[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Studies in the Quinoline Series. VI. The Preparation of Some Substituted Lepidylamines[1]

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In view of the high antimalarial activity shown by the 4-aminoquinolines, it became desirable to learn whether any of that activity would be retained if a methylene group were interposed between the amino side chain and the quinoline nucleus. In this connection we undertook the synthesis of some lepidylamines derived from 6-chloro- and 7-chlorolepidines.

Work[4] prepared several substituted lepidylamines by converting the corresponding N-alkylcinchonamides to the amido dichlorides, and reducing these with stannous chloride. While the present work was in progress Tarbell and his co-workers[5] reported the preparation of some 2-phenyllepidylamines. In most cases these were made by the method of Work[4] but in one case the lepidylaldehyde was condensed with a primary amine, and the product hydrogenated.

Many lepidines can now be prepared in good yield and in one step from the substituted aniline[6] and lepidines can in general be oxidized in one step to the corresponding aldehydes by means of selenium dioxide.[5,6,7] It seemed to us, therefore, that the shortest route to lepidylamines lay in the hydrogenation of the corresponding aldimines; this method was found to be very satisfactory in the cases reported here.

Experimental[8]

6-Chloro-4-quinoline Aldehyde.—A solution of 18.3 g. (0.165 mole) of sublimed selenium dioxide[9] in a mixture of 50 ml. of purified dioxane[10] and 12 ml. of water was added during one hour to a well-stirred solution of 29.3 g. (0.165 mole) of 6-chlorolepidine[11] in 55 ml. of purified dioxane, kept at 65–75°. The mixture was stirred at 85–90° for five hours and then filtered through a sintered glass funnel. The dioxane was evaporated from the filtrate to give 31 g. of crude aldehyde. Attempts to free this material of traces of selenium by recrystallization and treatment with Norite were unsuccessful, and it was finally purified by steam distillation. The aldehyde crystallized from the steam distillate in long white needles, m. p. 152–153°, obtained in 17.2 g. (54%) yield. The compound separated from ligroin as short, stout needles, m. p. 152.5–153°.

Anal. Calcd. for $C_{10}H_6NOCl$: C, 62.7; H, 3.16; N, 7.3; Cl, 18.5. Found: C, 63.1; H, 3.24; N, 6.9; Cl, 18.6.

The aldehyde semicarbazone melted at 234°.

6-Chloro-4-quinolinemethanol.—When the aldehyde was warmed at 70° with 50% potassium hydroxide solution there was isolated 6-chloro-4-quinolinemethanol, which crystallized from absolute alcohol as fine white needles, melting at 140–142°, resolidifying and remelting at 187–190° with decomposition.

Anal. Calcd. for $C_{10}H_8NOCl$: C, 62.0; H, 4.16; N, 7.24; Cl, 18.3. Found: C, 62.3; H, 4.26; N, 7.6; Cl, 18.6.

From the alkaline solution remaining, acidification precipitated 6-chlorocinchoninic acid, identical with that obtained by oxidation of 6-chloro-4-styrylquinoline.[11]

7-Chlorolepidine.—This was prepared by the general procedure of Campbell and Schaffner[6] using 148 g. (1.0 mole) of 1,3,3-trimethoxybutane and 205 g. (1.25 mole) of *m*-chloroaniline hydrochloride. The reaction mixture was made basic, evaporated to dryness and extracted four times with boiling benzene. Distillation of the extract yielded 119 g. (67%) of a semi-solid oil, b. p. 110–123° (2 mm.), which was a mixture of the 5- and 7-chlorolepidines. By systematic redistillation and recrystallization from ligroin there was isolated 70–80 g. of 7-chlorolepidine, m. p. 59–61°.

Anal. Calcd. for $C_{10}H_8NCl$: C, 67.6; H, 4.54; N, 7.90; Cl, 19.96. Found: C, 68.0; H, 4.8; N, 7.4; Cl, 20.1.

The lepidine formed a hydrochloride which melted at 220–222°, and a picrate which melted at 223°.

7-Chloro-4-quinoline Aldehyde.—This was prepared as described above for the 6-chloro isomer. There was obtained a 40% yield of compound which crystallized from ligroin in white needles, m. p. 112–113.5°.

Anal. Calcd. for $C_{10}H_6NOCl$: C, 62.7; H, 3.16; N, 7.3; Cl, 18.5. Found: C, 62.6; H, 3.5; N, 7.0; Cl, 18.7.

The aldehyde formed a semicarbazone, m. p. 263°.

