[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Ring Enlargement by Rearrangement of the 1,2-Aminochloroalkyl Group; Rearrangement of 1-Ethyl-2-chloromethylpyrrolidine to 1-Ethyl-3-chloropiperidine

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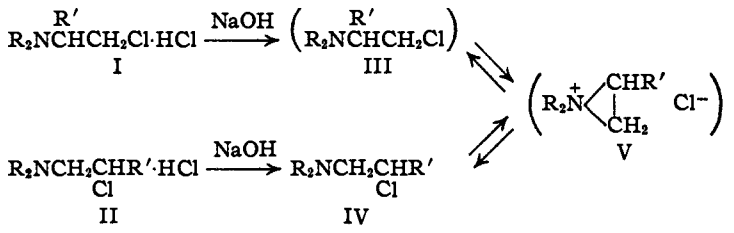
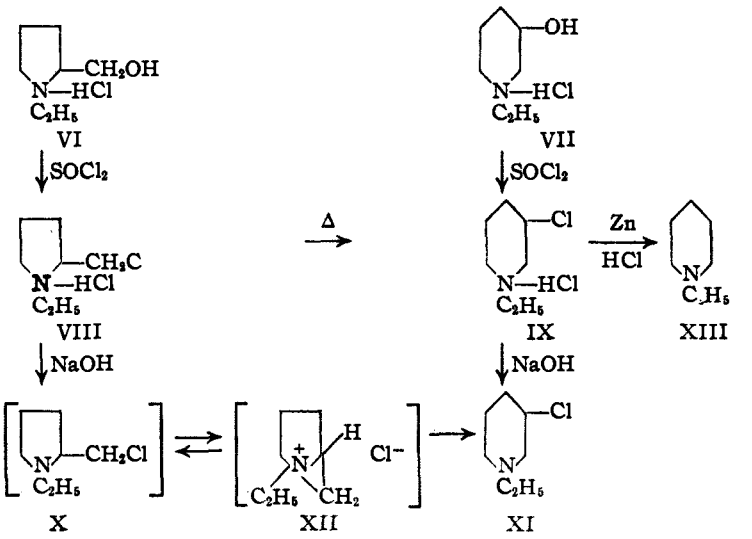
Recently it has been found that 1,2-aminochloroalkanes undergo a rearrangement[2] analogous to that of 2-chloroisopropyl sulfides.[3] In all examples thus far studied, the amines liberated from the isomeric 1,2-aminochloroalkane hydrochlorides (I and II) are identical and possess the normal structure (IV).[2b,c,d,4] This rearrangement of



chloro amines of structure I is believed to occur through the cyclic imonium chloride intermediate (V). It has been shown that ethyleneimonium salts of this type are formed in other reactions of 2-haloalkylamines.[5]

This behavior of 2-chloroalkylamines suggested the interesting possibility that 1-alkyl-2-chloromethyl cyclic imines—compounds in which the chlorine is in the 2-position to a cyclic tertiary amino group—by a similar rearrangement might undergo ring enlargement, providing a route to 1-alkyl-3-chloro cyclic imines having one more carbon in the ring. We have accomplished such a ring enlargement by rearrangement of 1-ethyl-2-chloromethylpyrrolidine hydrochloride (VIII) to 1-ethyl-3-chloropiperidine (XI).

It was found that when 1-ethyl-2-chloromethylpyrrolidine hydrochloride (VIII), prepared from the corresponding amino alcohol hydrochloride (VI) by treatment with thionyl chloride, was treated with alkali, the free base obtained was not the pyrrolidine derivative (X) but the isomeric 1-ethyl-3-chloropiperidine(XI). Presumably the 1-ethyl-2-chloromethylpyrrolidine (X) underwent rearrangement as rapidly as it was formed, the cyclic imonium salt (XII) being the intermediate. That the chloromethyl pyrrolidine (X) did not rearrange when in the form of its hydrochloride (VIII) was demonstrated by the fact that the picrate formed from the salt was different from that obtained from the free amine. The picrate of the distilled amine was identical with that prepared from the crude base, indicating that no change in the chloro amine occurred during distillation. The chloropiperidine (XI), prepared from 1-ethyl-3-hydroxypiperidine hydrochloride (VII), did not rearrange when liberated from its salt (IX). The free amine after being distilled formed a picrate identical with



that from the original piperidine hydrochloride and that of the free base obtained from the chloromethylpyrrolidine hydrochloride (VIII). For additional proof that the amine isolated from the isomeric chloro amine salts was the piperidine derivative, 1-ethyl-3-chloropiperidine hydrochloride (IX) was converted to 1-ethylpiperidine (XIII) by means of zinc and hydrogen chloride in glacial acetic acid.

