *Ber.*, **30**, 922 (1897).
5. Roser, *Ann.*, **245**, 311 (1888); **254**, 334 (1889).

B-54. 7(7H),9-Epoxydibenzo[*a,g*]-quinolizine. R.I. 3030

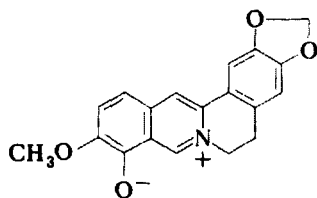


and

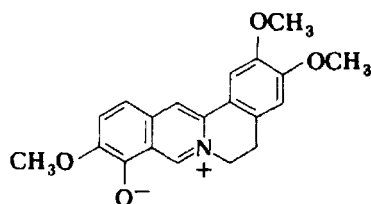
B-55. 7(7H),9-Epoxy-1,3-dioxolo-[*g*]isoquinolo[3,2-*a*]isoquinoline. R.I. 3461



Berberrubin (I)^{1,2} and *palmatrubin* (II)^{2,3} are dark red "anhydro" compounds obtained by heating *berberine* or *palmatine* chlorides with urea or carbon dioxide.



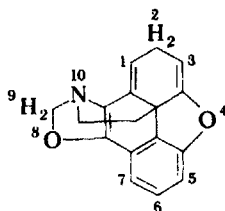
(I)



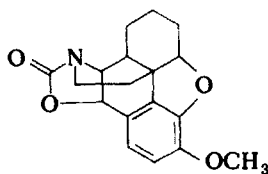
(II)

References

1. Frerichs and Stoepel, *Arch. Pharm.*, **251**, 321 (1913); *Chem. Zentr.*, **II**, 1407 (1913).
2. Späth and Burger, *Ber.*, **59**, 1486 (1926).
3. Feist and Dschu, *Arch. Pharm.* **263**, 294 (1925).

B-56. 2*H*,9*H*-10,10*c*-Ethanofuro[4,5]-phenanthro[9,10]oxazole

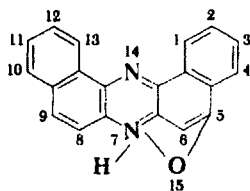
Compound I was obtained¹ during stereochemical studies upon 10-hydroxydihydrodesoxycodine derivatives.



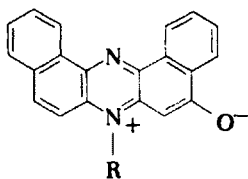
(I)

Reference

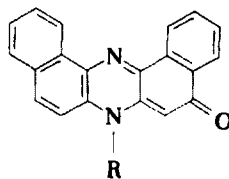
1. Rapoport and Masamune, *J. Am. Chem. Soc.*, **77**, 4330 (1955).

B-57. 5,7(7*H*)-Epoxydibenzo[*a*,*j*]-phenazine.* R.I. 3493

“Anhydro” compounds¹ of type I were given by the *Ring Index* as examples of this nucleus. Even if such a structure is accepted as representing this nucleus, it is probable that structure II, originally used,² more accurately portrays these products.



(I)

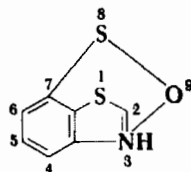


(II)

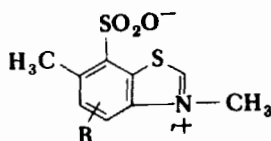
References

1. Fischer and Hepp, *Ber.*, **31**, 2485 (1898).
2. Fischer and Hepp, *Ann.*, **272**, 306 (1892).

B-58. 3(3H),7-Epoxythiobenzothiazole. R.I. 1531



Compounds of structure I ($R = H$ or NO_2)¹ are listed by the *Ring Index* as examples of this nucleus.

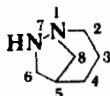


(I)

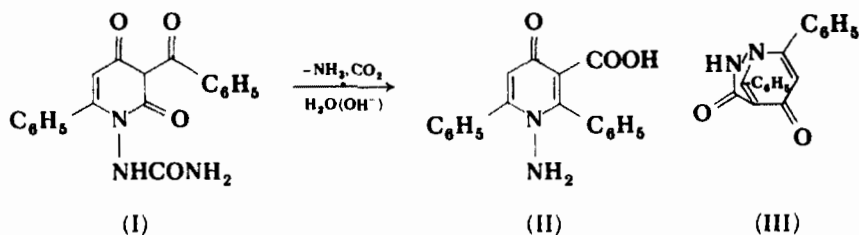
Reference

1. Rassow and Reim, *J. prakt. Chem.*, **93**, 214 (1916).

B-59. 1,7-Diazabicyclo[3.2.1]octane. R.I. 767



One example of this ring system has been claimed. Treatment of dehydrobenzoylacetic acid with semicarbazide yielded¹ a substance thought to have structure I, and treatment of this with alcoholic potassium hydroxide afforded a product (m. 160–1°) thought to be II. The lactam of this acid may be written as III, which em-

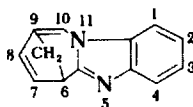


phasizes the relationship to the present ring system. Further evidence for these structures would be welcome, since III violates Bredt's rule.

Reference

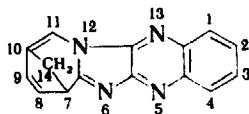
1. Schottle, *J. Russ. Phys. Chem. Soc.*, **47**, 645 (1915); *Chem. Zentr.*, **I**, 929 (1916).

B-60. 6,9-Methano-6*H*-azepo[1,2-*a*]-benzimidazole. R.I. 2275

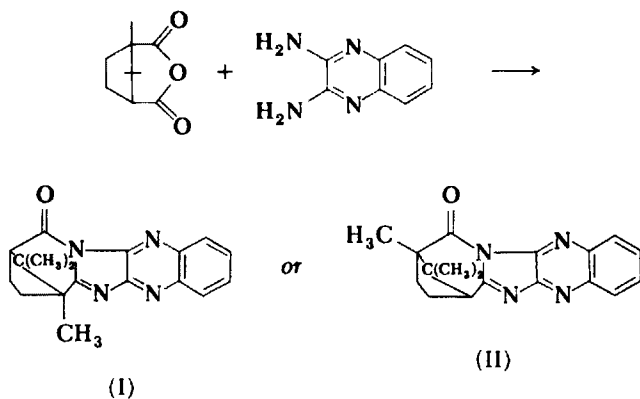


See Pyrido[1,2-*a*]benzimidazole (Section A-274).

B-61. 7,10-Methano-7*H*-azepo[1,2-*a*]-quinoxalo[2,3-*d*]imidazole. R.I. 2944



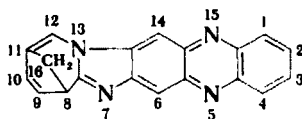
Condensation of camphoric anhydride with 2,3-diaminoquinoxaline yielded¹ a yellow crystalline product (m. 280°), having, presumably, either structure I or II.



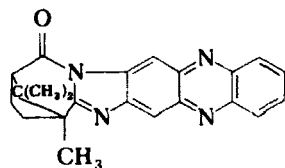
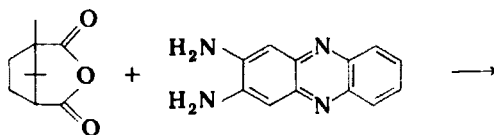
Reference

1. Sircar and Pal, *J. Indian Chem. Soc.*, **9**, 527 (1932); *Chem. Zentr.*, **I**, 1947 (1933); *Chem. Abstracts*, **27**, 1882 (1933).

B-62. 8,11-Methano-8*H*-azepo[1,2-*a*]-quinoxalo[2,3-*f*]benzimidazole. R.I. 3466

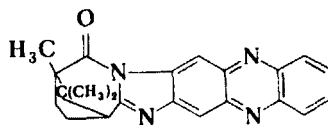


Sircar and De¹ obtained a yellow product (sinters 202°, m. 215–9°), presumably either I or II, from the reaction of camphoric anhydride with 2,3-diaminophenazine.



(I)

or

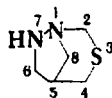


(II)

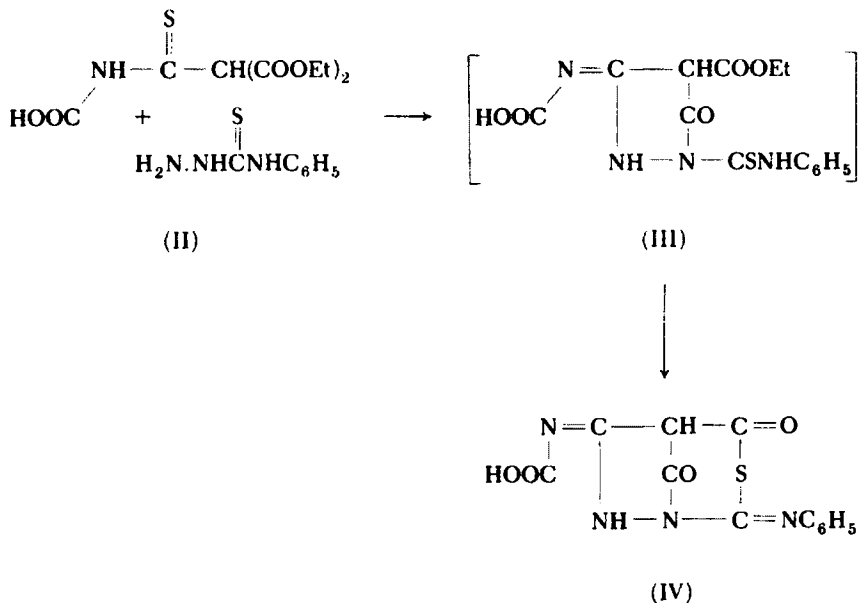
Reference

1. Sircar and De, *Quart. J. Indian Chem. Soc.*, **2**, 312 (1925); *Chem. Zentr.*, **1**, 2697 (1926); *Chem. Abstracts*, **20**, 1805 (1926).

B-63. 3-Thia-1,7-diazabicyclo[3.2.1]-octane. R.I. 746



The reaction of I with II is claimed¹ to yield a product (m. 183°d.) of structure IV, formed presumably via the intermediate III. Compound IV is soluble both in bicarbonate solution and in hydrochloric acid, and it is not desulfurated by mercuric oxide (taken as evidence for cyclic sulfur). Treatment with acetic anhydride gave phenyl isothiocyanate and tarry material. Further study of these compounds would seem necessary to confirm the proposed structures.

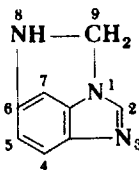


Compound IV was named *3-carboximino-5-keto-7-phenylimino-1,4-carbonyl-1,2,6-thioheptadiazine* and *2-(phenylimino)-5-(carboxyimino)-7-keto-3,6-carbonyl-1,3,4-heptathiodiazine* in addition to the *Chemical Abstracts* name: *6-(carboxyimino)-2-phenylimino-3-thia-1,7-diazabicyclo[3.2.1]octane-4,8-dione*.

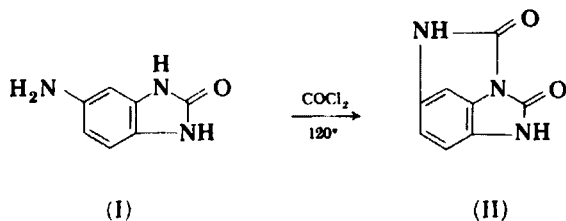
Reference

1. Ghosh, J. *Indian Chem. Soc.*, **13**, 86 (1936); *Chem. Zentr.*, **II**, 2910 (1936); *Chem. Abstracts*, **30**, 4860 (1936).

B-64. 6,1-Iminomethanobenzimidazole. R.I. 1568



When an amine thought to be I was heated in a sealed tube with phosgene, a base-soluble product assigned structure II, was obtained.¹ Since structure II is unreasonable, if structure I is assumed to

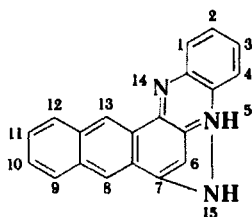


be correct, the product must be a urea, or possibly an isocyanate, formed via the primary amino group.

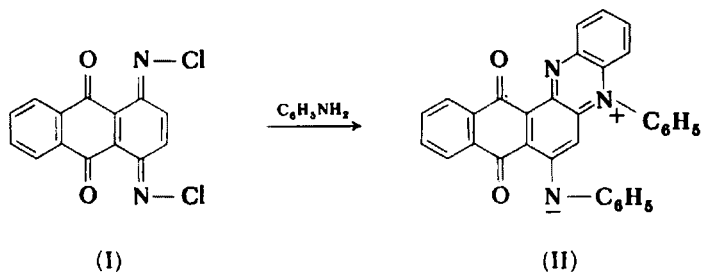
Reference

1. Jentzsch, *J. prakt. Chem.*, **38** 121 (1888).

B-65. 5,7(5H)-Iminonaphtho[2,3-*a*]-phenazine. R.I. 3497



Compound II, prepared¹ by heating I with aniline, sodium acetate and cupric acetate, was thought by the *Ring Index* to represent this nucleus. The accuracy of this structure seems questionable.

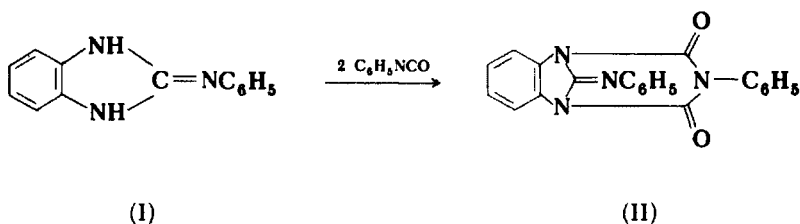


Reference

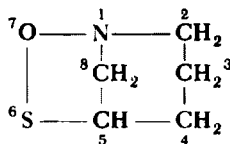
1. Sanin, *J. Russ. Phys. Chem. Soc.*, **59**, 867 (1927); *Chem. Abstracts*, **22**, 3408 (1928); *Brit. Chem. Abstracts*, **A**, 763 (1928).

B-66. 1,5(2*H*)-Methano-1,3,5-benzotriazepine. R.I. 1557

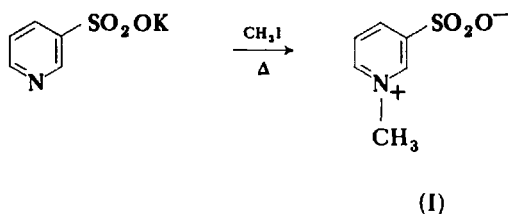
The reactions of I with different reagents were studied by Keller.¹ The product obtained from the reaction of I with phenyl isocyanate was assigned structure II, and several other structures, also undoubtedly incorrect, were assigned to the products of related reactions. A re-examination of these products is needed.

*Reference*

1. Keller, *Ber.*, **24**, 2498 (1891).

B-67. 7-Oxa-6-thi-1-azabicyclo[3.2.1]-octane. R.I. 677

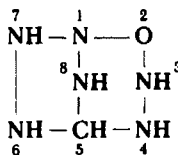
Sulfobetaines such as I^{1,2} are the only representatives of this class.



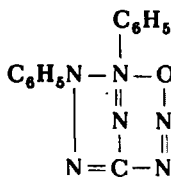
References

1. Hantzsch, *Ber.*, **19**, 31 (1886).
2. Meyer, *Monatsh.*, **24**, 195 (1903).

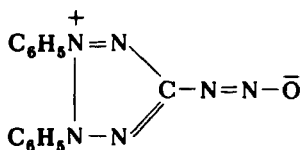
B-68. 2-Oxa-1,3,4,6,7,8-hexazabicyclo-[3.2.1]octane. R.I. 670



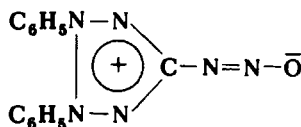
The product assigned¹ structure I is actually an inner salt, which might be written as II, or better yet, as a mesoionic compound III.



(I)



(II)

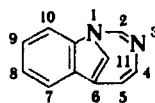


(III)

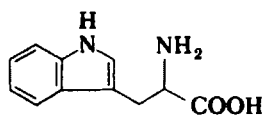
Reference

1. Bamberger, Padova and Ormerad, *Ann.*, **446**, 260 (1926).

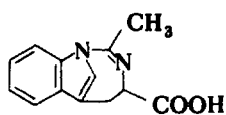
B-69. 1,6-Metheno-1,3-benzodiazocine. R.I. 1787



Treatment of tryptophane (I) with acetyl chloride yielded¹ an amphoteric product (yellow, m. 202° unc.; aurichloride, m. 179°; platinichloride, d. 240°), which was assigned structure II and named



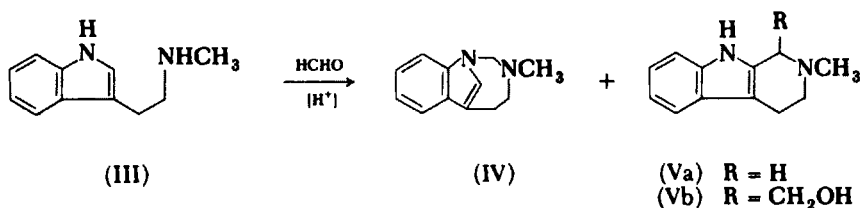
(I)



(II)

N,N'-ethenyltryptophane. Diazomethane reacted with II to yield an oily methyl ester, which gave no crystalline salts. An amide (d. $\sim 180^\circ$) resulted from the treatment of II with thionyl chloride followed by ammonia.

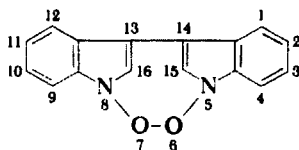
Violation of Brecht's rule by structure II has been noted,² although a very similar structure (IV) was assigned recently to one of the products (m. $225-6^\circ$; picrate, m. $237-8^\circ$; picrolonate, d. 223° ; methiodide, d. $272-3^\circ$) obtained from the treatment of *N*-methyltryptamine (III) with formaldehyde and acid. Two other products, Va and Vb, were formed with IV in this reaction.



References

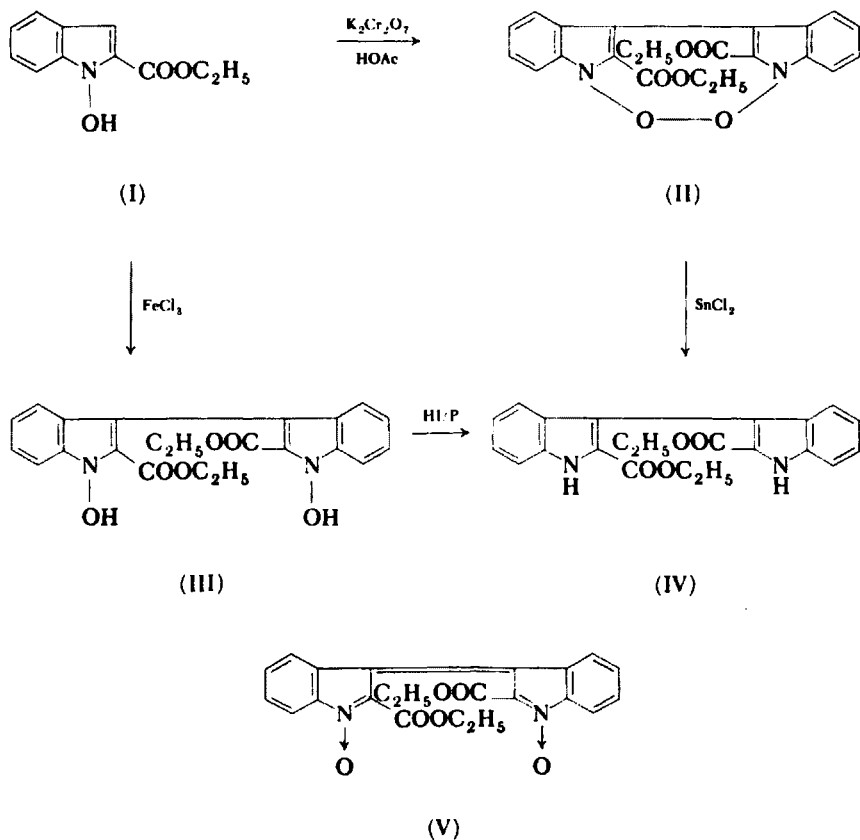
1. Wrede and Feuerriegel, *Ber.*, **66**, 1073 (1933).
2. Fawcett, *Chem. Rev.*, **47**, 219 (1950).
3. Yurashevskii, *Zhur. Obshchei Khim.*, **24**, 729 (1954); *Chem. Abstracts*, **49**, 6271 (1955).

B-70. 5,14,8,13-Dimethenodibenzo- [*d,h*][1,2,3,10]dioxadiazecine. R.I. 3021



A product (red, with green reflex, m. 189°) thought to have structure II was prepared by Gabriel and Wolter¹ from I by oxidation with potassium dichromate. Oxidation of I with ferric chloride solution afforded a different product, formulated as III. Both II and III yielded IV on reduction.

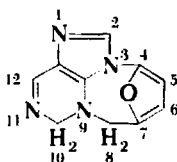
Structure II, if correct, is quite unique and further work would be desirable to establish its accuracy. A structure such as V would seem more reasonable.



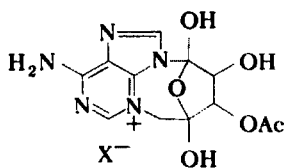
Reference

1. Gabriel and Wolter, *Ber.*, **56**, 1024 (1928).

B-71. 4,7-Epoxy-8H,10H-[1,3]-diazoco[1,2,3-cd]purine



This nucleus is represented only by quaternary nucleotide salts such as I (X = *p*-toluenesulfonate).¹

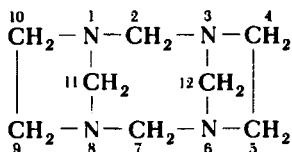


(1)

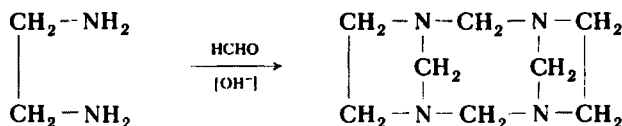
Reference

1. Andersen, Hayes, Michelson and Todd, *J. Chem. Soc.*, **1954**, 1882.

**B-72. 1,3,6,8-Tetrazatricyclo-
[6.2.1.1^{3,6}]dodecane.
R.I. 1469**



The prototype is the only known example of this ring system, and it has also been called *1,3,6,8-diendomethylene-1,3,6,8-tetrazacyclodecane* and *diethylenetetramethylenetetramine*. This compound¹⁻⁴ (I, m. 196°, b. 250°) is formed from the reaction of ethylenediamine with formaldehyde. It is stable under alkaline conditions, but rather readily decomposes in the presence of acids. Treatment³ of an ethereal solution of I with hydrogen chloride gives the monohydrochloride (m. 96–100°), which decomposes rapidly even at low temperatures. An unstable dinitrate salt (m. 15–9°) can similarly be obtained.³



(I)

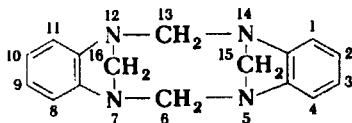
References

1. Bischoff, *Ber.*, **31**, 3248 (1898).
2. Bischoff, *Ber.*, **36**, 35 (1902).

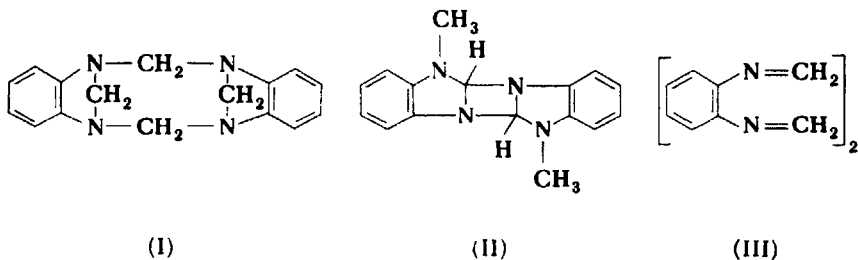
3. Simkins and Wright, *J. Am. Chem. Soc.*, **77**, 3157 (1955).

4. Krässig, *Makromol. Chem.*, **17**, 77 (1956); *Chem. Abstracts*, **50**, 13953 (1956).

**B-73. 5,14,7,12-Dimethanodibenzo-
[d,i][1,3,6,8]tetrazocine.**
R.I. 3020

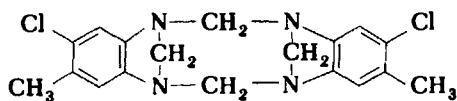


The formation of benzimidazoles from the condensation (in acidic media) of aldehydes with aromatic 1,2-diamines is well known. Under neutral conditions, however, other products are formed from the condensation of two moles of the diamine with four equivalents of aldehyde.^{1,2,3} For the reaction product thus formed from *o*-phenylenediamine and formaldehyde (m. 144°; chloroplatinate, m. 240°), Fischer³ suggested three possible structures: I, II and III. Because of the instability of the salts, which readily lose formaldehyde, he preferred

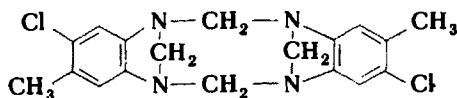


structure I, although both structures II¹ and III² had earlier been used. The 2,9- (or 2,10-) dimethyl (m. 222°)¹ and 6,13,15,16-tetramethyl (oil, b. >300°)² derivatives have similarly been prepared. The condensation of 4-chloro-5-methyl-1,2-phenylenediamine with formaldehyde was reported⁴ to yield two isomeric products (m. 170-5° and m. 225°), which were formulated as IV and V.

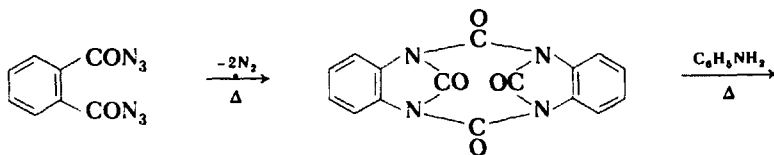
When phthalyl azide (VI) was subjected to the Curtius rearrangement, there resulted a product (m. 325°) named⁵ *dibenzimidazolonediuarea*. Since treatment with aniline yielded a mixture of VIII, IX and X, the product was assigned⁵ structure VII. In view of the recent work on the structure of aromatic isocyanate dimers, this



(IV)



(V)



(VI)

(VII)



(VIII)

(IX)

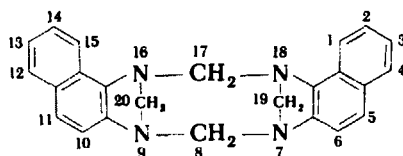
(X)

product might bear reinvestigation. Also, structure VII represents a flagrant violation of the "bridgehead amide" interdict.⁶

References

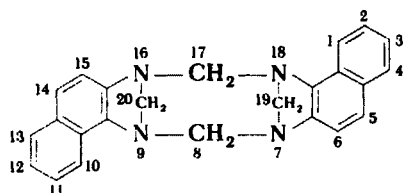
1. Fischer and Wreszinski, *Ber.*, **25**, 2711 (1892).
2. Hinsberg and Koller, *Ber.*, **29**, 1497 (1896).
3. Fischer, *Ber.*, **32**, 245 (1899).
4. Morgan and Challenor, *J. Chem. Soc.*, **119**, 1537 (1921).
5. Lindemann and Schultheis, *Ann.*, **464**, 237 (1928).
6. Lukeš, *Collection Czechoslov. Chem. Commun.*, **10**, 148 (1938).

B-74. 8*H*,17*H*-7,18,9,16-Di-methanodinaphtho-[1,2-*d*, 2',1'-*i*][1,3,6,3]-tetrazecine*



and/or

B-75. 8*H*,17*H*-7,18,9,16-Di-methanodinaphtho-[1,2-*d*, 1',2'-*i*][1,3,6,8]-tetrazecine*

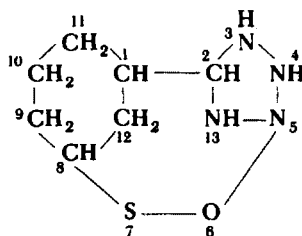


The condensation of formaldehyde with 1,2-naphthalenediamine in neutral solution is reported¹ to yield a product (m. 165°), which might be either of the above structures, or a mixture. For a discussion concerning closely related products see Section B-73.

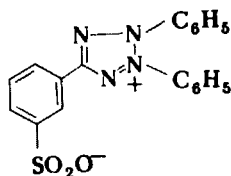
Reference

1. Fischer and Wreszinski, *Ber.*, **25**, 2711 (1892).

B-76. 6-Oxa-7-thia-3,4,5,13-tetrazatricyclo[6.3.1.1^{2,5}]tridecane. R.I. 1793



Compound I¹ was considered by the *Ring Index* to be a representative of this ring system.

