393. *Amidone. Some Isomeric Chlorodialkylaminopropanes and their Reaction with Diphenylmethyl Cyanide.*

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The preparation and some reactions of 1(and 2)-chloro-2(and 1)-dialkylaminopropanes have been studied in order to clarify conflicting experimental evidence. 1-Chloro-2- and 2-chloro-1-dimethylaminopropane are distinct entities, stable in solution in inert solvents under conditions employed in the preparation of amidone and its analogues. The relative proportion of the two isomers formed in the alkylation reactions of diphenylmethyl cyanide with 2-chloro-1-dimethylamino- and 2-chloro-1-piperidino-propane varies with the nature of the basic group.

Two isomeric basic cyanides are known to be produced by condensation of diphenylmethyl cyanide with 1-chloro-2- or 2-chloro-1-dialkylaminopropane. The present paper clarifies conflicting experimental evidence concerning the distinct nature and stability of some isomeric dialkylaminopropanols and chlorodialkylaminopropanes under conditions employed in the preparation of amidone and its analogues (*J.*, 1949, 648; 1950, 2158).

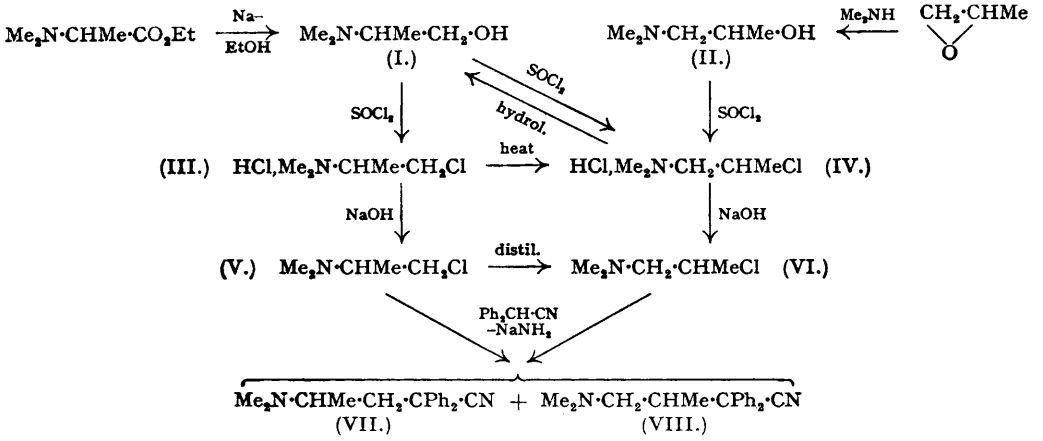
The preparation and some of the reactions of the 1(and 2)-chloro-2(and 1)-dimethylaminopropanes are shown in the reaction scheme.

It was confirmed that 1-dimethylaminopropan-2-ol (II) and 2-dimethylaminopropan-1-ol (I) were distinct entities as indicated by differences in their boiling points and in the melting points of their picrates (cf. Brode and Hill, *J. Amer. Chem. Soc.*, 1947, **69**, 724; Schultz *et al.*, *ibid.*, 1948, **70**, 48; Bockmuhl *et al.*, *Annalen*, 1948, **561**, 52). Although (I), prepared by the Bouveault–Blanc reduction of ethyl α-dimethylaminopropionate, was isolated from a strongly alkaline solution, yet (II) could not be detected in the product.

While (II) was readily converted into 2-chloro-1-dimethylaminopropane hydrochloride (IV) by thionyl chloride, the corresponding reaction with (I) yielded (III) or (IV) according to the conditions employed: mild heat led to (III), whereas, if during isolation the salt was heated more strongly, (IV) was formed (cf. also Schultz *et al.*, *loc. cit.*). A mixture of the two hydrochlorides melted below the melting point of the heat-labile (III) and could be separated into its constituents by making use of the large difference in solubility in acetone.

2- and 3-Chloro-1-piperidinopropane hydrochlorides, prepared by the action of thionyl chloride on the corresponding alcohols, were distinct entities; attempts to add hydrogen chloride to the double bond of 1-allylpiperidine were unsuccessful. This is in agreement with the reported absence of 1 : 1-diphenyl-4-piperidino-*n*-butyl cyanide from the product of the reaction of diphenylmethyl cyanide with the base obtained on treatment of 1-piperidinopropan-2-ol with thionyl chloride (cf. Ofner and Walton, *J.*, 1950, 2158). The action of thionyl chloride

on the amino-alcohols thus involves direct replacement of the hydroxyl group by chlorine rather than dehydration followed by addition of hydrogen chloride to the double bond.



