The Preparation of 3-Aminoanthyridine

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Nitration of anthyridine-2,6-dione (I) gave 7-nitroanthyridine-2,6-dione (II). Treatment of this compound with phosphorus pentasulfide afforded 7-aminoanthyridine-2,6-dithione (III). Desulfurization of the thioderivative III with Raney Nickel and subsequent aromatization of 3-amino-5,10-dihydroanthyridine (VI) in boiling nitrobenzene, gave 3-aminoanthyridine (VII) in satisfactory yield. The structure of 3-aminoanthyridine was demonstrated and its physicochemical features are not in agreement with that previously reported in literature. The preparation of 3-aminoanthyridine-5-one (XII) is also described.

Previously T. Takahashi and coworkers (1) described the isolation of 3-aminoanthryridine (VII) by treatment of 5-amino-2,2'-dipyridilamine hydrochloride with oxalic acid and glycerol at 130°. 3-Aminoanthyridine is reported to be a colourless solid melting at 125-128°. No other physicochemical data were reported by Takahashi and no structural proof was given. We recently reported the syntheses of several anthyridine derivatives (2a,b,c,d,e) and also the preparation of the parent nucleus (3) (m.p. 295-297°). The structures of these compounds were unequivocally assigned based upon chemical and physical evidence. In general, these substances are very high-melting crystalline solids, slightly soluble in the usual organic solvents. The relatively low melting point of the product isolated by Takahashi led us to repeat the reaction. However, various attempts to prepare the substance melting at 125-128° failed giving almost quantitative recovery of starting material.

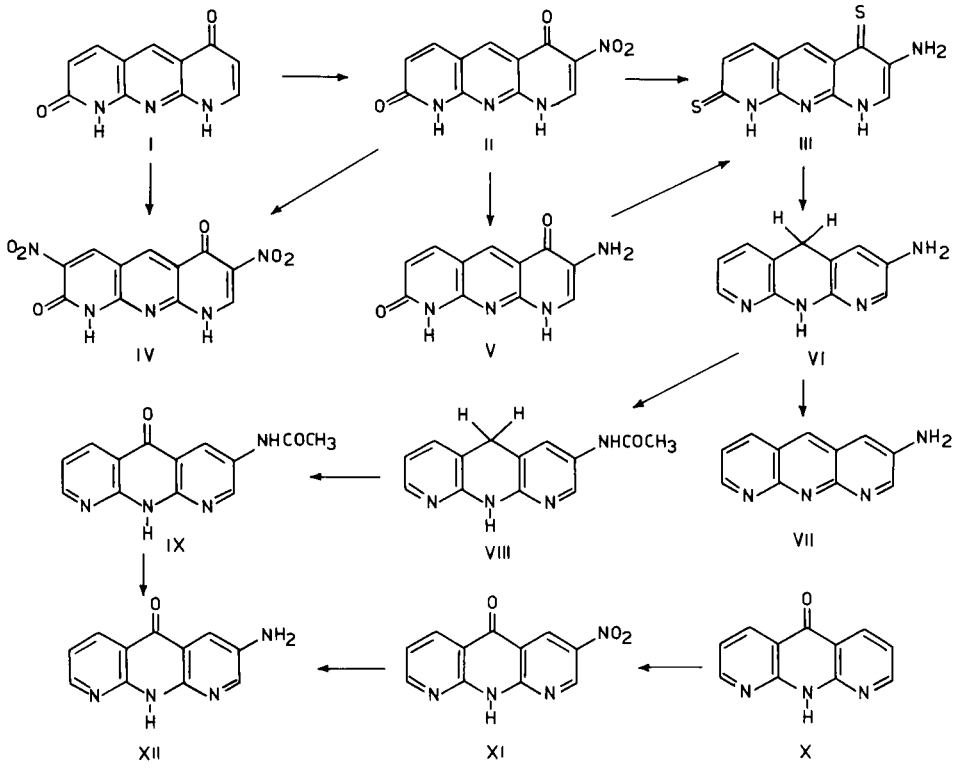
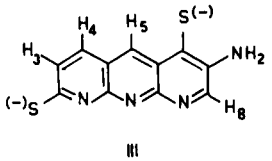