(1) Smith, Kline and French Laboratories Walter G. Karr Fellow 1947–1948.

(2) (a) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188 (1947); **69**, 2454 (1947); (b) Schultz and Sprague, *ibid.*, **70**, 48 (1948); (c) Brode and Hill, *ibid.*, **69**, 724 (1947); (d) Kerwin, Ullyot, Fuson and Zirkle, *ibid.*, **69**, 2961 (1947); (e) Ross, *ibid.*, **69**, 2982 (1947).

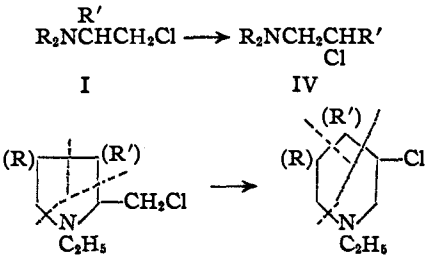
(3) Fuson, Price and Burness, *J. Org. Chem.*, **11**, 475 (1946).

(4) Schultz and Sprague (ref. 2b) reported that 2-dimethylamino-1-chloropropane did not rearrange immediately when liberated from its hydrochloride at room temperature, but did change to the isomeric 1-dimethyl-2-chloropropane upon distillation.

(5) (a) Gilman and Phillips, *Science*, **103**, 409 (1946); (b) Golumbic, Fruton and Bergmann, *J. Org. Chem.*, **11**, 518 (1946); (c) Golumbic and Bergmann, *ibid.*, **11**, 536 (1946); (d) Fruton and Bergmann, *ibid.*, **11**, 543 (1946); (e) Golumbic, Stahmann and Bergmann, *ibid.*, **11**, 550 (1946); (f) Bartlett, Ross and Swain, THIS JOURNAL, **69**, 2971 (1947); (g) Bartlett, Davis, Ross and Swain, *ibid.*, **69**, 2977 (1947); (h) Cohen, Van Artsdalen and Harris, *ibid.*, **70**, 281 (1948).

The experiments described above indicate that 1-ethyl-2-chloromethylpyrrolidine is stable in the form of its hydrochloride (VIII). In fact, this salt sublimed without change at temperatures below its melting point. The picrate formed from the sublimed hydrochloride was identical with that obtained from the original chloromethylpyrrolidine hydrochloride. At temperatures above its melting point, however, the pyrrolidine salt rearranged to 1-ethyl-3-chloropiperidine hydrochloride. This property has been found to be general for 1,2-aminochloroalkane hydrochlorides of type I.[2a,b,c,d] Upon rapid heating the pyrrolidine salt (VIII) melted at 165–170°, solidified, and remelted at 193.5–194.0°. When the temperature was raised slowly the isomeric hydrochlorides and a mixture of the two salts had the same melting point (193.5–194.9°), although the picrates prepared from the hydrochlorides differ in melting point.

The direction of rearrangement in this isomeric pair of cyclic chloro imines is that observed in other 1,2-aminochloroalkanes, *i. e.*



However, in some of their reactions, *e. g.*, hydrolysis and alkylation,[2a,b,c,d,e] the 2-chloro-*n*-propylamines (IV, R = CH_3) sometimes yield products containing the isopropylamino group—a change which is the reverse of that found in the isomerization of these chloro amines. Undoubtedly the ease and direction of rearrangement is determined by the steric and polar nature of both the intermediate cyclic imonium ion and the attacking nucleophilic agent. When the latter is chloride ion, the product appears to be that of structure IV exclusively.

