205. *Syntheses in the Piperidine Series. Part I. A Facile Synthesis of Piperidin-4-ol, and the Preparation of Related Compounds.*

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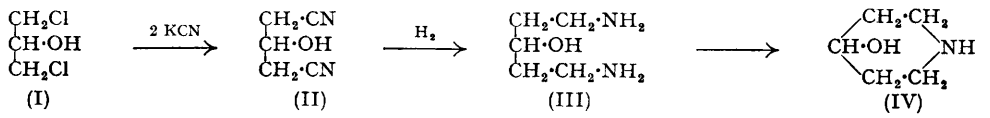
Contrary to earlier work, 1 : 3-dichloropropan-2-ol reacts with potassium cyanide to give 1 : 3-dicyanopropan-2-ol. This, on catalytic hydrogenation, yields piperidin-4-ol, making an easy synthesis of this compound available. Even when the hydrogenation is carried out in the presence of liquid ammonia the formation of piperidin-4-ol predominates over the formation of the open-chain diamine, 1 : 5-diaminopentan-3-ol. 4-Hydroxypiperidinium bromide with phosphorus tribromide gives 4-bromopiperidinium bromide which may be readily converted into 1-benzoyl-4-bromopiperidine. 1-Acetylpiperidin-4-ol may be prepared by the action of either acetamide or methyl acetate on piperidin-4-ol. 1-Methylpiperidin-4-ol is readily obtained by the reductive methylation of piperidin-4-ol with formaldehyde and formic acid. 1-Methylpiperid-4-one can be prepared from bis-2-chloroethyl ketone and methylamine.

A programme of synthetical work, which will be reported later, aimed at the preparation of potential chemotherapeutic agents required piperidin-4-ol and related compounds as intermediates. The recorded methods of synthesising piperidin-4-ol generally required difficultly accessible starting materials and, besides being time-consuming, gave low overall yields (Koenigs and Neumann, *Ber.*, 1915, **48**, 956; McElvain and McMahon, *J. Amer. Chem. Soc.*, 1949, **71**, 901). It therefore seemed worth while to investigate the following route which would involve only three stages and would require as starting material easily accessible 1 : 3-dichloropropan-2-ol (I) :



Simpson (*Annalen*, 1865, **133**, 75) unsuccessfully attempted to prepare 1 : 3-dicyanopropan-2-ol (II) from (I) and potassium cyanide; Morgensen and Zerner (*Monatsh.*, 1910, **31**, 778) claimed the isolation of (II), describing it as an amorphous solid unstable to distillation, but this was later shown to be incorrect by Lespieau (*Compt. rend.*, 1923, **176**, 754) and Legrand (*Bull. Soc. chim. Belg.*, 1944, **53**, 166), who prepared the compound from 1-chloro-3-cyanopropan-2-ol and found it to be a stable liquid.

Contrary to Simpson (*loc. cit.*) we found that (II) can be prepared from (I) and sodium

cyanide. The use of water as solvent gave higher yields than when alcohol was employed, and sodium cyanide was superior to potassium cyanide for the reaction. Some commercial samples of (I) were unsatisfactory as starting materials even after careful distillation, but consistent results were obtained with (I) prepared by the usual method from 3-chloropropylene oxide and hydrogen chloride (Hill and Fischer, *J. Amer. Chem. Soc.*, 1922, **44**, 2584).

The preparation of 1 : 5-diaminopentan-3-ol (III) by reduction of (II) with sodium and alcohol was claimed by Morgensen and Zerner (*loc. cit.*), who characterized their product as a picrate, but in view of the doubtful nature of their starting material, the lack of analytical data, and the melting point of the derivative, their results must be accepted with some reserve. We found that reduction of (II) with sodium and either ethyl or *n*-butyl alcohol gave indifferent yields of (III), and difficulties were experienced in the isolation of the product.

Catalytic reduction of cyanides is frequently a suitable method of preparing amines and the presence of ammonia usually suppresses the formation of secondary amines (Schwoegler and Adkins, *J. Amer. Chem. Soc.*, 1939, **61**, 3501; Huber, *ibid.*, 1944, **66**, 876; Biggs and Bishop, *Org. Synth.*, 1947, **27**, 18). The cyanide (II) was therefore catalytically hydrogenated in alcoholic ammonia and also in anhydrous ammonia. Although the products from these reactions contained some of the open-chain diamine (III), in all cases piperidin-4-ol (IV) predominated. Hydrogenation of (II) in the absence of ammonia further increased the yield of (IV). Rapid hydrogenation of (II) gave the best yield of (IV), slow hydrogenation producing some high-molecular weight material, formed probably by the polymerization of intermediate imine. Thus there was available a two-stage synthesis of piperidin-4-ol requiring only simple starting materials.