TABLE I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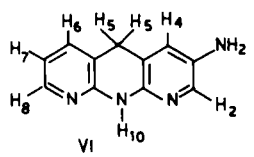
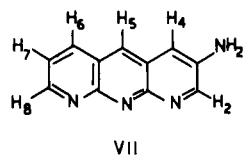

VI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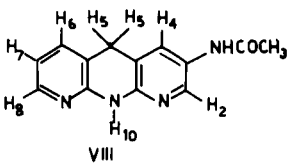
VIII

	Chemical shifts (δ)									Coupling const. cps					
Compound	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_{10}	$-NH_2$	$J_{2,4}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$	$J_{3,4}$	Solvent
III (a)	-----	7.33	7.66	8.98	-----	-----	8.36	-----	-----	-----	-----	-----	-----	9.0	NaOD-D_2O
VI	7.64	-----	6.90	4.08	7.48	6.80	8.12	9.68	4.90	2.4	7.5	1.2	5.0	-----	DMSO-d_6
VII	9.00	-----	7.30	8.82	8.50	7.56	9.13	-----	6.25	3.0	8.2	1.9	3.8	-----	DMSO-d_6
VIII (b)	8.20	-----	7.69	4.10	7.40	6.78	8.01	9.83	-----	2.4	7.6	1.2	5.0	-----	DMSO-d_6

(a) 2,2,3,3-Tetradeutero-3-(trimethylsilyl)propionic acid sodium salt as internal reference. (b) The -NH-CO- and -CO-CH_3 signals appear at δ 9.83 and δ 2.03 respectively.

In this paper we describe the synthesis and the characterization of 3-aminoanthyridine (VII). Anthyridine-2,6-dione (I) (2c) was considered the ideal starting material for this synthesis since it is readily available from the reaction of 2-amino-7-hydroxy-1,8-naphthyridine with diethyl ethoxymethylenmalonate. Upon treatment of I in concentrated sulfuric acid with a slight excess of nitric acid (molar ratio 1:1.2) there was obtained the mononitroderivative II, while the use of a large excess of nitric acid led to the formation of the dinitroderivative IV. In order to eliminate the oxygen functions, a procedure which had been applied in the preparation of anthyridine (4) was followed. Thus, treatment of 7-nitroanthyridine-2,6-dione (II) with phosphorus pentasulfide in anhydrous pyridine affording 7-aminoanthyridine-2,6-dithione (III), involved both the replacement of oxygen by sulfur and reduction of the nitro group to amino group. This was proven by the reduction of II with sodium dithionite to give 7-aminoanthyridine-2,6-dione (V), which upon action of phosphorus pentasulfide also gave III.

The assignment of the position of the amino group, and consequently the position of the nitro group in structure II, was proven by spectral data (see Table). In fact, the nmr spectrum of III showed two proton-signals at δ 7.33 and δ 7.66 with a large coupling (J = 9.00 cps). Clearly, these signals are due to H_3 and H_4, respectively, because the high value of the coupling constant excludes the possibility that substitution has occurred at C_3. If the amino group was located at C_3 we could expect to observe a coupling constant of 4-5 cps between H_7 and H_8 (3,4,5,6a,b,c).

Treatment of 7-aminoanthyridine-2,6-dithione (III) with Raney nickel in alcoholic sodium hydroxide solution resulted in the formation of 3-amino-5,10-dihydroanthyridine (VI). The elemental analysis and the nmr spectrum (see Table) of this product were consistent with the assigned structure. Since the conversion of aminoacridanes into aminoacridines, *via* the acetylderivative, has been easily effected by potassium dichromate (7), 3-acetylamino-5,10-dihydroanthyridine (VIII) (nmr data, see Table) was allowed to react in acetic acid with this oxidant. However, the major product was 3-acetylaminoanthyridine-5-one (IX), while a small amount of the target compound, 3-aminoanthyridine (VII), was isolated from the mother liquors. Attempts to obtain VII from VI using ferric chloride (5) were completely unsuccessful. However, the dihydroderivative VI underwent facil aromatization to 3-aminoanthyridine (VII) on refluxing in nitrobenzene. Elemental analysis, ir and nmr spectra (see Table) are all consistent with the assigned structure.

