## [CONTRIBUTION FROM THE NOVES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

## The Synthesis of 7-Chloro-4-(1-ethyl-4-piperidylamino)-quinoline (SN-13,425)<sup>1</sup>

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In a search for a superior antimalarial drug attention was directed to 7-chloro-4-(1-ethyl-4piperidylamino)-quinoline (I) because of its relation to 7-chloro-4-(3-diethylaminopropylamino)quinoline (II), which is known to have high antimalarial activity.



The method chosen for the synthesis involved the condensation of 4,7-dichloroquinoline (III) with 1-ethyl-4-aminopiperidine (IV).



The 1-ethyl-4-aminopiperidine is new and is unusual among aminopiperidines in having a primary amino group in the 4 position. Many amines of this general type, most of which have a secondary or tertiary amino group in the 4 position, have been made by Cerkovnikov and Prelog<sup>2</sup> who were interested in these amines because of their high spasmolytic activity.

Reductive amination of the corresponding piperidones appeared to be a promising method for the preparation of 4-aminopiperidines having a primary amino group in the 4 position. The most satisfactory method for the synthesis of 1-alkyl-4piperidones is that of Bolyard and McElvain.<sup>3</sup> It involves condensation of ethyl  $\beta$ -bromopropionate with a primary amine and subsequent ring closure by the Dieckmann method.

The Survey Number, designated by SN, identifies a drug in the files of the Survey of Antimalarial Drugs. The activities of these drugs will be tabulated in a forthcoming monograph.

(2) Cerkovnikov and Prelog. Ber., 74B, 1648, 1658 (1941); Helv. Chim. Acta, 26, 1132 (1943).

(3) Bolyard and McElvain, THIS JOURNAL, 51, 922 (1929).

It seemed likely that the bis-( $\beta$ -carbethoxyethyl)-alkylamines could be made more conveniently by the addition of alkylamines to ethyl acrylate.<sup>4</sup> When this method was used with ethylamine a 91–94% yield of bis-( $\beta$ -carbethoxyethyl)-ethylamine (V) was obtained. The ring

$$C_{2}H_{5}NH_{2} + 2CH_{2} = CHCO_{2}C_{2}H_{5} \rightarrow C_{2}H_{5}N(CH_{2}CO_{2}C_{2}H_{5})_{2} \rightarrow V$$

$$V$$

$$C_{2}H_{5}N \begin{pmatrix} CH_{2}CH_{2} \\ CH_{2}CH_{2} \end{pmatrix} CO \xrightarrow{CH_{2}CH_{2}} CO \xrightarrow{CH_{2}CH_{2}} CO \xrightarrow{CH_{2}CH_{2}} CO \xrightarrow{CH_{2}CH_{2}} CO \xrightarrow{CH_{2}CH_{2}} VI$$

closure and decarboxylation gave 82-87% yields of 1-ethyl-4-piperidone hydrochloride, based upon the bis-( $\beta$ -carbethoxyethyl)-ethylamine used.

Since it is known that low molecular weight piperidones of this type are unstable,<sup>5</sup> no attempt was made to isolate 1-ethyl-4-piperidone (VI). Instead, the hydrochloride was decomposed with potassium carbonate and the ketone taken up in ether and reduced directly in the presence of ammonia, Raney nickel being used as a catalyst. The yield of 1-ethyl-4-aminopiperidine (IV) was 51%. 1-Ethyl-4-aminopiperidine fumes in the air and readily deposits a solid carbonate. It formed a dipicrate.

1-Ethyl-4-hydroxypiperidine was obtained in 12% yield as a by-product of the reduction. It was identified by means of its neutralization equivalent and by preparation of its phenyl urethan derivative. This alcohol is of especial interest since the corresponding halides are the logical reagents to use in attaching the new side chain to compounds of the 8-aminoquinoline type.

The condensation of an equimolar mixture of 4,7-dichloroquinoline and 1-ethyl-4-aminopiperidine to give 7-chloro-4-(1-ethyl-4-piperidylamino)-quinoline (I) was easily effected, phenol being used as a solvent. The yield of once crystallized material (m.p.  $195-197^{\circ}$  dec.) was  $80_{CC}^{\circ}$ .