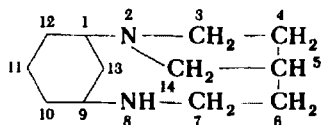


(I)

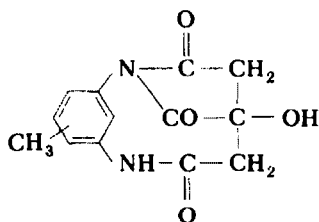
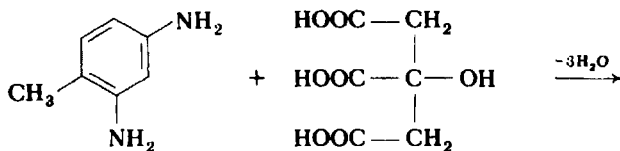
Reference

1. Fichter and Schiess, *Ber.*, **33**, 747 (1900).

**B-77. 2,8-Diazatricyclo-
[7.3.1.1^{2,5}]tetradecane.
R.I. 1795**



The reaction of citric acid with 2,4-diaminotoluene is reported¹ to yield a product (d. 187°) of structure I. This unusual structure could bear confirmation.

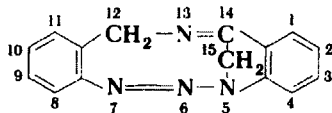


(I)

Reference

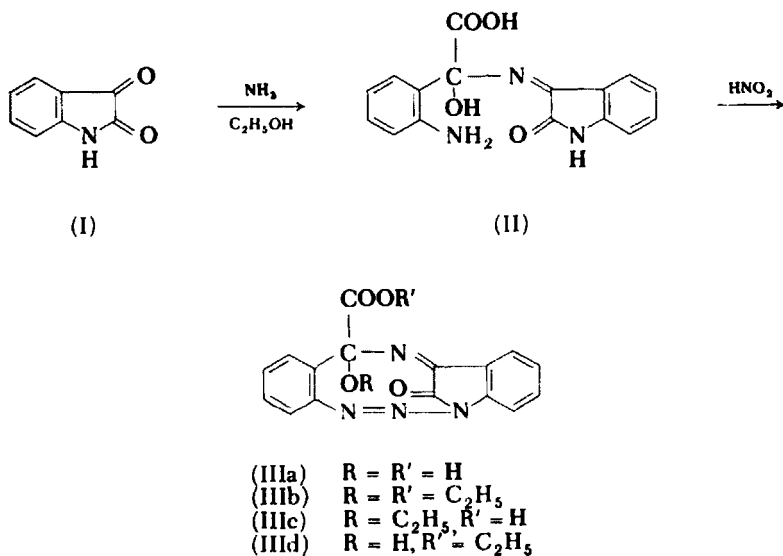
1. Schneider, *Ber.*, **21**, 660 (1888)

**B-78. 5(12*H*),14-Methanodibenzo-
[*d,i*][1,2,3,7]tetrazonine.
R.I. 2585**



Reissert and Hoppmann¹ treated an ethanolic solution of isatin (I) with ammonia and isolated an amino acid to which they assigned structure II. It was named *β-isatinimidyl-o-aminomandelic acid*.

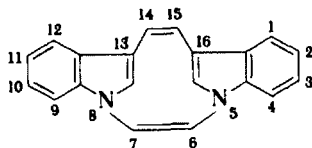
Treatment of II with nitrous acid gave a product (yellow, m. with sudden d. $\sim 140^\circ$), which they considered to have structure IIIa. When IIIa was allowed to react with ethyl nitrite in acidified ethanolic solution, the diethyl derivative IIIb (yellow, m. $214-5^\circ$) resulted, and this could be saponified to the ethoxy acid IIIc (yellow, m. 195°). Esterification of IIIa by the normal Fischer-Speier method yielded the hydroxy ester IIId (yellow, m. $214-5^\circ$). Further evidence for these unusual structures would be welcome.



Reference

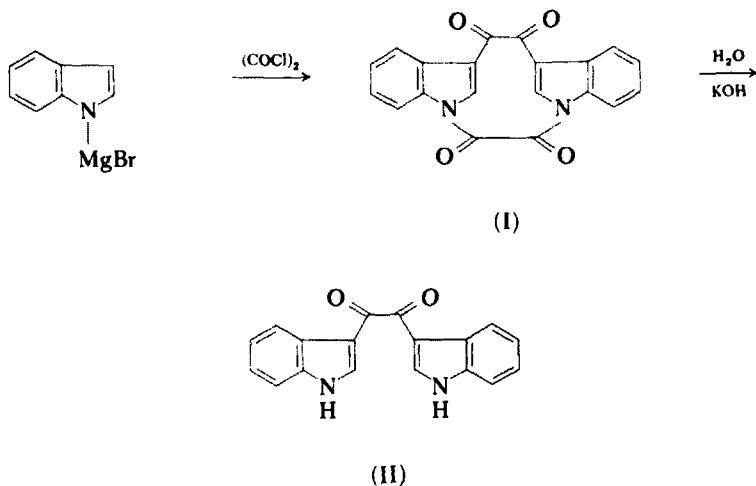
1. Reissert and Hoppmann, *Ber.*, **57**, 972 (1924).

**B-79. 5,16,8,13-Dimethenodibenzo-
[e,h][1,4]diazacyclododecine.
R.I. 3024**



One of the products (see Section A-708) obtained by Oddo and Sanna¹ from the treatment of indole magnesium bromide with oxalyl chloride was a material, m. 200° , thought to have structure I. Treat-

ment of this product with aqueous caustic gave II, which was also formed in the first reaction. Additional evidence for structures I and II would be welcome.



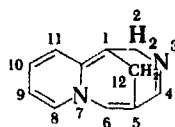
Reference

1. Oddo and Sanna, *Gazz. chim. ital.*, **51**, 337 (1921); *Chem. Zentr.*, **I**, 1032 (1922); *Chem. Abstracts*, **16**, 1423 (1922).

CHAPTER XVII

Bridged 6/6 Ring Systems

B-80. 1,5-Methano-2-pyrido[1,2-*a*][1,5]-diazocine. R.I. 1945

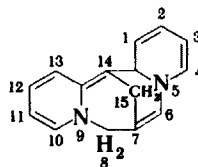


All of the compounds which are reported to contain this ring system have been studied in connection with the investigation of the alkaloid *cytisine*. Excellent reviews of this field have been given by Leonard¹ and Henry,² and no useful purpose would be served by their repetition here. The synthesis of racemic cytisine has very recently been reported.³⁻⁵

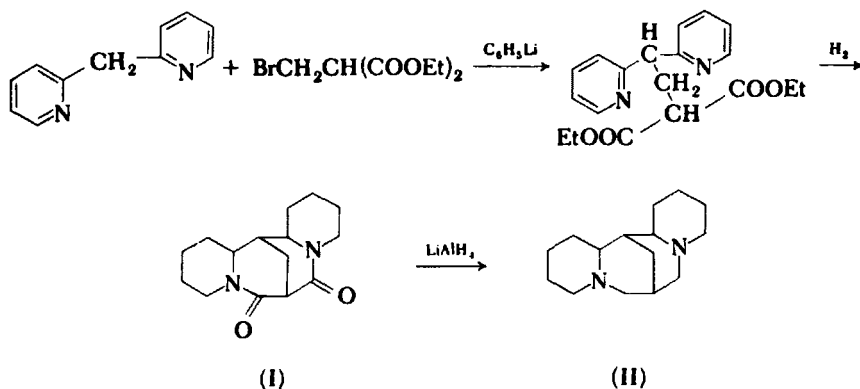
References

1. Leonard, in Manske and Holmes, *The Alkaloids*, Academic Press, New York, 1953, Vol. 3, pp. 143ff.
2. Henry, *The Plant Alkaloids*, 4th Ed., The Blakiston Co., Philadelphia, 1949, pp. 142ff.
3. van Tamelen and Baran, *J. Am. Chem. Soc.*, **77**, 4944 (1955).
4. Bohlmann, *Angew. Chem.*, **67**, 531 (1955).
5. Bohlmann, Englisch, Ottawa, Sander and Weise, *Angew. Chem.*, **67**, 708 (1955).
6. Galinovsky, Sparatore and Langer, *Monatsh.*, **87**, 100 (1956).

B-81. 7,14-Methanodipyrido[1,2-*a*, 1',2'-*d*]-[1,5]diazocine



Derivatives of this nucleus were obtained by Leete and Marion.¹ Two stereoisomeric forms of I were obtained (m. 262-3° and 161-2°). By reduction the corresponding two forms of II (b_{0.2} 80°,

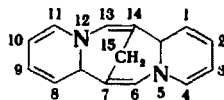


n_D^{20} 1.5308 and $b_{0.2}$ 80–90°, n_D^{20} 1.5295, named ψ -sparteines A and B, respectively) were obtained.

Reference

1. Læete and Marion, *Can. J. Chem.*, **30**, 563 (1952).

B-82. 7,14-Methanodipyrido[1,2-*a*, 1',2'-*e*]-[1,5]diazocine. R.I. 2691

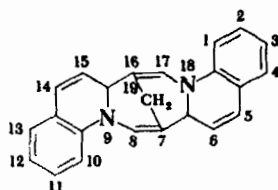


The only representatives of this ring system are certain of the lupine alkaloids (*sparteine*, *lupanine*, *anagryne*, etc.) and the related compounds prepared during the investigation of their structures. As this subject is beyond the scope of this book, and recently has been extensively reviewed by Leonard¹ and Henry,² it will not be discussed. Some more recent references³⁻⁷ are, however, listed.

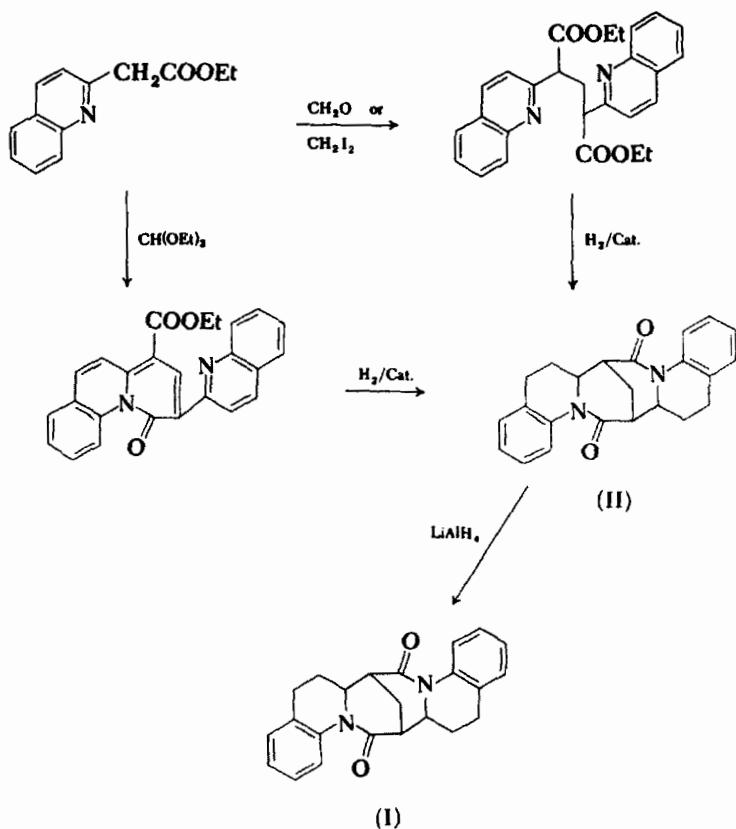
References

1. Leonard in Manske and Holmes, *The Alkaloids*, Academic Press, New York, 1953, Vol. 3, p. 156ff.
2. Henry, *The Plant Alkaloids*, 4th Ed., The Blakiston Co., Philadelphia, 1949, p. 116ff.
3. Marion and Leonard, *Can. J. Chem.*, **29**, 355 (1951).
4. Leonard, Thomas and Gash, *J. Am. Chem. Soc.*, **77**, 1552 (1955).
5. van Tamelen and Baran, *J. Am. Chem. Soc.*, **78**, 2913 (1956).
6. Clemo, Raper and Seaton, *J. Chem. Soc.*, **1956**, 3390.
7. Bohlmann, Weise, Sander, Hanke and Winterfeldt, *Chem. Ber.*, **90**, 653 (1957).

B-83. Methanodiquino[1,2-*a*, 1',2'-*e*]-[1,5]diazocine

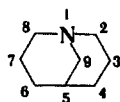


This nucleus has also been called *dibenzo[*c,k*]sparteine* by Clemo and Nath¹ who have prepared the prototype. Compounds I and II are both oils ($b_{0.5}$ 115–22° and $b_{0.5-0.6}$ 130–5°, respectively) and II yields a dipicrate (m. 156–8°).



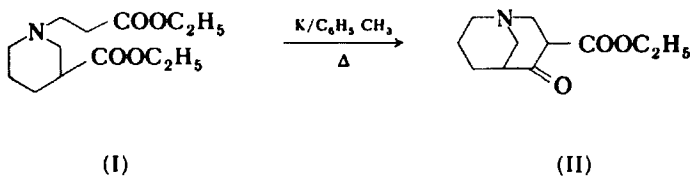
Reference

1. Clemo and Nath, *J. Chem. Soc.*, **1952**, 2196.

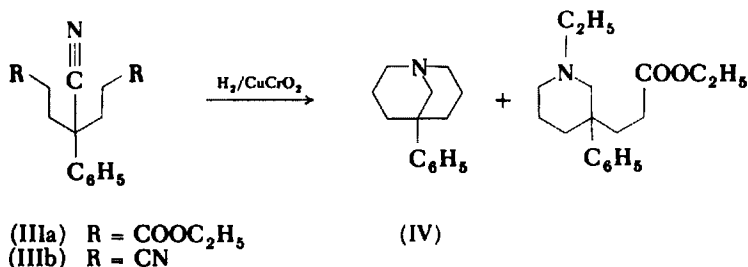
B-84. 1-Isogranatanine. R.I. 1014

Although the above trivial name has gained acceptance, the systematic name *1-azabicyclo[3.3.1]nonane* is often encountered.

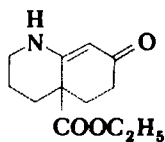
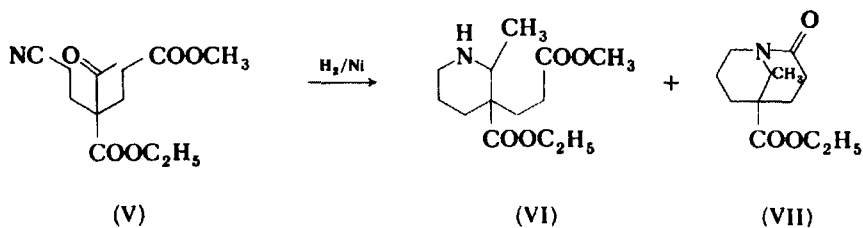
The first synthesis of this ring system was accomplished by McElvain and Adams,¹ who obtained II from the Dieckmann cyclization of I. Apparently unaware of the earlier work, Clemo, Ormston and Ramage² reported the failure of this reaction in their hands. However, the preparation of 1-azabicyclo[3.3.1]nonan-4-one³ and its 2-methyl homolog^{3,4} in approximately 25% yield confirms the utility of this reaction. The location of the carbethoxy group of II in the 3- rather than the 5-position was evidenced¹ by the positive ferric chloride color test shown by the ester.



The hydrogenation of IIIa, in dioxane solution using a copper chromite catalyst, gave,⁵ *inter alia*, about 20% of IV, which was also formed in the reduction of IIIb.

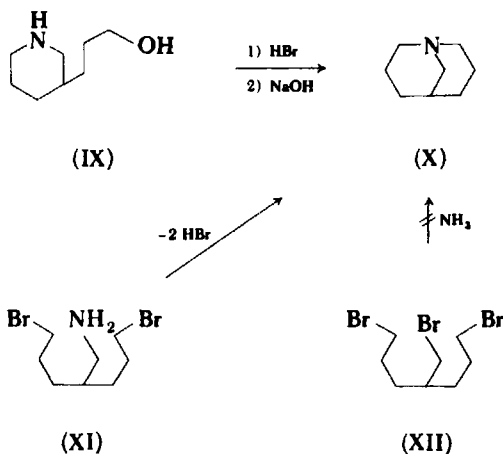


In a somewhat related reduction, Albertson^{6,7} claimed to have obtained from V, 43% of VI and 36% of a product thought, at first, to be VII, but later⁸ considered to be VIII.

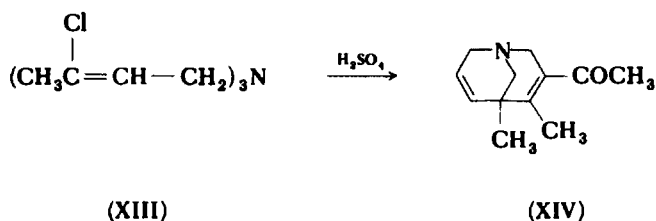


(VIII)

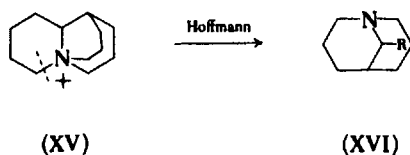
The prototype (X) of this ring system was prepared by Prelog, Heimbach and Seiwert⁹ from both IX and XI. It is interesting that treatment of XII with alcoholic ammonia failed⁹ to yield X.



Hudlicky¹⁰ found that treatment of XIII with sulfuric acid gave a mixture of products from which could be isolated a chlorine-free, basic solid. On the basis of degradation studies, the product was assigned structure XIV. The selective action of various reducing agents upon XIV was carefully elaborated.

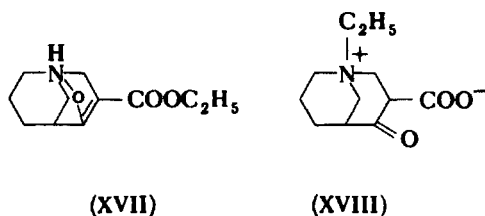


Clemo and Rudinger¹¹ subjected XV to a Hofmann degradation and isolated three products, one of which (by the elimination of probable alternative structures) was thought to be XVI (R = CH₂CH₂CH=CH₂), formed by scission of XV at the dotted line.



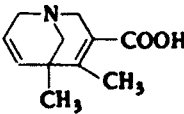
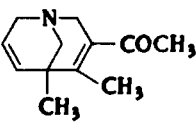
Prelog and Balenović¹² were unable to isolate any definite products from the dehydrogenation of X with selenium or with palladium charcoal catalysts.

It was noted by McElvain and Adams¹ that, on standing, II was partially converted into a crystalline salt-like product for which they proposed structure XVII. For several reasons this structure is unattractive, and a more reasonable formulation might be XVIII.



The antispasmodic activity of several esters¹³ of this series was studied.¹⁴ The benzoyl ester of II, which structurally somewhat resembles cocaine, was more toxic and had less anesthetic activity than cocaine.¹

Derivatives of 1-Isogranatanine

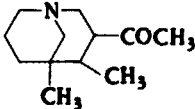
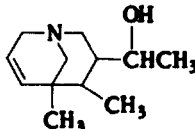
Empirical formula	Substituents or structure	Properties and derivatives	Refs.
$C_8H_{13}NO$	4-Oxo-	m. 95-8°. HCl salt, 3,15 m. 248-9°. Picrate, m. 225-6°.	
$C_8H_{15}N$	Unsubstituted	Volatile, waxy cryst., 9 m. 114°, b. ~175°. HCl salt, subl. ~350° without m. Picrate, m. 283°. Picrolonate, m. 231°. Chloroplatinate, m. 226°. Methiodide, m. 351°.	
$C_8H_{15}NO$	4-Hydroxy-	m. 169-70°, HCl salt, m. >300°. Benzylic acid ester hydrochloride, m. 214-6°.	3,4,13, 15
$C_9H_{15}NO$	2-Methyl-4-oxo-	HCl salt, m. 206-7°.	3,4,15
$C_9H_{17}NO$	4-Hydroxy-2-methyl-	m. 70.3°. HCl salt, m. 250-4°. Picrate, m. 262-3°. Benzylic acid ester hydrochloride, m. 188-90°.	3,4,13, 15
$C_{11}H_{15}NO_2$		m. 280-5°.	10
$C_{11}H_{17}NO_3$	3-Carbethoxy-4-oxo-	b _g 137-9°; n _D ¹⁸ 1.5070; d ₂₀ ²⁰ 1.1381.	1
$C_{11}H_{19}NO_3$	3-Carbethoxy-4-hydroxy-	Two stereoisomers, the hydrochlorides of both of which m. 199-201°.	1
$C_{12}H_{17}NO$		m. 64°; d ₄ ²⁰ 1.0849; n _D ²⁰ 1.53766. Acid oxalate, m. 172-3°.	10

(continued)

Derivatives of 1-Isogranatanine (*continued*)

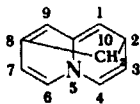
Empirical formula	Substituents or structure	Properties and derivatives	Refs.
		Acid tartrate, m. 201°. Perchlorate, m. 175–80°. Picrate, m. 222–5° d. Oxime, m. 196–7°. Semicarbazone, d. ~210°.	
$C_{12}H_{18}BrNO$		HBr salt, m. 202–3°.	10
$C_{12}H_{19}N$		b_{21} 119–21°; b_3 93–8°; n_D^{20} 1.51105. Picrate, m. 210–1°.	10
$C_{12}H_{19}NO$		m. 102–3°. Picrate, m. 194–5°.	10
		m. 52°; $n_D^{19.5}$ 1.522. 10 Picrate, m. 241–2°. Methiodide, m. 255–6°. Oxime, m. 196–7°.	10
$C_{12}H_{19}NO_2$		m. 102–3°. Picrate, m. 235–47°.	10
$C_{12}H_{21}N$		b_3 95–6°. Picrate, m. 237°.	10
		b_{15} 115°. Picrate, m. 114°. Methiodide, m. 232–3°.	11

Derivatives of 1-Isogranatanine (*continued*)

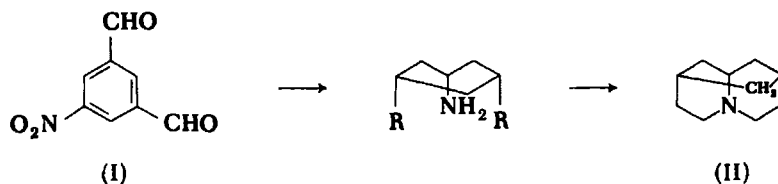
Empirical formula	Substituents or structure	Properties and derivatives	Refs.
$C_{12}H_{21}NO$		m. 122°. Picrate, m. 234-5°.	10
		b ₅ 162-3°. Picrate, m. 225-7°.	10
$C_{12}H_{23}N$	9-(n-Butyl)-	Picrate, m. 84-5°.	11
$C_{13}H_{23}NO_2$	 (R = $CH_2CH_2COOC_2H_5$)	b ₁ 125°. Picrate, m. 75-6°. Methiodide, m. 125°.	11
$C_{14}H_{19}N$	5-Phenyl-	b _{0.4} 130-5°; m. 64°. Picrate, m. 178°. Methiodide, m. 236°.	5

References

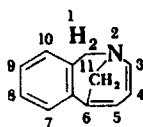
- McElvain and Adams, *J. Am. Chem. Soc.*, **45**, 2738 (1923).
- Clemo, Ormston and Ramage, *J. Chem. Soc.*, **1931**, 3185.
- Sternbach and Kaiser, *J. Am. Chem. Soc.*, **74**, 2215 (1952).
- Sternbach, Brit. Pat. 694,067; *Chem. Abstracts*, **48**, 11498 (1954).
- Badger, Cook and Walker, *J. Chem. Soc.*, **1949**, 1141.
- Albertson, *J. Am. Chem. Soc.*, **72**, 2594 (1950).
- Albertson, U. S. Pat. 2,585,210.
- Albertson, *J. Am. Chem. Soc.*, **74**, 249 (1952).
- Prelog, Heimbach and Seiwert, *Ber.*, **72**, 1319 (1939).
- Hudlický, *Collection Czechoslov. Chem. Commun.*, **13**, 206 (1948).
- Clemo and Rudinger, *J. Chem. Soc.*, **1951**, 2714.
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- Sternbach and Kaiser, *J. Am. Chem. Soc.*, **74**, 2219 (1952).
- Randall, Benson and Stefkó, *J. Pharmacol. Exptl. Therap.*, **104**, 284 (1952); *Chem. Abstracts*, **46**, 6739 (1952).
- Sternbach, U. S. Pat. 2,648,667.

B-85. 2,8(2H)-Methanoquinolizine

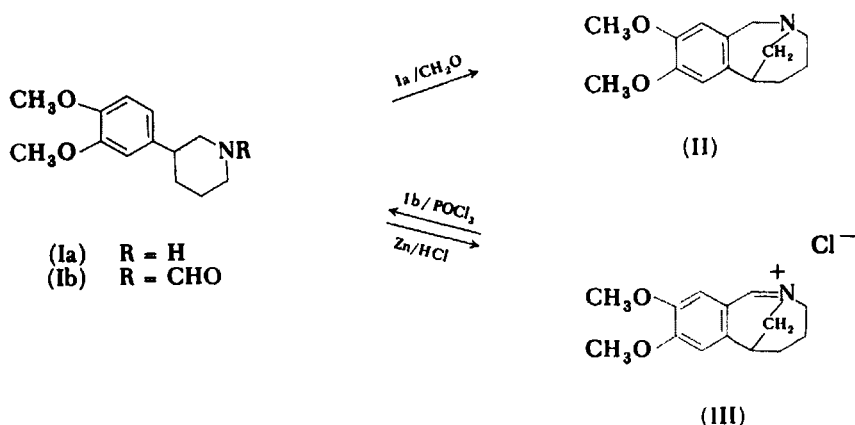
Attempts¹ to prepare the perhydro compound II (*1-azatricyclo-[4.4.1^{4,8}]undecane*) from I were unsuccessful.

*Reference*

1. Jennings, *J. Chem. Soc.*, **1957**, 1172.

B-86. 1H-2,6-Methano-2-benzazocine

Treatment of Ia with aqueous formaldehyde yielded^{1,2} II (*b*_{4,5} 164–6°; hydrochloride, m. 265–6°; picrate, m. 197.5–9°), which was named *1-aza-3,4:1',2'-(4',5'-dimethoxybenzo)bicyclo[3.3.1]nonane*. Cyclization of Ib yielded a resinous product thought to be III, which, upon reduction with zinc and acid, underwent scission to regenerate Ia.

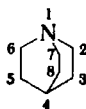


Compound II exhibited about one third of the analgesic activity of morphine.

References

1. Sugimoto and Kugita, *J. Pharm. Soc. Japan*, **75**, 183 (1955); *Chem. Abstracts*, **50**, 1815 (1956).
2. Sugimoto and Kugita, *Jap. Pat.* 1677('56); *Chem. Abstracts*, **51**, 9710 (1957).

B-87. Quinuclidine. R.I. 1013



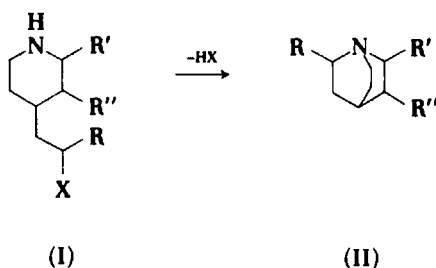
The systematic name for this ring system is *1-azabicyclo[2.2.2]octane*.

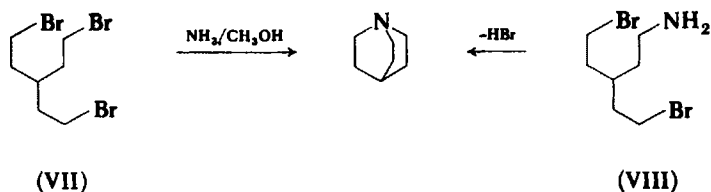
A voluminous literature has accumulated concerning quinuclidine and its derivatives, and, as has been customary in other Sections, references concerning chiefly natural products and their degradation products, have been excluded from this discussion. Thus the extensive studies upon the Cinchona alkaloids,¹ such as those by Rabe *et al.*,^{2,3} are not included here, and the compounds described in these references are not listed in the table of quinuclidine derivatives.

I. Synthesis of Quinuclidines

As might be expected from the symmetry and simplicity of the molecule, relatively few methods have been used to prepare quinuclidine and its homologs. The synthesis most commonly employed, by a wide margin, is that discussed first.

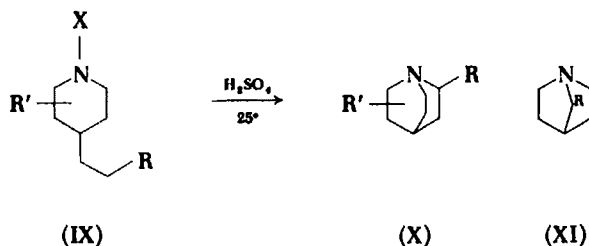
1. *Dehydrohalogenation of 4-(2-Haloalkyl)-piperidines*. This method was employed by Koenigs^{4,5} to prepare the first known quinuclidine, the 3-ethyl homolog, and it has found subsequently a wide application. Piperidines of type I are treated with base to produce the quinuclidine II. The cyclization of 4-(2-iodoethyl)-pyridine to III





good, the requisite halides (VII and VIII) are less readily available than the piperidines employed in the first method.