Work is now in progress to determine whether other 1-alkyl-2-chloromethyl cyclic imines also undergo this rearrangement.

Experimental

1-Ethyl-2-hydroxymethylpyrrolidine.—This amino alcohol was prepared by the synthesis of Signaigo and Adkins.[6a] Hydrogenation[7] of 1,2-dicarbethoxypyrrole[6b] over Raney nickel in dry methanol at 70° and 1500 lb. pressure gave a 95% yield of 1,2-dicarbethoxypyrrolidine[6a]; b. p. 133–135° (8 mm.) (Signaigo and Adkins reported 133–134° (8 mm.)). The latter (33.6 g., 0.156 mole) in absolute ethanol upon hydrogenation at 250° and 100 atm. in the presence of 10 g. of copper chromite yielded 6.3 g. (31%) of 1-ethyl-2-hydroxymethylpyrrolidine; b. p. 78–79° (17 mm.); $n^{25}D$ 1.4659 (reported: b. p. 82–84° (24 mm.); $n^{25}D$ 1.4662). The hydrochloride, prepared by saturating a dry toluene solution of the amine with hydrogen chloride, separated as an oil which resisted all attempts at recrystallization. The benzoate hydrochloride of the amino alcohol separated as an oil when a mixture of the alcohol and an equimolar amount of benzoyl chloride in dry toluene was heated for an hour on the steam-bath. On standing overnight in the ice-box the oil solidified as waxy needles but all attempts to recrystallize the solid failed. A picrate was formed by adding a concentrated solution of the benzoate hydrochloride to a saturated aqueous solution of picric acid; m. p. 170.5–171.5° after two recrystallizations from acetone.

Anal. Calcd. for $C_{20}H_{22}O_9N_4$: C, 51.95; H, 4.80; N, 12.12. Found: C, 51.68; H, 4.62; N, 12.16.

1-Ethyl-3-hydroxypiperidine.—By the method of Paul,[8] diethyltetrahydrofurfurylamine[8] was converted to 1-ethyl-3-hydroxypiperidine in 43% yield; $n^{25}D$ 1.4744. The benzoate hydrochloride melted at 198–199° (203–204° (cor.)) (Paul reported a boiling point of 97–98° (21 mm.); $n^{25}D$ 1.47427; benzoate hydrochloride, m. p. 204°). A benzoate picrate was prepared as described above for comparison with that of 1-ethyl-2-hydroxymethylpyrrolidine. The yellow crystals recrystallized from acetone melted at 181.5–182.5°.

Anal. Calcd. for $C_{20}H_{22}O_9N_4$: N, 12.12. Found: N, 12.08.

The amino alcohol formed a hydrochloride (VII) which melted at 157–158° after recrystallization from ethyl acetate–ethanol.

Anal. Calcd. for $C_7H_{16}ONCl$: C, 50.75; H, 9.74; N, 8.46. Found: C, 50.93; H, 9.64; N, 8.26.

1-Ethyl-2-chloromethylpyrrolidine Hydrochloride (VIII).—To a flask equipped with a mechanical stirrer and a condenser fitted with a calcium chloride tube was added 4.0 g. (0.031 mole) of 1-ethyl-2-hydroxymethylpyrrolidine in 25 ml. of dry chloroform. The flask was immersed in an ice–salt-bath and the solution saturated with dry hydrogen chloride to form the salt of the amino alcohol (VI). With stirring 4.8 g. (0.040 mole) of thionyl chloride in a few milliliters of chloroform was added dropwise to the cold solution of amine hydrochloride. After all the thionyl chloride was added the mixture was stirred for thirty minutes at room temperature, then refluxed for one hour. The dark crystalline product after removal of solvent was triturated with acetone and collected on a filter. Two recrystallizations of the slightly discolored solid from acetone–ethanol gave 3.2 g. (56%) of the chloro amine hydrochloride. When the bath temperature was raised rapidly (20° per minute), the hydrochloride melted at 165–170°, solidified, and remelted at 193.5–194.0° (rate of heating, two degrees per minute). When the temperature was raised slowly, the sample contracted without melting at 165° and melted at 193.5–194.0°. A mixture melting point with 1-ethyl-3-chloropiperidine hydrochloride (IX) showed no depression. These observations indicate that upon heating the two isomeric salts rearrange to the same compound.

