

Synthesis of 1,9,10-Anthyridine

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1,9,10-Anthyridine (VIII) was synthesized by oxidation of 5,10-dihydro-1,9,10-anthyridine (VII) with chromic acid. The structures of VII and VIII were determined by UV and NMR analyses.

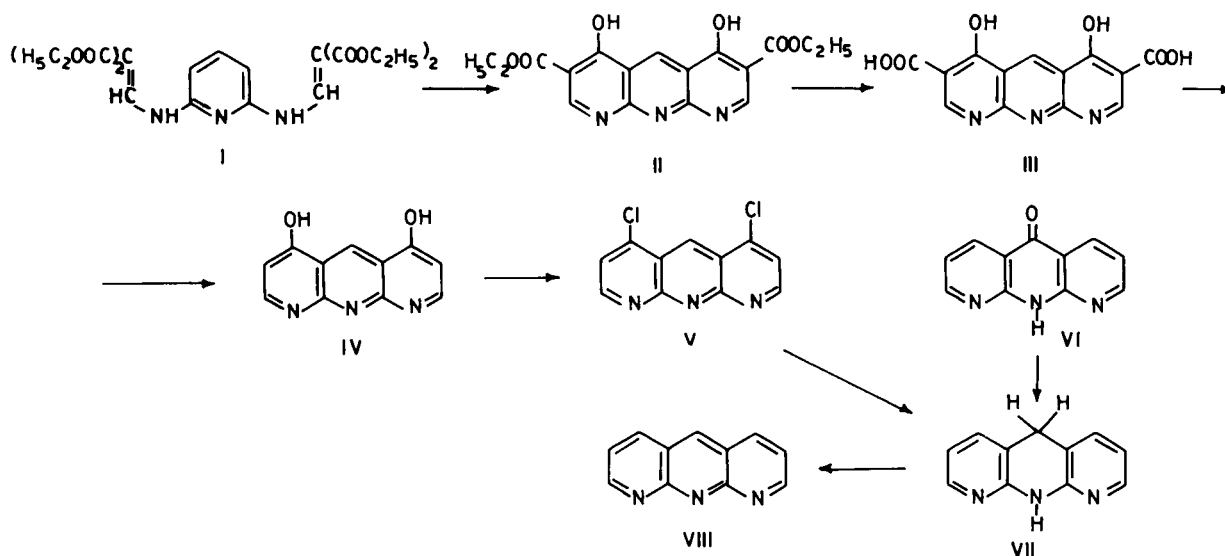
The preparation of various derivatives of 1,9,10-anthyridine both by the closure of a pyridine ring on a side of a preformed 1,8-naphthyridine system and by the closure of a central pyridine ring on two side pyridine rings has already been described (1,2). New 1,9,10-anthyridine derivatives have now been obtained by the direct closure of two pyridine side rings on one central one.

Treatment of 2,6-diaminopyridine with diethyl ethoxy-methylenemalonate gives I. The structure of this compound has been established by NMR spectral data. In fact signals attributable to the system -NH-CH=C are present (3).

The product I when refluxed in diphenyl ether cyclizes to the dihydroxydicarboxyanthyridine II; this gives 4,6-dihydroxy-1,9,10-anthyridine (IV) upon hydrolysis and decarboxylation. We attributed the anthyridine structure to this product, and consequently to II and III, because its properties are similar to the dihydroxyanthyridines previously obtained (1,2): high stability to acids,

alkalis and heat, very low solubility in all organic solvents, fluorescence in solution, even when very dilute, in Wood's light. All of these properties suggested the anthyridine structure which was confirmed in the following manner.

The treatment of IV with excess phosphorus oxychloride and phosphorus pentachloride gave the dichloroderivative V (NMR spectrum, see Table II) from which a non-halogenated product 5,10-dihydro-1,9,10-anthyridine (VII) was obtained by hydrogenation. The structure of VII was assigned based upon its NMR spectrum (see Table II) and UV spectrum which shows a behaviour closely analogous to that of 5,10-dihydroacridine (4) (see Table I), as well as upon analytical data. The product VII was also isolated from 5,10H-1,9,10-anthyridin-5-one (VI) previously obtained (2) by heating VI with a mixture of zinc, zinc chloride and sodium chloride. Thus all of the suggested structures of II, III, IV and V were confirmed. 1,9,10-Anthyridine (VIII) was isolated after treatment of VII with potassium dichromate in an analogous manner to the



transformation of acridanes into acridines (5). The structure of this compound is clearly confirmed by the NMR spectrum (see Table II) and the UV spectrum which shows two absorption bands analogous to anthracene (6) and acridine (7) (see Table I).