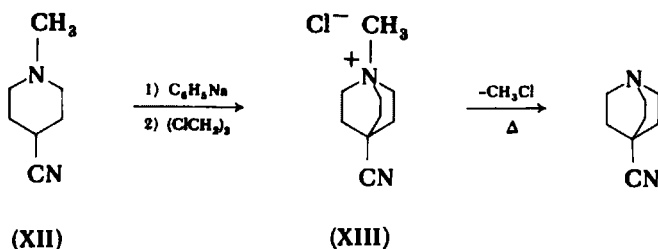
3. *The Löffler-Freytag Reaction.* The cyclodehydrohalogenation, by treatment with sulfuric acid, of certain *N*-halo secondary alkyl- and cycloalkylamines has become known as the Löffler-Freytag reaction. The reaction was first used by Hofmann to prepare δ -coniceine (see Section A-183) and has been used to synthesize pyrrolizidines (see Section A-64). Wawzonek *et al.*³⁸ irradiated with ultraviolet light solutions of *N*-halopiperidines of type IX in 85% sulfuric acid. From the reaction mixtures, quinuclidines (X) were isolated (as the picrates) in yields of 1–27%. The reaction appeared to produce the best yields when run at about 25°, and the nature of the halogen (chlorine or bromine) seemed inconsequential. The worst yields resulted from 2-alkylpiperidines. The properties of the quinuclidines thus obtained agree with those reported for the same products prepared by other routes.



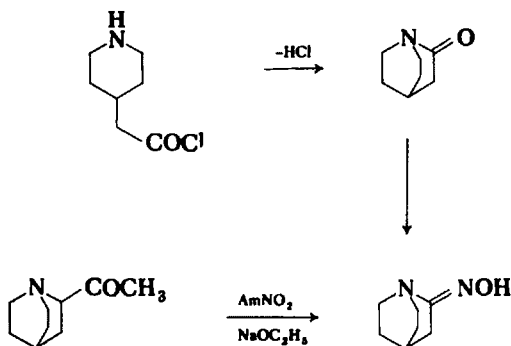
Lukeš and Ferles reported³⁹ a 5.5% yield of quinuclidine from a similar reaction upon 1-chloro-4-ethylpiperidine without ultraviolet radiation. However, later they concluded⁴⁰ that the product formed actually was 7-methyl-1-azabicyclo[2.2.1]heptane (XI, see Section B-20), and further, that 1-chloro-4-ethyl-4-methylpiperidine yielded 4,7-dimethyl-1-azabicyclo[2.2.1]heptane. The properties of these two products are clearly different from those of quinuclidine and its

4-methyl homolog,³⁷ and evidently further work is needed to clarify the factors controlling this reaction.

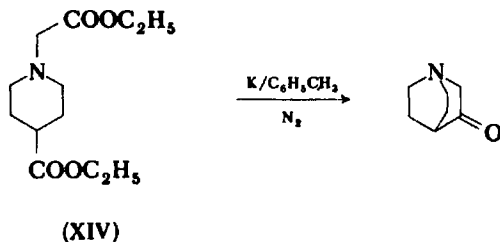
4. *Miscellaneous Syntheses.* Treatment of 1-methylisonipecotonitrile (XII) with phenyl sodium followed by ethylene dichloride afforded⁴¹ a 17% yield of XIII, which could be pyrolyzed to 4-cyanoquinuclidine in 86% yield.



Recently, the synthesis of 2-quinuclidone was reportedly achieved⁴² by the cyclization of the acid chloride of piperidyl-4-acetic acid, and the corresponding oxime was said to be obtained by degradation of 2-acetylquinuclidine. This is the only known 2-oxo derivative of quinuclidine, and in view of the "bridgehead amide" interdict,⁴³ the meagre evidence for its structure could well be augmented.



The Dieckmann cyclization of XIV was first used to prepare 3-quinuclidone by Clemo and Metcalfe.⁴⁴ As this ketone provides a convenient precursor for numerous derivatives, the reaction has been employed several times,⁴⁵⁻⁴⁷ and the yield has been raised⁴⁷ to 53-60% by the use of powdered potassium, a powerful stirrer and a nitro-



gen atmosphere. The purity of XIV was found⁴⁷ also to be a critical factor in obtaining high yields.

II. Properties of Quinuclidines

Quinuclidine itself is a very volatile, white solid, m. 158° in a sealed tube. Most of the simple alkyl homologs are liquids or low-melting solids, but many other derivatives are solids with surprisingly high melting-points. The Raman spectrum of quinuclidine has been reported,⁴⁸ and the crystal structures of the base⁴⁹⁻⁵¹ and its salts⁵² have been studied. Kinetic studies⁸ of the reaction of alkyl iodides with tertiary alkylamines and with quinuclidine have shown much faster rates in the case of quinuclidine, and the adduct formed with trimethylboron⁵³ is more stable than similar trimethylboron adducts with tertiary alkylamines. The high base strength (pK_a 10.95,⁵⁴ 11.10⁸⁰) and the ready availability of the nitrogen electron pair through reduced "F-strain,"⁵³ have led to the use of quinuclidine in place of pyridine and collidine in dehydrohalogenation reactions, etc. The base strengths^{54,55} and ultraviolet spectra⁵⁴ of a number of quinuclidine derivatives have been reported.

Quinuclidines of various structures exhibit several physiological actions. The activity of the quinine alkaloids is, of course, well known,¹ and quinuclidine compounds containing pyridine,^{12,15} quinoline⁵⁶ and acridine⁵⁷ groups also have been examined for anti-plasmodial activity. Quinuclidine hydrochloride has been reported⁵⁸ to lower blood pressure in cats and rabbits, and a number of aminoalkylquinuclidinium salts have been patented⁵⁹ as hypotensive agents. The sympathicomimetic properties of a variety of 3-substituted quinuclidines have been claimed.^{46,60-64} 4-Phenylquinuclidine and its 3-oxo homolog, though toxic, are stated²⁹ to possess analgesic activity.

III. Reactions of Quinuclidines

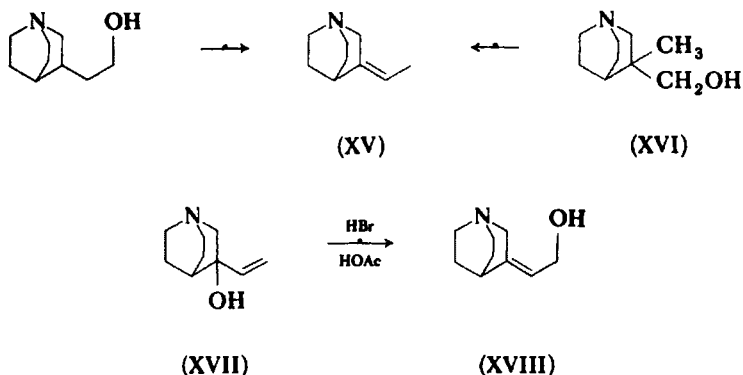
Although quinuclidines have been obtained via the pyrolysis of 1-methylquinuclidinium acetates^{23,65} or chlorides⁴¹ and by the hydrogenolysis of 1-benzylquinuclidinium salts,²⁹ the Hofmann degradation of quinuclidine was shown³¹ to yield 1-methyl-4-vinylpiperidine and 1-methyl-4-(2-hydroxyethyl)-piperidine.

Quinuclidine-2-carbohydrazide has been subjected⁶⁶ successfully to the Curtius rearrangement, and the silver salt of the corresponding acid was shown¹⁴ to undergo the Hunsdiecker reaction, while the ester has been employed⁴² in the Claisen condensation. A variety of quinuclidine esters have been reduced to carbinols by the Bouveault-Blanc method⁶⁷ or by the action of lithium aluminum hydride.^{16,22,68-70} A number of primary, secondary and tertiary amides have been reduced with this reagent to aminomethylquinuclidines,⁷⁰⁻⁷² although quinuclidine-2-aldehyde has been obtained⁷³ from the methylanilide of quinuclidine-2-carboxylic acid. The 4-aldehyde has been prepared⁶⁸ by oxidation of the hydroxymethyl derivative with bichromate. The 2-aldehyde has been used⁷⁴ in a Knoevenagel reaction with malonic ester.

As mentioned earlier, 3-quinuclidone serves as the starting compound for numerous derivatives. Reaction with acetylene^{47,75,76} yields 3-ethynyl-3-hydroxyquinuclidine, which may be reduced to either 3-ethyl-3-hydroxy^{75,76} or to 3-hydroxy-3-vinylquinuclidine⁷⁶ (XVII). Some discrepancies appear in the reported properties of the former substance, and in those of the ethynyl compound also.

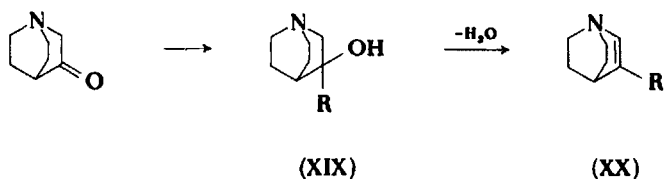
Several rearrangements involving 3-substituted quinuclidines have been reported. Attempts to dehydrate 3-(2-hydroxyethyl)-quinuclidine by heating with hydrochloric acid at 180°, or with phosphorus pentoxide in toluene led⁷⁶ only to XV, although the use of benzenesulfonic acid in boiling phthalic anhydride did produce 3-vinyl quinuclidine.⁷⁷ Dehydration of XVI also produced²⁴ XV, while XVII underwent an allylic rearrangement to XVIII.

Reduction of 3-quinuclidone by a variety of reagents always led⁴⁵ to the same 3-hydroxyquinuclidine, from which the 3-bromo⁴⁵ and 3-chloro⁴⁷ compounds could be obtained. 3-Quinuclidylamine has been prepared⁴⁵ by reduction of the oxime. The



reaction of 3-quinuclidone with benzaldehyde, followed by catalytic hydrogenation yielded⁴⁵ 2-benzyl-3-hydroxyquinuclidine.

3-Quinuclidone readily forms the cyanhydrin (XIX, R = CN) in nearly quantitative yield,⁶⁴ and this may be converted into the unsaturated nitrile, amide or ester (XX, R = CN, CONH₂ or COOCH₃).^{47,64} Similarly, reaction with alkyl⁶² or aryl⁴⁷ lithium compounds or with Grignard reagents⁴⁷ affords, generally, good yields of carbinols with structure XIX. Dehydration, followed by hydrogenation of the unsaturated compounds (XX) produces 3-substituted quinuclidines.^{47,64}



An interesting method for the introduction of certain substituents into the 2-position was demonstrated⁴⁷ by the 1,4 addition of *i*-propylmagnesium bromide to the unsaturated ester XX (R = COOCH₃). Also, nitration of 3-phenyl- Δ^2 -dehydroquinuclidine (XX, R = C₆H₅) yielded⁴⁷ a mixture containing 18% of 2-nitro-3-phenyl- Δ^2 -dehydroquinuclidine and 36% of 2-nitro-3-(4-nitrophenyl)- Δ^2 -dehydroquinuclidine.

Reduction of 3-quinuclidones by the Clemmensen⁴⁴ or Wolff-Kishner^{29,44} techniques produced quinuclidines, but decomposition

of 3-quinuclidone tosylhydrazone by Bamford and Stevens' method⁷⁹ yielded⁴⁷ a mixture of quinuclidine and its Δ^2 -dehydro homolog. The latter compound also has been obtained⁴⁷ by pyrolysis of 3-(*p*-toluenesulfonyl)-quinuclidine.

Quinuclidines more highly unsaturated than the Δ^2 -dehydro compound have not been described. Quinuclidine is not dehydrogenated by treatment with mercuric acetate, presumably⁴⁷ because the reaction would proceed via the Δ^1 -dehydroquinuclidinium salt, and the existence of the latter is forbidden by Bredt's rule. Attempts to dehydrogenate quinuclidine by heating with palladium-charcoal or selenium⁷⁸ 4-ethylpyridine.

Quinuclidines			
Empirical formula	Substituents or structure	Properties	Refs.
$C_7H_{11}N$	Δ^2 -Dehydro-	b ₄₀ 70-5°; waxy crystals; pK _a 9.82. HCl salt, HClO ₄ salt and methiodide all m. > 300°. Picrate, m. 262-5° d. Oxalate, m. 141-2°. Oil, d. upon distn. Oxime, m. 171-2°.	47, 54
$C_7H_{11}NO$	2-Oxo- 3-Oxo-	b ₁₂ 110°; m. 147-8° (138°). HCl salt, m. 311-3° d. (294-5° unc.). Picrate, m. 209-11° (208-10°, 210°). Methiodide, m. 310° d. Oxime, m. 213-7°; HCl salt, m. 233-6°. <i>p</i> -Toluenesulfonylhydrazone, m. 200-1° d.; HCl salt, m. 233-5° d.	42 24, 44-47, 64, 76
$C_7H_{12}BrN$	2-Bromo-	Oil. Picrate, m. 175°.	14
$C_7H_{12}ClN$	3-Bromo-	m. 231-3°. HBr salt, m. 243-5°.	45, 47
$C_7H_{13}N$	3-Chloro- Unsubstituted	HCl salt, m. 215-7°. Volatile, m. 158-9° (158°, 156°, 155-6°); pK _a 10.95 (11.10). HCl salt, m. 369-74° (364-5°, 315°). Picrate, m. 275-6° (274-5°, 275° d., 271-3°). Picrolonate, m. 255°. Methiodide, m. 357-8° (343°). Ethiodide, 270-1° (270°). Aurichloride, m. 271-3°. Chloroplatinate, m. 238-40°.	47 6-10, 30-33, 38-40, 44, 47-54, 58, 78, 80
$C_7H_{13}NO$	3-Hydroxy-	m. 225-7° (221-3°). HCl salt, m. > 300°. Picrate, m. 214°. O-Acetyl cpd., b ₁₁ 113-5°; n_D^{25} 1.4675. O-Acetyl methiodide,	45-47

(continued)

Quinuclidines (*continued*)

Empirical formula	Substituents or structure	Properties	Refs.
$C_7H_{14}N_2$ $C_8H_{10}N_2$	3-Amino-	m. 165–6°. <i>p</i> -Toluenesulfonate, HCl salt, m. 202°.	45
	3-Cyano- Δ^2 -dehydro-	m. 218–20°. Di-HCl salt, m. >280°. b_{11} 73–5°; waxy, m. 41°; pK_a 5.84; λ_{max} 260 m μ . HCl salt, m. 225–6° d. $HClO_4$ salt, m. 180° d. Picrate, m. 195° d. Methoperchlorate, m. 212–4° d.	47, 54
$C_8H_{11}NO_2$	3-Carboxy- Δ^2 -dehydro-	HCl salt, m. 210–1° d. Methyl ester hydrochloride, m. 178–9°. Amide, m. 160–1°, pK_a 7.32; HCl salt, m. 248–50°; $HClO_4$ salt, m. 218° d.; picrate, m. 198–9°; methoperchlorate, m. 220–2° d. HCl salt hydrate, d. 230°.	47, 54
$C_8H_{12}Cl_3N$ $C_8H_{12}N_2$	2-Trichloromethyl-	Oil. Picrate, m. 212°.	21
	2-Cyano-	pK_a 7.81. HCl salt, m. 212–3°.	14
	3-Cyano-	m. 135°. Picrate, m. 286–9° d. Methiodide, m. >310°.	47, 54
	4-Cyano-		41
$C_8H_{12}N_2O$ $C_8H_{13}N$	3-Cyano-3-hydroxy-	m. 172–3° d. Picrate, m. 133–4° d.	64
	3-Methylene-	b_{70} 170–1°; n_D^{20} 1.4908; d_4^{20} 0.9388. Picrate, m. 200–1°. Chloroplatinate, m. 194° d. Methopicrate, m. 257–8°.	65
$C_8H_{13}NO$	2-Formyl-	$b_{0,4}$ 80–2°; n_D^{20} 1.5296. HCl salt, m. 228°. Picrate, d. 218–9°. Phenylhydrazone, m. 147–8°. Semicarbazone, d. 244°.	73
	4-Formyl-	Semicarbazone, m. 284–7°.	68

$C_8H_{13}NO_2$	2-Carboxy-	m. $\sim 280^\circ$ d. (d. $275-8^\circ$). HCl salt. d. $292-4^\circ$ ($290-1^\circ$, 286°). HBr salt, m. $277-8^\circ$ d. Methochloride, m. 298° d. Methoberaine, m. $215-20^\circ$. Ethyl ester, $b_{0.3}$ $87-9^\circ$, b_{12} $122-3^\circ$; n_D^{20} 1.4723. Methyl ester, b_{12} 115° ; picrate, m. 174° ; methiodide, m. $176-8^\circ$. <i>i</i> -Amyl ester, $b_{0.6}$ $110-2^\circ$; n_D^{16} 1.4671. Amide, m. $143-5^\circ$ ($142-3^\circ$). Methylanilide, $b_{0.6}$ $161-2^\circ$, m. $95-6^\circ$. Dimethylamide, $b_{0.34}$ $97-100^\circ$; m. $48-50^\circ$. Diethylamide, $b_{0.35}$ $100-2^\circ$. Diethylaminoethylamide, b_7 $170-80^\circ$. <i>S</i> -Diethylamino-2-pentylamide, $b_{0.3}$ $150-1^\circ$. Benzylamide, $b_{0.2}$ $183-5^\circ$; HCl salt, m. $166-8^\circ$. 2-Pyridylamide, $b_{0.3}$ $149-50^\circ$; m. $109-10^\circ$. Pentamethyleneamide, $b_{0.35}$ $129-30^\circ$; m. $72-4^\circ$. 2-Thiazolylamide, m. $114-6^\circ$. HCl salt, m. $273-5^\circ$ d. Amide, m. $196-9^\circ$; pK_a 9.67; picrate m. $192-4^\circ$; HCl salt, m. $209-12^\circ$. Methyl ester, pK_a 9.40; HCl salt, m. $167-9^\circ$; picrate, m. $155-6^\circ$. m. $> 370^\circ$. HCl salt, m. $> 360^\circ$. Picrate, m. $268-9^\circ$ d. Methyl ester, m. $48-9^\circ$; HCl salt, m. $288-92^\circ$ d.; picrate, m. $214-6^\circ$; methiodide, m. $271-4^\circ$. Ethyl ester, oil; HCl salt, double m.p. $255-6^\circ$ and $298-9^\circ$; picrate, m. $261-4^\circ$ d.	14,17,18, 21,34,55, 66,67,71- 73
	3-Carboxy-		47,54,55,64
	4-Carboxy-		41,55

(continued)

Quinuclidines (*continued*)

Empirical formula	Substituents or structure	Properties	Refs.
$C_8H_{13}NO_3$	3-Carboxy-3-hydroxy-	HCl salt, m. 252-5° d. Methochloride, m. 259-61° d. Methopicate, m. 233-6° d. 1-Methylbetaine, m. 278-81° d. Methyl ester, m. 122°; HCl salt, m. 140-1°; picrate, m. 188-9°; methiodide, m. 191-2°.	64
$C_8H_{14}BrN$	2-Bromomethyl-	HBr salt, m. 239.5-40.5°.	56
$C_8H_{14}ClN$	2-Chloromethyl-	HCl salt, m. 234-5°.	67
	3-Chloromethyl-	HCl salt, m. 243-4°.	69
$C_8H_{15}N$	2-Methyl-	b. 161°. HCl salt, m. 327°. HI salt, m. 229°. Picrate, m. 286° (282-3° d.). Styphnate, m. 208.5°. Picrolonate, m. 226°. Methiodide, m. 346.5° d.	11, 35, 38
	3-Methyl-	b. 169-71° (171°). HCl salt, m. 312-24°. Picrate, m. 229-30° (226-8°, 227°, 225°). Picrolonate, m. 205-6°. Chloroplatinate, m. 219° d. Methiodide, m. 316° d. Methopicate, m. 300° d.	36, 38, 65, 69
	4-Methyl-	b ₇₃₈ 158-60°; m. 49-50°. Picrate, m. 292-4° (291°). Methiodide, m. 264-5° d. (265°). Methopicate, m. 257-8°.	37, 68
$C_8H_{15}NO$	2-Hydroxymethyl-	b ₁₄ 118-20°. HBr salt, m. 308°. Picrate, m. 230-1°. O-Benzoyl deriv. HCl salt, m. 245.5-6.5°.	67
	3-Hydroxymethyl-	Oil. Picrate, m. 188-90°. Methiodide, m. 278-80° d.	69

$C_8H_{16}N_2$ $C_9H_{13}NO$	4-Hydroxymethyl-	m. 138°. Picrate, m. 261-4° d.	68
	3-Hydroxy-3-methyl-	m. 109-11°. HCl salt, m. 291-2°.	62
	2-Aminomethyl-	b ₅ 83-5°. Di-HCl salt, m. 277-9°.	71
	3-Ethinyl-3-hydroxy-	m. 159-60° (191-2° ?). Picrate, m. 176.0-6.5° (153° ?).	75, 76
	3-Ethylidene-	b ₇₉ 187-8°; n_D^{20} 1.4968; d_4^{20} 0.9430. Picrate, m. 127.5-8.0°. Chloroplatinate, m. 179-80°.	24, 76
$C_9H_{15}NO$	3-Vinyl-	b ₁₅ 85°; b ₁₈ 80°; n_D^{20} 1.4969; d_4^{20} 0.9409. Picrate, m. 150-1° (149-50°). Styphnate, m. 186-7°.	25, 77
	2-Acetyl-	Oil. HCl salt, m. 183-4°. Phenylhydrazone, m. 184°.	42
	3-(2-Hydroxyethylidene)-	Form A: m. 93.5-5.0°. Picrate, m. 123.0-3.5°.	76
	3-Hydroxy-3-vinyl-	Form B: m. 48.0-8.5°. Picrate, m. 151-2°.	76
	3-Acetyl-3-hydroxy-	m. 89-90.5°. Picrate, m. 157-8°.	47
$C_9H_{15}NO_2$	3-Carboxymethyl-	m. 104-5°. Methiodide, m. 190-2°.	28
	2-Carboxy-3-methyl-	HCl salt, d. 238°. Ethyl ester, b _{0.15} 91-3°.	22
		HCl salt, m. 292°. Ethyl ester, b _{0.25} 75-6°.	
		Amide, m. 127.5-8°. Hydrazide, m. 77-82°; picrate, m. 175-7°.	
	3-(2-Bromoethyl)-	HBr salt, m. 167-8°. Picrate, m. 148-9°.	76
$C_9H_{16}BrN$ $C_9H_{16}BrNO$	3-Bromomethyl-3-hydroxymethyl-	Methobromide, m. 200-4°. O-Acetate methobromide, m. 190°.	23
	3-(2-Chloroethyl)-	Picrate, m. 136.5-7°.	76

(continued)

Quinuclidines (*continued*)

Empirical formula	Substituents or structure	Properties	Refs.
C ₉ H ₁₇ N	2-Ethyl-	b. 180-1°. HCl salt, m. 239°. Picrate, m. 172° d. (170-1°). Picrolonate, m. 219°. Chloroplatinate, m. 227°. Methiodide, m. 290.0-0.5°.	35, 38
	3-Ethyl-	b ₁₂ 78-9°; b ₇₂₀ 190-2°. HBr salt, m. 230-1°. HCl salt, m. 208-11°. HI salt, m. 233°. Chloraurate, m. 178.5-9° (176.5-8°). Chloroplatinate, m. 220-3° (221° d.). Picrolate, m. 155.5-7.5° (153-4.5°). Picrolonate, m. 187-8°. Methiodide, m. ~55° (130°?).	4, 5, 24, 36
C ₉ H ₁₇ NO	2-Hydroxymethyl-3-methyl-	b ₀₂ 78°; n _D ²⁰ 1.4992.	22
	3-Hydroxymethyl-3-methyl-	HBr salt, m. 312° d. (310-1°). HCl salt, m. 312° d. (280° d.). Picrate, m. 193-4°. Methobromide, d. ~335°.	23, 24, 26
	3-(2-Hydroxyethyl)-	m. 34-6°. Picrate, m. 94-5.5°.	76
	3-Ethyl-3-hydroxy-	b ₀₁ 97-101°; m. 110.5°. Picrate m. 159° (175°?).	75, 76
C ₉ H ₁₇ NO ₂	3,3-Bishydroxymethyl-	Methobromide, m. <300°.	23
C ₁₀ H ₁₄ N ₂ O ₂	3-Acetoxy-3-cyano-	b ₀₀₅ 96-9°; n _D ²⁰ 1.4848. Methiodide, m. 245-8° d.	47
C ₁₀ H ₁₅ NO ₂	2-(2-Carboxyvinyl)-	HCl salt, m. 197-8°.	74
		b ₀₄ 140°; m. 137-9°. HCl salt, d. 310-2°. Picrate, m. 234-6°.	27

$C_{10}H_{15}NO_4$	2-Carboxy-3-carboxymethyl-	m. 265-7° (273°, 180-2°). HCl salt, d. 254-5°. Diethyl ester, b_{03} 126°; n_D^{20} 1.4797; methiodide, m. 140-1°. Diamide, m. 198-200°. Bisdimethylamide, m. 117-8°. Bisdieethylamide, b_{04} 163-5°; m. 45°. Bismonobenzylamide, m. 139-41°. $b_{0,23}$ 120-2°. HCl salt, m. 139-40°. Methiodide, m. 136°.	16,71
$C_{10}H_{17}Cl_2N$	3-(2-Chloroethyl)-2-chloromethyl-	m. 132-3°.	47
$C_{10}H_{17}NO$	3-(2-Hydroxypropyl)- Δ^2 -dehydro-	HCl salt, d. 215-6°. Ethyl ester methiodide, m. 87-9°.	74
$C_{10}H_{17}NO_2$	2-(2-Carboxyethyl)-		
$C_{10}H_{17}NO_3$	3-Carboxymethyl-3-hydroxymethyl-	Hydrazide, m. 145-8°. Phenylhydrazide, d. 151-3°.	27
$C_{10}H_{18}N_2O_2$	2-Carboxy-3-(2-hydroxyethyl)-	Ethyl ester, $b_{0,26}$ 102-15°.	19,20
$C_{10}H_{19}NO$	2-(Carbethoxyamino)-	m. 166-8°. HCl salt, m. 136-8°.	66
	3-(2-Methoxyethyl)-	Picrate, m. 128-9°.	76
	3-(2-Hydroxypropyl)-	m. 111-2°.	47
$C_{10}H_{19}NO_2$	3-(2-Hydroxyethyl)-2-hydroxymethyl-	$b_{0,4}$ 156-7°.	16
$C_{10}H_{19}NS$	3-(2-Methylthioethyl)-	m. 191.5-2°.	76
$C_{10}H_{20}N_2$	2-Dimethylaminomethyl-	$b_{7,3}$ 89-90°. Dipicrate, m. 211.5-3.5°.	71
$C_{10}H_{20}N_2O$	2-Aminomethyl-3-(2-hydroxyethyl)-	$b_{0,3}$ 157-60°. Dipicrate, m. 202-4°.	70
$C_{11}H_{15}NO_2$	3-Acetoxy-3-ethyl-	HCl salt, m. 234-40° d. Picrate, m. 181-3° d. Methiodide, m. 275-7° d.	47
$C_{11}H_{17}N_3S$	2-(2-Thiazolylaminomethyl)-	$b_{0,2}$ 150-2°; m. 76-8°.	72
$C_{11}H_{19}NO_2$	3-Carboxy-2-(2-propyl)-	HCl salt, m. 308-9°. Picrate, m. 243-6°. Methyl ester, b_{11} 123-5°; n_D^{20} 1.4701; HCl salt, m. 198-9°; perchlorate, m. 175-7°; picrate, m. 188-90°; methiodide, m. 190-1°.	47

(continued)

Quinuclidines (continued)

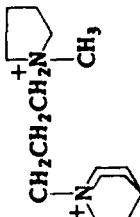
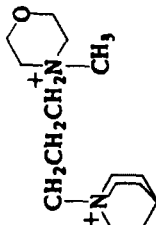
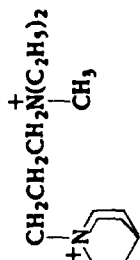
Empirical formula	Substituents or structure	Properties	Refs.
$C_{11}H_{10}NO_3$	2-Carboxy-5-(2-methoxyethyl)-	HCl salt, d. 190-1°. Ethyl ester, $b_{0.4}$ 185-95°; picrate, m. 152-3°.	20
$C_{12}H_{10}NO$	2-(Carboxyoxycetyl)-	m. 115-6°.	42
$C_{12}H_{10}NO_4$	3-(Carboxyoxymethyl)-2-carboxy-	HCl salt, m. 228-9°.	70
$C_{12}H_{10}NO_5$	2,2-Dicarboxy-5-(2-methoxyethyl)-	HCl salt, m. 182°. Diethyl ester, $b_{0.4}$ 132-70°; n_D^{20} 1.4809; d_{20} 1.097.	20
$C_{12}H_{20}N_2O_3$	3-Carboxyoxymethyl-2-carboxamido-	m. 102-3°.	70
$C_{12}H_{24}N_2$	2-Diethylaminomethyl-	b_{20} 131-2°. Dipicrate, m. 196-8°.	71
$C_{12}H_{25}N_2$	$\begin{array}{c} CH_2CH_2N^+(CH_3)_3 \\ + \text{N} \end{array}$ 	Iodide, m. 164-6°.	59
$C_{13}H_{13}N_3O_4$	2-Nitro-3-(4-nitrophenyl)- Δ^2 -dehydro-	Pale yel., m. 201-2°. Weak base; does not form a methiodide.	47
$C_{13}H_{14}N_2O_2$	2-Nitro-3-phenyl- Δ^2 -dehydro-	Yel., m. 66-7°. Weak base; does not form a methiodide.	47
$C_{13}H_{15}N$	3-Phenyl- Δ^2 -dehydro-	b_{11} 150-3°; m. 55-7°; n_D^{24} 1.4989; pK_a 9.10; λ_{max}^{EtOH} 249 $m\mu$. Picrate, m. 159-60°. Perchlorate, m. 163-8°. Methopchlorate, m. 169-70°; λ_{max}^{EtOH} 247 $m\mu$.	47, 54
$C_{13}H_{15}NO$	3-Oxo-4-phenyl-	m. 157-8°. HCl salt, m. 255-70°. Methiodide, m. 189-90°. Semicarbazone, m. 267-8°. 1-Benzyl bromide, m. 290-5°. 1-Benzyl nitrate, m. 255-6°.	29

