[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Synthesis of Antimalarials. VI.[1] Synthesis of Certain 1,5- and 1,8-Naphthyridine Derivatives[2]

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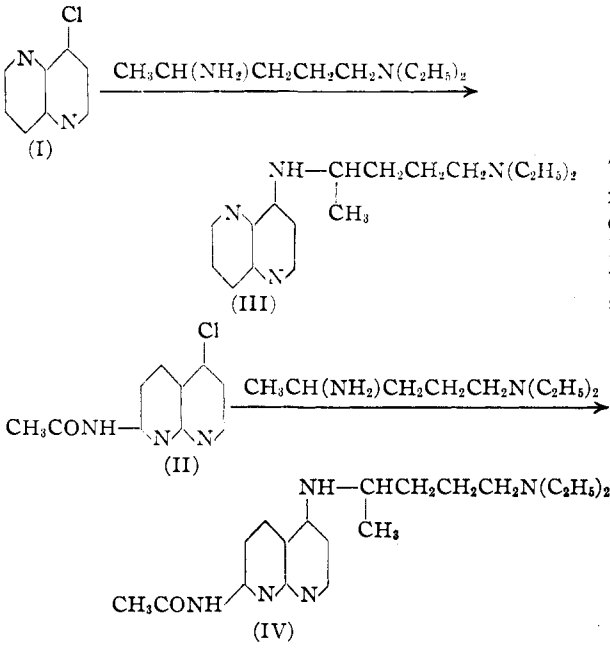
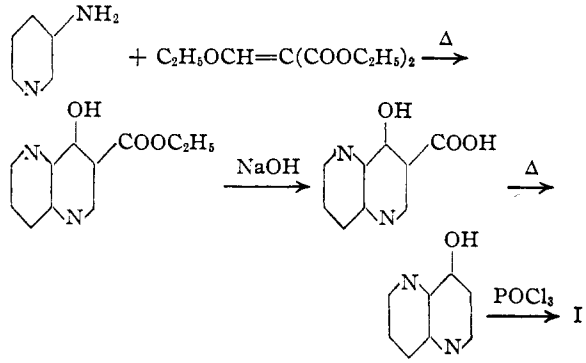
The present paper describes the synthesis of 4-chloro-1,5-naphthyridine (I) and 4-chloro-7-acetamino-1,8-naphthyridine (II), and the coupling of these compounds with 1-diethylamino-4-aminopentane to form 4-(4′-diethylamino-1′-methylbutylamino)-1,5-naphthyridine (III) and 4-(4′-diethylamino-1′-methylbutylamino)-7-acetamino-1,8-naphthyridine (IV), respectively. Compound (III) promised to be of particular interest, since it may be regarded as a derivative of either a 4- or 8-aminoquinoline, both series of which have furnished useful antimalarials. Compound (IV) may be regarded as a derivative of a 4-aminoquinoline.



4-Hydroxy-1,5-naphthyridine, from which the chloro derivative (I) is obtained, has been described previously by Klisiecki and Sucharda,[5] but their method of preparation was rather complicated and their yield was apparently very poor. We have prepared this hydroxy compound in satisfactory yield by the cyclization of 3-aminopyridine with ethoxymethylenemalonic ester followed by hydrolysis of the resulting ester and decarboxylation of the acid. The hydroxy compound was converted to the corresponding chloro derivative (I) by means of phosphorus oxychloride. These reactions may be represented as



The cyclization of 3-aminopyridine with ethoxymethylenemalonic ester was effected by heating a dilute solution of the reactants in Dowtherm A. High dilution appears to be required for satisfactory results not only in this but also in certain similar reactions.[6] The cyclization of aniline derivatives with ethoxymethylenemalonic ester has previously been described by Gould and Jacobs.[7] Recently, Price and co-workers[6] have developed this method for the preparation of various 4-hydroxyquinolines. The hydrolysis of the ester and decarboxylation of the acid were readily effected, but the conversion of the hydroxy compound to the chloro derivative was accomplished satisfactorily only when the hydroxy compound was heated with a large excess of phosphorus oxychloride. The coupling was effected by heating the chloro derivative (I) with a large excess of 1-diethylamino-4-aminopentane at 100°, the final compound (III) being purified by distillation at low pressure. It was obtained as an orange oil which would not crystallize and would not form a crystalline salt with hydrochloric, hydriodic, phosphoric or citric acids. It did, however, form a crystalline dipicrate.

An attempt to effect the coupling of (I) with 1-diethylamino-4-aminopentane at 100° using phenol as solvent in a manner similar to that used for the coupling of acridines with primary amines led to an interesting result. The only compound isolated was a compound which analyzed correctly for 4-phenoxy-1,5-naphthyridine. A phenoxy compound has been postulated as the inter-

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(2) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University.