It is of interest to compare the nmr spectra of 3-aminoquinoline, 3-amino-1,8-naphthyridine (8) and 3-aminoanthyridine with their unsubstituted nuclei; the one interesting feature is the increase in $J_{2,4}$ when going from quinoline ($J_{2,4}$ = 1.77 cps) (5) to 3-aminoquinoline ($J_{2,4}$ = 2.47 cps; ΔJ = +0.7 cps) (9), from 1,8-naphthyridine ($J_{2,4}$ = 2.0 cps) (6a,b,c) to 3-amino-1,8-naphthyridine ($J_{2,4}$ = 2.77 cps; ΔJ = +0.77 cps) (9) and finally from anthyridine ($J_{2,4}$ = 2.1 cps) (3) to 3-aminoanthyridine ($J_{2,4}$ = 3.0 cps; ΔJ = +0.9 cps). The relatively large $J_{2,4}$ in 3-aminoanthyridine is not surprising. 3-Aminoanthyridine is a red-orange solid which darkens without melting below 320° and exhibits a marked yellow green fluorescence in ethanolic solution even when very dilute. Although it is impossible to assign a structure to the compound isolated by Takahashi, it appears that its structure was incorrectly assigned. With regard to 3-acetylaminoanthyridine-5-one (IX), its structure was pro-

vided by alkaline hydrolysis which gave compound XII, identical with that obtained by nitration of anthyridine-5-one (X) (2e) and subsequent reduction of the nitro derivative XI.

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 Zeiss Model PMQ II spectrophotometer in ethanol. The nmr spectra were obtained on a Jeol Model C 60 HL spectrometer.

7-Nitroanthyridine-2,6-dione (II).

A solution of anthyridine-2,6-dione (I) (2c) (2.00 g.) in concentrated sulfuric acid (25 ml.) was treated with 0.76 ml. of nitric acid (d 1.4, 1:1.2 moles) and heated at 100° for 30 minutes. After cooling, the solution was poured onto ice and the resulting precipitate was collected and washed with water (2.25 g., 93%); yellow crystals, m.p. above 320° (from DMSO); principal ir peaks: 5.96, 6.09, 6.16, 6.30, 7.10, 7.50, 7.86, 11.90, 12.45 μ.

Anal. Calcd. for $C_{11}H_6N_4O_4$: C, 51.16; H, 2.32; N, 21.70. Found: C, 51.00; H, 2.43; N, 21.60.

3,7-Dinitroanthyridine-2,6-dione (IV).

From I.

To a solution of anthyridine-2,6-dione (5.0 g.) in concentrated sulfuric acid (50 ml.) was added 10 ml. of nitric acid (d 1.4). The solution was heated at 100° for 3 hours. After cooling, the reaction mixture was poured onto ice and the resulting solid collected and washed with water (5.8 g., 81.5%). The analytical sample was obtained by crystallization from DMSO, yellow crystals with m.p. above 320°. Principal ir peaks: 5.95, 6.17, 6.26, 6.52, 7.10, 7.40, 7.62, 11.85, 12.38, 12.50 μ. The nmr spectrum in DMSO-d_6 (TMS) shows three singlets at δ 8.95, 9.10, 9.15; however, the exact assignment of these could not be made on the basis of chemical shifts.

Anal. Calcd. for $C_{11}H_5N_5O_6$: C, 43.56; H, 1.65; N, 23.10. Found: C, 43.20; H, 1.80; N, 23.10.

From II.

The title compound was obtained in 89.4% yield by analogous treatment of II with excess nitric acid.