7-Chlorocinchoninic Acid and 7-Chloro-4-quinolinemethanol.—The aldehyde was warmed at 70° with 50% potassium hydroxide solution for six hours, and the cooled mixture was extracted with ether. Evaporation of the ether extract gave almost the theoretical yield of the carbinol. After recrystallization from absolute alcohol this was obtained as white needles, m. p. 188–190° after melting at 158–159° and resolidifying.

Anal. Calcd. for $C_{10}H_8NOCl$: C, 62.0; H, 4.16; N, 7.24; Cl, 18.3. Found: C, 62.4; H, 4.49; N, 7.30; Cl, 18.6.

The aqueous alkaline solution was acidified with dilute hydrochloric acid to a *p*H of 3, and the voluminous white precipitate collected. This material melted at 281–282° (dec.).

Anal. Calcd. for $C_{10}H_6NO_2Cl$: C, 57.9; H, 2.9; Cl, 17.1. Found: C, 57.9; H, 3.14; Cl, 17.1.

The ethyl ester prepared from this compound melted at 32–34°. 7-Chlorocinchoninic acid prepared from 6-chloroisatin of established structure has been found to melt at 285–286°, and to form an ethyl ester melting at 33–35°.[12]

6-Chloro-α-(β-hydroxyethylamino)-lepidine.—A mixture of 1.3 g. of redistilled ethanolamine and 3.8 g. of 6-

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(4) Work, *J. Chem. Soc.*, 426 (1942).

(5) Tarbell, Bunnett, Carlin and Wystrach, THIS JOURNAL, **67**, 1582 (1945).

(6) Campbell and Schaffner, *ibid.*, **67**, 86 (1945).

(7) Levitz and Bogert, *J. Org. Chem.*, **10**, 341 (1945).

(8) Most of the analyses reported here were carried out at Northwestern University.

(9) "Organic Syntheses," Coll. Vol. II, 510 (1943).

(10) Fieser, "Laboratory Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 369.

(11) Campbell and Kerwin, THIS JOURNAL, **68**, 1837 (1946).

(12) Koepfli, Seuear and co-workers, unpublished results.

chloro-4-quinoline aldehyde was heated at 90–95° for two hours. On cooling the aldimine crystallized. After two recrystallizations from benzene it weighed 2.9 g., and melted at 125–125.5°.

Anal. Calcd. for $C_{12}H_{11}N_2OCl$: C, 61.4; H, 4.73; N, 11.94. Found: C, 61.36; H, 4.96; N, 12.0.

A solution of 2.66 g. of the aldimine in 100 ml. of absolute alcohol containing 0.05 g. of pre-reduced platinum oxide was shaken with hydrogen at 40 lb./sq. in. until absorption ceased (forty minutes). The product crystallized on evaporation of part of the solvent, and melted at 147–150° (dec.).

Anal. Calcd. for $C_{12}H_{13}N_2OCl$: C, 60.9; H, 5.54; Cl, 15.0. Found: C, 60.7; H, 5.23; Cl, 15.2.

6-Chloro-α-(4-diethylamino-1-methylbutylamino)-lepidine.—A mixture of 4.1 g. of pure Noval diamine and 4.8 g. of 6-chloro-4-quinoline aldehyde was warmed at 75–80° for forty minutes. It was then dissolved in 75 ml. of absolute ethanol and shaken with hydrogen in the presence of 0.1 g. of pre-reduced platinum oxide. Absorption was complete in ninety minutes. The alcohol was removed, the residue taken up in dilute hydrochloric acid, and the *p*H adjusted to 6, to precipitate any unreacted aldehyde or its reduction product. The filtrate was made strongly basic, and the amine taken up in ether. Distillation of the extract gave 5.6 g. (67%) of a light yellow oil, b. p. 171–174° (0.04 mm.), $n^{20}D$ 1.5587–1.5593. The oil was dissolved in *n*-propanol and two equivalents of propanolic hydrogen chloride added. On cooling the dihydrochloride separated, m. p. 149–151.5°.

Anal. Calcd. for $C_{19}H_{30}N_3Cl_3 \cdot H_2O$: C, 53.7; H, 7.59; N, 9.89; Cl, 25.0. Found: C, 53.8; H, 7.6; N, 10.3; Cl, 24.6.