	3-(4-Hydroxyphenyl)- Δ^2 -dehydro-	m. 230-1°. Methide, m. 205-7°. Metho- perchlorate, m. 180° d.	47
$C_{13}H_{16}N_2O$	2-Picolinoyl-	m. 71.5-3°. Di-HBr salt, d. 170-1°.	15
	2-Isonicotinoyl-	m. 117-8°. Di-HCl salt, m. 221-3° d.	12
$C_{13}H_{17}N$	3-Phenyl-	pK _a 10.23. Perchlorate, m. 152°. Picrate, m. 143-5°.	47,54
	4-Phenyl-	m. 125°. HCl salt, m. > 350°. Perchlorate, m. 271-3°. Methiodide, m. 280-1°.	29
$C_{13}H_{17}NO$	3-(4-Hydroxyphenyl)-	m. 201-2°.	47
	3-Hydroxy-3-phenyl-	m. 166-8°.	47
	3-Hydroxy-4-phenyl-	m. 198-200°. HCl salt, m. 339-40°. O- Acetate, m. 92-3°; HCl salt, m. 275-9°. O-Propionate, m. 60°; HCl salt, m. 208- 10°.	29
$C_{13}H_{18}N_2O$	2-(2-Pyridylhydroxymethyl)-	<i>Two racemates</i> : A: m. 118-9°; HCl salt, m. 232-3°. B: m. 80-2°; HCl salt, m. 175-7°	15
	2-(4-Pyridylhydroxymethyl)-	<i>Two racemates</i> : A: m. 57-8°; di-HCl salt, m. 206-7°; oxalate, m. 174-5°. B: m. 158-9°; di-HCl salt, m. 167-9°.	12
$C_{13}H_{19}N_2$	2-(2-Pyridylaminomethyl)-	b ₀₂₅ 160°; m. 64-6°.	72
$C_{13}H_{21}NO_4$	2,2-Dicarboxy-	b ₉ 153-5°. Picrate, m. 177-8°.	13,14
$C_{13}H_{24}N_2$	2-(1-Piperidylmethyl)-	b ₀₂ 91-3°. Methiodide, m. 140-2°.	72
$C_{13}H_{24}N_2O_2$		b ₀₆ 105-8°; n _D ²⁰ 1.4587	66

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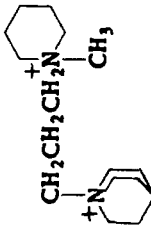
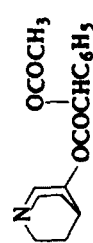
Quinuclidines (*continued*)

Empirical formula	Substituents or structure	Properties	Refs.
$C_{13}H_{28}N_2$	$ \begin{array}{c} CH_2CH_2CH_2\overset{+}{N}(CH_3)_3 \\ \\ \text{Quinuclidine ring} \end{array} $	Dibromide, m. 292-3°.	59
$C_{14}H_{17}NO$	3-(4-Methoxyphenyl)- Δ^2 -dehydro-	$b_{0.05}$ 100-2°; m. 63-7°; $\lambda_{\text{EtOH}}^{260}$ m μ . Perchlorate, m. 161°. Picrate, m. 195-7°. Methiodide, m. 184-8° d. Methoperchlorate, m. 163-5° d.; $\lambda_{\text{EtOH}}^{268}$ m μ .	47, 54
$C_{14}H_{19}NO$	3-(4-Methoxyphenyl)-	Perchlorate, m. 127-9°.	47
	2-Benzyl-3-hydroxy-	m. 154-6°. HCl salt, m. 201-5°.	45
$C_{14}H_{19}NO_2$	3-Hydroxy-3-(4-methoxyphenyl)-	m. 160-1°.	47
$C_{14}H_{28}N_2$	$ \begin{array}{c} \text{Quinuclidine ring} \\ \\ CH_2CH_2\overset{+}{N}(CH_3) \end{array} $	Bromide, m. 349-52°.	59
$C_{14}H_{29}N_2$	2-(2-Diethylaminoethyl)aminomethyl-	b_{13} 171-3°. Tripicrate, m. 164.5-6.5°.	72
$C_{14}H_{29}N_3$	3-(2-Dimethylaminoethyl)-2-dimethylaminomethyl-	$b_{0.3}$ 98°. Tripicrate, m. 196-7°.	71
$C_{15}H_{20}N_2$	3-(4-Dimethylaminophenyl)- Δ^2 -dehydro-	m. 76-8°; pK_a 9.39; $\lambda_{\text{EtOH}}^{295}$ m μ . Perchlorate, m. 234-6°. Picrate, m. 205-6°.	47, 54
		Methiodide, m. 235-7° d. Methoperchlorate, m. 245-8° d.; $\lambda_{\text{EtOH}}^{227}$ and 312 m μ .	
$C_{15}H_{20}N_2O$	5-Ethyl-2-picolinoyl-	$b_{0.3}$ 155-6°; $[\alpha]_D^{20}$ 75.2°.	15

$C_{13}H_{22}N_2$	3-(4-Dimethylaminophenyl)- 2-Benzylaminomethyl-	m. 65-7°; pK_a 10.29. $b_{0.23}$ 191°. Di-HCl salt, m. 202-4°. Dipi- crate, m. 190-1°.	47, 54 72
$C_{13}H_{22}N_2O$	3-(4-Dimethylaminophenyl)-3-hydroxy-	m. 75-80°, then resolidifies and m. 127-8°. Picrate, m. 149-50°.	47
$C_{13}H_{23}NO_4$	5-Ethyl-2-(2-pyridylhydroxymethyl)-	$b_{0.3}$ 139-43°; $[\alpha]_D^{20}$ 70.8° (EtOH).	15
$C_{13}H_{23}N_3O$	2-(2,2-Dicarboethoxyvinyl)- 3-(2-Hydroxyethyl)-2-(2-pyridylamino- methyl)-	b_g 142-3°; n_D^{20} 1.4821. m. 137-9°.	74 70
$C_{13}H_{28}N_2O$	3-(2-Hydroxyethyl)-2-(1-piperidylmethyl)-	m. 116-7°.	70
$C_{13}H_{30}N_2$		Bromide, m. 298° d.	59
$C_{13}H_{30}N_2O$		Bromide, m. 265-6°.	59
$C_{13}H_{32}N_2$		Bromide, m. 255-6°.	59

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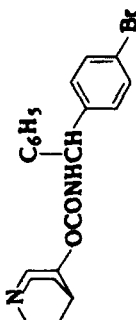
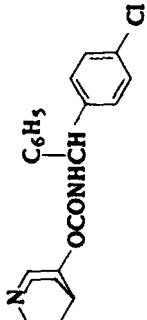
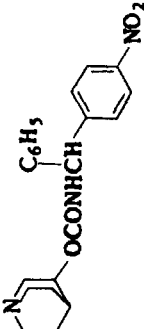
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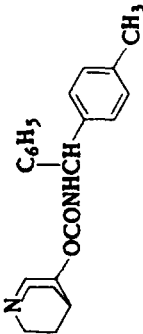
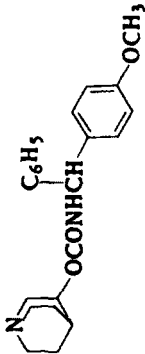
Empirical formula	Substituents or structure	Properties	Refs.
	$\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$ 	Bromide, m. 295-8°.	59
$\text{C}_{16}\text{H}_{32}\text{N}_2$		Bromide, m. 284-6°.	59
$\text{C}_{16}\text{H}_{33}\text{N}_3\text{O}$	2-(2-Diethylaminoethylaminoethyl)-3-(2-hydroxyethyl)-	$b_{0.35}$ 170-2°.	70
$\text{C}_{17}\text{H}_{21}\text{NO}_4$		HCl salt, m. 169-78°.	46,62
$\text{C}_{17}\text{H}_{23}\text{N}_3\text{O}_3$	3-Carbethoxymethyl-2-[N-(2-pyridyl)-carboxamido]-	$b_{0.3}$ 210-2°; m. 56-8°.	70
$\text{C}_{17}\text{H}_{25}\text{NO}_6$	2,2-Dicarbethoxy-5-(2-acetoxyethyl)-	$b_{0.3}$ 110-70°; n_D^{20} 1.4809; d_{20}^{20} 1.133.	19
$\text{C}_{17}\text{H}_{27}\text{NO}_6$	2,2-Dicarbethoxy-3-carbethoxymethyl-	$b_{0.25}$ 147-8°; n_D^{20} 1.4793. Methiodide, m. 139-41°.	16
$\text{C}_{17}\text{H}_{28}\text{N}_2\text{O}_3$	3-Carbethoxymethyl-2-(N,N-pentamethyl-enecarboxamido)-	$b_{0.4}$ 160-2°; m. 45-7°.	70
$\text{C}_{17}\text{H}_{33}\text{N}_2$	2-(5-Diethylamino-2-pentylaminomethyl)-	$b_{0.3}$ 144-6°.	72

$C_{18}H_{19}NO$	2-(1-Naphthoyl)-	m. 98.5–100°. HCl salt, m. 246–7°.	15
$C_{18}H_{21}NO$	2-(1-Naphthylhydroxymethyl)-	<i>Two Racemates</i> : A: m. 200–1°; HCl salt, m. 203.5–5.5°. B, m. 63–5°; HCl salt, m. 267.5–9°.	15
$C_{18}H_{23}N_3O$	2-(6-Methoxy-8-quinolylaminomethyl)-	b_{02} 200–2°. Di-HCl salt, yel., m. 218–9°. Dipicrate, m. 194–5°.	56
$C_{18}H_{33}N_3O_3$	3-Carboxymethyl-2-[N-(2-diethylaminoethyl)-carboxamido-]	b_{04} 185–6°.	70
$C_{18}H_{37}N_3$	3-(2-Diethylaminoethyl)-2-diethylaminomethyl-	b_{0x} 125–7°.	71
$C_{19}H_{39}N_3O$	2-(5-Diethylamino-2-pentylaminomethyl)-	b_{03} 185–6°.	70
$C_{20}H_{24}NO$	2-(Diphenylhydroxymethyl)-	HCl salt, m. 265°. Picrate, m. 253–4°.	67
$C_{21}H_{21}NO_2$	3-(Fluorenyl-9-carboxoxy)-	Oil. HCl salt, m. 201–5°.	46, 60
$C_{21}H_{23}NO_2$	3-Diphenylacetoxy-	m. 95–6° (<i>L</i> - and <i>d</i> -forms, m. 89–90°). Sulfate. $2H_2O$, m. 95–103°. Methobromide, m. 212–3°. Ethobromide, m. 205–6°.	46, 60, 62
		Allyl bromide, m. 149–50°. Benzyl bromide, m. 171–3°.	
$C_{21}H_{23}NO_3$	3-Benziloyloxy-	m. 164–5°. HCl salt, m. 239–41°. Methobromide, m. 240–1°. Methopicrate, m. 171–3°. Methocamphorsulfonate, <i>d</i> -, m. 221–3°; <i>l</i> -, m. 209–10°. Ethobromide, m. 229–30°. Propyl bromide salt, m. 251–4°. Allyl bromide salt, m. 181–2°. Butyl bromide salt, m. 246–7°. Benzyl bromide salt, m. 169–78°.	46, 60, 62

(continued)

Quinuclidines (continued)

Empirical formula	Substituents or structure	Properties	Refs.
$C_{21}H_{23}BrN_2O_2$		m. 125-7° (135°).	63
$C_{21}H_{23}ClN_2O_2$		m. 136°.	63
$C_{21}H_{23}N_3O_4$		m. 82-8°. HCl salt, m. 238-40° d.	63
$C_{21}H_{24}N_2O$	3-Diphenylacetamido-	m. 177-9°.	60
$C_{21}H_{24}N_2O_2$	3-(N-Benzhydrylcarbamoyloxy)-	m. 148-9°. HCl salt, m. 239-41°. Methobromide, m. 235°. Ethobromide, m. 230-1°. Butyl bromide salt, m. 234-5°.	63
$C_{21}H_{30}N_2O_2$		m. 163-4°. HCl salt, m. 225-8°. Methobromide, m. 243-4°.	63

$C_{21}H_{39}N_3O_3$	3-Carboxymethyl-2-[(N-(5-diethylamino-2-pentyl)-carboxamido]-	b_{03} 190-1°.	70
$C_{22}H_{24}ClN_3O$	2-(3-Chloro-7-methoxyacridinylamino-methyl)-	m. 157°. Tri-HCl salt, m. 282°.	57
$C_{22}H_{23}NO_2$	3-Diphenylacetoxy-3-methyl-	m. 88-9°. Sulfate, m. 205-6°. Methobromide, m. 176-7°.	62
$C_{22}H_{26}N_2O_2$		m. 139-40°. HCl salt, m. 220-1°.	63
$C_{22}H_{26}N_2O_3$		Two forms: m. 166-7.5° and m. 111-22°.	63
$C_{22}H_{41}N_3O_4$	2-(2-Diethylaminoethoxycarbo)-3-(2-diethylaminoethoxycarbomethyl)-	b_{03} 187-9°. Trimethiodide, d. 197-9°.	16
$C_{23}H_{28}N_2O_4$		HCl salt, m. 221.5-2°.	63
$C_{24}H_{27}NO_2$		HCl salt, m. 185-91°.	60
$C_{24}H_{33}N_3$	3-(2-Benzylaminoethyl)-2-benzylamino-methyl-	b_{03} 230-2°.	71
$C_{28}H_{29}NO_2$	2-Benzyl-3-diphenylacetoxy-	HCl salt, m. 250-2°.	60

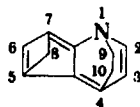
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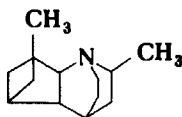
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B-88. 1,4-Ethano-5,7-methano-1-pyridine. R.I. 2208



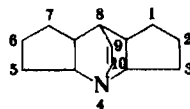
One of the bases isolated from California petroleum is the product (m. 24.5°; b_{750} 225.6°; n_D^{25} 1.4833; n_D^{30} 1.4811; d_4^{20} 0.8700; picrate, m. 158.7°; bisulfate, m. 155°; chloroplatinate, m. 205°d.; mercuric chloride-hydrochloride complex, m. 131.6°) $C_{13}H_{21}N$, which was assigned ^{1,2} structure I. There is little to support such a structure assignment, and it is almost certainly incorrect. See Sections B-21 and B-89/91.



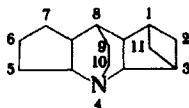
(I)

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B-89. 4,8-Ethenopyrindacine. R.I. 2318

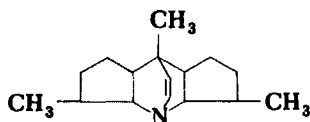
and

B-90. 4,8-Ethano-1,3-methanodicyclopenta[*b,e*]pyridine

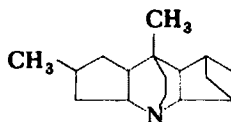
and

B-91. 4,8-Ethano-3,8 α -methanodicyclopenta[*b,e*]pyridine. R.I. 2876

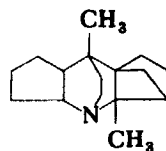
A basic product (b_{746} 278.2°; d_4^{20} 0.9391; n_D^{20} 1.5129; picrate, m. 151°; hydrochloride, m. 251°; bisulfate, m. 196°; nitrate, m. 141°; methiodide, softens at $\sim 250^\circ$ and decomposes without melting; chloroplatinate, d. 240°; mercuric chloride complex, m. 157.5°; zinc chloride complex, m. 171°) analyzing for $C_{16}H_{25}N$ was isolated^{1,4} from California petroleum, and was assigned successively structures I,¹ II² and III.³



(I)

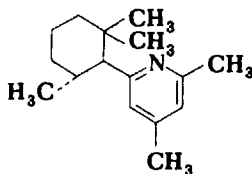


(II)



(III)

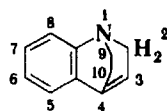
This product was shown subsequently^{5,6} to have structure IV.



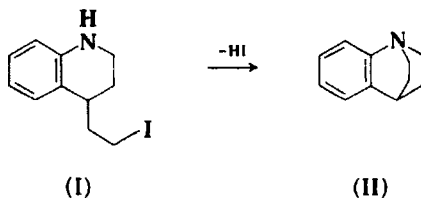
(IV)

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B-92. 2H-1,4-Ethanoquinoline. R.I. 1961

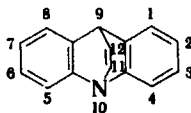
The above name and numbering are currently used by *Chemical Abstracts*, but the nucleus was previously named *benzoquinuclidine*. Treatment of I with a base resulted in the formation¹ of II (m. 68–9°; $pK_a^{25^\circ}$ 7.79; picrate, m. 195–6°; chloroplatinate, sinters at $\sim 225^\circ$ and d. 230° ; ethiodide, m. 217–8°). The absence of appreci-



able resonance interaction (because of noncoplanarity) between the nitrogen atom and the aromatic ring was demonstrated by studies of the ultraviolet absorption spectrum² and base strength³ of II.

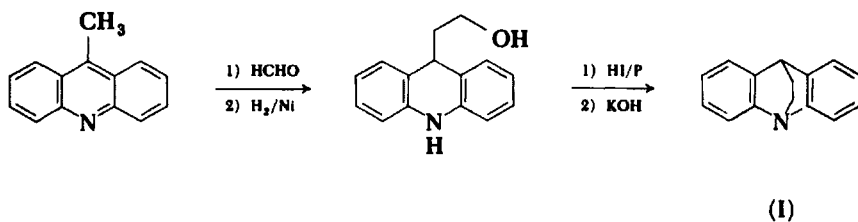
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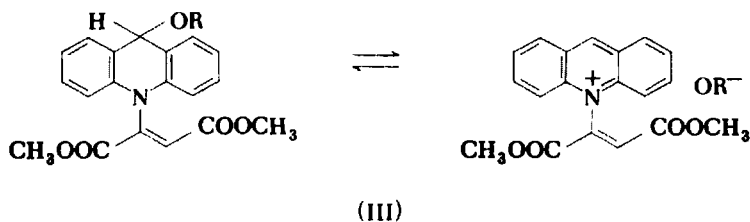
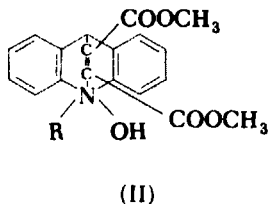
B-93. 9H-9,10-Ethenoacridine

The 11,12-dihydro derivative of this nucleus is also called *dibenzoquinuclidine*.

Van der Krogt and Wepster¹ obtained I (m. 111–2°; $pK_a^{25^\circ}$ 4.46 in water) by the reactions shown, and measured its ultraviolet spectrum to demonstrate the lack of resonance interaction between the nitrogen atom and the benzenoid rings.



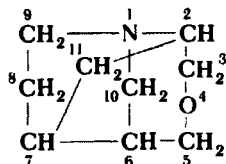
Diels and Thiele² treated acridine in alcoholic solutions with acetylenedicarboxylic ester and obtained red adducts, which they considered to have structure II ($R = CH_3$, m. 104°; $R = C_2H_5$, m. 71°). However, recently Acheson and Burstall³ obtained evidence that these adducts have structure III.



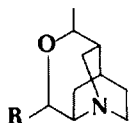
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**B-94. 4-Ox-1-azatricyclo-
[4.3.1.1^{2,7}]hendecane.
R.I. 2039 and 2042**



The acid-catalyzed internal cyclization of the alkaloid *cinchonine* yields two epimeric compounds, α -, and β -*isocinchonine*, having structure I (R = 4-quinoly). This cyclization has been discussed briefly by Turner and Woodward.¹

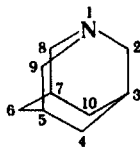
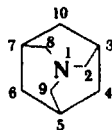
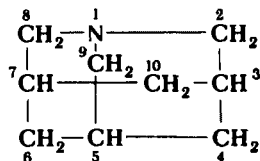


(I)

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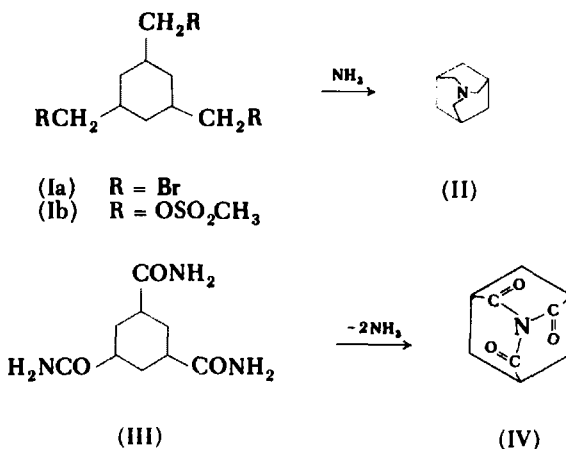
B-95. 1-Azatricyclo[3.3.1.1^{3,7}]decane



The three structures shown are equivalent, and this nucleus is often referred to as *1-azaadamantane*.

By converting trimesic acid into Ia, and treatment of this with ammonia, Lukeš and Galík^{1,2} and Fusco and Biachetti^{3,5} succeeded

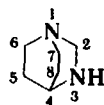
in preparing II (m. 257–8°; picrate, m. 300–1°). Newman and Lowrie⁴ attempted a similar ammonolysis of Ib, but evidently failed to obtain II. Their efforts to prepare IV from III were also without success.⁴



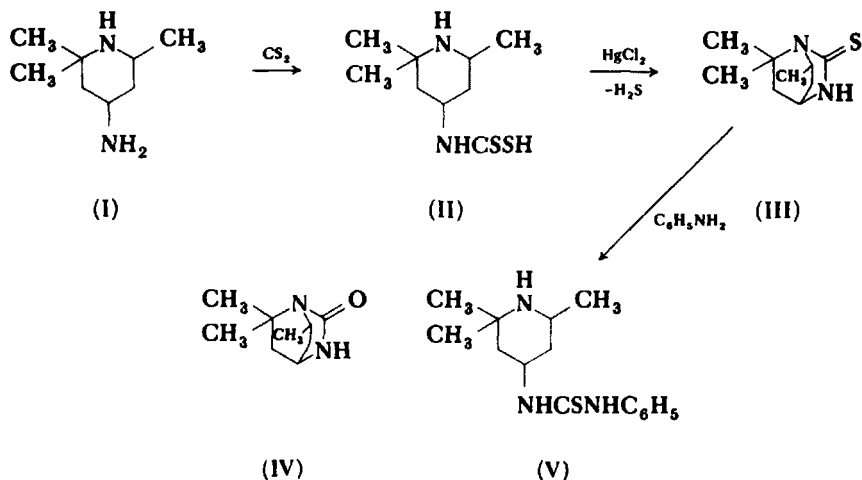
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5. Fusco and Bianchetti, *Atti accad. nazl. Lincei, Rend., Classe sci. fis., mat. e nat.*, **15**, 420 (1953); *Chem. Abstracts*, **49**, 6264 (1955).

B-96. 1,3-Diazabicyclo[2.2.2]-octane. R.I. 973



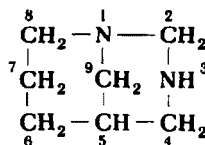
The reaction of the amine I with carbon bisulfide yielded the dithiocarbamic acid II, which was converted¹ into III (m. 77–8°; hydrochloride, m. 254–5°; chloraurate, m. 108–9°) by treatment with mercuric chloride. Efforts to convert III into IV by treatment with mercury oxide yielded² only I. The reaction¹ of an ethanolic solution of III with aniline gave V.



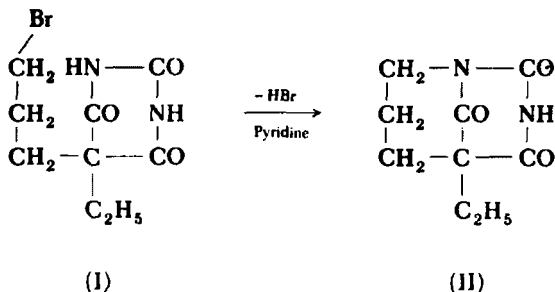
References

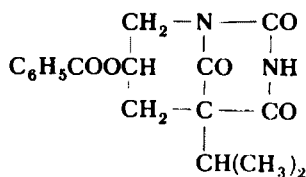
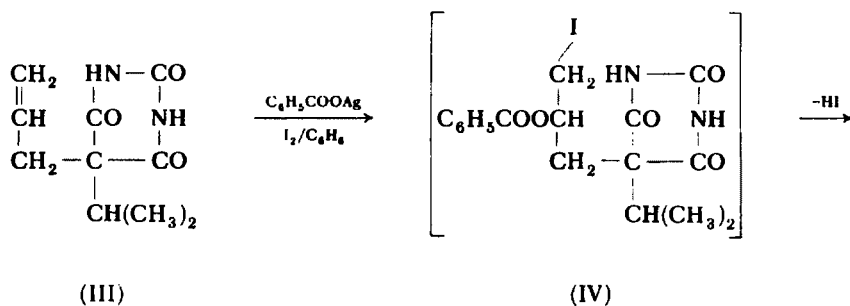
1. Harries, *Ann.*, **294**, 336 (1897).
2. Harries, *Ann.*, **417**, 107 (1918).

B-97. 1,3-Diazabicyclo[3.3.1]nonane



Compound II (m. 346–50°d.) was reported¹ to result from the cyclodehydrohalogenation of I. Similarly, the Prevost oxidation of III yielded² a product thought to be V (m. 172.0–3.5°), presumably formed via the intermediate IV.



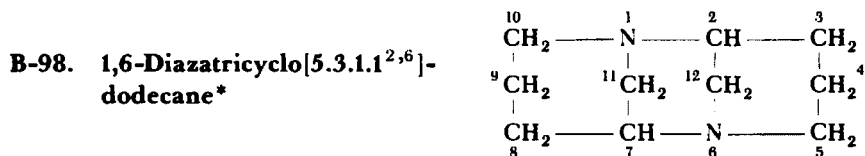


(V)

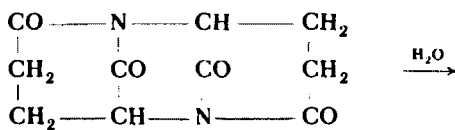
These products would seem to be examples of the "forbidden" bridgehead amide type.³ Although many 5,5-dialkylbarbituric acids exhibit hypnotic activity, compound II appeared inactive.

References

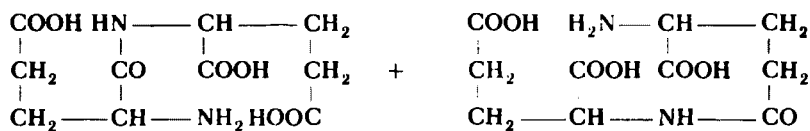
1. Baumler, Sarkin and Erlenmeyer, *Helv. Chim. Acta*, **34**, 459 (1951).
2. Meltzer and Lewis, *J. Org. Chem.*, **21**, 256 (1956).
3. Lukeš, *Collection Czechoslov. Chem. Commun.*, **10**, 148 (1938).



By heating glutamic acid in glycerol at 150°, Blanchetière^{1,2} obtained a product which he considered to have structure I. The product gave a negative biuret test, and on alkaline hydrolysis yielded two glutamylglutamic acids II and III. Further information would be welcome.



(I)



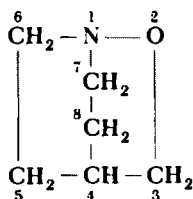
(II)

(III)

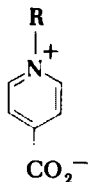
References

1. Blanchetière, *Bull. soc. chim. France*, [4]31, 1045 (1922); *Chem. Zentr.*, **III**, 1084 (1923).
2. Blanchetière, *Bull. soc. chim. France*, [4]35, 1317 (1924); *Chem. Zentr.*, **I**, 220 (1925).

B-99. 2-Ox-1-azabicyclo[2.2.2]octane.
R.I. 942



Betaines^{1,2} of type I were considered by the *Ring Index* to represent this ring system.

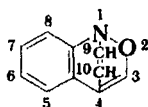


(I)

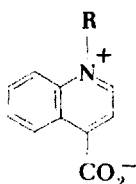
References

1. Ternárgó, *Monatsh.*, **21**, 446 (1900).
2. Camps, *Arch. Pharm.*, **240**, 345 (1902).

B-100. 1,4-Etheno-2,1-benzoxazine.
R.I. 1840



Cinchoninic acid betaines¹⁻³ of type I were considered by the *Ring Index* to represent this nucleus. No true examples have been reported.