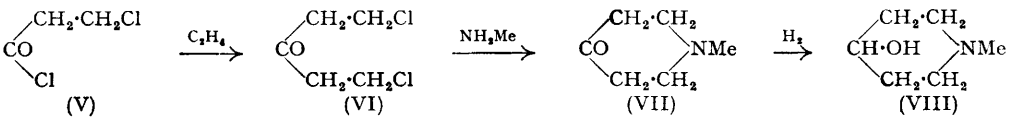
Many simple salts of piperidin-4-ol are hygroscopic, but we found that the sulphate tetrahydrate, m. p. 66—88°, is non-hygroscopic; it is converted into the anhydrous sulphate, m. p. 272—274°, when dried in a vacuum desiccator, and in air reverts to the tetrahydrate. The hydrated salt, being soluble in hot 95% alcohol, is useful for separating (IV) from (III), the sulphate of which is insoluble in the same solvent.

4-Bromopiperidine was prepared by Koenigs and Neumann (*loc. cit.*) by the action of fuming hydrobromic acid on (IV) in a sealed tube. We were unable to obtain the yield quoted, and the product was difficult to decolourize. We found that the compound could be readily prepared from phosphorus tribromide and the hydrobromide of (IV), and that the product was easily purified.

Leffler and Adams's acylation method (*J. Amer. Chem. Soc.*, 1937, **59**, 2256) was used for the preparation of 1-benzoyl-4-bromopiperidine but failed with (IV). The 1-acetyl derivative of (IV) was readily obtained from (IV) by the action of (*a*) acetamide in boiling *cyclo*hexanol or (*b*) methyl acetate.

The preparation of 1-methylpiperidin-4-ol (VIII) has been attended in the past by the same difficulties as are encountered in the preparation of (IV). Reductive methylation of (IV) with formaldehyde and formic acid gave excellent yields of (VIII) (cf. Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571).

The preparation of (VIII) from 1-methylpiperid-4-one (VII) has already been reported (McElvain and Rorig, *J. Amer. Chem. Soc.*, 1948, **70**, 1826). The following route to (VIII) was therefore explored :



The formation of (VI) from (V) has been described elsewhere (B.P. 459 537), but we found that to obtain good yields it was necessary to add the ethylene and aluminium chloride simultaneously to (V). During the course of this work, Cardwell and McQuillin (*J.*, 1949, 708) described the use of nitromethane as solvent in this reaction.

By the reaction of methylamine with (VI) in aqueous sodium carbonate (VII) was

formed, but in view of the ease of preparation of (VIII) from (IV) this route was not investigated further. The simple salts of (VIII), with the exception of the picrate, were hygroscopic.

Experimental

1 : 3-*Dicyanopropan*-2-*ol* (II).—To sodium cyanide (54 g.) in warm water (60 ml.) was added 1 : 3-dichloropropan-2-ol (65 g.) in one portion, and whilst vigorously stirred, the mixture was warmed to 50°. The temperature was held at 50—55° for 40 minutes by ice-water cooling; the mixture was then allowed to cool and was stirred overnight. After neutralisation (litmus) with 5N-hydrochloric acid, the mixture was filtered and the residue and filtrates extracted with ethyl acetate (4 × 50 ml.). The extracts were dried (Na_2SO_4) and distilled under reduced pressure, giving 1-chloro-3-cyanopropan-2-ol (6·3 g.), b. p. 85—105°/0·01—0·03 mm., followed by 1 : 3-dicyanopropan-2-ol. The latter, a pale yellow, viscous oil (23·3 g.), b. p. 145—155°/0·02—0·05 mm., was characterized by conversion into 2-bromo-1 : 3-dicyanopropane, m. p. 91° (from water) (Lespieau, *loc. cit.*, gives m. p. 87—88°); and into 2-bromo-1 : 3-dicyanopropane bromohydrate which formed long needles, m. p. 228° (from water) (Lespieau, *loc. cit.*, gives m. p. 230°). No increase in yield was obtained when 1 : 3-dibromopropan-2-ol replaced the dichloro-compound.

