127. *Pharmacodynamic Compounds. Part II.* Some Rearrangements in the Pyrrolidine–Piperidine Series.*

By E. G. Brain, F. P. Doyle, and M. D. Mehta.

Two types of rearrangement in the pyrrolidine–piperidine series are distinguished. Thermal rearrangement of 2-chloromethyl-1-methylpyrrolidine to 3-chloro-1-methylpiperidine has been extended to several esters of 2-hydroxymethyl-1-methylpyrrolidine. Replacement reactions of 3-chloro-1-methylpiperidine with nucleophilic reagents result in partial rearrangement in the reverse direction.

It is known that 1-chloro-2-dialkylaminopropanes when in the form of free bases readily undergo rearrangement to the isomeric 2-chloro-1-dialkylaminopropanes.[1] Fuson and Zirkle [2] have similarly shown that 2-chloromethyl-1-ethylpyrrolidine hydrochloride when treated with alkali or heated above its melting point produces 3-chloro-1-ethylpiperidine or its hydrochloride, respectively.

We have now found that, although 2-chloromethyl-1-methylpyrrolidine hydrochloride (I) and 3-chloro-1-methylpiperidine hydrochloride (II) have distinct melting points, the former appears to be partially isomerised to the latter when heated above its melting point. When carefully neutralised with cold sodium hydroxide the hydrochlorides afford

* Part I, *J.*, 1958, 4458.

[1] Kerwin, Ullyot, Fuson, and Zirkle, *J. Amer. Chem. Soc.*, 1947, **69**, 296; Brode and Hill, *ibid.*, 1947, **69**, 724; Schultz and Sprague, *ibid.*, 1948, **70**, 48.

[2] Fuson and Zirkle, *J. Amer. Chem. Soc.*, 1948, **70**, 2750.

distinct bases without isomerisation; these were purified by low-temperature distillation and characterised as picrates and by infrared spectra.

2-Chloromethyl-1-methylpyrrolidine (III) when heated for 1 hr. at 100° was converted into 3-chloro-1-methylpiperidine (IV) to the extent of ~60%, as determined by infrared absorption measurements, a solid by-product also being formed. The recovery of the chloropiperidine (IV) unchanged after heating under the same conditions showed that this rearrangement was not an equilibration.

When the chloropyrrolidine (III) had been refluxed in propan-2-ol for 4 hr. only the chloropiperidine (IV) could be isolated. These conditions are those normally used in the Hörenstein–Pählicke method for the synthesis of esters from amino-alcohols and suggested to us that the preparation of esters from the chloride (III) by this method might lead to a mixture of pyrrolidine and piperidine derivatives. Blicke and Lu [3] reported the preparation of the benzilic ester [VI; R = $Ph_2C(OH)\cdot CO$] by this method, but by fractional crystallisation we have now found that the material obtained by following their procedure was a mixture of the pyrrolidine ester [VI; R = $Ph_2C(OH)\cdot CO$] and the piperidine ester [VII; R = $Ph_2C(OH)\cdot CO$]. Infrared analysis of the mixture indicated that the pyrrolidine ester predominated in the ratio of 7 : 3. [The hydroxymethylpyrrolidine (VI; R = H) used as starting material by Blicke and Lu [3] was probably obtained from L-glutamic acid and therefore optically active, whereas ours was racemic; this does not invalidate our finding].

This formation of a mixture could at first sight be explained by thermal rearrangement of (III) during the reaction. The proportion of pyrrolidine and piperidine esters present in the product would then depend on the relative rates of the thermal rearrangement and nucleophilic attack on the two isomeric chloro-compounds by the benzilate ion. However, nucleophilic replacements with both the bases (III) and (IV) probably proceed by way of the ion (V). Thus, the replacement reactions of 1-alkyl-3-chloropiperidine with certain nucleophilic reagents, for example, with amines,[4] hydrazines,[5] and cyanide ion [6] have been reported to yield only the corresponding 1-alkyl-2-pyrrolidylmethyl derivatives. In other reactions, a mixture of pyrrolidine and piperidine products resulted.[6,7] We have now found that the product from the reaction of the chloropiperidine (IV) and benzilic acid in propan-2-ol is a mixture of esters (VI) and (VII) [R = $Ph_2C(OH)\cdot CO$] in a similar ratio (7 : 3) to that obtained when the 2-chloromethylpyrrolidine (III) was used. This ratio was not significantly altered by the use of alkali benzilates in place of free benzilic acid or by other changes in reaction conditions.