The chloro-base (VI) from the hydrochloride (IV) was found to be stable, in agreement with Schultz *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 48). The same crystalline picrate was obtained, whether the base was liberated from an aqueous solution of its hydrochloride at 0° with dilute aqueous ammonia or isolated at room temperature with excess of 40% sodium hydroxide solution. The base was distilled *in vacuo* without change. Hydrolysis of (IV) yielded 2-dimethylaminopropan-1-ol (I) (cf. Ross, *ibid.*, 1947, **69**, 2982).

It has now been established that the base liberated from an aqueous solution of the hydrochloride (III) at room temperature by the addition of excess of 40% sodium hydroxide solution is identical with the 1-chloro-2-dimethylaminopropane (V) isolated by Schultz *et al.* (*loc. cit.*) by the addition of 20% sodium hydroxide solution to an ice-cold solution of its hydrochloride. This result was unexpected in view of the reported isolation of 2-chloro-1-diethylaminopropane from an aqueous solution of 1-chloro-2-diethylaminopropane hydrochloride (cf. Kerwin *et al.*, *ibid.*, p. 2961; Brode and Hill, *loc. cit.*). The chloro-base (V) may be heated in an inert solvent and may be agitated in an inert solvent with sodium hydroxide solution or an excess of sodamide without undergoing decomposition or isomerisation. On distillation of the base *in vacuo* isomerisation occurred, contrary to the observations of Attenburrow *et al.* (*J.*, 1949, 510); the isomeric chloro-bases (V) and (VI) were separated by fractional crystallisation of the picrates.

It is therefore concluded that the 1(and 2)-chloro-2(and 1)-dimethylaminopropanes are distinct chemical entities and that the action of sodamide does not cause isomerisation to their equilibrium mixture The production of two basic cyanides by sodamide alkylation of diphenylmethyl cyanide with the base from (III) is therefore significant It follows that if a reaction mechanism of the type suggested by Schultz *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 188, 2454) operates, any rearrangement product of the chloro-base must be of a transient nature and produced in the presence of the alkali-metal derivative of diphenylmethyl cyanide.

The relative proportions of the isomers formed in the alkylations of diphenylmethyl cyanide with 2-chloro-1-dimethylaminopropane and 2-chloro-1-piperidinopropane were determined by effecting as complete as possible a separation of the isomer giving the more sparingly soluble salts. In the dimethylamino-series the *n*-compounds form the more sparingly soluble salts, whereas in the analogous piperidino-series the salts of the *iso*-compounds have the lower solubilities (cf. *J.*, 1949, 648; 1950, 2158). In the former series at least 60% of the cyanide was formed by isolation as 6-dimethylamino-4 : 4-diphenylheptan-3-one hydrobromide, and in the latter at least 45% of the *iso*cyanide as 3-imino-5-methyl-4 : 4-diphenyl-6-piperidinohexane dihydrochloride. It appears that the relative proportions vary according to the nature of the basic group of the chloro-base employed in the alkylation.

Experimental.

(M.p.s are uncorrected.)

2-Dimethylaminopropan-1-ol (I).—Ethyl α-dimethylaminopropionate was reduced by the Bouveault–Blanc procedure (Karrer, *Helv. Chim. Acta*, 1922, **5**, 477) to 2-dimethylaminopropan-1-ol (55% yield), b. p. 145—148°. Redistilled 2-dimethylaminopropan-1-ol in ether gave the *picrate* which crystallised from alcohol in orange-yellow bars, m. p. 182—183° (Found : N, 16·8. $C_5H_{13}ON,C_6H_3O_7N_3$ requires

N, 16·9%). The presence of the picrate of the isomeric 1-dimethylaminopropan-2-ol could not be detected in the mother-liquors.

1-*Chloro*-2-*dimethylaminopropane Hydrochloride* (III).—2-Dimethylaminopropan-1-ol (20 g.) in benzene (45 c.c.) was added during 20 minutes to an ice-cold solution of thionyl chloride (23 g.) in benzene (90 c.c.) kept at 0° and stirred vigorously. The mixture was allowed to warm to room temperature and then refluxed for 1·5 hours to remove the gases formed. After cooling, the dark supernatant liquor was poured off, leaving a black gum which was washed several times with dry ether by decantation and then dried in a vacuum-desiccator over sodium hydroxide pellets. On recrystallisation from acetone (150 c.c.), the crude salt (29 g.) yielded the pure hydrochloride (18 g.; 59%) as broad deliquescent needles, m. p. 103—104° (cf. Walton, Ofner, and Thorp, *J.*, 1949, 648).

