A New Synthesis of Anthyridine Derivatives

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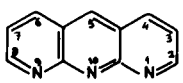
An Ullmann reaction between 2-bromonicotinic acid and 2,6-diaminopyridine gave 6′-amino-2,2′-dipyridylamino-3-carboxylic acid (V). The latter was converted into 7-amino-5*H*-dipyrido-[1,2-*a*:2′,3′-*d*]pyrimidin-**5**-one (VII) by heating with polyphosphoric acid and into 2-amino-5,10 *H*-anthyridin-5-one (VIII) by heating with concentrated sulfuric acid. Structure proofs of VII and VIII are given and some derivatives of VIII are described.

In view of the importance of acridine derivatives in the pharmaceutical field, it appeared interesting to study the synthesis and properties of related compounds such as anthyridines.



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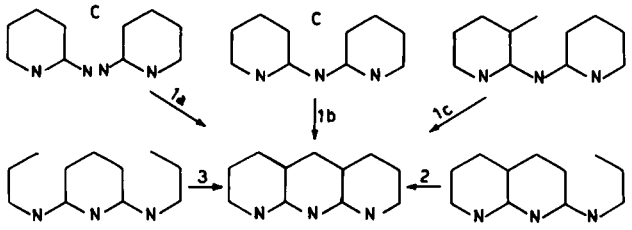
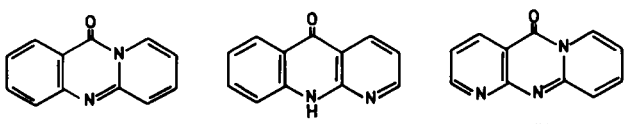
Anthyridine (1,9,10-triazaanthracene or pyrido[2,3-*b*]-1,8-naphthyridine) (I) is still unknown and only some 5-alkyl-2,8-diaminoanthyridines (1) and 3-aminoanthyridine (2) had been reported in the literature up to 1964. These compounds had been prepared by the routes **1a** and **1b** (Table I), but only very scarce details on their synthesis had been given.

We have recently reported the preparation of 4,6-dihydroxy-2,8-dimethylanthyridine and 2,6-dihydroxy-4,8-dimethylanthyridine (3) by a new method (Table I, Scheme 2) involving the closure of a pyridine ring on the side of a preformed 1,8-naphthyridine system. This method was found useful for the preparation of a series of anthyridine derivatives (4,5). Another method used was based on the closure of two pyridine rings on the sides of a central one (Table I, Scheme 3). This method was only used indirectly, since the formation of an intermediate naphthyridine, followed by the cyclization of the second side-chain, led us to the same product (3,6).

Table I
Schemes of Anthyridine Syntheses



In this paper we have described another route for the preparation of anthyridine derivatives which is analogous to the general method of synthesis of acridones from diphenylamine-2-carboxylic acids (7). However, some difficulties were foreseen because of the deactivating influence of the pyridine nitrogen atom in an intramolecular electrophilic attack. Cyclization of 2-(2′-pyridylamino)benzoic acid indeed gave 11 *H*-pyrido[2,1-*b*]-quinazolin-11-one (II) (8,9) and not 5,10 *H*-benzo[*b*]-1,8-naphthyridin-5-one (III) (10,11). The latter compound was instead obtained from 2-phenylaminonicotinic acid (12). Also, the cyclization of 2-(2′-pyridylamino)nicotinic acid gave 5*H*-dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one (IV) (13) and not the isomeric XVI.