TABLE I

Comparison of Ultraviolet Absorption Spectra

Compound	λ max, $m\mu$ ($\log \epsilon$)
5,10-Dihydroacridine	289 (4.14)
5,10-Dihydro-1,9,10-anthryridine	303 (4.19)
Anthracene	252 (5.30), 375 (3.90)
Acridine	248 (5.30), 353 (4.04)
1,9,10-Anthryridine	234 (4.85), 350 (4.14)

This preparation of 1,9,10-anthryridine seems worthy of note since this compound represents a fundamental ring system in heterocyclic chemistry.

EXPERIMENTAL

All melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Model 137 spectrophotometer in Nujol mulls. Ultraviolet spectra were recorded on a Beckman Model DU spectrophotometer in ethanol. The proton NMR spectra were obtained on a Jeol Model C 60 HL spectrometer in deuteriochloroform solution with tetramethylsilane as internal reference.

2,6-Di-(diethyl aminomethylenemalonate)pyridine (I).

A mixture of 3.5 g. of 2,6-diaminopyridine and 14.5 g. of diethyl ethoxymethylenemalonate (1:2.1 moles) was heated at 110° for 30 hours. After cooling, the resulting solid was treated with ether and the insoluble material collected by filtration to yield 12.0 g. (83.3% yield) of I. The analytical sample was obtained by crystallization from benzene. Yellow crystals m.p. 136-138°; NMR (deuteriochloroform) δ 10.94 (d, NH) δ 8.98 (d, CH), J = 12.6 cps.

Anal. Calcd. for $C_{21}H_{27}N_3O_8$: C, 56.12; H, 6.06; N, 9.35. Found: C, 55.80; H, 6.15; N, 9.45.

3,7-Dicarbethoxy-4,6-dihydroxy-1,9,10-anthryridine (II)

To 100 ml. of diphenyl ether was added 10 g. of I and the mixture was refluxed for 6 hours using a short air condenser in order to facilitate the elimination of ethanol formed in the reaction. The warm reaction mixture was then filtered and the residue washed with ethanol and ethyl ether yielding 5.9 g. of II (74.2%). The analytical sample was obtained by crystallization from dimethylsulfoxide, pale yellow crystals with m.p. above 320°. Principle IR peaks: 5.80, 5.91, 6.24, 6.52, 6.98, 8.45, 9.22 and 12.40 μ .

Anal. Calcd. for $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23; N, 11.76. Found: C, 56.87; H, 4.39; N, 11.99.

4,6-Dihydroxy-1,9,10-anthryridin-3,7-dicarboxylic Acid (III)

A mixture of II (5.0 g.), 2 N sodium hydroxide (100 ml.) and ethanol (40 ml.) was refluxed on a steam bath for 1 hour. After cooling, acidification of the reaction mixture with hydrochloric acid gave 4.0 g. of III (95.2%). The analytical sample was obtained by crystallization from dimethylsulfoxide-water, yellow-brown crystals with m.p. above 320°; principle IR peaks: 5.89, 6.30, 7.10, 8.09, 8.47, 12.20 and 12.81 μ .

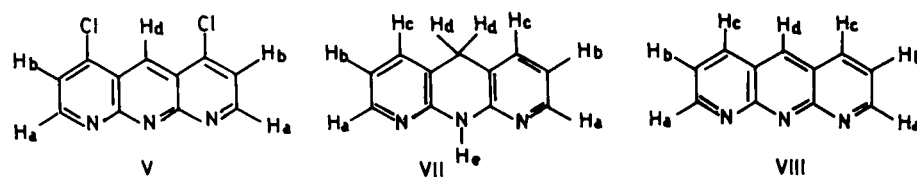
Anal. Calcd. for $C_{13}H_7N_3O_6$: C, 51.83; H, 2.34; N, 13.95. Found: C, 51.50; H, 2.50; N, 14.21.

4,6-Dihydroxy-1,9,10-anthryridine (IV)

A mixture of 4,6-dihydroxy-1,9,10-anthryridin-3,7-dicarboxylic acid (5.0 g.) and copper chromite (0.4 g.) in quinoline (20 ml.)

TABLE II

NMR Spectral Data of 4,6-Dichloro-1,9,10-anthryridine (V), 5,10-Dihydro-1,9,10-anthryridine (VII) and 1,9,10-Anthryridine (VIII) in Deuteriochloroform.