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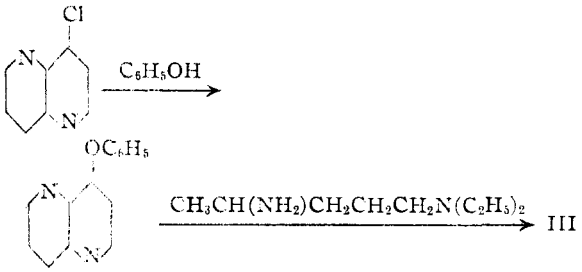
(5) Klisiecki and Sucharda, *Roczniki Chem.*, **7**, 204 (1927); *cf. C. A.*, **22**, 778 (1928).

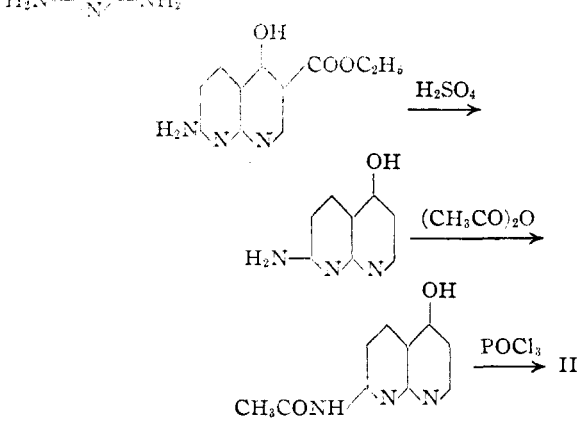
(6) C. C. Price and co-workers, University of Illinois, private communication.

(7) Gould and Jacobs, THIS JOURNAL, **61**, 2890 (1939).

mediate in the coupling of 9-chloroacridines with amines. On refluxing this compound with a large excess of 1-diethylamino-4-aminopentane (III) was obtained. The reactions may be represented thus



4-Hydroxy-1,8-naphthyridine, which would correspond to the 4-hydroxy-1,5-naphthyridine described above, has been prepared by Sucharda,[8] but the reactions are complicated and the over-all yield was apparently very poor. We have attempted to prepare this compound from 2-aminopyridine and ethoxymethylenemalonic ester in a manner analogous to that described above with 3-aminopyridine, but the cyclization failed. However, we have successfully effected the corresponding cyclization with 2,6-diaminopyridine, in which the 3-position is activated by the 6-amino group. The resulting ester was hydrolyzed and decarboxylated to form 4-hydroxy-7-amino-1,8-naphthyridine, which was acetylated and converted to the chloro derivative (II) by means of phosphorus oxychloride.



The ester failed to be hydrolyzed with sodium hydroxide, apparently because of its insolubility. However, it was readily hydrolyzed by heating with 50% sulfuric acid; decarboxylation also took place under these conditions. An attempt to remove the 7-amino group by diazotization was unsuccessful, as was the attempt to convert the 4-hydroxy-7-amino compound to the chloro derivative by means of phosphorus oxychloride, but the corresponding reaction was accomplished with the acetamino compound. All the compounds but the last were so insoluble that they could not be purified for analysis.

The coupling of the chloro derivative (II) with 1-diethylamino-4-aminopentane was effected by heating the two compounds together at 150–155° for nine hours. The isolation of (IV) was difficult, since it decomposed on distillation. It was converted into a dipicrate, which was too insoluble for recrystallization but which analyzed correctly after washing with acetone. The free base showed a blue-purple fluorescence in dilute solution.

Experimental[9]

4-(4'-Diethylamino-1'-methylbutylamino)-1,5-naphthyridine, I (SN 12,017).[10]—3-Aminopyridine was prepared by the amination of 3-bromopyridine[11] according to the procedure of Maier-Bode.[12]

To one liter of Dowtherm A[11] contained in a three-necked flask equipped with a mercury-sealed stirrer and air condenser were added 23.5 g. (0.25 mole) of 3-aminopyridine and 54.0 g. (0.25 mole) of ethoxymethylenemalonic ester.[13] The mixture was stirred and heated to 150°, at which temperature alcohol was evolved. It was then refluxed for one hour, cooled and the precipitated ester was removed by centrifuging. It was washed with petroleum ether (30–60°) until the washings were colorless, 40–45 g. (73–82%) of 3-carbethoxy-4-hydroxy-1,5-naphthyridine being obtained as a brown powder.

The crude ester (68 g., 0.31 mole) was refluxed for six hours with 700 ml. of 4% sodium hydroxide. The hot solution was charcoaled, filtered and acidified to *p*H 3. 3-Carboxy-4-hydroxy-1,5-naphthyridine was filtered off after cooling, washed with water and dried at 110°; 38–44 g. (68–78%) was obtained as a tan powder.