II III IV

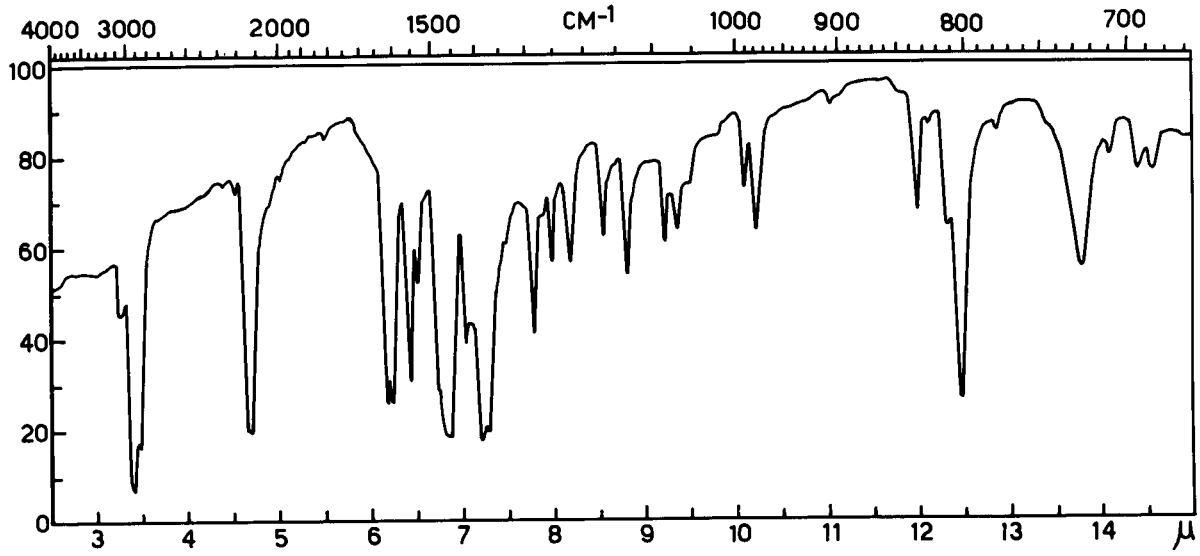


Figure 1. Infrared Spectrum of 6-Azidotetrazolo[1,5-*a*]anthyridine (XV).

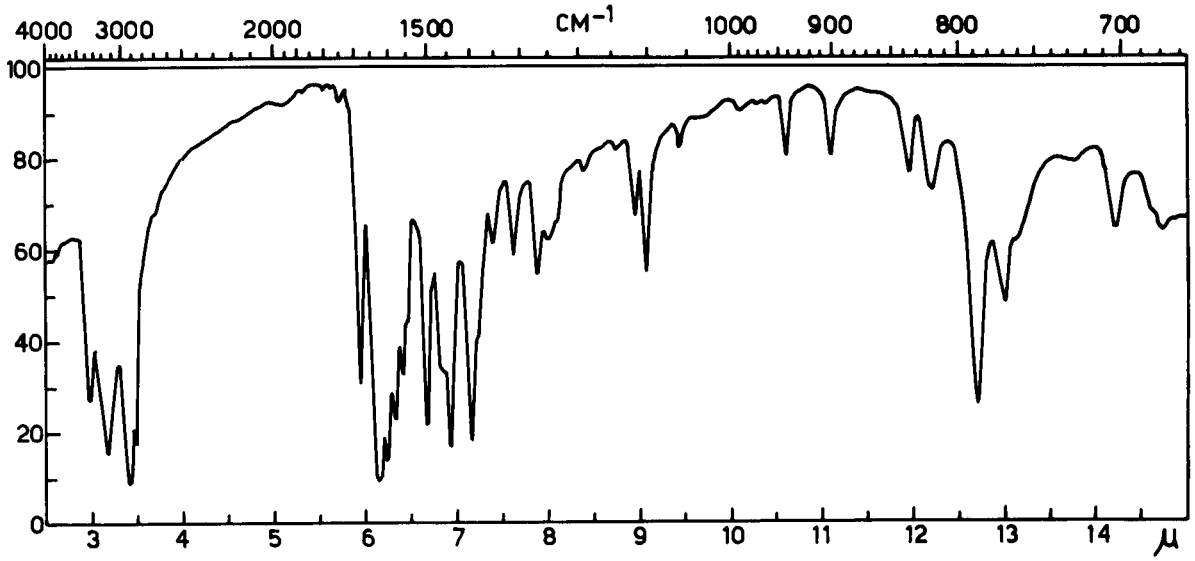


Figure 2. Infrared Spectrum of 2-Amino-5,10 *H*-anthyridin-5-one (VIII).