7-Chloro-α-(β-hydroxyethylamino)-lepidine, SN-8646.[13]—A mixture of 5.44 g. of 7-chloro-4-quinoline aldehyde and 1.8 g. of ethanolamine was heated at 80–90° for forty minutes, and then hydrogenated in 100 ml. of absolute ethanol in the presence of 0.1 g. of pre-reduced platinum oxide. The solvent was evaporated and the residue washed with a little cold acetone to remove adhering oil. The white crystalline product melted at 123–125° and weighed 3.7 g. (55%). It was soluble in alcohol and hot dioxane, insoluble in acetone.

(13) The numbers are those assigned by the Survey of Antimalarial Drugs to identify the drugs in their records. The antimalarial properties of these substances will be tabulated in a forthcoming monograph.

Anal. Calcd. for $C_{12}H_{13}N_2OCl$: C, 60.9; H, 5.54; Cl, 15.0. Found: C, 61.2; H, 5.4; Cl, 14.9.

The hydrochloride was prepared by evaporating a solution of the base in dilute hydrochloric acid. The hygroscopic hydrochloride melted at 110°.

7-Chloro-α-(4-diethylamino-1-methylbutylamino)-lepidine, SN-11,197.—This was prepared as described for the 6-chloro isomer. The product was a light yellow oil, b. p. 179–184° (0.07 mm.) and was obtained in 67% yield. The dihydrochloride, prepared in propanol, melted at 106–108°.

Anal. Calcd. for $C_{18}H_{30}N_3Cl_3 \cdot 2H_2O$: C, 51.5; H, 7.74; N, 9.5; Cl, 24.0. Found: C, 51.66; H, 7.89; N, 9.1; Cl, 24.3.

6-Ethylaminohexylamine.—6-Bromohexylphthalimide (67 g.) was added to a solution of 45 g. of ethylamine in 100 ml. of dry benzene, at 10°, and the reaction mixture was allowed to stand with occasional cooling, for twenty-four hours. The benzene solution was extracted with dilute hydrochloric acid, and the extract made strongly basic. The dark oil was hydrolyzed with hydrazine hydrate and hydrochloric acid.[14] The amine, obtained in 10–15 g. yield, had b. p. 82–84° (5 mm.), $n^{20}D$ 1.4512, d^{20}_4 0.8431, MR_D obs. 46.0, MR_D calcd. 46.2.

Anal. Calcd. for $C_8H_{20}N_2$: N, 19.42. Found; N, 19.61.

The diamine dihydrochloride melted at 200–203°.

7-Chloro-α-(6-ethylaminohexylamino)-lepidine, SN-13,154.—This was prepared from 7.2 g. of 6-ethylaminohexylamine and 9.5 g. of 7-chloro-4-quinoline aldehyde. The product, a light yellow oil, was obtained in 7 g. (44%) yield; it had b. p. 190–195° (0.2 mm.), $n^{20}D$ 1.5563. The dihydrochloride, prepared in propanol, melted at 195–200°.

Anal. Calcd. for $C_{18}H_{28}N_3Cl_3$: C, 55.0; H, 7.16; Cl, 27.1. Found: C, 54.7; H, 7.43; Cl, 27.3.

Summary

1. Several lepidylamines derived from 6-chlorolepidine and 7-chlorolepidine have been prepared.

2. 7-Chlorolepidine, 6-chloro- and 7-chloro-4-quinoline aldehyde and the corresponding carbinols have been synthesized.

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Transference Numbers and Activity Coefficients in Zinc Iodide Solutions at 25°

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A comparison of the activity coefficients of the halides, perchlorates and nitrates of zinc with those of magnesium has shown[2] that the halides of zinc exhibit increasing abnormality in passing from the iodide through the bromide to the chloride. A parallel behavior is found in the transference numbers, for while that of zinc perchlorate is normal up to the highest concentration measured (4 *M*), the cationic transference numbers of the chloride and bromide fall rapidly with increasing concentration, reaching negative values above 2 *M* in zinc chloride solutions[3] and above 2.7 *M* in zinc bromide solutions.[4] The only work on concentrated solutions of the iodide appears to be that of Hittorf,[5] who made only three measurements. The present paper reports activity coefficients and transference numbers of zinc iodide from 0.05 to 10 *M*, derived from isopiestic vapour pressure data and e. m. f. measurements on cells with transference, at 25°.

Experimental.—The technique of isopiestic measurements on zinc iodide solutions has been

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(4) H. N. Parton and J. W. Mitchell, *ibid.*, **35**, 758 (1939).

(5) W. Hittorf, *Pogg. Ann.*, **106**, 513 (1859).