1-*Dimethylaminopropan*-2-*ol* (II).—This was prepared from propylene oxide and dimethylamine (cf. Goldfarb, *J. Amer. Chem. Soc.*, 1941, **63**, 2280). From ethereal solutions the *picrate* was precipitated immediately as a sticky gum which crystallised during 12 hours at 0°. It crystallised from alcohol in orange-yellow rectangular plates, m. p. 83—84° (Found: N, 16·8. $C_5H_{13}ON,C_6H_3O_7N_3$ requires N, 16·9%).

2-*Chloro*-1-*dimethylaminopropane Hydrochloride* (IV).—(*a*) 1-Dimethylaminopropan-2-ol (20 g.), treated with thionyl chloride (23 g.) as described above, gave the hydrochloride (IV) which crystallised from alcohol (100 c.c.)–dry ether (200 c.c.) in long silky needles, m. p. 190—191° (24 g., 73%; cf. Walton, Ofner, Thorp, *loc. cit.*). A mixture of equal parts of (III) and (IV) melted from 59° to 110°, was clear at 153°, solidified again at 160°, and re-melted at 183°.

(*b*) 2-Dimethylaminopropan-1-ol (20 g.) in benzene (45 c.c.) was treated with thionyl chloride (23 g.) in benzene (90 c.c.) as above. The solvent was removed from the reaction mixture by distillation to dryness under reduced pressure, and the gummy residue refluxed with acetone (150 c.c.). A crystalline solid separated which crystallised in long needles [from alcohol (50 c.c.)–dry ether (100 c.c.)] (10·5 g., 34%), m. p. 190—191° alone or mixed with (IV).

2-*Chloro*-1-*piperidinopropane*.—1-Piperidinopropan-2-ol [b. p. 198—201°/762 mm.; picrate, m. p. 134—135° (Ofner and Walton, *loc. cit.*)], prepared from propylene oxide and piperidine, was treated with thionyl chloride as described for (II). The hydrochloride of 2-chloro-1-piperidinopropane crystallised from alcohol in rectangular plates (65%), m. p. 202—203° (cf. Wenker, *J. Amer. Chem. Soc.*, 1938, **60**, 158). The base liberated from the aqueous solution of the hydrochloride with dilute ammonia gave a *picrate* which crystallised from alcohol in long parallelepipeds, m. p. 132—133° (Found: N, 14·3; Cl, 9·0. $C_8H_{16}NCl,C_6H_3O_7N_3$ requires N, 14·3; Cl, 9·1%).

1-*Allylpiperidine*.—This was prepared in good yield by the action of allyl bromide on piperidine (cf. Beilstein, Vol. XX, p. 21); it gave a *picrate*, m. p. 72—73°, as rectangular bars from alcohol (Found: N, 15·9. $C_8H_{15}N,C_6H_3O_7N_3$ requires N, 15·8%).

1-*Chloro*-3-*piperidinopropane*.—1-Piperidinopropan-3-ol (picrate, m. p. 66—67°; cf. Hromatka, *Ber.*, 1942, **75**, *B*, 131, records m. p. 69°), treated with thionyl chloride as described for (II), gave 1-chloro-3-piperidinopropane hydrochloride which crystallised from alcohol–ether in slender rectangular plates, m. p. 213—214° (Ofner and Walton, *loc. cit.*). This compound, m. p. 208—209°, was previously prepared by Adams *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 735) by treating piperidine with 3-chloropropyl bromide. The hydrochloride, on treatment with alkali, yielded a stable base, b. p. 79—80°/10 mm. (picrate, m. p. 111—112°) (cf. Beilstein, Vol. XX, p. 18, gives b. p. 210°/742 mm. for the base and m. p. 110—111° for the picrate). The mother-liquors from the salts of 2-chloro-1-piperidinopropane and 1-chloro-3-piperidinopropane were tested for the presence of the salts of the respective isomer and 1-allylpiperidine but none was found.