The compound selected for our synthesis was 6'-amino-2,2'-dipyridylamino-3-carboxylic acid (V) since the presence of an amino group in the 6'-position should facilitate cyclization in the 3'-position. An analogous situation occurs in the synthesis of several 1,8-naphthyridines (14). However, the possibility of cyclization occurring on the nitrogen atom-1' (15) was not to be excluded.

Compound V was prepared in > 50% yield *via* an Ullman reaction between 2-bromonicotinic acid and 2,6-diaminopyridine. The use of 2-chloronicotinic acid decreased the yield to 15-20%.

Difficulties were incountered in the subsequent conversion of V to VIII. The heating of V on a steam bath with phosphorus oxychloride, under the conditions

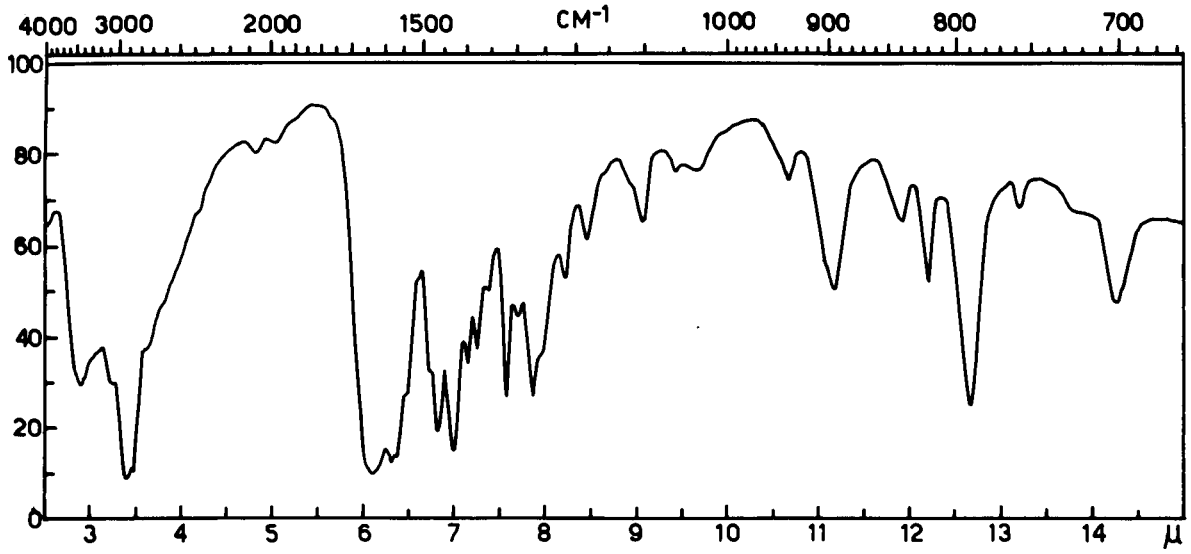


Figure 3. Infrared Spectrum of 2-Hydroxy-5,10*H*-anthyridin-5-one (XI).

utilized for the cyclization of diphenylaminocarboxylic acids to acridones (7), as well as the treatment with a mixture of polyphosphoric acid and phosphorus oxychloride, did not produce VIII. However, these reagents were useful instead in the synthesis of III (12).

Addition of V to polyphosphoric acid at 170° produced an orange red compound to which we attributed the structure of 7-amino-5*H*-dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one (VII). It melted at a relatively low temperature (220-222°) and easily gave, by hydrolysis, the starting compound V, and, by alcoholysis with methanol, the methyl ester VI which was also directly obtained from V.