## Experimental

bis-(6-Carbethoxyethyl)-ethylamine.—The method was similar to that employed in the synthesis of the corresponding 1-methyl compound.<sup>4</sup> From 3 moles of ethylamine and 6.4 moles of ethyl acrylate was obtained 694 g. (94%) of product boiling at 110-111° (1.1 mm.);  $n^{20}$ D (1.4404-1.4395. A small sample was redistilled and submitted for analysis.

Anal. Caled. for  $C_{12}H_{23}O_4N$ : N, 5.71. Found: N, 5.53.

**1-Ethyl-4-piperidone Hydrochloride.**—It was necessary to adapt the general procedure of Bolyard and McElvain<sup>3</sup> to large-scale operation. Since the preparation was carried out many times, opportunity was provided of develop-

(4) Mozingo and McCracken. "Organic Syntheses," 20, 35 (1940).
(5) F. J. Wolf, Ph.D. Thesis, University of Illinois, 1942.

<sup>(1)</sup> The work described in this paper was done under a contract recommended by the National Defense Research Committee and the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

ing a detailed technic, which proved to be very valuable chiefly in avoiding certain mechanical difficulties. To a mixture of 35 g. of powdered sodium in 400 ml. of

boiling xylene was added 2 ml. of absolute ethanol and then 387 g. of  $bis - (\beta$ -carbethoxyethyl)-ethylamine at such a rate as to maintain gentle reflux (44-50 minutes). Throughout the period of addition the mixture was agitated vigorously by means of a Hershberg stirrer. The reaction mixture was heated under reflux for an hour after addition was completed, allowed to cool for about five minutes and poured into a mixture of 200 g. of ice and 400 ml. of ice water. The mixture was shaken vigorously and the layers were allowed to separate. An additional amount of water (250-300 ml.) was used to wash the xylene layer. The salt which separated during the extraction was collected on a filter and washed with ether. The filtrate was then extracted with two 150-ml. portions of ether. The ether and xylene extracts contained no appreciable amount of either starting material or product, and were discarded.

The aqueous solution combined with the salt from the filtration was cooled below  $10^{\circ}$  and while the temperature was kept at this point, the solution was made acid to congo red with concentrated hydrochloric acid (260-275 ml.). The acidic solution was neutralized with solid technical potassium carbonate, cooled below  $0^{\circ}$  and placed in a 4-liter separatory funnel. Approximately 800 g. of potassium carbonate was added in two portions, with shaking. An orange layer of amine separated and was drawn off. The aqueous layer was cooled to  $10^{\circ}$ , an additional 400 g. of potassum carbonate was added and the mixture extracted with a total of 1 liter of ether. The organic layer and ether extracts were combined and shaken with two 50-ml. portions of a saturated solution of sodium chloride.

The ether solution of 1-ethyl-3-carbethoxy-4-piperidone was extracted with a total of 430 ml. of hydrochloric acid (270 ml. of concentrated hydrochloric acid in 160 ml. of One hundred and fourteen milliliters of concenwater). trated hydrochloric acid was then added to this solution (these amounts of reactants are calculated to give a solution of 1-ethyl-3-carbethoxy-4-piperidone hydrochloride in 20% hydrochloric acid), the dissolved ether was removed by heating, and the whole heated under reflux until a drop of the solution failed to give a red color when added to a 1% solution of ferric chloride (approximately four hours). The aqueous solution of 1-ethyl-4-piperidone hydrochloride (light orange in color) was evaporated to dryness on a steam-bath at water-pump pressure. The weight of light orange solid was  $211{-}223$  g.  $(82{-}87\%$  based on the bis- $(\beta$ -carbethoxyethyl)-ethylamine used).

1-Ethyl-4-aminopiperidine.-Sixty-five grams of the 1ethyl-4-piperidone hydrochloride, prepared as directed above, was dissolved in 50 ml. of water and the resulting solution cooled to  $-2^\circ$ . To it was added 75 ml. of cold ether and then 100 g. of technical potassium carbonate in portions with choleing. The other large the solution of the solution of the solution of the solution of the solution. portions, with shaking. The ether layer was separated and the remaining pasty material extracted with three 75-ml. portions of ether. The ether extracts were combined and dried over 15 g. of anhydrous magnesium sulfate. The solution was filtered through a sintered glass funnel and then twice through a single thickness of filter paper. The ether was removed under reduced pressure, the temperature of the residue being kept below 25° Approxi-The oil was mately 50 ml. of a light orange oil remained. placed in a 270-ml. high-pressure bomb together with 40 ml. of absolute ethanol, a few cc. of Raney nickel catalyst and 55 ml. of liquid ammonia. An initial pressure of 2900 lb. of hydrogen was established and the bomb was heated to  $150^{\circ}$  and shaken for fifteen to twenty minutes. The bomb was cooled to room temperature and opened. The Raney nickel was removed by filtration and the bomb washed well with dry ether. The organic solvents were removed under reduced pressure (water pump) and the residue was distilled through a 6-in. column