Compound	Chemical Shifts (δ)					Coupling Constants, cps			
	Ha	Hb	Hc	Hd	He	Jab	Jbc	Jac	Jcd
V	9.30	7.66	---	9.66	---	4.5	---	---	---
VII	8.25	6.84	7.40	4.16	9.19	4.8	7.9	1.2	$\lll 1$
VIII	9.46	7.62	8.52	8.98	---	4.2	8.6	2.1	$\lll 1$

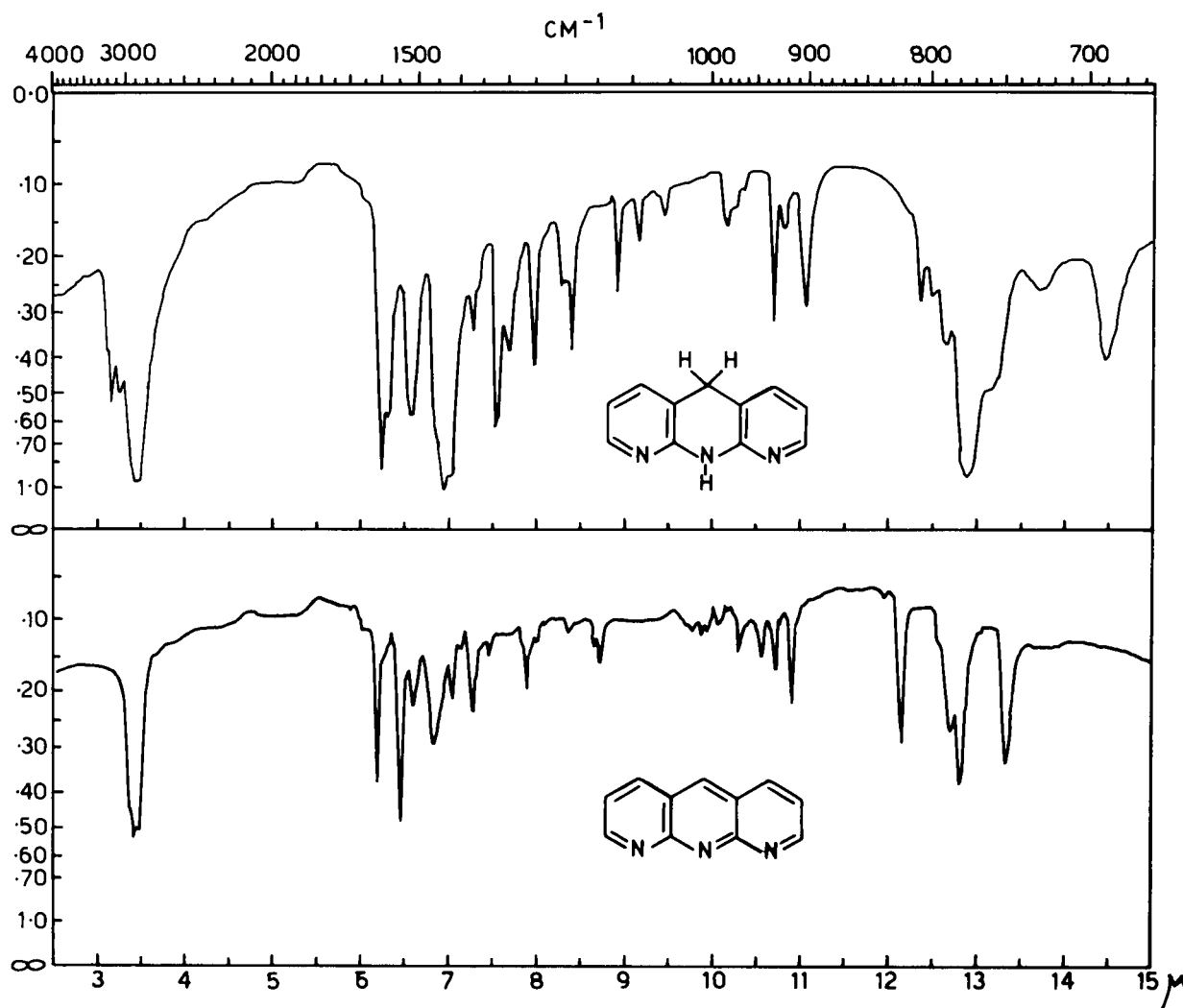


Fig. 1 - Infrared spectra of VII and VIII in nujol mulls.

was refluxed with stirring until the evolution of carbon dioxide had ceased (2-3 hours). The excess quinoline was then removed by distillation at reduced pressure and the residue was diluted with ethyl ether, collected and washed with ether. The mixture (3.9 g.) was extracted with 50 ml. of 35% aqueous potassium hydroxide. After standing overnight the resulting yellow product (potassium salt of IV) was collected and the mother liquors were utilized for a second extraction of the insoluble residue to give another fraction of potassium salt. The acidification of the combined fractions with dilute hydrochloric acid gave 2.8 g. (79.2%) of pure 4,6-dihydroxy-1,9,10-anthridine (IV). A small amount of the starting material (III) was recovered by acidification of the alkaline mother liquors.