The crude acid (44 g., 0.23 mole) was added with stirring to 1.5 liters of mineral oil at 320–330°. Heating and stirring were continued for thirty minutes, the reaction mixture was cooled and the precipitate was filtered off. It was washed with petroleum ether to remove mineral oil and then recrystallized from one liter of hot water; 26–30 g. (78–90%) of 4-hydroxy-1,5-naphthyridine was obtained as a yellow powder. It sublimed without melting above 300°.[14]

4-Hydroxy-1,5-naphthyridine (10 g., 0.069 mole) was heated on a steam-bath for one hour with 200 ml. of phosphorus oxychloride. The excess phosphorus oxychloride was removed under reduced pressure on the steam-bath, the residue was cooled and then 100 g. of ice and 100 ml. of water were added. The mixture was stirred until the gummy solid had dissolved, the solution was filtered and neutralized with concentrated ammonium hydroxide, keeping the temperature below 10°. The resulting solution was evaporated to dryness *in vacuo* on a steam-bath and the residue was extracted with hot benzene. Evaporation of the benzene left 6–7 g. (53–61%) of fairly pure 4-chloro-1,5-naphthyridine. The compound was recrystallized once from ligroin (70–90°), m. p. 102–102.5°.

Anal. Calcd. for $C_8H_5N_2Cl$: C, 58.4; H, 3.06; N,

(8) Sucharda, Kosmos, Lwow, 1920, p. 123; *cf. C. A.*, **22**, 777 (1928).

(9) Analyses by Dr. T. S. Ma, Department of Chemistry, University of Chicago, Chicago, Illinois, and by Arlington Laboratories, Fairfax, Virginia.

(10) The Survey Number, designated SN-, identifies a drug in the files of the Survey of Antimalarial Drugs. The activities of those drugs to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(11) We are indebted to the Dow Chemical Company for a generous supply of this chemical.

(12) Maier-Bode, *Ber.*, **69**, 1536 (1936).

(13) We are indebted to Dr. R. C. Elderfield of Columbia University and Dr. C. C. Price of the University of Illinois for a supply of this compound.

(14) Klisiecki and Sucharda[8] say it sublimes at 340°.

17.0; Cl, 21.5. Found: C, 58.2; H, 3.14; N, 17.0; Cl, 21.5.

4-Chloro-1,5-naphthyridine (9.7 g., 0.059 mole) and 1-diethylamino-4-aminopentane (47.5 g., 0.30 mole) were heated on a steam-bath for thirty-six hours. The reaction was initially slightly exothermic, the temperature rising to 102°. The reaction mixture was cooled, 50 ml. of 20% sodium hydroxide was added and the oil was extracted with ether. The ether solution was dried over potassium carbonate, the solvent removed and the excess diamine distilled; 36 g. was recovered, b. p. 92–93° at 20 mm. The residue was transferred to a 50-ml. Claisen flask and distilled at less than 0.01 mm. After a small, low-boiling forerun came over, a white solid sublimed, probably unreacted chloro compound. This was removed from the condenser and compound (III) was then collected at 150–160°, 14.3 g. (85%) being obtained as an orange oil. This was redistilled twice, b. p. 145–148° at 0.004 mm. Potentiometric titration gave a neutral equivalent of 147 compared to the calculated value of 143.

Anal. Calcd. for $C_{17}H_{26}N_4$: C, 71.3; H, 9.15; N, 19.6. Found: C, 70.4; H, 9.10; N, 19.6.

A portion was converted into a dipicrate, which was recrystallized from dilute ethanol, m. p. 182°.

Anal. Calcd. for $C_{29}H_{32}O_{14}N_{10}$: C, 46.8; H, 4.33; N 18.8. Found: C, 46.9; H, 4.47; N, 19.4.

4-Phenoxy-1,5-naphthyridine.—4-Chloro-1,5-naphthyridine (6.5 g., 0.04 mole) was stirred and heated on a steam-bath with 35 g. of phenol for ten minutes. 1-Diethylamino-4-aminopentane (7.9 g., 0.05 mole) was added to the hot solution with stirring and the reaction mixture was heated for an additional three hours. It was cooled, poured into acetone and then excess alcoholic hydrogen chloride was added. The hydrochloride was precipitated with ether, the solvent was decanted and the residual oil was dissolved in water. The solution was made alkaline with ammonia, the oil was extracted with ether and the ethereal solution was dried over potassium carbonate. The solvent was removed and the residue was distilled from a small Claisen flask, 4.2 g. (48%) of yellow oil being obtained, b. p. 140–150° at 0.005 mm. On standing it solidified to a yellow solid, m. p. 93–94° after recrystallization from ligroin (70–80°). A sodium fusion test showed the absence of chlorine. It would not titrate at all using methyl red as an indicator, showing the absence of any strongly basic groups.