Attempts to cyclize V with sulfuric acid under mild conditions failed. The addition of V to sulfuric acid at 200° gave instead a pale yellow product (78% yield) which was isomeric with VII. The stability of this compound to acids, alkalies, and to heat led us to attribute to it the anthyridine structure VIII. Additional proof of this structure was obtained from the reaction of VIII with nitrous acid which gave 2-hydroxy-5,10 *H*-anthyridin-5-one (XI). The latter compound was also converted into a mixture of the monochloro XIV and dichloro XIII derivatives upon heating with phosphorus oxychloride at 60° for 15 hours. The dichloro derivative XIII was probably the main product of the reaction, but it was isolated only in low yield since it is easily hydrolyzed to the monochloro derivative XIV. Further proof of the anthyridine structure was provided by the reaction of the dichloro derivative XIII with sodium azide giving 6-azidotetrazolo-[1,5-*a*]anthyridine (XV). The I.R. spectrum of XV (Nujol mull) showed the characteristic absorption band at 2120 cm^{-1} of the azidic group and other bands at 1000-1100 cm^{-1} for the tetrazole ring (Figure 1).

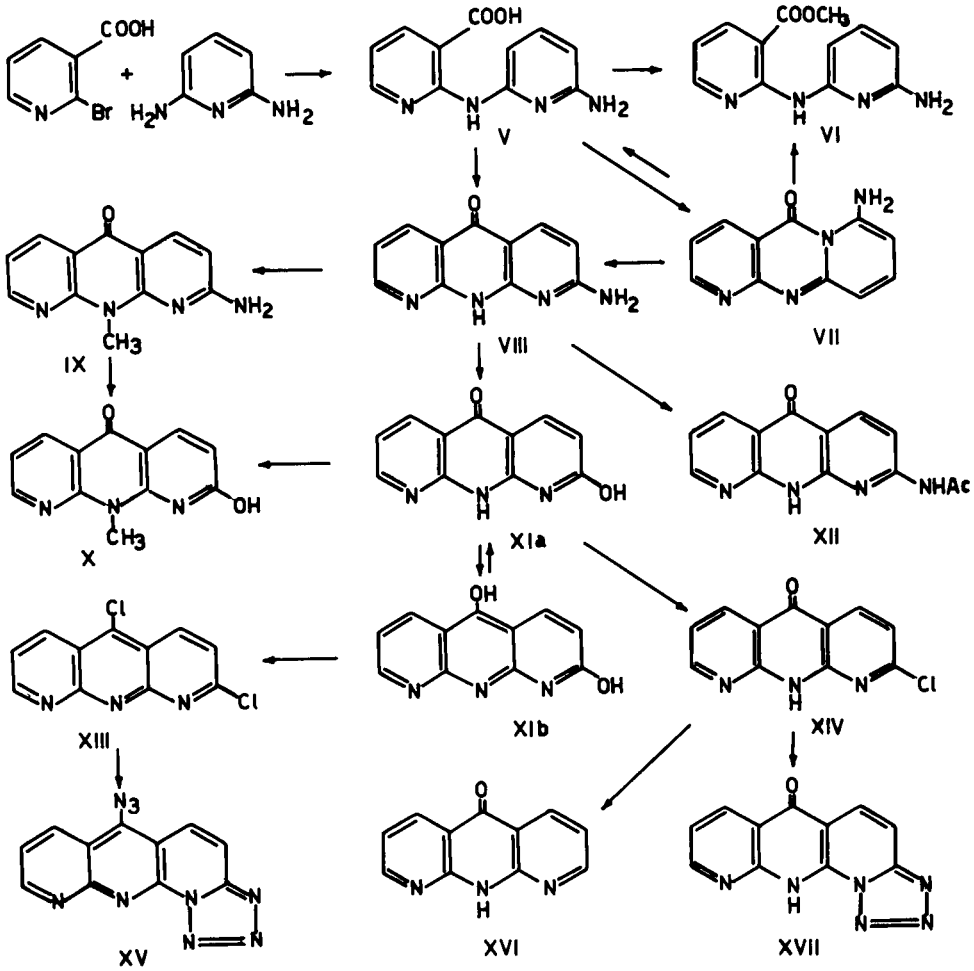
Treatment of the monochloro derivative XIV with sodium azide gave 6,11*H*-tetrazolo[1,5-*a*]anthyridin-6-one (XVII), whose I.R. spectrum showed tetrazole (1000-1100 cm^{-1}) but not azide bands.