Piperidin-4-*ol* (IV).—1 : 3-Dicyanopropan-2-ol (45 g.) in ethanol (400 ml.; 95%) was hydrogenated in a magnetically stirred autoclave (750 ml. capacity) in the presence of Raney nickel (10 g.) at 50° and 50 atmospheres. Hydrogenation was complete in 2 hours. The solution was then filtered and distilled under reduced pressure to give (IV) (17·6 g.) as a colourless, highly viscous oil, b. p. 110—115°/10 mm., which crystallized in the receiver. The platinichloride, prepared in alcoholic solution, had m. p. 195° (decomp.) [Koenigs and Neumann, *loc cit.*, give m. p. 184—187° (decomp.)] [Found : C, 19·75; H, 4·0. Calc. for $(C_5H_{11}ON)_2PtCl_6$: C, 19·6; H, 3·9%]. The crude hydrogenation product, on neutralization with dilute sulphuric acid and evaporation to dryness, gave a solid which was treated with hot 95% ethanol. From the filtrates 4-*hydroxypiperidinium sulphate tetrahydrate* crystallized as needles, m. p. 66—68° (Found : C, 32·4; H, 8·2; S, 8·4. $2C_5H_{11}ON,H_2SO_4,4H_2O$ requires C, 32·3; H, 8·6; S, 8·6%). When kept in a vacuum desiccator this compound changed into the anhydrous sulphate, m. p. 272—274° (Koenigs and Neumann, *loc. cit.*, give m. p. 263—266°) (Found : C, 39·8; H, 8·2; S, 11·0. Calc. for $2C_5H_{11}ON,H_2SO_4$: C, 40·0; H, 8·0; S, 10·7%). The ethanol-insoluble material was dissolved in a minimum of water, and added to an excess of saturated sodium picrate in water. Yellow needles separated and were crystallized from hot water giving 1 : 5-*diaminopentan*-3-*ol dipicrate*, m. p. 238° (decomp.) (Found : C, 35·8; H, 3·6; N, 19·4. $C_5H_{14}ON_2,2C_6H_3O_7N_3$ requires C, 35·5; H, 3·5; N, 19·4%) [Morgensen and Zerner, *loc. cit.*, reported m. p. 272° (decomp.) for this compound, but gave no analytical figures].

4-*Bromopiperidinium Bromide*.—Piperidin-4-ol (3 g.) was dissolved in aqueous hydrobromic acid (10 g.; 47%) and the solution concentrated to dryness under reduced pressure. The residue was dissolved in hot ethanol (10 ml.), and the solvent then removed under reduced pressure to give a crystalline hydrobromide, m. p. 104—106°. Phosphorus tribromide (5 g.) was added and the mixture refluxed for 10 minutes. When the mixture was cold, excess of phosphorus tribromide was removed under reduced pressure and the residue was extracted three times with sodium-dried ether, and then with three lots of hot absolute alcohol, from which crystals, m. p. 192—193° (decomp.), were deposited. These were recrystallized from *n*-butanol, giving 4-bromopiperidinium bromide (2·8 g.), m. p. 192—193° (decomp.) (cf. Koenigs and Neumann, *loc. cit.*). By the addition of an aqueous solution of this salt to a saturated solution of sodium picrate in water the *picrate* was obtained as yellow prisms, m. p. 162—163° (from hot water) (Found : C, 33·8; H, 3·3; N, 14·0; Br, 20·4. $C_5H_{10}NBr,C_6H_3O_7N_3$ requires C, 33·6; H, 3·3; N, 14·2; Br, 20·3%). The *sulphate* was prepared from a saturated solution of silver sulphate in water and the bromide. After removal of silver bromide, the sulphate was obtained by evaporation followed by recrystallization of the residue from 95% ethanol; it formed prisms, m. p. 163—164° (Found : C, 28·5; H, 5·3; N, 6·3. $2C_5H_{10}NBr,H_2SO_4$ requires C, 28·2; H, 5·2; N, 6·6%).