7-Aminoanthyridine-2,6-dione (V).

To a boiling suspension of 7-nitroanthyridine-2,6-dione (II) (2.2 g.) in 5% sodium hydroxide solution (200 ml.) was added portionwise an excess of sodium dithionite until the solid was dissolved. The solution was acidified with hydrochloric acid and refluxed for 15 minutes. The resulting precipitate was collected, washed with water and dried (1.94 g., 100%). The product was extracted with hot 40% potassium hydroxide solution and the potassium salt of V left to crystallize. Treatment of this latter with hydrochloric acid gave the analytical sample, orange powder m.p. above 320°. Principal ir peaks: 2.92, 3.00, 6.00, 6.18, 6.42, 7.52, 7.75, 8.06, 8.36, 11.72, 12.65 μ. Attempts to determine nmr spectrum were not successful due to its insolubility.

Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 57.50; H, 3.38; N, 24.22.

7-Aminoanthyridine-2,6-dithione (III).

From II.

To a boiling suspension of 2.25 g. of 7-nitroanthyridine-2,6-dione (II) in 300 ml. of anhydrous pyridine, was added 5.0 g. of phosphorus pentasulfide. After refluxing for 20 hours, the warm reaction mixture was decanted and the dark residue treated with boiling water. The solid material was collected, dried and extracted with carbon disulfide to remove a small quantity of sulfur; there was obtained 0.7 g. of III. The pyridine mother liquors were diluted with 300 ml. of water and left to stand overnight. The sulfur which separated was removed by filtration and the filtrate was evaporated under reduced pressure to give a residue which was treated with water (50 ml.), collected and extracted with carbon disulfide. There was obtained 1.5 g. of III (total yield 97.0%); dark-brown crystals, m.p. above 320° (from DMF-water). Principal ir peaks: 2.90, 3.05, 6.19, 7.26, 7.45, 7.96, 8.42, 8.96, 10.71, 12.79 μ; nmr data, see Table.

Anal. Calcd. for $C_{11}H_8N_4S_2$: C, 50.77; H, 3.10; N, 21.53; S, 24.60. Found: C, 50.65; H, 3.03; N, 21.20; S, 25.00.

From V.

The thioderivative III was also obtained from 7-aminoanthyridine-2,6-dione using the above procedure (93.7% yield).

3-Amino-5,10-dihydroanthyridine (VI).

To a boiling solution of 7-aminoanthyridine-2,6-dithione (III) (1.0 g.) in ethanolic sodium hydroxide solution (50 ml. of 10% sodium hydroxide solution and 50 ml. of ethanol) was added portionwise Raney nickel (about 15 g.) during 15-20 minutes until the colour changed from red to yellow. The catalyst was then removed and the solution was concentrated to 20-30 ml. at reduced pressure and extracted with methylene chloride (10 x 100 ml.).

The combined extracts were dried over magnesium sulfate and evaporated to dryness at reduced pressure to give 0.2 g. (26.3%) of VI. The analytical sample was obtained by crystallization from benzene as pale yellow crystals which decompose at 195-200°. Principal ir peaks: 2.89, 2.96, 3.15, 6.24, 6.55, 6.98, 7.96, 8.05, 10.83, 12.91 μ uv λ max (ethanol), 222 mμ (log ε 3.97 inflection), 317 mμ (log ε 4.07); nmr data, see Table.

Anal. Calcd. for $C_{11}H_{10}N_4$: C, 66.65; H, 5.09; N, 28.27. Found: C, 66.80; H, 4.84; N, 28.00.

3-Aminoanthyridine (VII).

A solution of 3-amino-5,10-dihydroanthyridine (VI) (0.2 g.) in 6 ml. of nitrobenzene was refluxed for 5 minutes. After cooling, the precipitate was collected and washed with ethyl ether (0.13 g., 65.7%). Crystallization from ethanol afforded orange-red needles that darken without melting below 320°. Principal ir peaks: 2.96, 3.13, 6.11, 6.45, 7.00, 10.10, 11.09, 12.32, 13.39 μ; uv λ max (ethanol), 222 (log ε 4.32), 262 (log ε 4.54), 350 mμ (log ε 3.62); vis λ max (ethanol), 434 mμ (log ε 3.80); nmr spectrum, see Table.