Several attempts to convert XIII to I were unsuccessful, and the reduction of XIV gave 5,10 *H*-anthyridin-5-one (XVI).

The methylation of VIII gave 2-amino-10-methyl-5,10-*H*-anthyridin-5-one (IX) which was converted with nitrous acid into X. Compound X was also obtained on methylation of XI.

The methylation product of VIII is thought to correspond to the *N*-methyl derivative IX and not to the isomeric *O*-methyl derivative based on its high melting point (315-317°) and a carbonyl band at 1660 cm^{-1}.

The lack of reactivity of the carbonyl group of VIII towards phenylhydrazine and hydroxylamine denotes vinylogous amide character similar to that represented by acridone, 4-quinolone, and 4-pyridone. The mechanism of the cyclization of V to VIII was not investigated. However, we think that it may be similar to the mechanism reported for the conversion of diphenylamine-2-carboxylic acids to acridones (16).



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.

6′-Amino-2,2′-dipyridylamino-3-carboxylic Acid (V).

Ten grams of 2,6-diaminopyridine and 6.7 g. of 2-bromonicotinic acid (17) were intimately mixed with 5.0 g. of anhydrous potassium carbonate, 0.02 g. of Ullmann copper and a trace of potassium iodide. The mixture was slowly warmed to 170° and kept at this temperature for 4 hours after which the reaction mixture was cooled and extracted several times with boiling ethyl acetate to remove unreacted 2,6-diaminopyridine. The residual solid was extracted twice with 100 ml. of boiling water and 70 g. of potassium hydroxide (pellets) were added to the combined extracts. The potassium salt of V was filtered after standing overnight, treated with anhydrous acetic acid (to *p*H 5), diluted with water, and again allowed to stand overnight. The resulting pale yellow precipitate was collected, crystallized from water and dried. The yield of V was 4.0-5.0 g. (52-65%), m.p. 265-267° (dec.).

Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.36; H, 4.53; N, 24.26.

7-Amino-5*H*-dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one (VII).

One gram of V was added to 10.0 g. of polyphosphoric acid at 170° and the mixture was heated at the same temperature for 15 minutes. After cooling the solution was poured onto crushed ice and made basic with cold concentrated ammonium hydroxide. The orange red solid was collected by filtration, washed with water and dried at 120° (0.57 g., 62%). The compound could be crystallized from toluene or chloroform-petroleum ether (b.p. 40-60°), but the analytical sample was purified by sublimation (180-190°/0.2 mm.) since it has a tendency to retain the crystallization solvent. Orange red crystals m.p. 220-222°, were obtained.

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.60; H, 3.87; N, 26.07.

The above product VII when heated with water on a steam bath was quantitatively reconverted into V.

Methyl 6′-amino-2,2′-dipyridylamino-3-carboxylate (VI).

Method a. By Alcoholysis of VII.

A mixture of VII (0.1 g.) and 10 ml. of anhydrous methanol was left at room temperature until solution was complete. The

solution was then evaporated to dryness and the residue (0.1 g., 87%) was crystallized from aqueous methanol to give VI, m.p. 156-158°.

Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.04; H, 4.75; N, 23.06.

Method b. By Methylation of V.

Dry hydrogen chloride was passed through a boiling solution of 0.2 g. of V in 25 ml. of anhydrous methanol for 4 hours. Evaporation of the solvent gave a residue which upon neutralization with sodium carbonate solution gave 0.17 g. of VI (80%).