Anal. Calcd. for $C_{14}H_{10}ON_2$: C, 75.7; H, 4.54; N, 12.6. Found: C, 76.1; H, 4.59; N, 13.0.

4-Phenoxy-1,5-naphthyridine (3.2 g.) was refluxed for three hours with 20 ml. of 1-diethylamino-4-aminopentane. The excess diamine was removed by steam-distillation, the residual oil was extracted with ether, dried over potassium carbonate and distilled; 3.7 g. (90%) of compound (III) was obtained, b. p. 150–155° at 0.005 mm. It was identified by conversion into a dipicrate, m. p. 182°, mixed melting point with an authentic sample, 181–182°.

4-(4′-Diethylamino-1′-methylbutylamino)-7-acetamino-1,8-naphthyridine (II).—The cyclization of 2,6-diaminopyridine 39.5 g., 0.36 mole) and ethoxymethylenemalonic ester (84.5 g., 0.39 mole) was effected as described above. On cooling a precipitate formed, which was washed with benzene and air-dried. It still contained Dowtherm and could not be recrystallized. It was therefore hydrolyzed by refluxing it with 100 ml. of concentrated sulfuric acid and 200 ml. of water for eight hours. Carbon dioxide was evolved during the heating and the solid went into solution. The cooled solution was extracted with benzene to remove Dowtherm and was then neutralized with sodium hydroxide. The precipitated 4-hydroxy-7-amino-1,8-naphthyridine (39 g., 67%) was filtered and dried *in vacuo* at room temperature. It was yellow in color but rapidly turned green on continued exposure to light. It could not be recrystallized and decomposed without melting.

The above compound was refluxed for one hour with 400 ml. of acetic anhydride. On cooling an orange solid, unaffected by light, precipitated and was filtered off (28.6 g., 57%). Unlike the starting material, it gave no apparent reaction with nitrous acid. It could not be recrystallized and decomposed gradually on heating without any definite melting point.

Fifteen grams (0.074 mole) of presumably 4-hydroxy-7-acetamino-1,8-naphthyridine was stirred and heated on a steam-bath for ninety minutes with 450 ml. of phosphorus oxychloride. The excess phosphorus oxychloride was removed *in vacuo*, ice was added to the residue and then enough ammonium hydroxide to make the solution alkaline. The precipitate was dried at 110° and then was extracted for one hour with 1.5 liters of boiling benzene. Concentration of the benzene extract yielded 5.2–6.1 g. (32–37%) of 4-chloro-7-acetamino-1,8-naphthyridine as pale yellow crystals, m. p. about 240° with previous decomposition. A portion was recrystallized from dioxane–benzene and then from methyl ethyl ketone, the compound being obtained as small, colorless clusters of prisms, m. p. 244–246° with previous decomposition.

Anal. Calcd. for $C_{10}H_8ON_3Cl$: C, 54.2; H, 3.64; N, 19.0; Cl, 16.0. Found: C, 54.5; H, 3.83; N, 18.6; Cl, 16.0.

A mixture of 10.9 g. (0.049 mole) of the 4-chloronaphthyridine and 39.5 g. (0.25 mole) of 1-diethylamino-4-aminopentane was stirred and heated at 150–155° for nine hours. The clear solution was cooled and treated with 100 ml. of 20% sodium hydroxide. The two layers were separated and the oily layer was shaken with ether and water. The aqueous phases were combined and extracted thoroughly with ether. The combined ether layers were dried over potassium carbonate, the solvent was removed and the excess 1-diethylamino-4-aminopentane was distilled at 3 mm.; 21 g. was recovered. The residue was dissolved in 200 ml. of 10% acetic acid and the solution was charcoaled to remove any unreacted naphthyridine. The solution was then made alkaline with potassium carbonate, the oil was separated, dissolved in ethanol and added to a solution of 30 g. of picric acid in 500 ml. of ethanol. The picrate was filtered off and was washed thoroughly with acetone; 24.4 g. (62%) of a dipicrate was obtained, m. p. 202–203°.

Anal. Calcd. for $C_{31}H_{35}O_{15}N_{11}$: C, 46.4; H, 4.40. Found: C, 46.5; H, 4.79.

Summary

4-Chloro-1,5-naphthyridine and 4-chloro-7-acetamino-1,8-naphthyridine have been synthesized and coupled with 1-diethylamino-4-aminopentane to form 4-(4′-diethylamino-1′-methylbutylamino)-1,5-naphthyridine and 4-(4′-diethylamino-1′-methylbutylamino)-7-acetamino-1,8-naphthyridine, respectively.

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