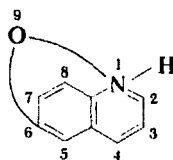


(I)

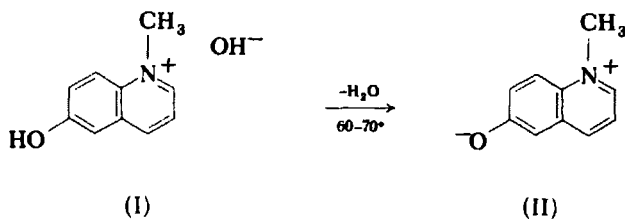
References

1. Claus, *Ann.*, **270**, 335 (1892).
2. Decker and Remfry, *J. prakt. Chem.*, **79**, 335 (1909).
3. Meyer, *Monatsh.*, **24**, 195 (1903).

B-101. 1(1H),6-Epoxyquinoline.
R.I. 1841



Thermal dehydration of I yielded^{1,2} II, considered by the *Ring Index* to represent this nucleus.



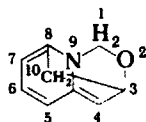
(I)

(II)

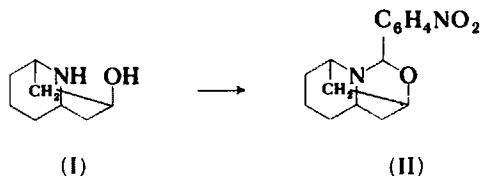
References

1. Decker and Engler, *Ber.*, **36**, 1169 (1903).
2. Claus and Howitz, *J. prakt. Chem.*, **43**, 505 (1891).

B-102. 3,8-Methano-1*H*,3*H*-pyrid-[1,2-*c*]-*m*-oxazine



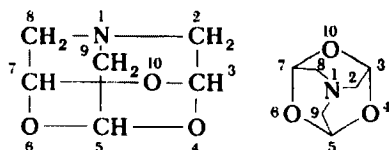
The reaction of I with *p*-nitrobenzaldehyde is reported¹ to yield II (m. 132–3°).



Reference

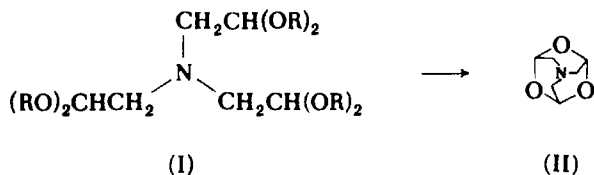
1. Alder and Dortmann, *Chem. Ber.*, **86**, 1544 (1953).

**B-103. 4,6,10-Triox-1-azatricyclo-[3.3.1.1^{3,7}]decane.
R.I. 1826 and 1834**



The first *Ring Index* number (1826) lists this ring system as C₃O₃-C₄NO-C₄NO, while the second (1834) classifies it as C₄NO-C₄NO-C₄NO. The nucleus has also been called *trimorpholine* and *azaparacetaldehyde*. The two structures shown are equivalent.

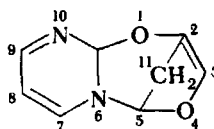
Treatment¹ of the acetal I with hydrochloric acid causes hydrolysis and dehydration, yielding II (becomes yellow at ~180°, and decomposes without melting at 210–20°; hydrochloride, d. ~255–60°; nitrate, d. ~240°; picrate, m. 210°; hydrochloride-mercuric chloride complex, d. >260°; hydrochloride-aurichloride complex, darkens without melting up to 220°; methiodide, d. >270°; methochloride, d. 308°; quaternary methyl hydroxide, m. 76–8°). The crystal structure of II has been studied extensively.¹



Reference

1. Wolff and Marburg, *Ann.*, **363**, 169 (1908).

B-104. 2,5-Methano-5H-pyrimido-[2,1-b][1,5,3]dioxazepine

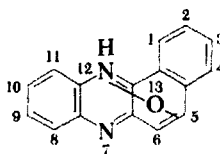


Cyclothymidines were reported¹ to be derivatives of this nucleus.

Reference

1. Michelson and Todd, *J. Chem. Soc.*, **1955**, 816.

B-105. 5,12(12H)-Epoxybenzo[a]-phenazine. R.I. 3197



The *Ring Index* lists anhydro derivatives¹ of type I (R = NH₂, N(Me)₂, etc.) as representatives of this nucleus.

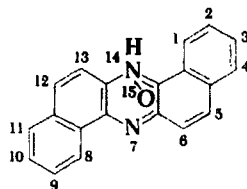


(I)

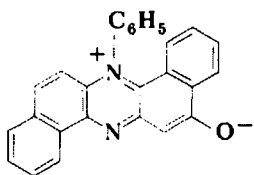
Reference

1. Kehrmann and Aebi, *Ber.*, **32**, 932 (1899).

B-106. 5,14(14H)-Epoxydibenzo[a,h]-phenazine. R.I. 3574



The "anhydro" compound I¹ was listed by the *Ring Index* as an example of this nucleus.

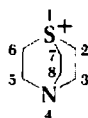


(I)

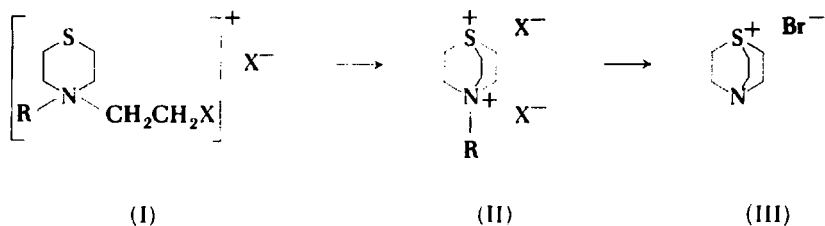
Reference

1. Kehrman and Sutherst, *Ber.*, **32**, 939 (1899).

B-107. 1-Thionia-4-azabicyclo[2.2.2]-octane*



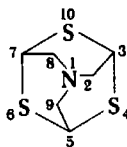
When I ($R = H$, $X = Cl$, or Br) was heated with hydrochloric or hydrobromic acid, respectively, II [$R = H$, $X = Cl$, m. $210-12^\circ$ ($208-10^\circ$); $R = H$, $X = Br$, m. $241-2^\circ$; $R = H$, $X = \text{picrate}$, m. $210-5^\circ$ d.] was obtained in good yield.¹ Treatment of II ($R = H$, $X = Br$) with silver oxide gave III (instantaneous m.p. $\sim 250^\circ$ d.). A quaternary salt of structure II ($R = CH_3$, $X = Br$, m. 270° d.) was obtained from I ($R = CH_3$, $X = Br$) in 92% yield.



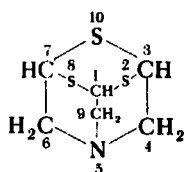
Compound III showed an LD_{50} of 80-100 mg./kg. when injected intraperitoneally into white mice, while the quaternary salt II ($R = CH_3$, $X = Br$) was non-toxic up to 100 mg./kg. under these conditions.

Reference

1. Cockburn and McKay, *J. Am. Chem. Soc.*, **77**, 397 (1955).

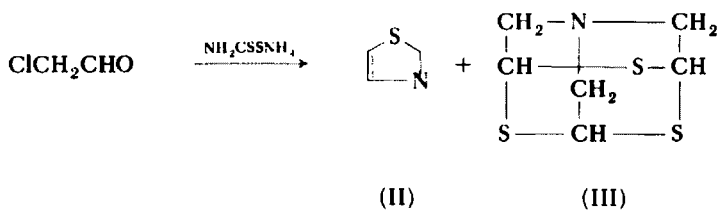
B-108. 4,6,10-Trithia-1-azaadamantane

This nucleus has also been named *5-aza-2,8,10-trithiaadamantane* (numbered as shown in I) and *trithiotrimorpholine*.



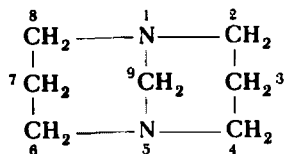
(I)

Accompanying the major product (II) of the reaction of chloroacetaldehyde with ammonium dithiocarbamate was a by-product (m. 147–8°) considered,¹ on the basis of its formula ($C_6H_9NS_3$) and infrared spectrum, to have structure III. Ammonium dithiocarbamate can, of course, readily decompose to, *inter alia*, ammonia and hydrogen sulfide. It was suggested¹ that the chloroacetaldehyde reacts with ammonia to yield nitrilotrisacetaldehyde, which then forms III by reaction with hydrogen sulfide.

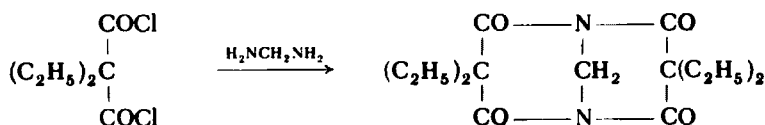
*Reference*

1. Craig, Shipman, Hawthorne and Fowler, *J. Am. Chem. Soc.*, **77**, 1283 (1955).

**B-109. 1,5-Diazabicyclo[3.3.1]nonane.
R.I. 962**



By reacting certain amides with formaldehyde and then hydrolyzing the resulting methylenebisamides, Einhorn and Mauermayer¹ prepared methylenediamine, which reacted with diethylmalonyl chloride to yield I (m. 138°).



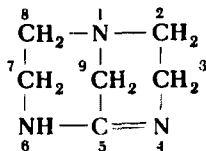
(I)

If structure I is accurate, it would seem to be one of the few examples of "bridgehead amides."²

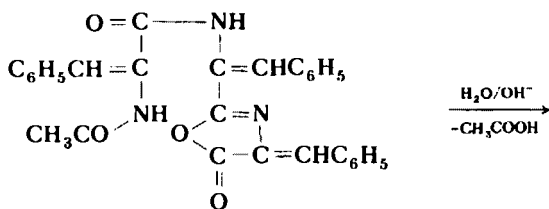
References

1. Einhorn and Mauermayer, *Ann.*, **343**, 282 (1905).
2. Lukes, *Collection Czechoslov. Chem. Commun.*, **10**, 148 (1938).

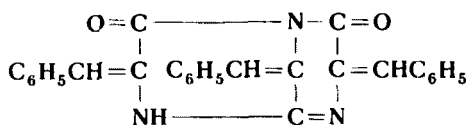
B-110. 1,4,6-Triazabicyclo[3.3.1]-4-nonene



When I was dissolved in an aqueous-acetone solution of caustic, a very small yield of a yellow crystalline material ($\text{C}_{27}\text{H}_{19}\text{N}_3\text{O}_2$, m. 288–9°d.) separated.¹ Structure II was assigned¹ to this product. In addition to violating Bredt's rule,² structure II has little in its favor over several of the other conceivable formulations, and further evidence would be welcome.



(I)

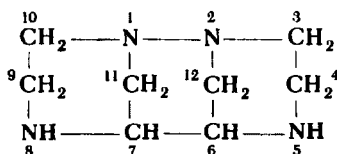


(II)

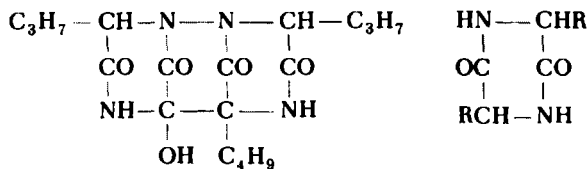
References

1. Tietzman, Doherty and Bergmann, *J. Biol. Chem.*, **151**, 387 (1943).
2. Fawcett, *Chem. Rev.*, **47**, 219 (1950).

B-111. 1,2,5,8-Tetrazatricyclo-
[5.3.1.1^{2,6}]dodecane.
R.I. 1870



Treatment of valyl-leucine anhydride (obtained from the hydrolysis of goose feathers) with cold concentrated hydrochloric acid was claimed¹ to yield a "dipeptine" assigned structure I. The term peptine refers to a diketopiperazine such as II. Even if the formation



(I)

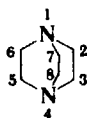
(II)

of a nitrogen-nitrogen bond in I is ignored, structure I seems improbable.

Reference

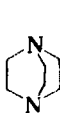
1. Salikov and Zelinskii, *Biochem. Z.*, **147**, 30 (1924); *Chem. Abstracts*, **19**, 994 (1925).

B-112. 1,4-Diazabicyclo[2.2.2]octane

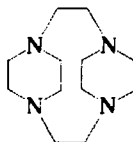


This nucleus is also known as *triethylenediamine*.

As long ago as 1859 A. W. von Hofmann became interested in triethylenediamine (I), and thought¹ that he had obtained it by the interaction of ethylene bromide with ammonia. Harries, who at that time was Hofmann's assistant, later² declared that the product obtained was probably hexaethylenetetramine (II, see Section B-131). Ladenburg³ attempted without success to bridge the two nitrogen atoms in piperazine, and Cherbuliez and Feer⁴ were unable to make 1,4-diazabicyclo[2.2.2]octane-2,5-dione from 1,4-bischloromethyldiketopiperazine.

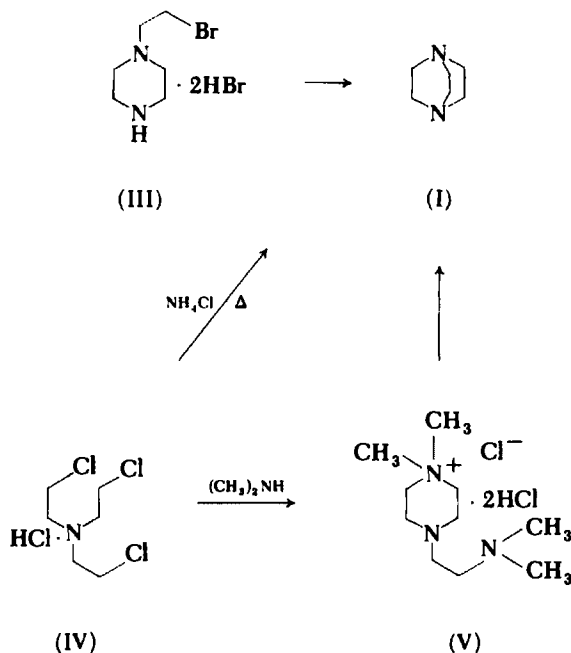


(I)

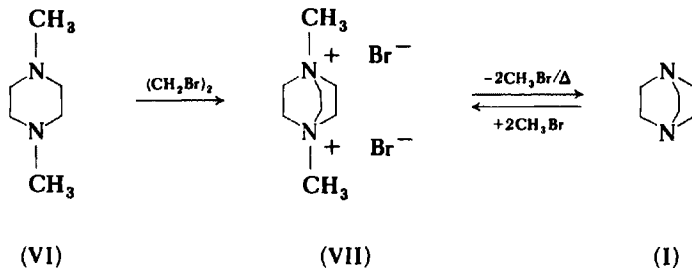


(II)

Treatment of III with caustic solution, a method analogous to those often used for the preparation of nuclei closely related to I, was, oddly, unsuccessful.⁵ However, the pyrolysis^{6,7} of III produced a mixture of products containing about 28% of I. Triethylenediamine is also obtained in about 2% yield by the pyrolysis of diethanolamine hydrochloride; in unspecified yield by heating triethanolamine with ammonium chloride;⁸ in 11% yield by heating IV with ammonium chloride,⁹ and in unspecified yield from the pyrolysis of V.¹⁰ Passage of *N,N'*-bis(2-hydroxyethyl)-piperazine over an alumina-silica catalyst at 325° is reported¹² to give a low yield of I.

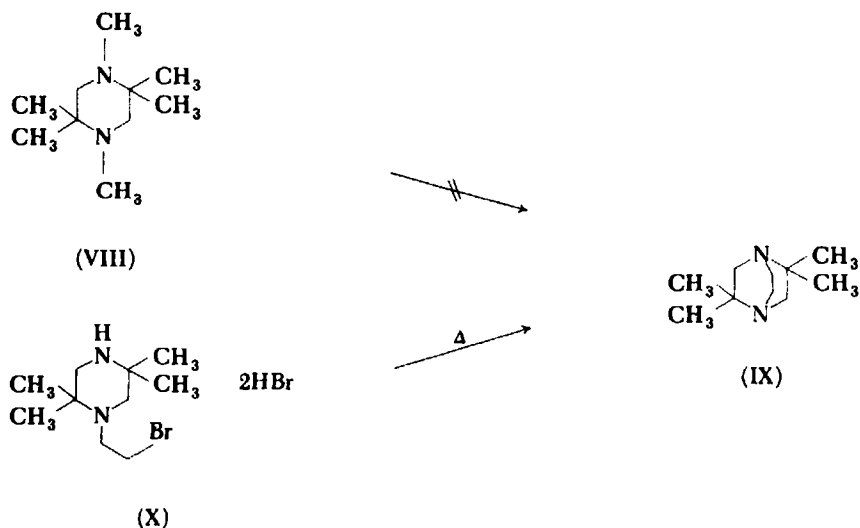


Probably the most convenient synthesis, and the one offering the lowest production of by-products, is that proceeding from dimethylpiperazine (VI). Reaction with ethylene bromide¹⁰ gives a 70% yield⁹ of VII, which can be pyrolyzed⁹ to I in 70% yield. In isolating I from reaction mixtures, secondary amines are usually removed from the crude mixture of bases by acylation. Hromatka introduced the technique of isolating I as the *p*-nitrophenolate⁸ or 2,4-dinitrophenolate⁹ salt. This last synthesis may not have wide general applicability since it was not found possible⁷ to prepare a bisquaternary analogous to VII from ethylene bromide and dibenzylpiperazine.



Triethylenediamine is a volatile solid, m. 158–60° in a sealed capillary, and gives the following derivatives: dihydrochloride, m. 310–1°D. (m. 290°d.),¹⁰ diperchlorate, m. 179–80°; dipicrate, m. 298°; acid oxalate, m. 287°d.; phenolate, m. 123°; *p*-nitrophenolate, m. 184–5° (183°);⁸ 2,4-dinitrophenolate, m. 159°; styphnate, d. > 280°; dimethobromide, m. 335°d. (298–300°d.);⁹ dimethopicrate, m. 331°d. Slightly different values for most of these melting points have recently been reported by Mann and Baker.¹⁷

Attempts^{7,18} to obtain IX by treatment of VIII with ethylene bromide failed because no quaternary salt could be produced. However, IX was isolated⁷ in less than 1% yield as the dipicrate salt (m. 250.2°) from the pyrolysis products of X. Compound IX is of interest because, like Troeger's base (see Section B-115), it should be resolvable into diastereoisomeric modifications.

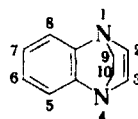


The Hofmann degradation of VII was shown¹¹ to yield VI and acetaldehyde. The stability of the complex formed between I and silver ions has been measured,^{13,14} and I has been evaluated¹⁵ as a decontaminating agent for mustard gas. The catalytic effect of the copper complex of I upon the decomposition of hydrogen peroxide has been studied.¹⁶

References

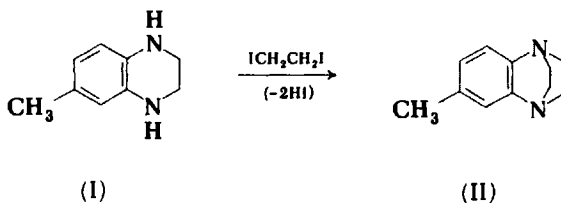
1. Hofmann, *Proc. Roy. Soc.*, **9**, 153 (1859).
2. Harries, *Ann.*, **294**, 350 (1897).
3. Ladenburg, *Ber.*, **30**, 1587 and 3043 (1897).
4. Cherbuliez and Feer, *Helv. Chim. Acta*, **5**, 678 (1922).
5. Prelog, Cerkovnikov and Ustricev, *Ann.*, **535**, 37 (1938).
6. Hromatka and Engel, *Ber.*, **76**, 712 (1943).
7. McElvain and Bannister, *J. Am. Chem. Soc.*, **76**, 1126 (1954).
8. Hromatka, *Ber.*, **75**, 1302 (1942).
9. Hromatka and Kraupp, *Monatsh.*, **82**, 880 (1951).
10. Mann and Mukherjee, *J. Chem. Soc.*, **1949**, 2298.
11. Hromatka and Skopalik, *Monatsh.*, **83**, 38 (1952).
12. Ishiguro, Kitamura, Matsumara and Ogawa, *J. Pharm. Soc. Japan*, **75**, 1370 (1955); *Chem. Abstracts*, **50**, 10106 (1956).
13. Schwarzenbach, Maissen and Ackermann, *Helv. Chim. Acta*, **35**, 2333 (1952).
14. Schwarzenbach, *Helv. Chim. Acta*, **36**, 23 (1953).
15. Stora and Genin, *Bull. soc. chim. France*, **1949**, 72.
16. Nikolaev, *Zhur. Fiz. Khim.*, **28**, 275 (1954); *Chem. Abstracts*, **49**, 5941 (1955).
17. Mann and Baker, *J. Chem. Soc.*, **1957**, 1881.
18. Mann and Senior, *J. Chem. Soc.*, **1954**, 4476.

B-113. 1,4-Ethanoquinoxaline. R.I. 1883



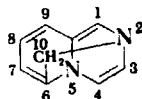
Moore and Doubleday¹ obtained a product (m. 175°d.) with structure II from the reaction of ethylene iodide with 1,2,3,4-tetrahydro-6-methylquinoxaline (I). It forms both mono- and dibasic salts.

However, the failure of 1,2,3,4-tetrahydroquinoxaline to yield 1,4-ethanoquinoxaline by reaction with ethylene dibromide, ethylene chlorobromide or ethylene chlorohydrin, has been recorded.²

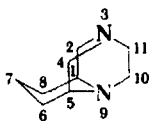


References

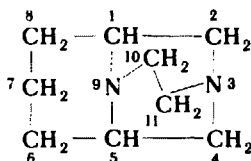
1. Moore and Doubleday, *J. Chem. Soc.*, **119**, 1170 (1921).
2. Meisenheimer and Wieger, *J. prakt. Chem.*, [2]**102**, 45 (1921).

B-114. 2,6-Methano-2H-pyrido[1,2]-pyrazine


The perhydro derivative of this nucleus has been called 3,9-diazatricyclo[3.3.1.2^{3,9}]undecane, and written as I identical with II.

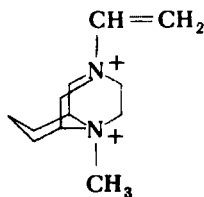


(I)

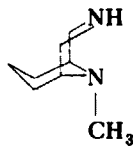


(II)

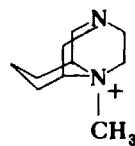
Treatment of III with ethylene bromide at 40° yielded the bromide of a product considered to have structure IV (bromide, m 243–7°; picrate, yellow, m. 275–80°d.). The reaction of III with excess ethylene bromide at 130° yielded a different product (dipicrate, yellow, m. 272–80°) thought to be V.



(V)



(III)

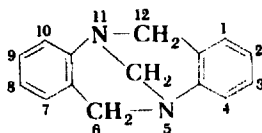


(IV)

Reference

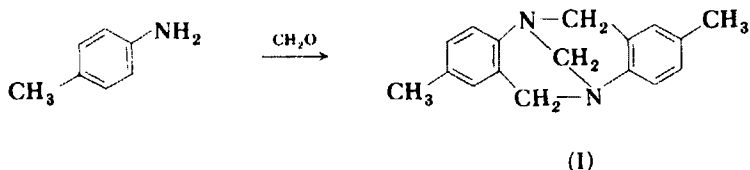
1. Fales and Barnes, *J. Am. Chem. Soc.*, **76**, 1947 (1954).

**B-115. 5,11 (6H,12H)-Methanodibenzo-
[b,f][1,5]diazocine. R.I. 2651**



This ring system has also been called *5:11-endomethylene-5:6:11:12-tetrahydrophenhomazine*, and the 2,8-dimethyl derivative is generally known as *Troeger's* (or *Tröger's*) *base*.

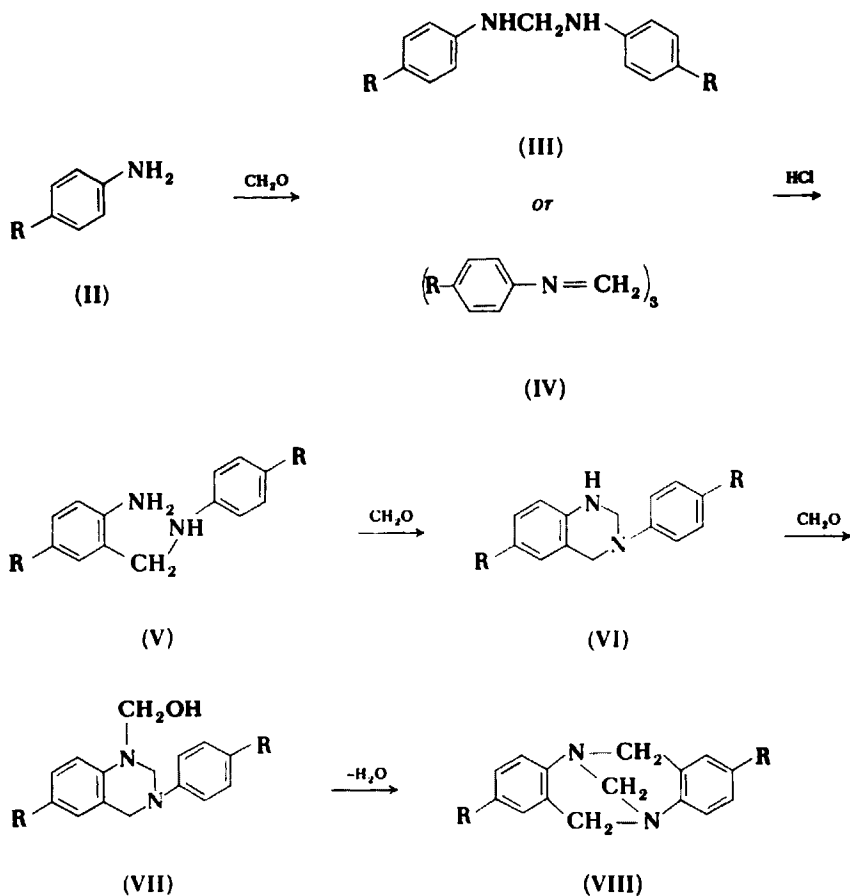
From the reaction of *p*-toluidine with methylal in hydrochloric acid solution, Troeger¹ isolated a crystalline base, m. 134°, of the formula C₁₇H₁₈N₂. The same base was subsequently obtained by others²⁻⁷ via several superficially different methods. There was some initial disagreement regarding the empirical formula and identity of these products, since other basic products were usually obtained with Troeger's base. However, the accuracy of Troeger's formula was finally confirmed,^{6,7} and Spielman⁸ proposed formula I for Troeger's base.



The mode of formation of Troeger's base was studied by Spielman⁸ and by Wagner,^{9,10} who showed that the same product could be obtained from either II, III, IV, V or VI (R = CH₃) by reaction with sufficient formaldehyde.

The scope of this condensation was investigated by Miller and Wagner,¹⁰ who showed that amines of type II gave VIII when R was a methyl, methoxyl or ethoxyl group, but that with amines in which R was a bromine or chlorine atom, the final reaction product was VII and not VIII. The condensation of *p*-anisidine^{5,11} and *p*-phenetidine^{5,6,11-15} with formaldehyde had been the subject of earlier investigations, but as in each case a mixture of bases was obtained, there was some dispute regarding the nature of the products.

The preparation of Troeger's base by the condensation of IX (R = CH₃) with formaldehyde was considered by Wagner,⁹ but

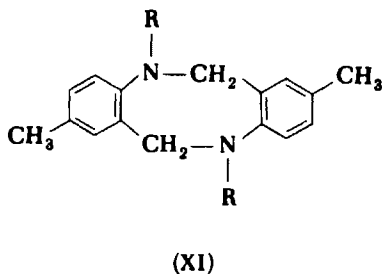
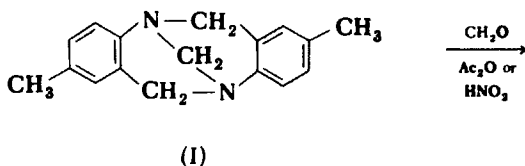


compounds of type IX were not then available. Recently, Cooper and Patridge^{16,23} succeeded in preparing IX ($R = \text{H}$ or CH_3) conveniently (paradoxically, from Troeger's base itself!), and condensed it ($R = \text{CH}_3$) with a variety of aldehydes and ketones to obtain X. While phosgene and ethyl carbonate failed to react with IX ($R = \text{CH}_3$), ethyl orthoformate reacted²³ to give X ($R = \text{CH}_3$, $R' =$

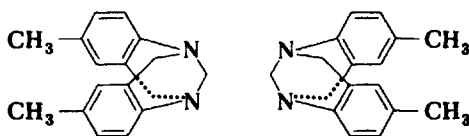


H, $R'' = OC_2H_5$). N,N' -Disubstituted derivatives, but no products of type X, were obtained from the reaction of IX with phenyl isocyanate, phenyl isothiocyanate, potassium cyanate, potassium thiocyanate or malonic ester.