Stability of 2-*Chloro*-1-*dimethylaminopropane* (VI).—(i) The base was liberated into ether (20 c.c.) by the addition of ice-cold dilute aqueous ammonia to a dilute solution (25 c.c.) of the hydrochloride (IV) (1·5 g.). The pure picrate (2·1 g.), m. p. 103—104°, obtained by precipitation from the ethereal solutions, crystallised from alcohol in yellow, rectangular plates (Found: N, 15·9; Cl, 10·1. Calc. for $C_5H_{12}NCl,C_6H_3O_7N_3$: N, 16·0; Cl, 10·1%) (cf. Schultz *et al.*, *loc. cit.*). (ii) A picrate of identical m. p. was obtained when the base was liberated by addition of 40% sodium hydroxide solution at room temperature in the absence of ether. In neither experiment was any other picrate isolated from the mother-liquors. (iii) The chloro-base isolated as described under (ii) distilled at 36—37°/35 mm. The picrates from an aliquot of the oily extract and the distillate were identical, and melted at 102—103° after recrystallisation from alcohol. (iv) The hydrochloride (IV) (5 g.) was hydrolysed as described by Ross (*J. Amer. Chem. Soc.*, 1947, **69**, 2982) for 2-chloro-1-diethylaminopropane hydrochloride. Fractional crystallisation of the picrate of the product yielded 2-dimethylaminopropan-1-ol picrate (0·5 g.), m. p. 179—180° alone or mixed with an authentic specimen.

Stability of 1-*Chloro*-2-*dimethylaminopropane* (V).—(i) The chloro-base from hydrochloride (III) (1·5 g.), liberated by the addition of dilute aqueous ammonia to the aqueous solution of (III) at 0°, gave a picrate, m. p. 161—162°, which crystallised from alcohol in light yellow, rectangular plates, m. p. 167—168° (2·3 g.) (Found: N, 16·0; Cl, 10·1%).

(ii) The m. p. of the picrate was not changed when the base was either liberated by 40% sodium hydroxide solution at room temperature in the presence of ether or left in contact with the strongly alkaline solution for 30 minutes in the absence of solvent before extraction.

A mixture of the hydrochlorides (III; 2 g.) and (IV; 2 g.) was refluxed with acetone (20 c.c.) for 30 minutes, and the suspension of undissolved hydrochloride was filtered hot. The residue was washed with hot acetone, then with ether, leaving 1·6 g., m. p. 189° (picrate, m. p. 101—102°). The acetone filtrate deposited on cooling a further quantity (0·3 g.) of hydrochloride (N.) (picrate, m. p. 101—103°). Ether precipitation of the acetone mother-liquors and preparation of the picrate yielded the pure salt (2·2 g.), m. p. 167—168°.

(iii) Aliquots of a benzene solution of the chloro-base were (*a*) stirred vigorously with 40% sodium hydroxide solution (24 mols. per mol.) at 40—50° for 30 minutes, (*b*) heated with an equal volume of xylene at 97° for 30 minutes, (*c*) refluxed and stirred vigorously with an equimolecular quantity of sodamide for 30 minutes, (*d*) added during 30 minutes to a suspension of sodamide (8 mols. per mol.) in dry benzene at 40—45° (the suspension was refluxed an additional 30 minutes), and (*e*) tested immediately after preparation and after 10 days at room temperature. Only the picrate of (V) was isolated in each case. An acetone-soluble hydrochloride was obtained from an aliquot which had been refluxed with sodamide as described under (*c*), filtered, and cautiously acidified with alcoholic hydrochloric acid at 0°.

(iv) Addition of alkali to an aqueous solution of the hydrochloride (III) (2 g.), followed by ether-extraction and distillation of the solvent, gave 1-chloro-2-dimethylaminopropane (V) (1·7) g., a light yellow, mobile liquid. No isomerisation had taken place during removal of the solvent, as a sample of the base (0·2 g.) gave a picrate (0·1 g.), m. p. 165—167°. The base distilled at 25—30°/5 mm. The colourless distillate (1 g.), in ether, gave a picrate (2 g.), m. p. (sintering at 100°) 120—144° (clear at 152°). Recrystallisation from alcohol (100 c.c.) gave a first fraction (1·2 g.), m. p. 164—166°; concentration to 25 c.c. and addition of ether (5 c.c.) yielded a second fraction (0·2 g.), m. p. (sintering at 140°) 150—155°; and further concentration (to 5 c.c.) gave the picrate of the isomeric 2-chloro-1-dimethylaminopropane (VI) (0·3 g.), m. p. 100—102°.

In the stability experiments described above all m. p.s were checked by mixed m. p. determinations with authentic materials.