Analogous reactions of the chloropiperidine (IV) in which this rearrangement might occur were also investigated. With acetate ion, the product was a mixture of the isomeric acetates in a ratio similar to that obtained in the case of the esters (VI and VII). With sodium benzyl oxide, however, rearrangement was complete and only 2-benzyloxymethyl-1-methylpyrrolidine (VI; R = CH_2Ph) was formed. Just as with 3-chloro-1-ethylpiperidine [6] the cyanide ion gave only the 2-cyanomethylpyrrolidine (VIII) the identity of which was established by conversion, through the ester (IX), into the known 2-2′-hydroxyethyl-1-methylpyrrolidine (X). The nitrile (VIII) was also shown by means of infrared spectra and preparation of the picrate to be different from an authentic sample of 3-cyano-1-methylpiperidine obtained from ethyl nicotinate.

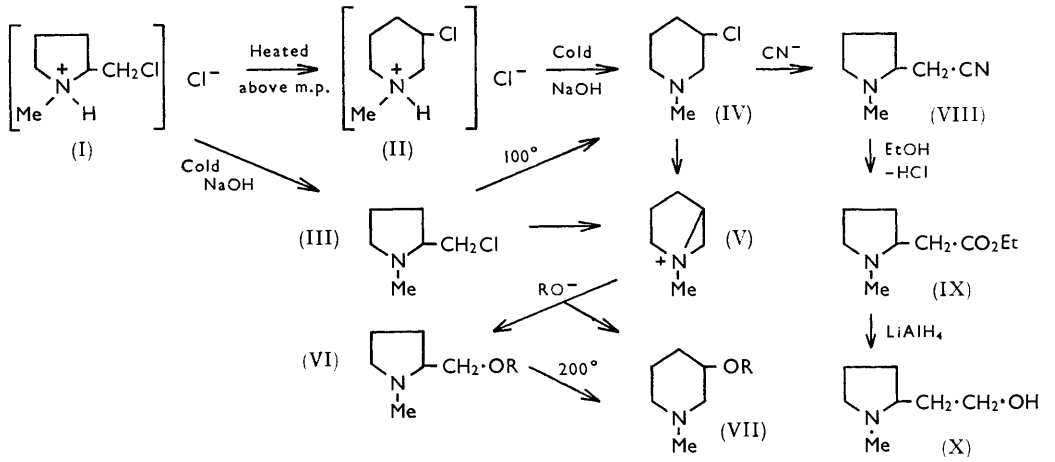
Attack on an aziridinium ion by hydroxyl ion has been shown in the open-chain series to lead preferentially to the primary alcohol.[8] This appears to apply also to 3-chloro-1-methylpiperidine, since the only product isolated from alkaline hydrolysis was 2-hydroxymethyl-1-methylpyrrolidine.

[3] Blicke and Lu, *J. Amer. Chem. Soc.*, 1955, **77**, 29.
[4] Reitsema, *J. Amer. Chem. Soc.*, 1949, **71**, 2041; Biel, U.S.P. 2,874,163.
[5] Biel, Hoya, and Leiser, *J. Amer. Chem. Soc.*, 1959, **81**, 2527.
[6] Paul and Tchelitcheff, *Bull. Soc. chim. France*, 1958, 736.
[7] Biel, *J. Amer. Chem. Soc.*, 1955, **77**, 2250.
[8] Ross, *J. Amer. Chem. Soc.*, 1947, **69**, 2982.

In the above nucleophilic replacement reactions the major, or sole, product was always the pyrrolidine derivative and it seemed surprising therefore that other workers had obtained mainly piperidine compounds from 1-alkyl-3-chloropiperidines by such reactions.[9,10] The possibility of thermal rearrangement of the products (possibly during isolation), as has been demonstrated for the chloro-compounds, has not hitherto been considered. This has now been shown to occur with several simple esters of 2-hydroxymethyl-1-methylpyrrolidine.