2-Amino-5,10 *H*-anthyridin-5-one (VIII).

Method a. From V.

To 20 ml. of preheated (200°) concentrated sulfuric acid was added 2.5 g. of V and the solution was maintained at this temperature for 10 minutes. After cooling, the reaction mixture was poured onto crushed ice and made alkaline with concentrated ammonium hydroxide. After several hours the precipitate was collected, washed with water, and crystallized from dimethyl sulfoxide to give 1.8 g. (78%) of yellow product, m.p. above 320°. U.V., λ max (log ε) 232 (4.44), 251 (4.30), 288 (4.05), 329 (4.19), 358 (4.05), 370 (4.03, inf.), 373 mμ (4.04); I.R. spectrum (see Figure 2).

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.17; H, 3.90; N, 26.25.

Method b. From VII.

This compound was converted under the conditions described under Method a into the aminoanthyridone VIII, in 80% yield. Compound VIII was collected unchanged after reflux with 10% sodium hydroxide solution.

2-Acetylamino-5,10 *H*-anthyridin-5-one (XII).

A mixture of 0.25 g. of VIII and 5 ml. of acetic anhydride was refluxed for 5 hours. After cooling, the reaction mixture was poured onto water and the precipitate was collected (0.2 g., 66.7%), washed with water and crystallized from dimethylformamide. The compound (small white crystals) slowly sublimes above 250° without melting.

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.29; H, 4.01; N, 22.19.

2-Hydroxy-5,10 *H*-anthyridin-5-one (XI).

Compound VIII (4 g.) was dissolved in 60 ml. of concentrated sulfuric acid, the solution was cooled to 0°, and excess sodium nitrite was added in small amounts. The reaction mixture was allowed to come to room temperature and held there for 1 hour with occasional stirring and was then poured onto crushed ice. The solution was neutralized with concentrated ammonium hydroxide and allowed to stand overnight. The precipitate was collected by filtration (3.2 g., 79.7%), washed with water and purified by crystallization from dimethylsulfoxide or by sublimation at 330°/2-3 mm giving small yellow needles, m.p. above 320°. U. V., λ max (log ε) 224 (4.46), 258 (4.16), 306 (4.40), 378 mμ (3.94); I. R. spectrum (see Figure 3).

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.86; H, 3.40; N, 19.64.

2-Amino-10-methyl-5,10 *H*-anthyridin-5-one (IX).

A mixture of 0.8 g. of VIII, 20 ml. of 10% aqueous potassium hydroxide, 10 ml. of ethanol and 4 ml. of methyl iodide was heated at 60° for 17 hours. After cooling, the solid was collected (0.45 g., 52.7%), washed with water and ethanol, and crystallized twice from dioxane-dimethylformamide (3:1) giving pale brown-yellow crystals which melted at 315-317°.

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.71; H, 4.75; N, 25.02.

2-Hydroxy-10-methyl-5,10 *H*-anthyridin-5-one (X).

Method a. From XI.

A mixture of 0.1 g. of XI and 2 ml. of 10% aqueous potassium hydroxide, 1 ml. of methyl iodide and 1 ml. of ethanol was heated at 60° for 3 hours and allowed to stand overnight at room temperature. Acidification of the filtered solution gave 0.02 g. (18.8%) of X, which was purified by crystallization from anhydrous acetic acid, m.p. above 320°.

Anal. Calcd. for $C_{12}H_9N_3O_2$: N, 18.49. Found: N, 18.03.

Method b. From IX.

To a cooled (0°) solution of 0.15 g. of IX in 3 ml. of concentrated sulfuric acid was added an excess of sodium nitrite in small amounts and the mixture, after standing at room temperature for 30 minutes, was poured onto ice. Treatment with ammonium hydroxide (to *p*H 2-3) gave a solid (X) which was collected by filtration, washed with water, and dried (0.13 g., 86.3%).

2-Chloro-5,10 *H*-anthyridin-5-one (XIV) and 2,5-dichloroanthyridine (XIII).