packed with glass helices. The first fraction consisted of 1-ethyl-4-aminopiperidine and the second proved to be 1-ethyl-4-hydroxypiperidine. The residue was a viscous red oil weighing 16 g. The aminopiperidine boiled at 73° (16 mm.);  $n^{19.5}$ D 1.4725; yield 26 g., or 51%.

Anal. Calcd. for  $C_7H_{16}N_2$ : C, 65.57; H, 12.58; N, 21.85. Found: C, 65.14; H, 12.65; N, 22.15.

The amine formed a carbonate rapidly when exposed to the atmosphere. The dipicrate of the amine was recrystallized from glacial acetic acid; m. p.  $254-255^{\circ}$  (dec.).

Anal. Calcd. for  $C_{19}H_{22}N_8O_{14}$ : C, 38.91; H, 3.78. Found: C, 39.07; H, 3.95.

1-Ethyl-4-hydroxypiperidine.—The 1-ethyl-4-hydroxypiperidine, which composed the second fraction of the distillate from the reductive amination, weighed 13 g. (12%); b. p.  $102-103^{\circ}$  (15 mm.);  $n^{10.8}$ p 1.4796. After redistillation the compound was found to have a neutralization equivalent of 127.8. The calculated value is 129.2. The phenyl urethan was recrystallized from high-boiling petroleum ether; m. p.  $125-128^{\circ}$ .

Anal. Calcd. for  $C_{14}H_{20}N_2O_2$ : C, 67.71; H, 8.12. Found: C, 67.95; H, 8.23.

7-Chloro-4-(1-ethyl-4-piperidylamino)-quinoline.—A mixture of 38.2 g, of 1-ethyl-4-aminopiperidine, 57.4 g, of 4,7-dichloroquinoline<sup>6</sup> and 30 g, of phenol was heated with stirring at 150-160° for ten hours and at 160-168° for two and one-half hours. While hot, the viscous material was poured into 160 ml, of a cold solution of 40 ml, of concentrated hydrochloric acid and 210 ml, of water. The remaining 90 ml, of hydrochloric acid solution was used to dissolve the material which remained in the reaction flask. About 100 ml, of water was used for washing purposes. The aqueous solution was filtered, cooled to approximately 10° and extracted with three 150-ml. portions of ether. The light orange aqueous solution was placed in a 2-liter beaker immersed in an ice-bath and, while being stirred, was made alkaline with cold 20% potassium hydroxide.

An orange-brown pasty material separated which, after being stirred for a short time, formed to a finely divided tan solid. The solid was collected on a filter, washed well with water and dried at  $80^{\circ}$ . The 7-chloro-4-(1-ethyl-4piperidylamino)-quinoline separated from benzene (2700 ml.) in white crystals melting at 195-197° (dec.). Recrystallization of the compound did not change the melting point. The yield was 80%.

Anal. Calcd. for  $C_{18}H_{20}N_8Cl$ : C, 66.31; H, 6.96; N, 14.50. Found: C, 66.29; H, 7.12; N, 14.26.

## Summary

1. bis-( $\beta$ -Carbethoxyethyl)-ethylamine has been prepared in 91–94% yield by the addition of ethylamine to ethyl acrylate.

2. 1-Ethyl-4-aminopiperidine has been prepared. The amine was characterized by the formation of a dipicrate. The over-all yield for this amine is high. The method is convenient and offers a satisfactory route to the synthesis of 1substituted 4-aminopiperidines.

3. 1-Ethyl-4-hydroxypiperidine, obtained as a by-product in the reductive amination of the piperidone, was isolated and characterized.

4. 7 - Chloro - 4 - (1 - ethyl - 4 - piperidylamino)quinoline has been prepared in connection with a study of compounds having antimalarial activity.

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(6) The 4,7-dichloroquinoline was kindly supplied by the National Aniline and Chemical Company.