Troeger obtained new derivatives from the reaction of I with acetic anhydride or with nitrous acid. This at first appeared inconsistent with the formulation of Troeger's base as I. However, Spielman⁸ showed that I reacts with these reagents by losing CH_2 (as formaldehyde) to give XI ($R = NO$ or CH_3CO). Other products of these types have also been obtained.^{10, 16}



Over the years, much time and thought have been devoted to the problem of resolving into optical isomers compounds containing an asymmetric nitrogen atom. It occurred to Prelog and Wieland¹⁷ that Troeger's base was ideally constituted for this purpose. In it, the customary oscillation of the nitrogen atom (through the plane of the substituent groups) would be prevented by the rigidity of the molecule. Using powdered *d*-lactose hydrate as an adsorbant, they were able, by chromatographic techniques, to resolve Troeger's base



into the *dextro* ($[\alpha]_D^{17} = +287^\circ (\pm 7^\circ)$, m. $126.0-7.5^\circ$) and *levo* ($[\alpha]_D^{17} = -278^\circ (\pm 7^\circ)$, m. $127-8^\circ$) forms. Mixture of the two antipodes regenerated the racemate (m. $136-7^\circ$).

The small extent of resonance interaction between the nitrogen atoms and the aromatic ring of Troeger's base was demonstrated¹⁹ by measurement of the ultraviolet spectrum^{16,19} and base strength¹⁹ (pK_a $25^\circ = 3.2$). Troeger's base and two homologs showed²³ slight antibacterial and antifungal activity, but no antiviral or antiprotozoal activity.

Derivatives of 5,11 (6*H*,12*H*)-Methanodibenzo[*b,f*][1,5]diazocine

Empirical formula	Substituents	Properties	Refs.
$C_{15}H_{14}N_2$	Unsubstituted	m. $138-9^\circ$. HCl salt shrinks $\sim 250^\circ$, but darkens unmelted $< 300^\circ$. Picrate, m. $190-1^\circ$.	16
$C_{17}H_{18}N_2$	2,8-Dimethyl- (Troeger's Base)	m. $137-8^\circ$ (136° , 135°) HCl salt, m. 215° (213°). Sulfate, m. 93° . Picrate, m. $188-9^\circ$ (186° , 172.6°). Monoquaternary cyclohexyl chloride, m. 240° d. Monoquaternary <i>p</i> -phenylphenacyl bromide, m. $249.5-50^\circ$.	1-10,16-19, 21,23
$C_{17}H_{18}N_2O_2$	2,8-Dimethoxy-	m. $172.0-2.5^\circ$. HCl salt, m. $213-5^\circ$ unc. Picrate, m. $207.5-8.5^\circ$.	5,10,11
$C_{19}H_{22}N_2$	13-Ethyl-2,8-dimethyl-	m. $80-1^\circ$.	23
	2,8,13,13-Tetramethyl-	m. $118-9^\circ$.	23
$C_{19}H_{22}N_2O$	13-Ethoxy-2,8-dimethyl-	m. $114-6^\circ$; λ_{max} 208, 238, 284 $m\mu$. ($\epsilon = 22,900, 8400, 2100$).	23

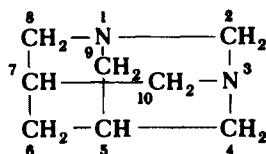
Derivatives of 5,11(6*H*,12*H*)-Methanodibenzo[*b,f*][1,5]diazocine (*continued*)

Empirical formula	Substituents	Properties	Refs.
C ₁₉ H ₂₂ N ₂ O ₂	2,8-Diethoxy-	m. 131.5–2°. HCl salt, m. 236–40°. Picrate, m. 196.5–7. Nitrate, m. 159°.	5,6,10–15
C ₂₀ H ₂₂ N ₂	2,8-Dimethyl-13-propenyl-	m. 121–2°	23
C ₂₁ H ₂₀ N ₂ O	13-(2-Furyl)-2,8-dimethyl-	m. 135.0–5.5°.	23
C ₂₁ H ₂₆ N ₂ O ₂	2,8-Dihydroxy-1,3,4,7,9,10-hexamethyl-	m. 279–80° d.	20
C ₂₂ H ₂₆ H ₂	13,13-Pentamethylene-2,8-dimethyl-	m. 195–6°.	23
C ₂₃ H ₂₁ N ₃ O ₂	2,8-Dimethyl-13-(4-nitrophenyl)-	m. 160.5–1°.	23
C ₂₃ H ₂₂ N ₂	2,8-Dimethyl-13-phenyl-	m. 182–3°. Monopicate, m. 205–6°.	23
C ₂₃ H ₂₂ N ₂ O	13-(2-Hydroxyphenyl)-2,8-dimethyl-	m. 182.5–3.5°.	23
	13-(4-Hydroxyphenyl)-2,8-dimethyl-	m. 220–1°.	23
C ₂₃ H ₃₀ N ₂ O ₂	2,8-Dimethoxy-1,3,4,7,9,10-hexamethyl-	m. 191–2°. HCl salt, m. 224–6°.	20
C ₂₄ H ₂₂ N ₂ O ₂	13-(3,4-Methylenedioxyphenyl)-2,8-dimethyl-	m. 160–1°.	23
C ₂₄ H ₂₄ N ₂ O	13-(2-Methoxyphenyl)-2,8-dimethyl-	m. 187–9°.	23
	13-(4-Methoxyphenyl)-2,8-dimethyl-	m. 155–6°. Monopicate, m. 195–6°.	23
C ₂₅ H ₂₄ N ₂	2,8-Dimethyl-13-styryl-	m. 142–3°.	23
C ₂₅ H ₂₆ N ₂ O ₂	13-(3,4-Dimethoxyphenyl)-2,8-dimethyl-	m. 147–8°.	23
C ₂₅ H ₂₇ N ₃	2,8-Dimethyl-13-(4-dimethylaminophenyl)-	m. 178–9°. Dipicrate, m. 95–7°.	23
C ₂₆ H ₃₂ N ₂ O	2,8-Dimethyl-13-(4-n-pentyloxyphenyl)-	A glass.	23
C ₄₀ H ₃₈ N ₄	2,2',8,8'-Tetramethyl-13,13'- <i>p</i> -phenylenebis-	m. 344–6°	23
C ₄₃ H ₃₈ N ₂ O ₄	2,3,8,9-Tetrabenzoyloxy-	m. 120–2°. Methiodide dihydrate, m. 200–2°.	22

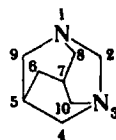
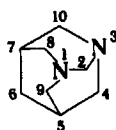
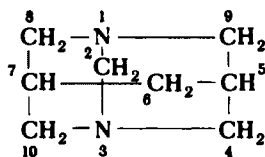
References

1. Troeger, *J. prakt. Chem.*, [2] **36**, 225 (1887).
2. Löb, *Z. Elektrochem.*, **4**, 428 (1898); *Chem. Zentr.*, **I**, 986 (1898).
3. Goecke, *Z. Elektrochem.*, **9**, 470 (1903); *Chem. Zentr.*, **II**, 238 (1903).
4. Erdmann, Ger. Pat. 122,474; *Frdl.*, **6**, 82 (1904); Fr. Pat. 301,450.
5. Lepetit and Maineri, *Atti accad. Lincei*, [5] **26**, 558 (1917); *Chem. Zentr.*, **II**, 609 (1917).
6. Lepetit, Maffei and Maineri, *Gazz. chim. ital.*, **57**, 862 (1927).
7. Eisner and Wagner, *J. Am. Chem. Soc.*, **56**, 1938 (1934).
8. Spielmann, *J. Am. Chem. Soc.*, **57**, 583 (1935).
9. Wagner, *J. Am. Chem. Soc.*, **57**, 1296 (1935).
10. Miller and Wagner, *J. Am. Chem. Soc.*, **63**, 832 (1941).
11. Goldschmidt, *Chem. Ztg.*, **21**, 395 (1897).
12. Goldschmidt, *Chem. Ztg.*, **24**, 97 (1900).
13. Goldschmidt, *Chem. Ztg.*, **25**, 178 (1901).
14. Lepetit, *Atti accad. Lincei*, [5] **26**, **I**, 172 (1917); *Chem. Zentr.*, **II**, 463 (1917).
15. Reverdin, *Helv. Chim. Acta*, **4**, 580 (1921).
16. Cooper and Partridge, *J. Chem. Soc.*, **1955**, 991.
17. Prelog and Wieland, *Helv. Chim. Acta*, **27**, 1127 (1944).
18. Havinga, *Chem. Weekblad*, **43**, 556 (1947); *Chem. Abstracts*, **43**, 9072 (1949).
19. Wepster, *Rec. trav. chim.*, **72**, 661 (1953).
20. Smith and Schubert, *J. Am. Chem. Soc.*, **70**, 2656 (1948).
21. Rutter, *J. Am. Chem. Soc.*, **74**, 3454 (1952).
22. Iwao and Kawazu, *J. Pharm. Soc. Japan*, **76**, 811 (1956); *Chem. Abstracts*, **51**, 1178 (1957).
23. Cooper and Partridge, *J. Chem. Soc.*, **1957**, 2888.

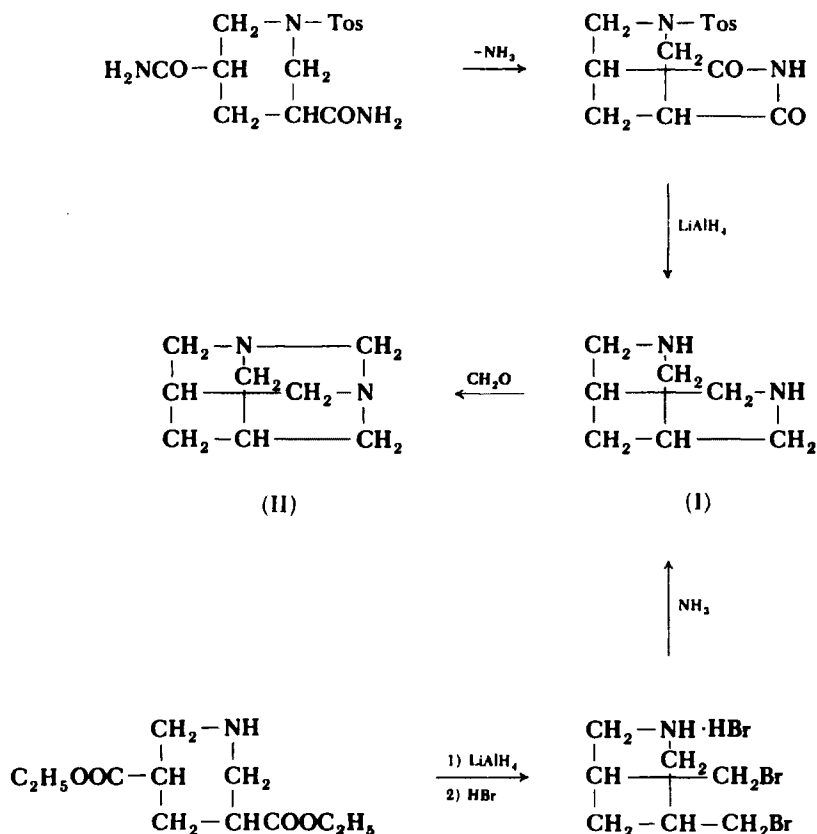
B-116. 1,3-Diazaadamantane



The structures shown are equivalent to that above, and the name *1,3-diazatricyclo[3.3.1.1^{3,7}]decane* has also been used.



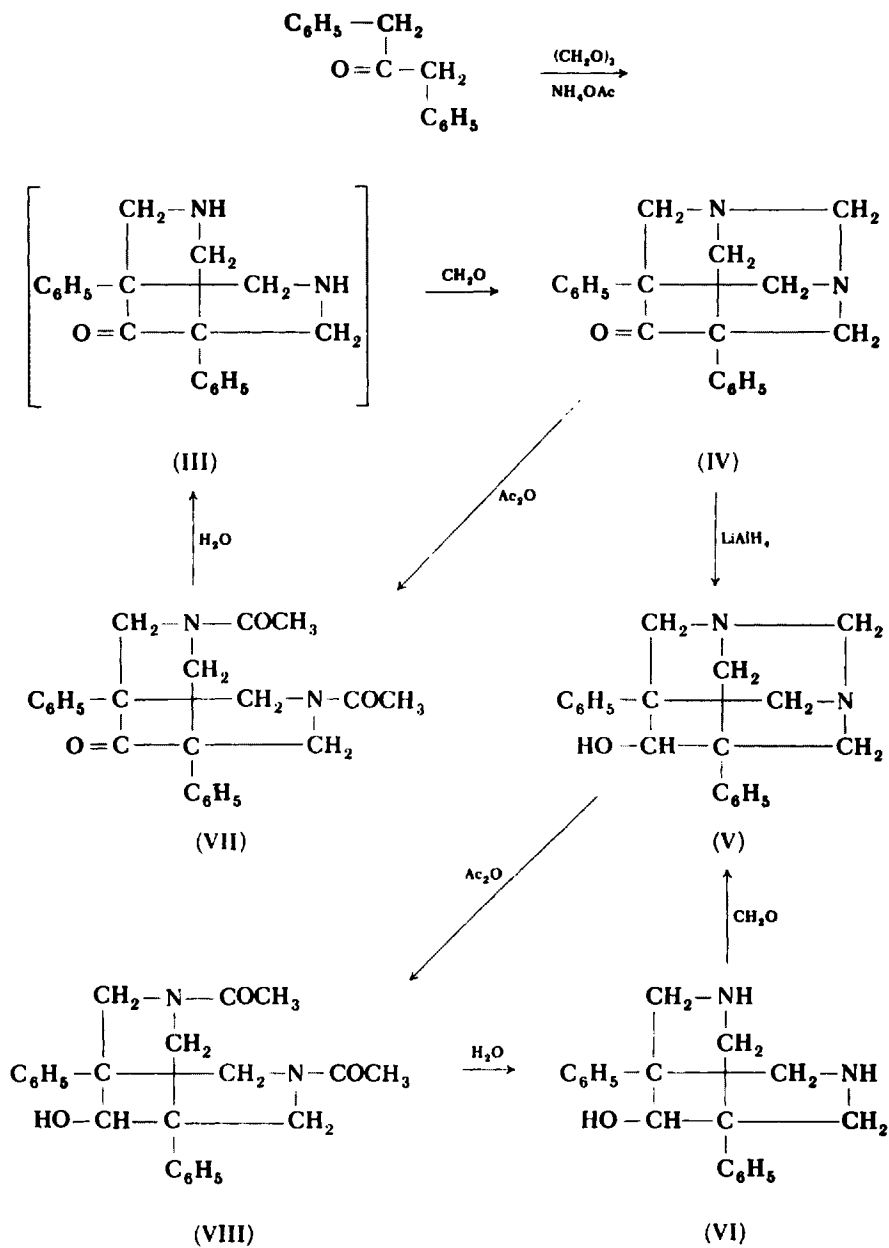
The bispidine I was prepared^{1,2} by two somewhat different routes, and converted by reaction with formaldehyde or methylene



iodide into II [m. 264–5° (260–2°); hydrochloride, m. 264–6°d.; picrate, m. 235°].

The condensation of dibenzyl ketone with formaldehyde and ammonium acetate in a Mannich reaction yielded^{3,4,7} a product (m. 256–7°; monohydrochloride, m. 251–2°) at first thought³ to be III, but later shown^{4,7} to be IV. Reduction of IV gave^{4,7} the carbinol V (m. 274°), which had been prepared previously,⁵ but was thought to have structure VI. The Wolff-Kishner reduction of IV produced⁷ 5,7-diphenyl-1,3-diazaadamantane (m. 217–9°).

Treatment of IV or V with acetic anhydride caused the elimination of formaldehyde and gave the diacetylbspidines VII and VIII. An analogous cleavage occurred⁶ in the reaction of II with *p*-toluenesulfonyl chloride. Hydrolysis of VII and VIII gave⁴ the bispidines III and VI, which could be reconverted into the tricyclic compounds

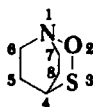


IV and V upon reaction with formaldehyde. When heated in ethanol with sodium ethoxide, IV underwent an interesting internal crossed Cannizzaro reaction to form VI (the carbonyl group being reduced by means of the formaldehyde eliminated).

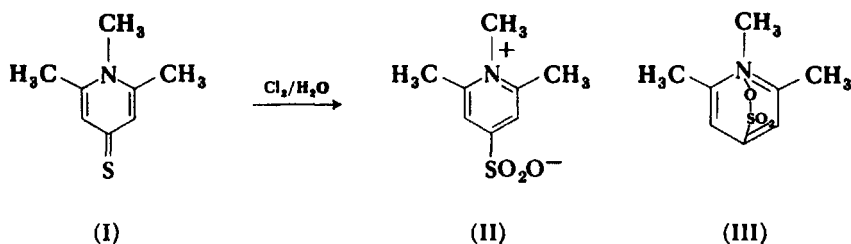
References

1. Stetter and Hennig, *Chem. Ber.*, **88**, 789 (1955).
2. Galinovsky and Langer, *Monatsh.*, **86**, 449 (1955); *Chem. Abstracts*, **50**, 11335 (1956).
3. Kyi and Wilson, *J. Chem. Soc.*, **1951**, 1706.
4. Stetter, Schäfer and Dieminger, *Angew. Chem.*, **70**, 52 (1958).
5. Chiavarelli, Settimj and Alves, *Gazz. chim. ital.*, **87**, 109 (1957).
6. Stetter and Merten, *Chem. Ber.*, **90**, 868 (1957).
7. Stetter, Schäfer and Dieminger, *Chem. Ber.*, **91**, 598 (1958).

B-117. 2-Oxa-3-thi-1-azabicyclo[2.2.2]-octane. R.I. 914



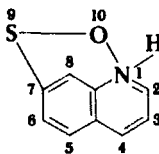
Oxidation of 1-methyl-4-thiolutidone (I) yielded the sulfobetaine II, which was once thought¹ to have structure III.



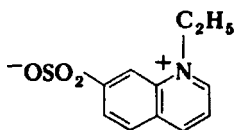
Reference

1. Michaelis and Hölken, *Ann.*, **331**, 245 (1904).

B-118. 1(1H),7-Epoxythioquinoline. R.I. 1803



The *Ring Index* considered the sulfobetaine I¹ to represent this ring system.

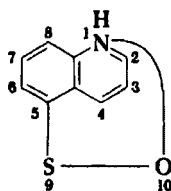


(I)

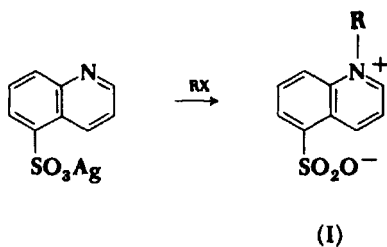
Reference

1. Claus, *J. prakt. Chem.*, **37**, 258 (1888).

**B-119. 1(1*H*),5-Epoxythioquinoline.
R.I. 1802**



Sulfobetaines of structure I¹ are the closest approach to examples of this nucleus.

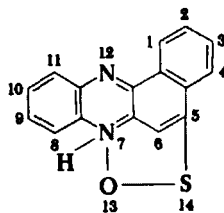


(I)

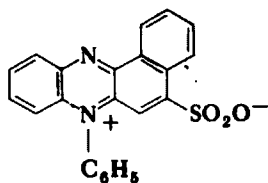
Reference

1. Claus and Steinitz, *Ann.*, **282**, 130 (1894).

**B-120. 7,5(7*H*)-Epoxythiobenzo[*a*]-
phenazine. R.I. 3185**



Compound I¹ was listed by the *Ring Index* as a representative of this nucleus.

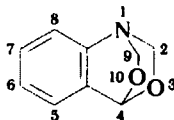


(I)

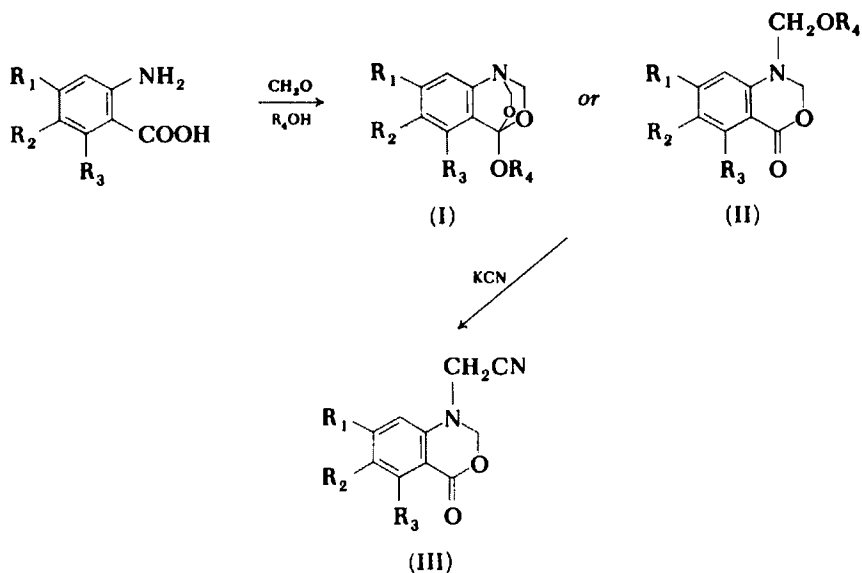
Reference

1. Kehrmann and Locher, *Ber.*, **29**, 2072 (1896).

B-121. 4,1(4)-Epoxyethano-3,1,2-benzoxazine. R.I. 1810



The reaction of dichloroanthranilic acids with formaldehyde in alcoholic solution was found by Villiger^{1,2} to yield products evidently having either structure I or II (Ia, $R_1 = H$, $R_2 = R_3 = Cl$, $R_4 = CH_3$, m. 152.5°; Ib, $R_1 = H$, $R_2 = R_3 = Cl$, $R_4 = C_2H_5$, m. 123-4°; Ic, $R_1 = R_2 = Cl$, $R_3 = H$, $R_4 = CH_3$, m. 118-21°; Id, $R_1 = R_2 = Cl$, $R_3 = H$, $R_4 = C_2H_5$, m. 95-7°), which he

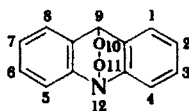


called *diformalides*. Treatment of these materials with potassium cyanide yielded III. It should prove possible to distinguish between structures I and II by means of infrared spectra.

References

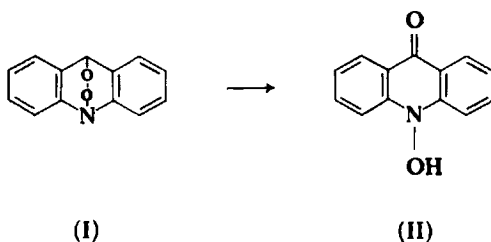
1. Villiger, *Ber.*, **42**, 3529 (1909).
2. Badische Anilin und Sodafabrik, Ger. Pat. 216,749; *Frdl.*, **10**, 341 (1913).

**B-122. 9,10(9*H*)-Epidioxyacridan.
R.I. 2592**



The above name and numbering were used by the *Ring Index*, while in *Chemical Abstracts* (Decennial Index, Vols. 21-30) are found the names *5-acridyl-10,10'-dioxide* and *acridine-5,10(5)-peroxide*.

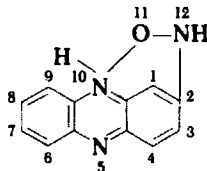
Compound I (m. 178°d. if immersed in the bath at 175°d, but m. ~340° if immersed below 175°) was obtained¹ by treating acridine with perbenzoic acid in benzene solution. Sulfuric acid or hot acetic acid or ethanolic caustic each converts I into II.



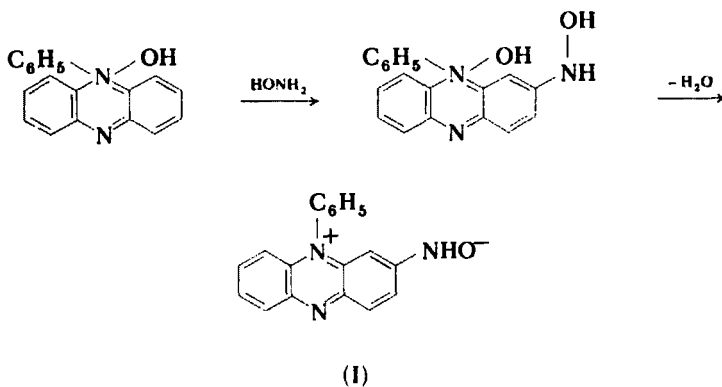
Reference

1. Lehmstedt and Klee, *Ber.*, **69**, 1514 (1936).

B-123. 10(10*H*),2-(Epoxyimino)-phenazine. R.I. 2593



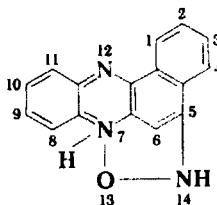
The anhydro compound I, obtained¹ as shown, is the nearest thing to a representative of this nucleus.



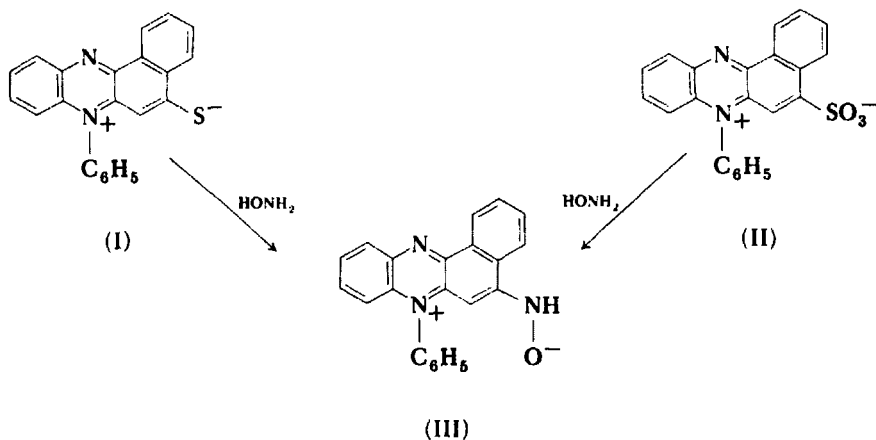
Reference

1. Kehrmann, Becker and Capatina, *Ann.*, **322**, 67 (1902).

B-124. 7,5(7H)-Epoxyiminobenzo- $[\alpha]$ phenazine. R.I. 3186



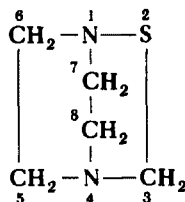
Treatment of either thiorosindone (I) or of II with hydroxylamine yielded^{1,2} III, the closest approach to a representative of this ring system.



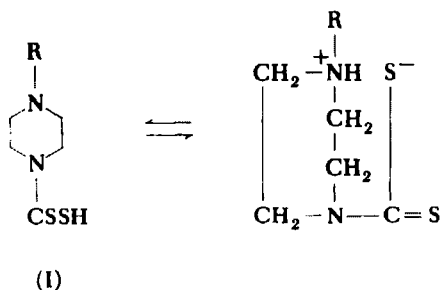
References

1. Kehrman and Locher, *Ber.*, **31**, 2428 (1898).
2. Fischer and Arntz, *Ber.*, **39**, 3807 (1906).

B-125. 2-Thia-1,4-diazabicyclo[2.2.2]-octane. R.I. 926

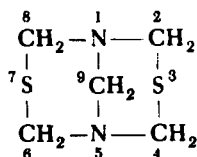


When written in zwitterionic form, acids of structure I (see Section B-26) were evidently considered representatives of this ring system.

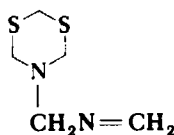


tem. No others have been reported, and, obviously, these acids are not true representatives.

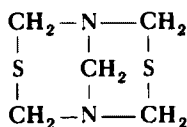
B-126. 3,7-Dithia-1,5-diazabicyclo[3.3.1]nonane. R.I. 925



The reaction of ammonium sulfide solutions with formaldehyde yields a product which was first obtained by Delépine^{1,2} and assigned structure I. The same reaction was investigated by Todtenhaupt³ and by Lefevre,^{4,5} who apparently were unaware of Delépine's work, and whose publications provoked assertions of priority by Delépine.⁶



(I)



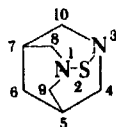
(II)

The more probable structure II was given this product by Lefevre.^{5,7} As first obtained from the reaction mixture, II is a gummy solid, but recrystallization gives a product melting at $200^{\circ}5$ (208°).³ Compound II is degraded by hot acid solutions to trithioformaldehyde. The heats of formation and combustion of II have been reported.⁸

References

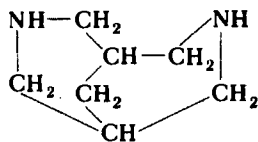
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B-127. 2-Thia-1,3-diazaadamantane

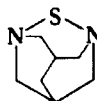
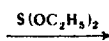


This ring system might also be named *2-thia-1,3-diazatricyclo-[3.3.1.1^{3,7}]decane*.

Condensation of bispidine (I) with ethyl sulfoxylate afforded¹ a fifty percent yield of II (pale yellow, m. with d. $\sim 160^{\circ}$ in a sealed



(I)



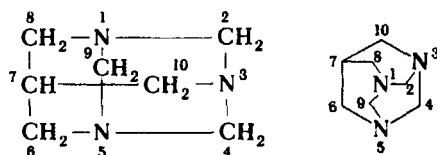
(II)

tube). Compound II dissolves in dilute acids, but the solutions soon deposit elemental sulfur; in alkaline solutions II dissolves slowly with decomposition.