A mixture of 1.0 g. of XI and 15 ml. of phosphorus oxychloride was heated at 60° for 15 hours. The excess phosphorus oxychloride was removed by vacuum distillation (60°) and the residue was poured onto a well-cooled mixture of ice and excess ammonium hydroxide. The brown solid was collected, washed with dilute ammonium hydroxide and dried at 120° (0.59 g.). It consisted (as indicated from its I.R. spectrum) of a mixture of XIII and XIV. The mixture was extracted with hot anhydrous benzene (30 ml.) and concentration of the extract to about one third of the original volume caused a small quantity of XIII to separate. The solution was then evaporated to dryness and the residue was combined with the benzene-insoluble fraction. The combined solids were purified by crystallization from toluene or preferably by sublimation at 250°/2-3 mm. to give pale yellow crystals of the monochloro derivative XIV, m.p. 310° (dec.).

Anal. Calcd. for $C_{11}H_6ClN_3O$: C, 57.03; H, 2.60; Cl, 15.30. Found: C, 56.87; H, 2.71; Cl, 15.35.

The initial basic filtrate, together with the washings, was extracted several times with methylene chloride. The combined extracts were dried (magnesium sulfate) and evaporated to dryness at reduced pressure. The residue (0.25 g. of crude XIII) was crystallized from benzene or benzene-petroleum ether (b.p. 40-60°), but no pure product was obtained after several recrystallizations. The pale yellow product decomposes above 240°.

An attempt to purify XIII by chromatography through a column of neutral alumina (eluent: methylene chloride) gave pure XIV.

6-Azidotetrazolo[1,5-*a*]anthyridine (XV).

To a suspension of 0.25 g. of XIII in 10 ml. of dimethylformamide was added 0.3 g. of sodium azide and the mixture was stirred at room temperature for 24 hours. The solution was poured onto water and the precipitate was collected, washed with water and dried (0.13 g., 49.5%). It was then crystallized from dimethylformamide, collected, washed with methanol, and dried *in vacuo* at 80° for 15 minutes to give pale yellow needles of XV which decompose above 150°. I.R. spectrum (see Figure 1).

Compound XV, when heated on a platinum plate, explodes

violently, and it acquires a greenish colour when exposed to the sunlight.

Anal. Calcd. for $C_{11}H_5N_9$: C, 50.20; H, 1.93; N, 47.95. Found: C, 50.60; H, 2.14; N, 48.10.

6,11 *H*-Tetrazolo[1,5-*a*]anthyridin-5-one (XVII).

To a suspension of 0.16 g. of XIV in 7 ml. of dimethylformamide was added 0.16 g. of sodium azide. The mixture was heated at 160° for 30 minutes. After cooling, the solution was diluted with water (40-50 ml.) and allowed to stand for several hours. The solid (XVII) was collected, washed with water, dried (0.06 g., 36.4%) and crystallized from dimethylformamide. The compound, upon heating, darkens above 250° without melting.

Anal. Calcd. for $C_{11}H_6N_6O$: C, 55.40; H, 2.52; N, 35.20. Found: C, 55.29; H, 2.60; N, 34.90.

5,10 *H*-Anthyridin-5-one (XVI).

To a suspension of 0.6 g. of XIV in 100 ml. of dioxane was added 2 ml. of triethylamine and 0.6 g. of 10% palladium on charcoal. The product was then hydrogenated at atmospheric pressure for 15 hours. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was treated with water (5-6 ml.) and the solid (XVI) was collected and washed (yield 0.11 g.). The catalyst was extracted with boiling dioxane (or dimethylformamide) and the extract was evaporated to dryness under reduced pressure. The residue, upon treatment with water, gave 0.145 g. of XVI (total yield 50%). The product was purified by crystallization from dimethylformamide, m.p. above 320° (subl.).

Anal. Calcd. for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 67.22; H, 3.49; N, 21.18.

Acknowledgment.

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