1-*Benzoyl*-4-*bromopiperidine*.—To a solution of benzoyl chloride (1·54 g.) in benzene (5 ml.) was added, with stirring, a solution of 4-bromopiperidinium bromide (2·45 g.) in water (15 ml.); followed by one of sodium carbonate (1·27 g.) in water (12·7 ml.), added dropwise, at 5°. After 2 hours' stirring, the mixture was extracted three times with benzene, and the extracts dried (Na_2SO_4). The solvent was removed under reduced pressure leaving an oil which slowly

solidified. Crystallization from light petroleum (b. p. 60—80°) gave 1-*benzoyl*-4-*bromopiperidine* as prisms (2 g.), m. p. 67—69° (Found: C, 53·6; H, 5·1; N, 5·1. $C_{12}H_{14}ONBr$ requires C, 53·7; H, 5·3; N, 5·2%).

1-*Acetylpiperidin*-4-*ol*.—(*a*) Piperidin-4-ol (5 g.) in methyl acetate (6 ml.) was refluxed for 78 hours, and the mixture then distilled under reduced pressure to give unchanged piperidin-4-ol (1·5 g.), followed by an oil, b. p. 176—178°/10 mm., which crystallized in the receiver. This product was recrystallized giving 1-*acetylpiperidin*-4-*ol* (3·0 g.) as hygroscopic prisms, m. p. 66—67° (Found: C, 58·3; H, 9·3; N, 9·7. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·2; N, 9·8%).

(*b*) Piperidin-4-ol (2·5 g.), acetamide (1·5 g.), and *cyclo*hexanol (5 g.) were refluxed for 6 hours in an apparatus equipped with a soda-lime tube. The resulting mixture was distilled under reduced pressure giving 1-acetylpiperidin-4-ol (1·5 g.), b. p. 180—182°/11 mm., identical with material obtained by method (*a*). The compound is readily soluble in water and insoluble in dry ether.

Di-2-*chloroethyl Ketone*.—Into β-chloropropionyl chloride (170 g.) was passed a steady stream of ethylene whilst powdered aluminium chloride (187 g.) was added portionwise. During the addition, which took 3½ hours, the temperature was kept at 20—25° and the ethylene was passed in as fast as it could be absorbed by the mixture. After addition of the aluminium chloride was complete, ethylene was passed in at the same temperature for 1 hour, whereupon no further absorption took place. Next morning the mixture was poured on a mixture of ice and dilute hydrochloric acid, whereupon a heavy oil separated. The mixture was extracted with ether, and the ethereal solution washed twice with water, dried (Na_2SO_4), and distilled through a fractionating column, giving di-2-chloroethyl ketone (89 g.), b. p. 79—89°/10 mm. (Caldwell and McQuillin, *loc. cit.*, give b. p. 78°/6 mm.—88°/10 mm.).

1-*Methylpiperid*-4-*one*.—A solution of sodium carbonate (6·3 g.) in water (70 ml.) was added dropwise during 45 minutes to a solution of di-2-chloroethyl ketone (4·65 g.) in absolute alcohol (30 ml.) at room temperature. Simultaneously methylamine gas was introduced into the mixture. When the addition was complete the mixture was refluxed for 1 hour. Next morning, after being evaporated to half its volume, the solution was treated with potassium hydroxide, and a dark oil separated. The mixture was extracted well with ether, the ethereal solution dried (Na_2SO_4), and the solvent evaporated giving methylpiperid-4-one (0·75 g.), b. p. 55—59°/14 mm. The product reacted with benzaldehyde to give 3 : 5-dibenzylidene-1-methylpiperid-4-one, m. p. 117° (cf. Howton, *J. Org. Chem.*, 1945, **10**, 279).

1-*Methylpiperidin*-4-*ol*.—To a cooled solution of piperidin-4-ol (5 g.) in 90% formic acid solution (8 g.) was added 40% aqueous formaldehyde solution (5 g.). The mixture was heated on the steam-bath for 8 hours. Next morning concentrated hydrochloric acid (10 ml.) was added, and the mixture refluxed for 5 minutes and then evaporated under reduced pressure, giving an oil. The oil was dissolved in water (5 ml.), and 50% aqueous potassium hydroxide (10 ml.) added, giving a brown oil. The mixture was extracted well with benzene and the extract dried (Na_2SO_4) and distilled, giving 1-methylpiperidin-4-ol (4·3 g.), b. p. 95—96°/10 mm. The *methiodide* crystallized from ethanol as prisms, m. p. 327° (decomp.) (Found: C, 32·9; H, 6·4; N, 5·3; I, 49·3. $C_6H_{13}ON,CH_3I$ requires C, 32·7; H, 6·3; N, 5·4; I, 49·4%).

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