Anal. Calcd. for $C_7H_{15}NCl_2$: C, 45.66; H, 8.21; N, 7.61; Cl, 38.52. Found: C, 45.56; H, 7.86; N, 7.45; Cl, 38.56.

A picrate prepared by adding a concentrated solution of the chloro amine hydrochloride to a saturated aqueous solution of picric acid was recrystallized from ethanol; m. p. 128.5–129.5°.

Anal. Calcd. for $C_{13}H_{17}O_7N_4Cl$: C, 41.44; H, 4.55; N, 14.87; Cl, 9.41. Found: C, 41.59; H, 4.45; N, 14.73; Cl, 9.43.

The pyrrolidine hydrochloride sublimed without change at 90° (2 mm.). The picrate prepared from the sublimed salt was identical with that obtained from the hydrochloride before sublimation.

Evaporation of the acetone with which the crude 1-ethyl-2-chloromethylpyrrolidine hydrochloride was washed

(6) (a) Signaigo and Adkins, THIS JOURNAL, **58**, 709 (1936); (b) **58**, 1122 (1936).

(7) The hydrogenations were performed by Mr. David J. Wallace.

(8) Paul, *Bull. soc. chim.*, **12**, 830 (1945).

yielded a dark water-soluble oil which formed a picrate (1.4 g.) when added to saturated aqueous picric acid solution. After repeated crystallizations from ethanol the picrate (0.4 g.) melted at 163.5–164.5°. The analytical values for this compound are in close agreement with those calculated for the picrate of 1-methyl-2-chloromethylpyrrolidine.

Anal. Calcd. for $C_{12}H_{15}O_7N_4Cl$: C, 39.73; H, 4.14; N, 15.45; Cl, 9.77. Found: C, 39.91; H, 3.99; N, 15.32; Cl, 9.79.

It is possible that the 1-ethyl-2-hydroxymethylpyrrolidine from which the corresponding chloro compound was prepared contained a small amount of 1-methyl-2-hydroxymethylpyrrolidine which would form the 1-methyl chloro compound upon treatment with thionyl chloride. Some of the N-methyl alcohol would be formed along with the N-ethyl alcohol if, upon hydrogenation of 1,2-dicarbethoxypyrrolidine, the 1-carbethoxy group were reduced to a methyl group instead of being removed by hydrogenolysis and replaced by an ethyl group from the ethanol present to form 1-ethyl-2-hydroxymethylpyrrolidine. Contamination of the latter compound by the 1-methyl alcohol would explain the fact that a pure crystalline hydrochloride and benzoate hydrochloride could not be obtained from 1-ethyl-2-hydroxymethylpyrrolidine.

If the unknown chloro amine is 1-methyl-2-chloromethylpyrrolidine, it was thought that the free base probably would rearrange to 1-methyl-3-chloropiperidine. An attempt to demonstrate this gave inconclusive results. The picrate of the unknown amine (0.3 g.) was treated with 20% sodium hydroxide and the free base separated by extraction with several small portions of chloroform. The combined extracts were dried for three hours over anhydrous calcium sulfate, filtered, and saturated with hydrogen chloride. Evaporation of the solvent left a crystalline residue of amine hydrochloride which formed a picrate (0.2 g.) when added to picric acid solution. After recrystallization from ethanol the picrate melted at 148–150°. Four additional crystallizations raised the melting point to 156–159°. A mixture melting point with the original unknown picrate (m. p. 163.5–164.5°) showed no depression. Evidently the picrate of the free base was a mixture, possibly of the unrearranged chloromethylpyrrolidine and 1-methyl-3-chloropiperidine picrates. An insufficient amount of material prevented further investigation of the unknown chloro amine.