The analytical sample of IV was obtained by crystallization of the potassium salt from water and by treatment of this with dilute hydrochloric acid, yellow crystals with m.p. above 320°; principle IR peaks: 6.20, 6.35, 6.62, 7.10, 8.35, 12.20 and 13.79 μ . The ethanolic solutions of the potassium salt fluoresce green in UV light.

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 62.02; H, 3.30; N, 19.90.

4,6-Dichloro-1,9,10-anthridine (V).

A mixture of 4,6-dihydroxy-1,9,10-anthridine (0.5 g.), phosphorus pentachloride (3.0 g.) and phosphorus oxychloride (25 ml.) was heated at 80° for 18 hours. The phosphorus oxychloride was removed by distillation with an oil-bath heated to 70-80° (at reduced pressure) and the residue was poured portionwise onto a well-cooled mixture of ice and sufficient ammonium hydroxide to maintain the reaction mixture at an alkaline pH. The alkaline mixture was extracted with five 200-ml. portions of methylene chloride and the combined extracts were dried over anhydrous magnesium sulfate and evaporated to dryness at reduced pressure to give 0.43 g. (73.3%) of V. The analytical sample was obtained by crystallization from toluene, yellow powder that sublimes above 200° and decomposes at 260°. Compound V decomposes slowly on standing.

Anal. Calcd. for $C_{11}H_5Cl_2N_3$: C, 52.84; H, 2.01; Cl, 28.36. Found: C, 53.07; H, 1.92; Cl, 28.30.

5,10-Dihydro-1,9,10-anthridine (VII).

Method a. From V.

The dichloro derivative V (0.11 g.) was treated with 0.15 g. of 10% Pd-C and 15 ml. of 5% KOH-methanol and hydrogenated at atmospheric pressure. The catalyst was removed by filtration and the solution was saturated with carbon dioxide and concentrated. The resulting precipitate (potassium carbonate) was removed by filtration, washed with methanol and the filtrate together with the washes, was evaporated to dryness (at reduced pressure). The residue sublimed at 160-170°/2-3 mm. giving 0.010 g. of VI (12.4%), colorless tablets, -m.p. 220° dec. For the IR spectrum see Figure 1.

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.36; H, 4.93; N, 22.79.

Method b. From VI.

5,10H-1,9,10-Anthyridin-5-one (0.280 g.) (2) was mixed intimately with 0.3 g. of zinc powder, 0.3 g. of sodium chloride and 1.5 g. of anhydrous zinc chloride. The mixture, which became wet from atmospheric moisture, was slowly heated up to 310-320° and maintained at this temperature for 5 minutes. After cooling, 15 ml. of water were added to the reaction mixture and the insoluble part was collected and boiled with 20 ml. of 2 N sodium hydroxide. The alkaline mixture was extracted with three 100-ml. portions of benzene. The combined extracts were dried over anhydrous magnesium sulfate and concentrated to a small volume (2-3 ml.) and left to crystallize. There was obtained 0.035 g. (13.4%) of 5,10-dihydro-1,9,10-anthyridine.

1,9,10-Anthyridine (VIII).

To a hot solution of 0.270 g. of 5,10-dihydro-1,9,10-anthyridine (VII) in 5 ml. of 2 N sulfuric acid was added 0.3 g. of potassium dichromate in 10 ml. of hot water. After cooling, the reaction mixture was made alkaline with 2 N sodium hydroxide and extracted with five 100-ml. portions of methylene chloride.

The combined extracts were dried over anhydrous magnesium sulfate and evaporated to dryness at reduced pressure: there was obtained 0.135 g. (50.5%) of 1,9,10-anthyridine. Crystallization from chloroform afforded white crystals with m.p. 295-297°. For the IR spectrum see Figure 1.

Anal. Calcd. for $C_{11}H_7N_3$: C, 72.91; H, 3.89; N, 23.19. Found: C, 72.98; H, 3.72; N, 23.30.

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