Reference

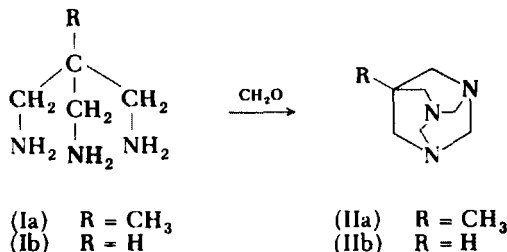
1. Stetter and Merten, *Chem. Ber.*, **90**, 868 (1957).

**B-128. 1,3,5-Triazatricyclo-
[3.3.1.1^{3,7}]decane**



The two formulae above are equivalent.

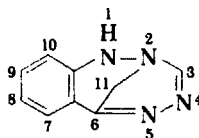
By the reaction of Ia with formaldehyde in benzene solution, Stetter and Böckmann¹ obtained IIa (sublimes $\sim 100^\circ$; m. 175° ; dihydrochloride, m. 195° d.). Compound IIb (sublimes $\sim 180^\circ$, m. 260° d.) was similarly obtained.²



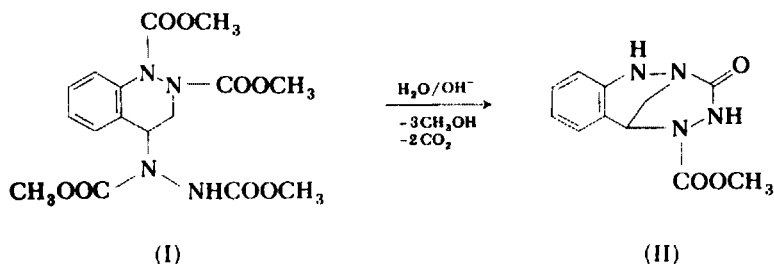
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3. Stetter, *Angew. Chem.*, **66**, 217 (1954).

B-129. 1H-2,6-Methano-1,2,4,5-benzotetrazocine



The reaction of styrene with azodicarboxylic ester^{1,2,3} gives a product now generally considered to be I, although it was at first

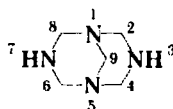


assigned other structures. Saponification of this material yields¹ a product (m. 183°d.) thought to have structure⁴ II.

References

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B-130. 1,3,5,7-Tetrazabicyclo[3.3.1]-nonane. R.I. 931

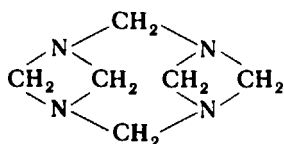


This ring system is commonly referred to as *pentamethylenetetramine*.

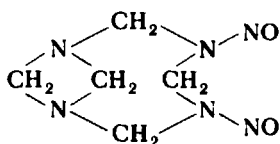
The prototype of this nucleus is unknown, and is, presumably, unstable. However, a number of derivatives have been prepared, the majority in connection with research upon explosives during World War II.

Treatment of hexamethylenetetramine with nitrous acid was shown^{1,2} to yield, depending upon the conditions,² two compounds having the formulae $C_3H_6N_6O_3$ and $C_5H_{10}N_6O_2$. The latter was called¹ dinitrosopentamethylenetetramine. Based upon the erroneous formulation of hexamethylenetetramine as I, Delépine³ proposed for this product structure II. However, Duden and Scharff,⁴ who formulated the now accepted structure of hexamethylenetetramine, showed that the compound $C_5H_{10}N_6O_2$ had structure III. They also obtained III from aqueous solutions of ammonia, formaldehyde and acetic and nitrous acids. It was later shown⁵ that III was also formed from the treatment of Henry's solution (ammonium hydroxide and formaldehyde) with nitrous acid. Bachmann and Deno

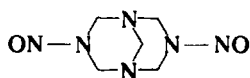
demonstrated⁶ that the reaction of hexamethylenetetramine with nitrous acid at a pH of 3 or higher⁴² gave exclusively III, while at pH 1, only Mayer's compound² $C_3H_6N_6O_3$ (structure IV) resulted. At pH values between 1 and 3, mixtures of III and IV were obtained. The heats of combustion and formation of III have been



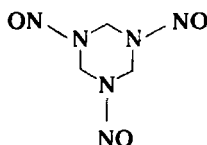
(I)



(II)



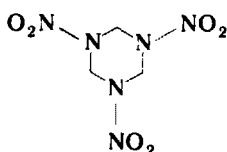
(III)



(IV)

measured.^{7,8} On boiling with dilute hydrochloric acid, III is decomposed⁹ to formaldehyde, ammonia and nitrogen, and the kinetics of this and related decompositions have been studied.^{10,39}

One of the byproducts formed in the production of "RDX" (*Cyclonite*, V) was found¹¹ to have structure VI. It was called

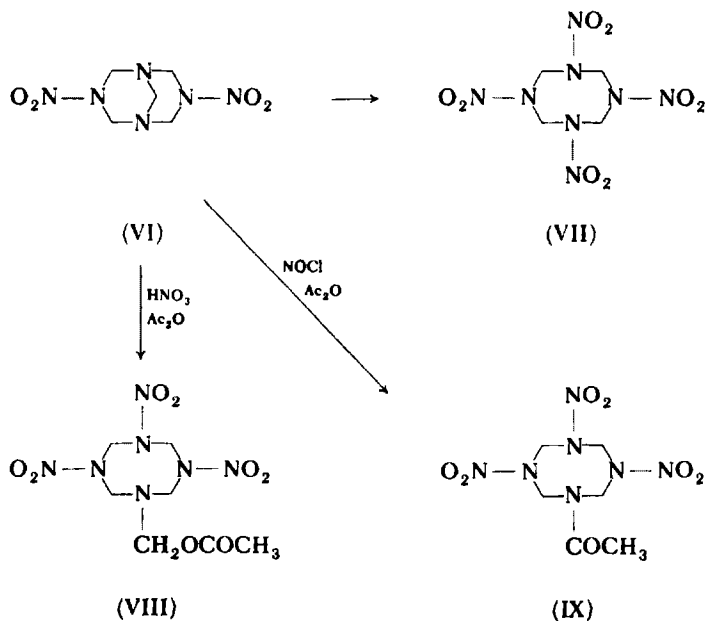


(V)

"DPT" and was synthesized by (a) the dehydration of hexamethylenetetramine dinitrate with sulfuric acid or acetic anhydride;^{11,12,13} (b) the condensation of bismethylolnitramine with methylene diamine,^{5,11} and (c) the reaction of methylenedinitroamine with formaldehyde and aqueous ammonia.¹⁴ The reaction of nitramine with formaldehyde and acetaldehyde gave¹¹ the 9-methyl

homolog of VI. Nitration of hexamethylenetetramine methonitrate (Knudsen's nitrate, v.i.) gave¹⁵ the quaternary 1-methyl salt of VI. The ultraviolet absorption spectrum of VI has been measured,^{16,17} and a method for the determination of VI developed.³⁰

When heated, VI gave¹¹ a sublimate composed of paraformaldehyde and hexamethylenetetramine. Refluxing VI in ethanol gave a 25% yield of hexamethylenetetramine, while in water a 76% yield of formaldehyde was obtained.¹¹ Treatment of VI with sulfuric acid¹² or with an ammonium nitrate-nitric acid mixture^{13,18} gave a mixture of VII ("homocyclonite" or "HMX") and V. The reaction of VI with nitric acid in excess acetic anhydride yielded¹⁹ VIII, while with nitrosyl chloride in acetic anhydride IX was formed.⁶

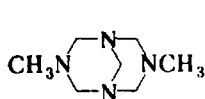


The immobility of the nitro groups in VI was shown by its failure to nitrate acetanilide in sulfuric acid solution.²⁰

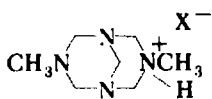
Other derivatives of pentamethylenetetramine have been obtained by the reaction of hexamethylenetetramine with various reagents. The 3,7-ditosyl derivative is formed in 46% yield,²¹ and the 3,7-diacetyl derivative²² in 5.2% yield.²³ With sodium hypochlorite the 3,7-dichloro derivative²⁴ is produced. This is converted into

N,N',N''-trichlorohexahydrotriazine by solution in acetic acid, and into 3,7-dinitropentamethylenetetramine by reaction with nitric acid in acetic anhydride.²⁵ The dichloro derivative has been used (as well as other *N*-chloro compounds) to cause the thiocyanation of the three toluidines.²⁶ Diazonium salts react with hexamethylenetetramine to give 3,7-bisarylazopentamethylenetetramines.⁴ Reduction of the 3,7-dinitroso compound (III) with sodium amalgam yielded⁴ the 3,7-diamine, which could not be isolated as such, but was converted into various Schiff's bases by condensation with aromatic aldehydes.

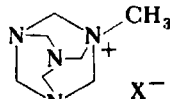
From the reaction of a solution of ammonium sulfate with formaldehyde, Knudsen²⁷ isolated salts (e.g. picrate, hydrochloride) of a base which was thought to have structure X, and the salts of Knudsen's base were generally assigned structure XI. The same picrate was obtained²⁸ by treating hexamethylenetetramine picrate in ethanol with formaldehyde. However, it has now been shown beyond doubt²⁹ that salts of Knudsen's base have structure XII.



(X)



(XI)



(XII)

Under the names "DNPMT" and "UND," 3,7-dinitrosopentamethylenetetramine has been used as a foaming (or blowing) agent for plastics and rubber.^{31-37,43-46} The inclusion of pentamethylenetetramine (salts?) in disinfectant mixtures has been claimed.³⁸

Derivatives of 1,3,5,7-Tetrazabicyclo[3.3.1]nonane

Empirical formula	Substituents	Properties	Refs.
$C_5H_{10}Cl_2N_4$	3,7-Dichloro-	Deflagrates at 78–82°; dec. slowly in air or solution.	24-6
$C_5H_{10}N_6O_2$	3,7-Dinitroso-	m. 207° (198°, 246°) d.	1-6,34,41
$C_5H_{10}N_6O_3$	3-Nitro-7-nitroso-	Methopicrate, m. 129°.	15
$C_5H_{10}N_6O_4$	3,7-Dinitro-	m. 222–3° (216°, 213°, 208–9°, 206–8°, 205–6°, 202–5°, 195–6°) d. Methonitrate, m. 143° (142°). Methopicrate, m. 141°.	5,6,11-20, 23,25,40

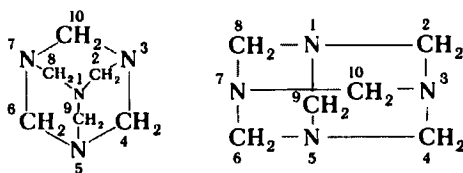
Derivatives of 1,3,5,7-Tetrazabicyclo[3.3.1]nonane (*continued*)

Empirical formula	Substituents	Properties	Refs.
C ₆ H ₁₂ N ₆ O ₄	9-Methyl-3,7-dinitro-	m. 175°.	11
C ₉ H ₁₆ N ₄ O ₂	3,7-Diacetyl-	m. 194.0–4.2° (186–7°).	22,23
C ₁₇ H ₁₈ N ₁₀ O ₄	3,7-Bis(<i>m</i> -nitro-phenylazo)-	Yel.-grn., m. 184° d.	4
	3,7-Bis(<i>p</i> -nitro-phenylazo)-	Yel., m. 244° d.	4
C ₁₇ H ₂₀ N ₈	3,7-Bisphenylazo-	Yel., m. 228° d.	4
C ₁₇ H ₂₀ N ₈ O ₆ S ₂	3,7-Bis(<i>p</i> -sulfo-phenylazo)-		4
C ₁₉ H ₂₀ N ₈ O ₄	3,7-Bis(<i>m</i> -nitro-benzalimino)-	m. 134°.	4
C ₁₉ H ₂₂ N ₆	3,7-Bis(benzalimino)-	m. 226–7°.	4
C ₁₉ H ₂₂ N ₆ O ₂	3,7-Bis(salicylidenimino)-	m. 213°.	4
C ₁₉ H ₂₄ N ₄ O ₄ S ₂	3,7-Ditosyl-	m. 236°.	21
C ₂₃ H ₂₄ N ₆	3,7-Bis(cinamyliidenimino)-	m. 207°.	4

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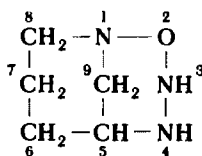
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B-131. Hexamethylene-tetramine. R.I. 1816

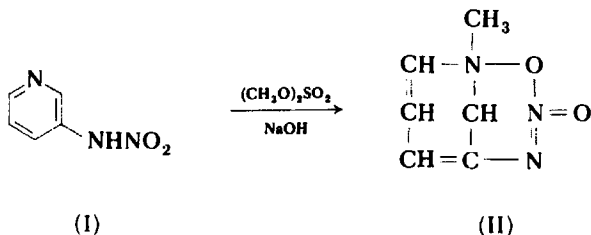
The two formulae shown are equivalent. This nucleus has also been named *1,3,5,7-tetrazatricyclo[3.3.1.1^{3,7}]decane*, *hexamine*, *hexamethyleneamine*, *urotropine*, *methenamine*, *aminoform* and *formin*. In view of the considerable age and several uses of this compound, a very extensive literature concerning it has accumulated. This subject has recently been reviewed¹ and little would be gained by a repetition here. Therefore, for information concerning hexamethylenetetramine this review,¹ and the references given therein, should be consulted.

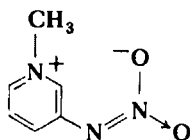
Reference

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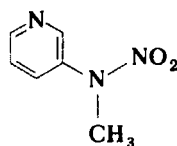
B-132. 2-Oxa-1,3,4-triazabicyclo-[3.3.1]nonane. R.I. 905

Since 2-nitraminopyridine was shown¹ to yield 1-methyl-2-nitriminopyridine when treated with dimethyl sulfate and alkali, the product similarly obtained from 3-nitraminopyridine (I) was assigned² structure II. If the position of methylation shown is correct, the product would now be written as III; however, no evidence was offered to exclude structure IV.





(III)

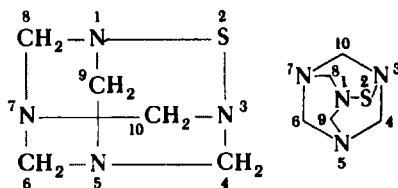


(IV)

References

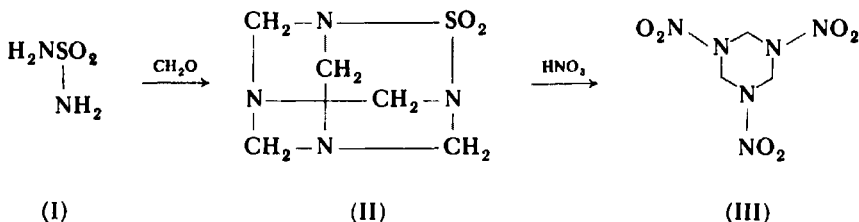
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B-133. 2-Thia-1,3,5,7-tetrazatri-cyclo[3.3.1.1^{3,7}]decane



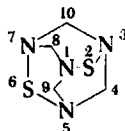
The above two formulae are equivalent.

Treatment of a solution of sulfamide (I) with formaldehyde produces, in good yield, a product (m. 224–5°) of structure II, called *pentamethylenetetraminesulfone*.^{1,2} When warmed with aqueous acids, II is readily hydrolyzed to its components, although with nitric acid it yields “hexogen” *Cyclonite*, III; see Section B-130). Compound II forms difficultly-soluble picrate and phosphate salts.

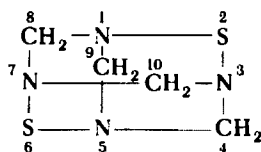


References

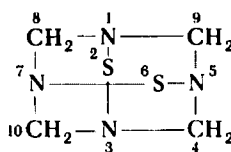
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3. Stetter, *Angew. Chem.*, **66**, 217 (1954).

B-134. 2,6-Dithia-1,3,5,7-tetraza-tricyclo[3.3.1.1^{3,7}]decane

Structures I and II represent alternative methods of depicting this nucleus.

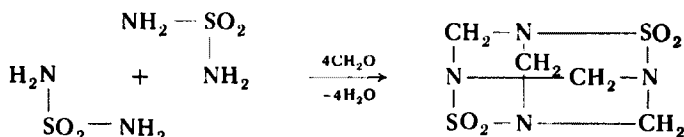


(I)



(II)

The existence of this ring system was made known in an unusual manner. Several cases of poisoning occurred amongst upholstery-factory workers using a product called "Crinexwolle," which was wool impregnated with a sulfamide-formaldehyde polymer.² The toxic constituent of Crinexwolle was isolated by Hecht and Henecka,² shown to be III (m. 255–60°d.), and named *tetramethylenedisulfotetramine*.



(III)

Compound III is a highly active convulsant and analeptic, more potent than picrotoxin³ and about five times as toxic as strychnine.¹ While extraordinarily effective as a rodenticide,^{4,5} its high toxicity for man probably precludes its use for this purpose.^{3,4} The high toxicity of such a simple structure is the more surprising in view of the absence of physiological activity in several closely related structures.⁶

References

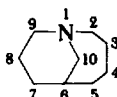
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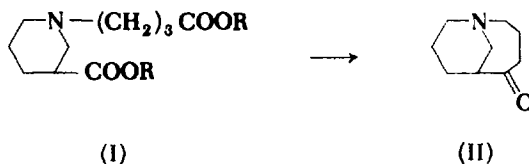
CHAPTER XVIII

Bridged 6/7 and Larger Ring Systems

B-135. 1-Azabicyclo[4.3.1]decane*



Unsuccessful efforts to obtain II by the Dieckmann cyclization of I ($R = C_2H_5$) and by pyrolysis of the thorium salt of the acid I

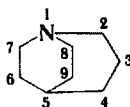


($R = H$) have been reported¹ by Clemo, Ormston and Ramage. However, the Dieckmann cyclization of I might bear further study since the cyclization of a closely related ester (reported¹ not to cyclize) has been successful (see Section B-84).

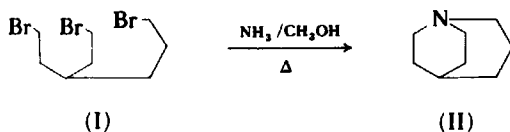
Reference

1. Clemo, Ormston and Ramage, *J. Chem. Soc.*, **1931**, 3185.

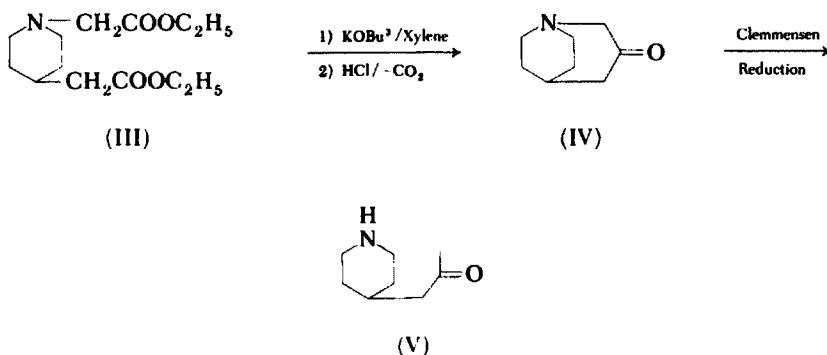
B-136. 1-Azabicyclo[3.2.2]nonane. R.I. 1064



Prelog and Cerkovnikov¹ obtained II (m. 129° ; picrate, m. $288-9^\circ$; chloroplatinate, orange, m. $238-40^\circ$; chloroaurate, d. $\sim 250^\circ$) in about 12% yield by treating I with alcoholic ammonia.



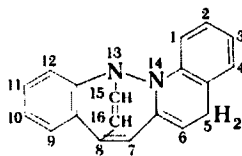
Leonard, Curry and Sagura² found the Dieckmann cyclization of III (and subsequent hydrolysis and decarboxylation of the resulting ketoester) gave less than 1% of IV (m. 128.5–31.5°), which on Clemmensen reduction gave, not II, but V.



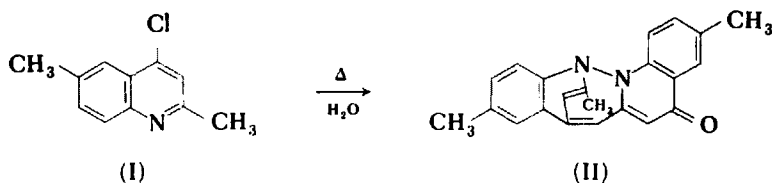
References

1. Prelog and Cerkovnikov, *Ann.*, **532**, 83 (1937).
2. Leonard, Curry and Sagura, *J. Am. Chem. Soc.*, **75**, 6249 (1953).

B-137. 8,13(5*H*)-Ethenoquino[1,2-*b*]-[1,2]benzodiazepine. R.I. 3394



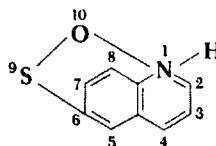
From the decomposition products of I was isolated a blue hydrochloride salt, from which a rose base was obtained.¹ It was assigned¹ the (improbable) structure II, which violates Bredt's rule.



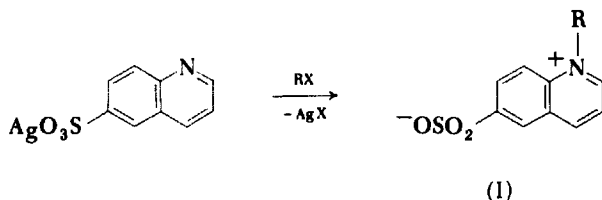
Reference

1. Meyer and Drutel, *Compt. rend.*, **207**, 923 (1938).

**B-138. 1(1*H*),6-Epoxythioquinoline.
R.I. 2043**



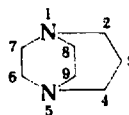
Sulfobetaines of structure I¹ were listed by the *Ring Index* as examples of this nucleus.



Reference

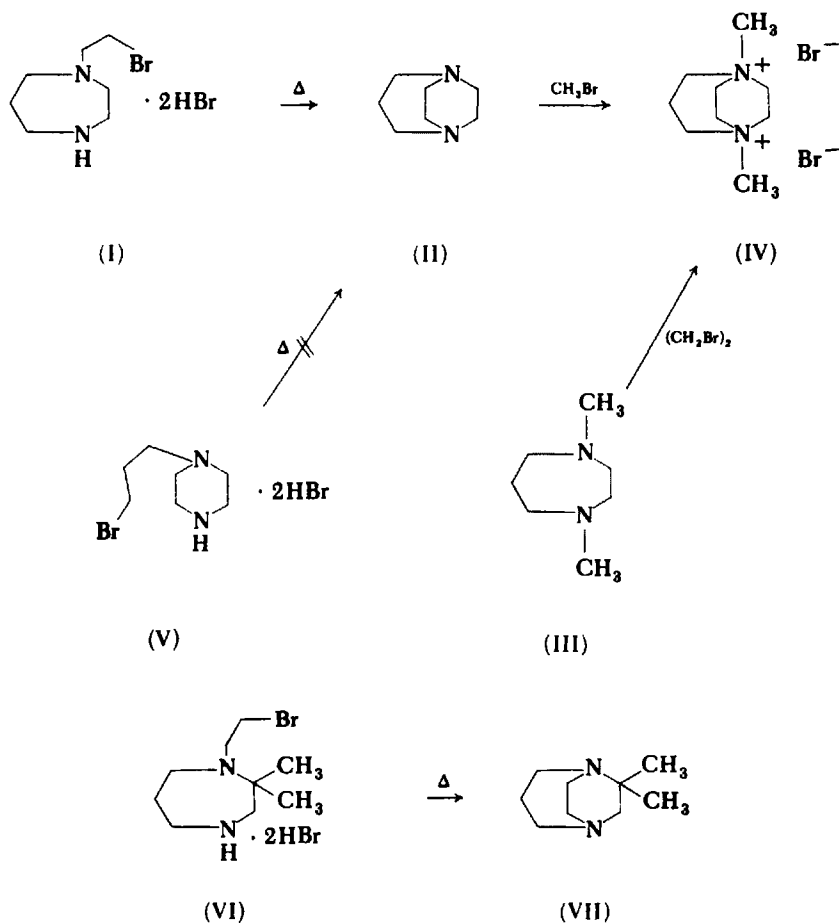
1. Claus and Steinitz, *Ann.*, **282**, 130 (1894).

B-139. 1,5-Diazabicyclo[3.2.2]nonane



The pyrolysis¹ of small amounts of I gave a 43% yield of II (m. 89–92°; dihydrochloride, m. 308°d.; dipicrate, m. 260–1°d.; bis-4-nitrophenolate, m. 116.5–7.0°; bis-2,4-dinitrophenolate, m. 169–70°; dimethobromide (IV), m. 252–3°d.; dimethopicrate, m. 278.0–9.5°). The dimethobromide of II (IV) could be formed from II or III, but unlike 1,4-diazabicyclo[2.2.2]octane dimethobromide (see Section B-112), which lost methyl bromide when heated, IV could not be pyrolyzed to II, nor did the pyrolysis of V yield II.

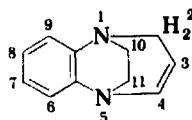
Similarly, the dimethyl derivate (VI) of I gave 13% of VII (oil; dipicrate, m. 241.5–2.5°; bis-2,4-dinitrophenolate, m. 138–40°) on pyrolysis.



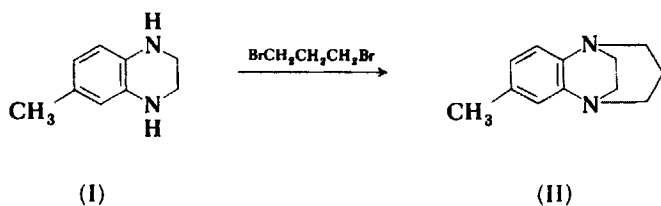
Reference

- McElvain and Bannister, *J. Am. Chem. Soc.*, **76**, 1126 (1954).

B-140. 1,5(2)-Ethano-1,5-benzodiazepine. R.I. 2038



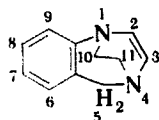
Treatment of I with trimethylene bromide yielded¹ II (m. 192°d.), which forms mono- and dibasic salts.



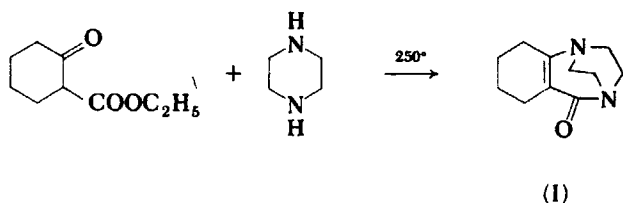
Reference

1. Moore and Doubleday, *J. Chem. Soc.*, **119**, 1170 (1921).

B-141. 1,4(5*H*)-Ethano-1,4-benzodiazepine. R.I. 2037.



By heating 2-carbethoxycyclohexanone with piperazine at 250°, Kötzt and Merkel¹ obtained a product (m. 280°) to which they assigned structure I. It has been called *N,N'*-[3.4.5.6-tetrahydrobenzoylene]-piperazine.

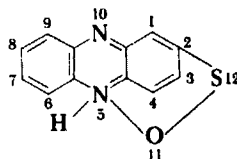


Structure I might be expected to be somewhat strained because of the coplanarity required of the nitrogen atoms and the ethylenic and carbonyl groupings, and, furthermore, it contains the "forbidden" bridgehead amide group.² Additional information on this product would be welcome.

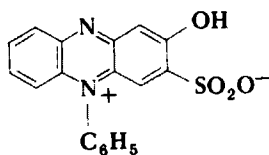
References

1. Kötzt and Merkel, *J. prakt. Chem.* [2] **79**, 102 (1909).
2. Lukeš, *Collection Czechoslov. Chem. Commun.*, **10**, 148 (1938).

**B-142. 5(5*H*),2-Epoxythiophenazine.
R.I. 2822**



The sulfobetaine I¹ was considered by the *Ring Index* to represent this nucleus.

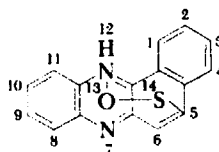


(I)

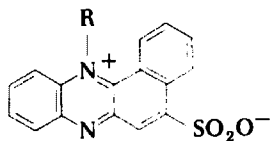
Reference

1. Jaubert, *Ber.*, **31**, 1178 (1898).

**B-143. 12,5(12*H*)-Epoxythiobenzo-
[a]phenazine. R.I. 3393.**



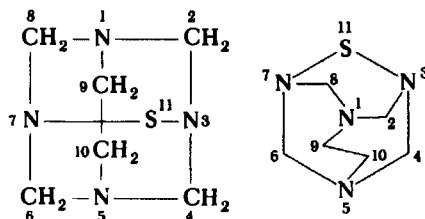
The sulfobetaines of type I¹ were considered by the *Ring Index* to represent this nucleus.