1-Ethyl-3-chloropiperidine Hydrochloride (IX).—To a suspension of 5.0 g. (0.030 mole) of 1-ethyl-3-hydroxypiperidine hydrochloride (VII) in 50 ml. of dry toluene was added 3.7 g. (0.031 mole) of thionyl chloride. The mixture was refluxed for three hours during which time the solid disappeared and two layers formed. Removal of the toluene at the water-pump left a dark solid residue which, after recrystallization from ethyl acetate–ethanol (activated carbon), gave 4.8 g. (87%) of slightly discolored crystals. After two additional crystallizations the 1-ethyl-3-chloropiperidine hydrochloride melted at 193.5–194.0°. A mixture of this salt with 1-ethyl-2-chloromethylpyrrolidine hydrochloride showed no depression in melting point. The picrate prepared from the hydrochloride melted at 159–160° after recrystallization from ethanol (Paul[9] reported a melting point of 156–157°).

The Free Amine from 1-Ethyl-2-chloromethylpyrrolidine Hydrochloride.—An ice-cold solution of 1.5 g. of the chloro amine hydrochloride (VIII) in 3 ml. of water was treated with 0.5 g. of sodium hydroxide in 2 ml. of water. The liberated amine was removed by extraction with three 5-ml. portions of chloroform. A small sample of the combined extracts was withdrawn immediately, the solvent evaporated rapidly under an air stream, and the residue added to a saturated aqueous solution of picric acid. The picrate after recrystallization from ethanol melted at 159–160° and showed no depression in melting point when mixed with that obtained from 1-ethyl-3-chloropiperidine hydrochloride, indicating that 1-ethyl-2-chloromethylpyrrolidine, when liberated from its salt, rearranges at room temperature to the piperidine isomer. The remainder of the chloroform solution of the free base was dried overnight over anhydrous calcium sulfate. After removal of the solvent the chloro amine (0.8 g.) distilled at 75–76° (20 mm.); $n^{20}D$ 1.4676 (reported for 1-ethyl-3-chloropiperidine:[9] b. p. 75° (20 mm.); $n^{19.5}D$ 1.46807). The picrate of the distilled amine was identical with that of the crude amine.

The Free Amine from 1-Ethyl-3-chloropiperidine Hydrochloride.—The chloro amine hydrochloride was treated with sodium hydroxide as described above. The isolated base distilled at 74–76° (20 mm.); $n^{20}D$ 1.4678. These constants agree well with those of the free amine from 1-ethyl-2-chloromethyl pyrrolidine hydrochloride. The picrate of the distilled amine was identical with that prepared from 1-ethyl-3-chloropiperidine hydrochloride, indicating that no rearrangement occurred during the liberation and distillation of the chloro amine.

Treatment of 1-Ethyl-3-chloropiperidine Hydrochloride with Zinc and Hydrogen Chloride.—To 1.5 g. of the chloro amine hydrochloride dissolved in glacial acetic acid was added 15 g. of zinc dust. The mixture was saturated with hydrogen chloride and heated on the steam-bath. Every two to three hours the solution was resaturated with hydrogen chloride. After all of the zinc was in solution another 15 g. of the metal was added and the process repeated. The reaction mixture was made strongly basic with sodium hydroxide and steam distilled into hydrochloric acid, the condenser outlet being kept slightly below the surface of the acid in the receiver. After evaporation of the distillate on the steam-bath, the residue of amine hydrochloride was treated with concentrated sodium hydroxide and the liberated base extracted with chloroform. The extract was dried overnight over anhydrous calcium sulfate. Removal of the solvent and distillation of the residue through a narrow 5-cm. Vigreux column yielded 0.4 g. of 1-ethylpiperidine, b. p. 129–130°.[10] About 0.4 g. of high-boiling material remained in the distillation flask. The picrate of the piperidine melted at 167–168°[10] and showed no depression when mixed with an authentic sample of 1-ethylpiperidine picrate.

Summary

1-Ethyl-2-chloromethylpyrrolidine, when liberated from its hydrochloride, undergoes ring enlargement by a rearrangement similar to that observed in other 1,2-aminochloroalkanes, to form 1-ethyl-3-chloropiperidine. The transformation probably occurs through an ethyleneimonium ion intermediate.

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(9) Paul, *Compt. rend.*, **221**, 412 (1945).

(10) Evans, *J. Chem. Soc.*, **71**, 524 (1897), reported a boiling point of 128°; picrate, m. p. 167.5°.