The Relative Proportion of Isomers.—(a) *Dimethylamino-series.* (i) The cyanide (VII) (20 g.; m. p. 90—91°) in redistilled xylene (20 c.c.) was added to the Grignard reagent from ethyl bromide (23·5 g.) and magnesium (5·3 g.) in ether. The mixture was heated on the steam-bath for 4 hours, the ether being allowed to evaporate. The product was then decomposed with water (20 c.c.), and 40% aqueous hydrobromic acid added until the reaction mixture was acid to Congo-red. The xylene was removed by distillation with water (200 c.c.) under reduced pressure. After 12 hours at 0°, the solid 6-dimethylamino-4 : 4-diphenylheptan-3-one (amidone) hydrobromide was filtered off, dried at 70° for 4 hours, and triturated with acetone. The white hydrobromide (22·1 g.), m. p. 223—225°, yielded a light yellow, solid base which crystallised from light petroleum (b. p. 80—100°) in hexagonal needles, m. p. 80—82° (16·8 g., 75% yield; in addition a small quantity of low-melting material). (ii) A mixture of cyanides (VII; 20 g.; m. p. 90—91°) and (VIII; 20 g.; m. p. 68—69°) in redistilled xylene (40 c.c.) was condensed with the Grignard reagent from ethyl bromide (47 g.) and magnesium (10·5 g.) in ether and amidone hydrobromide (22·6 g.), m. p. 222—224°, isolated as described under (i). Treatment of this salt with aqueous alkali and crystallisation from light petroleum (b. p. 80—100°) afforded amidone base (16·5 g.), m. p. 79—81°. (iii) The mixture of isomeric cyanides (750 g.) prepared by sodamide alkylation of diphenylmethyl cyanide with 2-chloro-1-dimethylaminopropane was dissolved in redistilled xylene (750 c.c.) and combined with ethylmagnesium bromide from ethyl bromide (881 g.), magnesium (197 g.), and dried ether (2 l.). By the procedure described under (i), a cream-coloured, solid hydrobromide (520 g.), m. p. 222—224°, was obtained after trituration with acetone and, on addition of alkali and crystallisation from light petroleum (b. p. 80—100°), amidone base (380 g.) m. p. 79—81°.

(b) *Piperidino-series.* (i) 2-Methyl-1 : 1-diphenyl-3-piperidino-*n*-propyl cyanide (9·6 g.; m. p. 105—106°) in redistilled xylene (10 c.c.) and the Grignard reagent from ethyl bromide (9·9 g.), magnesium (2·2 g.), and dry ether were caused to react as described by Ofner and Walton (*loc. cit.*). Reproducible and substantially higher yields of 4-imino-2-methyl-3 : 3-diphenyl-1-piperidinohexane dihydrochloride (9·3 g., 73%), m. p. 193° (decomp.), have now been obtained (average yield 75%). (ii) A mixture of the pure isomeric cyanides (11·5 g. of each) and ethylmagnesium bromide (3 mols.) in ether (100 c.c.) gave 4-imino-2-methyl-3 : 3-diphenyl-1-piperidinohexane dihydrochloride (11·2 g.), m. p. 193° (decomp.), isolated as described below. (iii) The mixture of isomeric cyanides (120 g.), produced by the alkylation of diphenylmethyl cyanide with 2-chloro-1-piperidinopropane, in xylene (80 c.c.) was added to ethylmagnesium bromide (3 mols.) in ether (275 c.c.). After distillation of the ether, the reaction mixture was heated at 95—100° for 4·5 hours. A solid adduct formed after 1 hour's heating; part of the xylene (40 c.c.) was then removed by distillation under reduced pressure. The basic reaction product was isolated as a dark brown, viscous oil by exhaustive ether-extraction of the alkaline reaction mixture and distilled to dryness under reduced pressure. The basic oil was treated with alcoholic hydrochloric acid till acid to Congo-red, then evaporated to dryness, and the residual paste refluxed with ethyl methyl ketone (300 c.c.) leaving the ketimine dihydrochloride in suspension. The solid was filtered off and again refluxed with ethyl methyl ketone (600 c.c.), to give the pure dihydrochloride (51 g.), m. p. 193° (decomp.). This treatment does not cause hydrolysis to the ketone; in each of the experiments (i), (ii), and (iii) the ethyl methyl ketone mother-liquors were evaporated, the base liberated by treatment with alkali and, in alcoholic solution, treated with 10% sulphuric acid. The hydrogen sulphate of the base was readily soluble in ethyl methyl ketone, whereas 5-methyl-4 : 4-diphenyl-6-piperidinohexan-3-one hydrogen sulphate (cf. Ofner and Walton, *loc. cit.*) was insoluble in boiling ethyl methyl ketone.

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