(I)

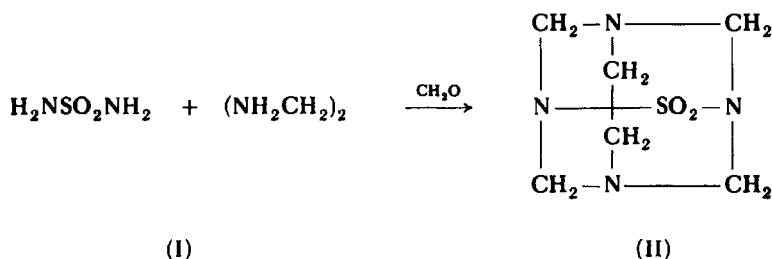
Reference

1. Kehrmann and Locher, *Ber.*, **29**, 2072 (1896).

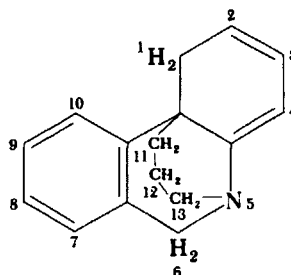
B-144. 11-Thia-1,3,5,7-tetraza-tricyclo[3.3.1.1^{3,7}]hen-decane

The above two formulae are equivalent.

The reaction of sulfamide (I) with formaldehyde and ethylene diamine provides, in 93% yield, II (m. 195–6°), which is hydrolyzed to its components by hot dilute acids.^{1,2} Compound II has been called *hexamethylenetetraminesulfone*.

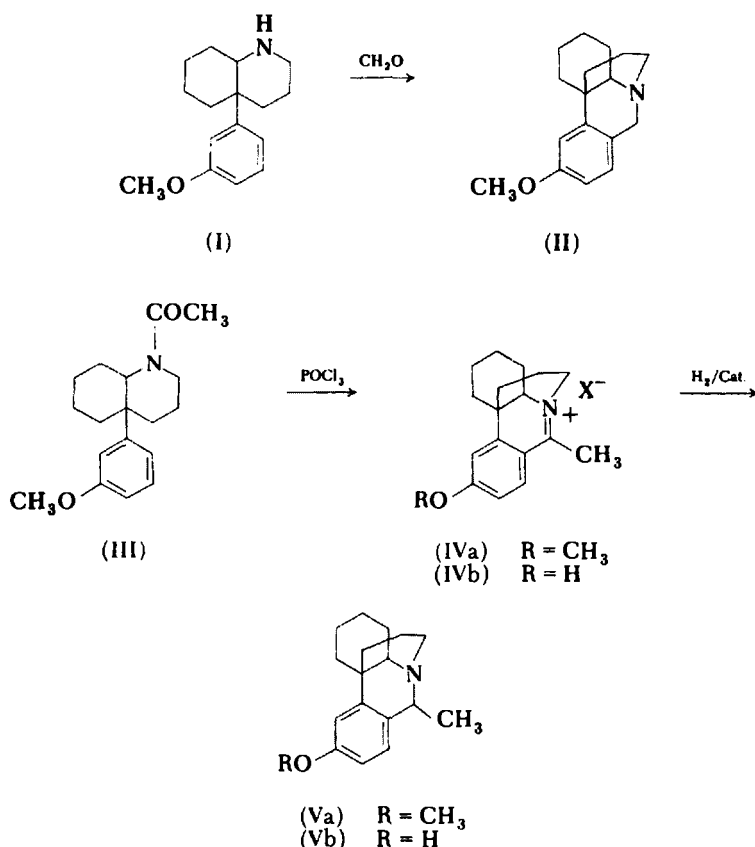
*References*

1. Paquin, *Angew. Chem.*, **60**, 316 (1948).
2. Farbwerke Höchst, Ger. Pat. 855,566.
3. Paquin, Ger. Pat. 851,497.

B-145. 1H,6H-5,10b-Propano-phenanthridine

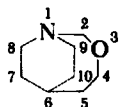
In spite of the intense interest in the morphine alkaloids, few analogs of morphine have been reported. By treating I with formalde-

hyde, Sugimoto and Kugita¹ obtained II ($b_{3.5}$ 160–2°; hydrochloride, m. 249–50°; picrate, m. 160–2°; methiodide, m. 235–6°). Also, the cyclodehydration of III ($R = CH_3$) yielded IVa ($R = CH_3$, $X = I^-$, m. 228–9°). Demethylation of IVa yielded IVb ($R = H$, $X = Br^-$, m. 160°), while upon catalytic reduction IVa gave Va ($R = CH_3$, hydrochloride, m. 285°; picrate, m. 217–9°). Cleavage of the methoxyl group in Va yielded Vb ($R = H$, m. 242–5°), which exhibited analgesic activity equal to that of morphine, but was more toxic.



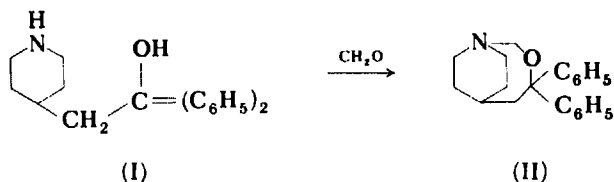
Reference

1. Sugimoto and Kugita, *Pharm. Bull. (Tokyo)*, **3**, 11 (1955); *Chem. Abstracts*, **50**, 1815 (1956).

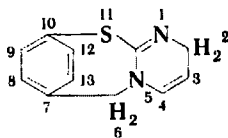
B-146. 3-Oxa-1-azabicyclo[4.2.2]-decane*

This nucleus was erroneously named *5-oxa-1-azabicyclo[4.2.2]decane*, and indexed as such by *Chemical Abstracts*.

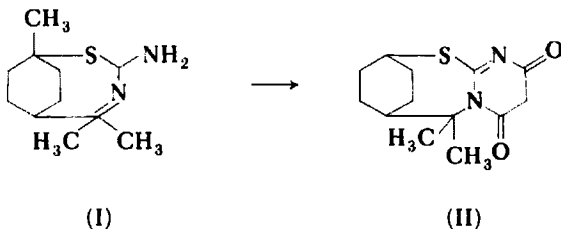
The reaction of the hydrochloride salt of I with formaldehyde produced¹ a 71% yield of II (hydrochloride, m. 277–8°).

*Reference*

1. Tilford and Van Campen, *J. Am. Chem. Soc.*, **76**, 2431 (1954).

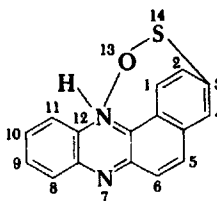
B-147. 2*H*,6*H*-7,10-Ethenopyrimido-[2,1-*b*][1,3]thiazocine *

The addition of thiourea to α -pinene yielded a product considered¹ to have structure I. Reaction of I with some sodiummalonic ester produced II (m. 249.0–9.5°), which was named *N,N'*-malonyl-1(*S*),8(*N*)-*p*-methyleneisothiourea.

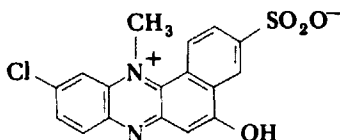
*Reference*

1. King, Subluskey and Stern, *J. Org. Chem.*, **21**, 1232 (1956).

**B-148. 12,3(12*H*)-Epoxythiobenzo-
[a]phenazine. R.I. 3405**



The only examples are sulfobetaines such as I. ¹

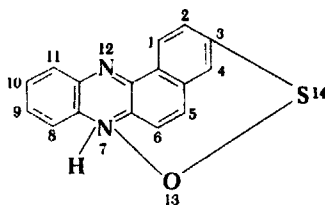


(I)

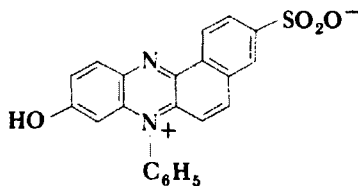
Reference

1. Kehrmann and Miller, *Ber.*, **34**, 1095 (1901).

**B-149. 7,3(7*H*)-Epoxythiobenzo-
[a]phenazine. R.I. 3415**



This nucleus is represented only by sulfobetaines ¹ such as I.

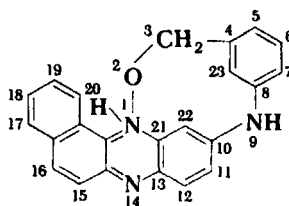


(I)

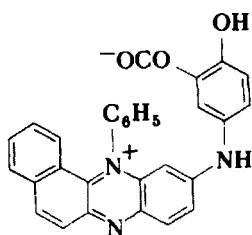
Reference

1. Kalle and Co., Ger. Pat. 72,343; *Frdl.*, **3**, 348 (1896).

- B-150.** 1*H*,9*H*, -10,1,13-Ethenylidene-4,8-metheno-3*H*-naphtho[1,2-*c*]-[1,2,5,10]oxatriazacyclohexadecine.* R.I. 3668



The zwitterionic compound I¹ was offered by the *Ring Index* as an example of this ring system.

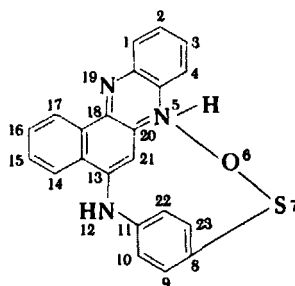


(I)

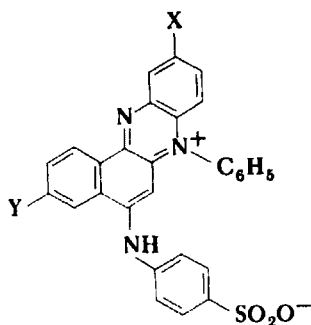
Reference

1. Kehrmann and Hiby, *Ber.*, **34**, 1085 (1901).

- B-151.** 5*H*,12*H*-Ethan-1(13)-ylidene-2(18,5)-ylidene-5*H*-dibenzo-[*c,g*][1,15,2,5,10]oxathiatriazacyclopentadecine.* R.I. 3670



The zwitterionic compound assigned^{1,2} structure I was cited by the *Ring Index* as an example of this ring system. However, uncertainty in determining which sulfonic acid group has ionized renders structure I open to question.

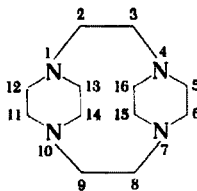


(I) X or $Y = \text{SO}_3\text{H}$

References

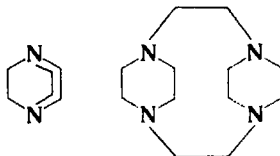
1. Kehrmann and Müller, *Ber.*, **34**, 1095 (1901).
2. Badische Anilin- und Sodafabrik, Ger. Pat. 79,953; *Frdl.*, **4**, 440 (1899).

B-152. 1,4,7,10-Tetrazatricyclo- [8.2.2.2^{4,7}]hexadecane



This system has also been named *hexaethylenetetramine*.

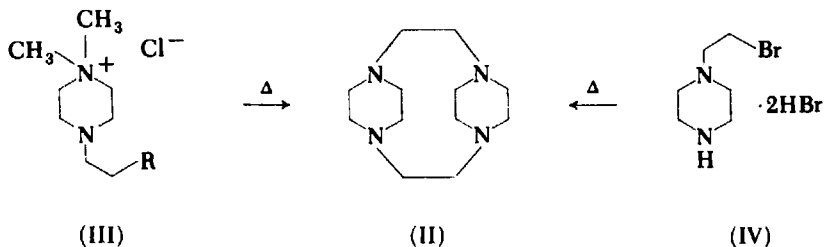
It has been asserted by Harries¹ that the product obtained by Hoffmann² from the interaction of ethylene bromide and ammonia and thought by him to have structure I (see Section B-112), has, actually, structure II.



(I)

(II)

Recently, II (tetrahydrochloride, m. 291°d.; tetrapicrate, m. 277°d.; tetramethobromide, m. 320°d.; monohydrate, m. 309–10°d.; tetramethopicrate, m. 298°) has been found among the pyrolysis products of both III³ (R = Cl, or N(CH₃)₂) and IV.⁴

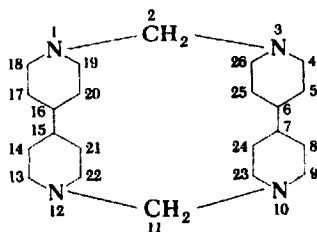


The strainless, non-coplanar configuration of II has been discussed.³

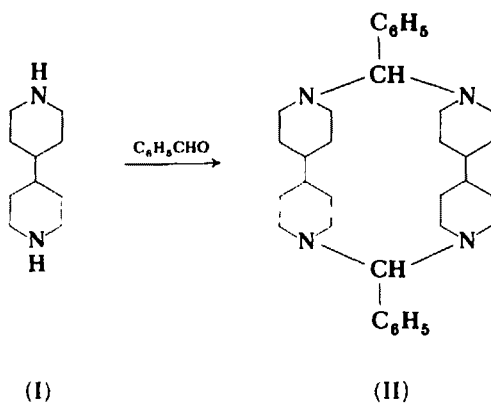
References

1. Harries, *Ann.*, **294**, 350 (1897).
2. Hofmann, *Proc. Roy. Soc.*, **9**, 153 (1859).
3. Mann and Mukherjee, *J. Chem. Soc.*, **1949**, 2298.
4. McElvain and Bannister, *J. Am. Chem. Soc.*, **76**, 1126 (1954).

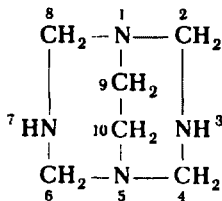
B-153. 1,3,10,12-Tetrazapentacyclo-
[14.2.2.3^{3,6}.2^{7,10}.2^{12,15}]-
cyclohexeicosane. R.I. 3432



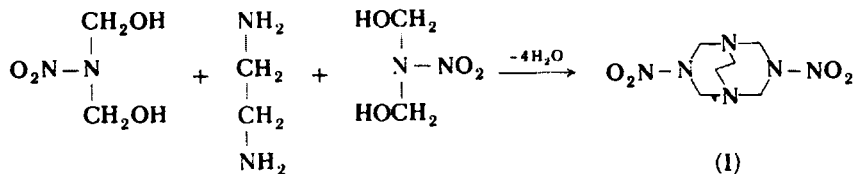
The reaction of 4,4'-dipiperidyl (I) with benzaldehyde yielded a product (m. 189°) for which formula II has been proposed.¹ Dilute hydrochloric acid readily hydrolyzed II to I and benzaldehyde. The reactions of I with formaldehyde, phosgene, methylene iodide and ethylene chloride were also studied, but no definite products were identified.

*Reference*

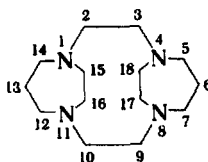
1. Emmert and Meixner, *Ber.*, **62**, 1731 (1929).

B-154. 1,3,5,7-Tetrazabicyclo[3.3.2]-decane

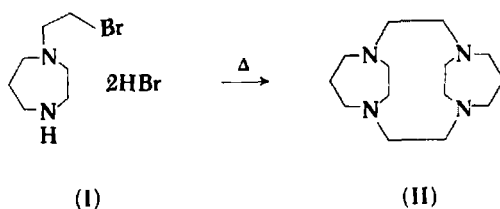
The reaction of ethylenediamine with two molecules of dimethylnitramine was shown¹ to yield I (m. 134–9°). See Section B-130.

*Reference*

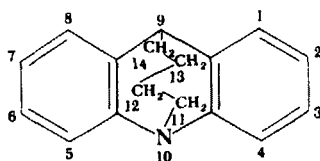
1. Chute, Downing, McKay, Myers and Wright, *Can. J. Research*, **27B**, 218 (1949).

B-155. 1,4,8,11-Tetrazatricyclo-[9.3.2.2^{4,8}]octadecane

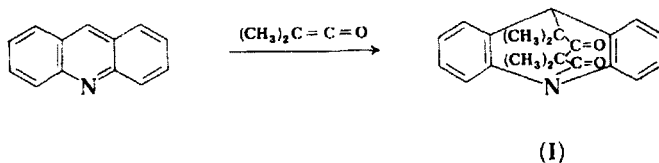
From the pyrolysis of I, McElvain and Bannister¹ isolated II (tetrapicrate, m. 236.5–7.5°) in about 11% yield. See Section B-152.

*Reference*

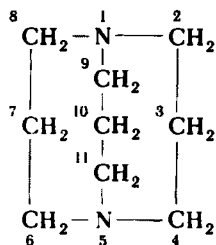
1. McElvain and Bannister, *J. Am. Chem. Soc.*, **76**, 1126 (1954).

B-156. 9,10-Butanoacridine. R.I. 2850

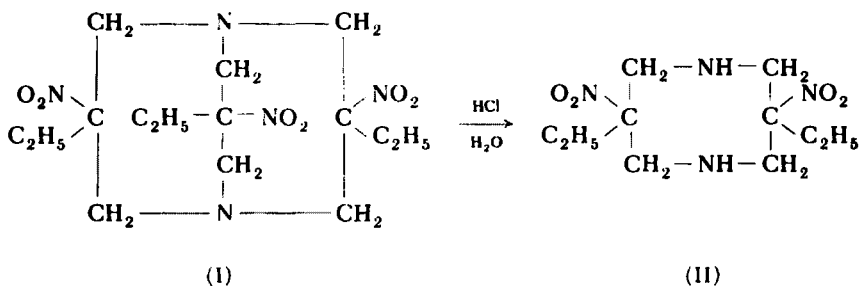
Staudinger and Klever^{1,2} treated acridine with dimethyl ketene and isolated a stable product (m. 127–8°), to which structure I was assigned.

*References*

1. Staudinger and Klever, *Ber.*, **40**, 1149 (1907).
2. Staudinger, Klever and Kober, *Ann.*, **374**, 1 (1910).

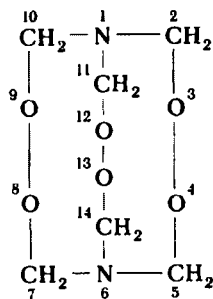
B-157. 1,5-Diazabicyclo[3.3.3]undecane

From the reaction¹ of nitropropane with formaldehyde and excess ammonia, compound I (m. 107–8°) is formed in about 30% yield. It is a weak base giving a monohydrochloride (m. 143–5°), but no picrate. Acidic hydrolysis of I yields II.

*Reference*

1. Jones, Kolinski, Piotrowska and Urbanski, *Bull. Acad. Polon. Sci., Classe III*, **4**, 521 (1956). *Roczniki Chem.*, **31**, 101 (1957); *Chem. Abstracts*, **51**, 14718 (1957).

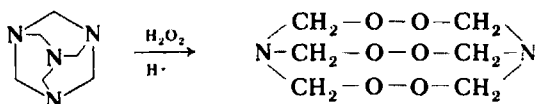
B-158. 3,4,8,9,12,13-Hexaoxa-1,6-diazabicyclo[4.4.4]tetradecane.
R.I. 1190



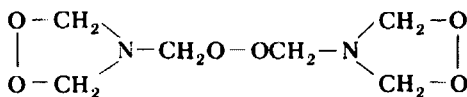
The single example and prototype is generally called *hexamethylenetriperoxidediamine*.

From the slow combustion of ether, Legler isolated a product^{1,2} ($C_2H_6O_4$?), which reacted with ammonia to give³ $C_6H_{12}N_2O_6$. Much more recently, Fujimoto isolated⁴ from the oxidation of methane in a silent arc discharge, a solid thought to be dihydroxymethylperoxide, which also reacts with ammonia to give hexamethylenetriperoxidediamine.

A more practical preparation was devised by Baeyer and Villiger,⁵ who treated ammonium salts with formaldehyde and hydrogen peroxide. They also assigned structure I to the product. The best preparative method was found by Girsewald,⁶ who treated urotropine with hydrogen peroxide in the presence of citric acid. Other weak acids such as acetic⁷ also are effective. From these reactants Leulier⁸ claimed to have isolated a product $C_4H_{11}NO_4$, but this was shown⁹ to be, in reality, $C_6H_{12}N_2O_6$. Formula II was later proposed¹⁰ by Girsewald and Siegens for this product, but has not found acceptance,⁷ although preparation⁷ of the product from trimethylolamine and hydrogen peroxide makes either structure possible.



(I)



(II)

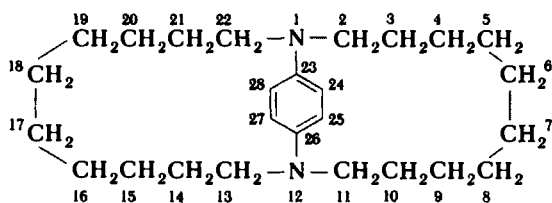
Hexamethylenetriperoxidediamine is a colorless solid, which is difficultly soluble in most solvents, but may, with care, be recrystallized from benzene, acetic acid, etc. It is very sensitive to friction, heat or shock and explodes readily. Hot water and hot dilute acids hydrolyze it to formaldehyde, but hot dilute bases yield ammonia.⁷ The use of hexamethylenetriperoxidediamine ("HMTD") in ex-

plosives has been studied^{11,12} and patented.^{13,14} It possesses excellent sensitivity, brisance and initiating characteristics, but is unstable in the presence of traces of (even atmospheric) moisture, and so is impractical.

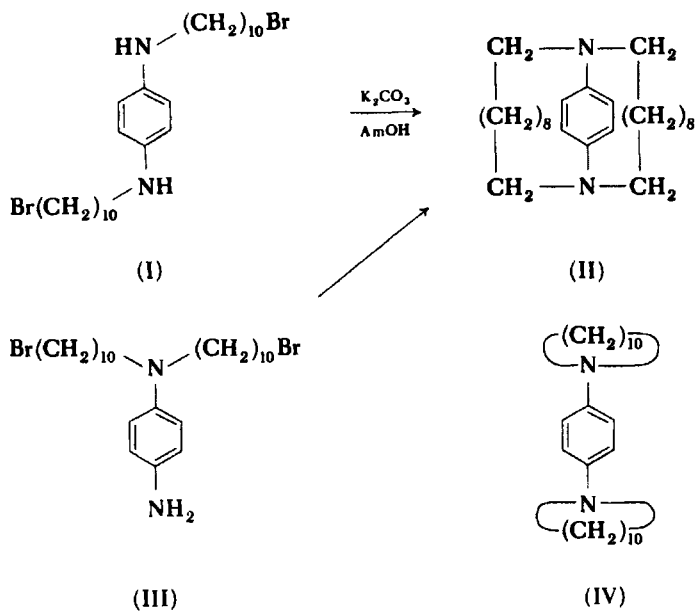
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B-159. 1,12-Diazatricyclo[10.10.4.2^{23,26}]-23,25,27-octacosatriene



By treatment of I with base, under conditions of high dilution, Lüttringhaus and Simon¹ obtained II (b_{0.01} 185–90°; m. 152°; picrate, m. 220°d.; dihydrochloride, turns brown > 220°). To exclude the possibility of structure IV, the product was also prepared from III.



Reference

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RING INDEX

Following is a list of the ring systems discussed in this book, arranged in the order of increasing complexity according to the system employed by *Chemical Abstracts* and the *Ring Index*. The right-hand column lists the Section(s) in which the ring system(s) given in the left-hand column is(are) discussed.

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CN ₂ -C ₂ N	A-2
CN ₂ -N ₂ O	A-4

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CN ₂ -C ₂ NO	A-7
N ₃ -CN ₃	A-11
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CNO-C ₃ N ₂	A-19
CNO-C ₄ N	A-16
CNS-C ₃ N ₂	A-20
CNSe-C ₃ N ₂	A-21
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CN ₂ -C ₃ N ₂	A-22
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CNS-C ₅ N	A-28
CNSe-C ₅ N	A-29
CN ₂ -C ₂ N ₄	A-36
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 $\text{CN}_2\text{Se}-\text{C}_3\text{N}_2$
 CN_3-CN_4
 $\text{CN}_3-\text{C}_2\text{N}_2\text{O}$
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 $\text{CN}_3-\text{C}_3\text{N}_2$
 $\text{C}_2\text{NO}-\text{C}_3\text{N}_2$
 $\text{C}_2\text{NO}-\text{C}_4\text{N}$
 $\text{C}_3\text{N}-\text{C}_3-\text{NS}$
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4/6 Systems

$\text{CN}_3-\text{C}_4\text{N}_2$
 $\text{C}_2\text{NO}-\text{C}_5\text{N}$
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4/9 Systems

$\text{C}_3\text{N}-\text{C}_7\text{N}_2$

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 $\text{CN}_4-\text{C}_4\text{N}$
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 $\text{C}_2\text{N}_2\text{S}-\text{C}_3\text{N}_2$
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 $\text{C}_2\text{N}_3-\text{C}_3\text{NS}$
 $\text{C}_2\text{N}_3-\text{C}_3\text{N}_2$
 $\text{C}_2\text{N}_3-\text{C}_4\text{N}$
 $\text{C}_3\text{NO}-\text{C}_3\text{NO}$
 $\text{C}_3\text{NO}-\text{C}_3\text{NS}$
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 $\text{C}_3\text{NS}-\text{C}_3\text{NS}$
 $\text{C}_3\text{NS}-\text{C}_3\text{N}_2$
 $\text{C}_3\text{NS}-\text{C}_4\text{N}$
 $\text{C}_3\text{NSe}-\text{C}_3\text{NSe}$
 $\text{C}_3\text{N}_2-\text{C}_3\text{N}_2$

$\text{C}_3\text{N}_2-\text{C}_4\text{N}$
 $\text{C}_4\text{N}-\text{C}_4\text{N}$

5/6 Systems

$\text{CN}_4-\text{CN}_4\text{O}$
 $\text{CN}_4-\text{C}_3\text{N}_3$
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C ₃ NS-C ₄ N ₂	A-487; A-504; A-544
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C ₃ N ₂ -C ₃ N ₃	A-614; A-616; A-630; A-633
C ₃ N ₂ -C ₄ NO	A-562
C ₃ N ₂ -C ₄ NS	A-514; B-63
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C ₃ N ₂ -C ₅ N	A-271; A-390; A-402; B-59
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 $C_3N_2-C_3N_2O-C_6$
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 $C_3N_2-C_3N_3-C_4N_2$
 $C_3N_2-C_3N_3-C_6$

 $C_3N_2-C_4NO-C_6$
 $C_3N_2-C_4N_2-C_4N_2$
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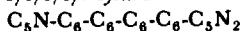
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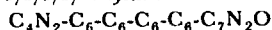
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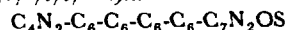
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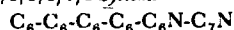
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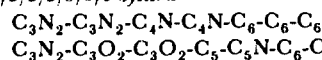
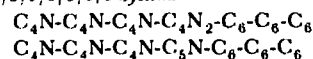
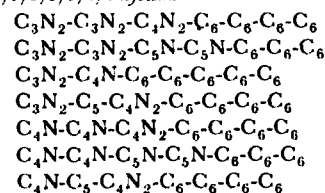
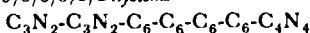
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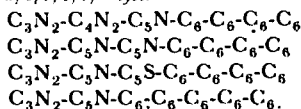
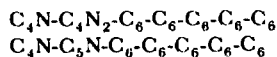
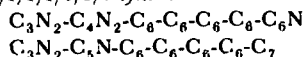
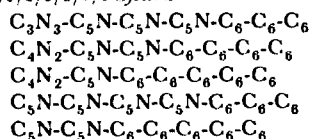
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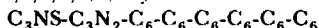
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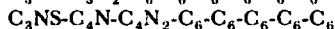
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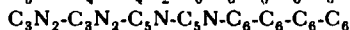
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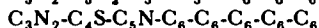
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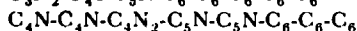
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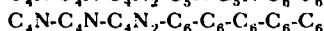
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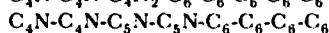
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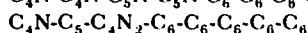
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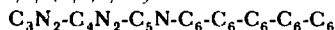
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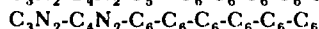
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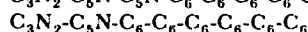
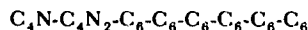
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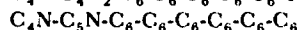
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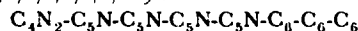
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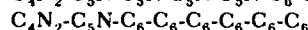
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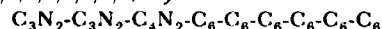
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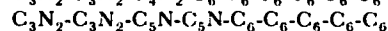


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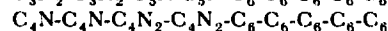
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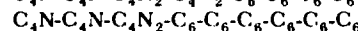
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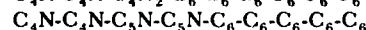
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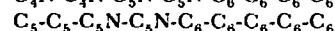
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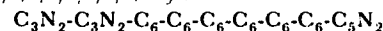
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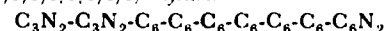
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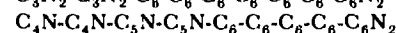
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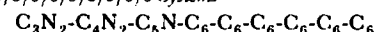
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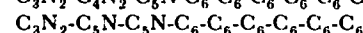
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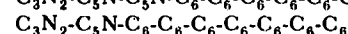
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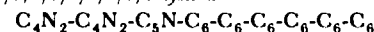
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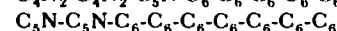
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