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.33; H, 4.11; N, 28.56. Found: C, 67.10; H, 4.20; N, 28.67.

3-Acetylamino-5,10-dihydroanthyridine (VIII).

A mixture of 3-amino-5,10-dihydroanthyridine (VI) (0.5 g.) and acetic anhydride (5 ml.) was heated at 100° for 15 minutes. The reaction mixture was diluted with water (10 ml.) and left to stand at room temperature until the solid was completely dissolved. The solution was then made basic with ammonium hydroxide and the resulting precipitate collected. There was obtained 0.548 g. of VIII (90.4%). Crystallization from dioxane gave brown crystals,

m.p. above 320°. Principal ir peaks: 6.08, 6.24, 6.95, 7.14, 7.30, 7.60, 10.80, 10.93, 11.20, 12.94 μ: nmr data, see Table.

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 65.20; H, 5.00; N, 23.68.

3-Acetylaminoanthyridine-5-one (IX).

To a hot solution (100°) of 3-acetylamino-5,10-dihydroanthyridine (VIII) (0.140 g.) was added dropwise a solution of 0.2 g. of potassium dichromate in 3 ml. of hot water. The mixture was heated on the steam bath for 15 minutes. After cooling, the solid was collected, treated with ammonium hydroxide and collected, yield 0.090 g. (60.7%). The analytical sample was obtained by crystallization from DMF, yellow crystals, m.p. above 320°. Principal ir peaks: 3.00, 5.91, 6.15, 6.27, 7.00, 7.80, 8.05, 10.78, 11.08, 12.62 μ.

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.30; H, 4.01; N, 21.70.

The acetic mother liquors, subjected to alkaline hydrolysis and extracted with methylene chloride, gave a trace of 3-aminoanthyridine (VII).

3-Nitroanthyridine-5-one (XI).

A solution of anthyridine-5-one (X)(2e) (0.5 g.) in concentrated sulfuric acid (4 ml.) was treated with 0.21 ml. of nitric acid (d 1.4, 1:1.2 moles) and heated at 100° for 30 minutes. After cooling, the solution was poured onto ice and the resulting precipitate was collected, washed with water and dried (0.580 g., 94.4%). Yellow crystals with m.p. above 320° (from DMSO). Principal ir peaks: 3.25, 6.02, 6.17, 6.26, 7.49, 8.03, 8.11, 11.00, 11.95, 12.57 μ.

Anal. Calcd. for $C_{11}H_6N_4O_3$: C, 54.54; H, 2.47; N, 23.14. Found: C, 54.20; H, 2.50; N, 22.98.

3-Aminoanthyridine-5-one (XII).

From IX.

Compound XII was obtained in 72% yield by hydrolysis of the acetylderivative IX with aqueous alkali and acidification of the solution with acetic acid; orange-yellow needles, m.p. above 320° (from DMSO-water). Principal ir peaks: 2.88, 2.96, 6.14, 6.28, 7.06, 7.91, 8.05, 10.82, 11.03, 12.73 μ.

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.35; H, 3.48; N, 26.37.

From XI.

A 0.1 g. sample of nitroderivative XI and 0.1 g. of palladium (10%) on charcoal were placed in 100 ml. of anhydrous ethanol and shaken under 15 atm. of hydrogen pressure at room temperature for 16 hours. The reaction mixture was heated to boiling and the catalyst removed. Evaporation of the solution to dryness yielded 0.035 g. of XII. Additional 0.015 g. of XII was obtained by further extraction of the catalyst with boiling ethanol (100 ml.); total yield 57%.

Acknowledgment.

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(8) The preparation of 3-aminonaphthyridine will be reported at a later date.

(9) The nmr spectrum of this substance was recorded in this laboratory.