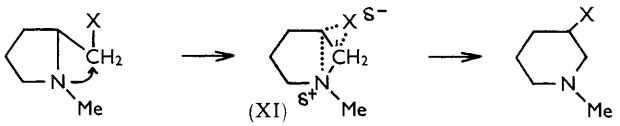
The acetate, benzoate, phenylacetate, and diphenylacetate were prepared unambiguously by the action of the appropriate acid chloride on the alcohol (VI; R = H). The corresponding esters of 3-hydroxy-1-methylpiperidine (VII; R = H) were prepared similarly for comparison.

The acetate (VI; R = Ac) was stable at 200°, but the remaining pyrrolidylmethyl esters all isomerised to some extent, as indicated by infrared measurements. The effect



of heat on 3-benzoyloxy-1-methylpiperidine (VII; R = Bz) was also investigated, but this showed none of the reverse rearrangement. Just as with the chloro-compounds (III) and (IV), therefore, the reaction is irreversible although completion is often slow.

Thermal rearrangement can thus account for the isolation of piperidine derivatives as the sole products when 3-chloropiperidines have been converted into esters,[9] since, where the ester has been isolated by distillation, it appears probable that any pyrrolidine ester formed during the initial nucleophilic reaction would revert to the piperidine isomer



by a second intramolecular thermal rearrangement during the isolation. While the nucleophilic replacement reaction is presumably ionic in character the thermal rearrangement is probably intramolecular, proceeding *via* the transition state (XI; X = halogen or acyloxy). As could be predicted, the ease of rearrangement increases with the ability of X to accommodate a negative charge in the transition state (Cl > O·CO·CHPh$_2$ > O·CO·CH$_2$Ph > O·CO·CH$_3$).

We have found that consideration must always be given to both types of rearrangement

[9] Cf. Biel, Friedman, Leiser, and Sprengler, *J. Amer. Chem. Soc.*, 1952, **74**, 1485; Buehler, Smith, Glenn, and Nayak, *J. Org. Chem.*, 1958, **23**, 1432.
[10] Biel, U.S.P. 2,831,862.

in any reaction, such as the Hörenstein–Pählicke ester synthesis, involving an unsymmetrical R·CH(NR_2)·CHR'Cl grouping.

Experimental

Infrared absorption spectra were determined by Mr. K. Austin using a Grubb–Parsons double-beam spectrometer. The specimens were examined as ~3% solutions in carbon tetrachloride or in cyclohexane. Racemic compounds were used throughout this work.

3-Chloro-1-methylpiperidine.—3-Hydroxy-1-methylpiperidine [11] with an excess of thionyl chloride in chloroform gave *3-chloro-1-methylpiperidine hydrochloride* (quantitative) as needles, m. p. 187—188° after several crystallisations from dioxan–ethanol (Found: C, 42·7; H, 7·8; N, 8·0; Cl, 41·4. $C_6H_{13}Cl_2N$ requires C, 42·3; H, 7·7; N, 8·2; Cl, 41·7%). The *picrate*, prepared directly from the hydrochloride, crystallised from ethanol as pale yellow needles, m. p. 168—169° (Found: C, 40·0; H, 4·0; N, 14·8; Cl, 9·2. $C_{12}H_{15}ClN_4O_7$ requires C, 39·8; H, 4·2 N, 15·5; Cl, 9·8%).

An aqueous solution of the above hydrochloride neutralised with an excess of sodium hydroxide solution at 0° gave *3-chloro-1-methylpiperidine* (55%), b. p. 52—53°/16—17 mm., n_D^{20} 1·4677 (Found: C, 53·7; H, 9·1; N, 10·5; Cl, 26·5. $C_6H_{12}ClN$ requires C, 54·0; H, 9·1; N, 10·5; Cl, 26·6%), $\nu_{max.}$ 8·22, 11·3, 12·67, 13·18 μ.

2-Chloromethyl-1-methylpyrrolidine.—2-Hydroxymethyl-1-methylpyrrolidine [11] was converted as above into *2-chloromethyl-1-methylpyrrolidine hydrochloride* (quantitative) which after several crystallisations from dioxan–ethanol was obtained as needles, m. p. 144° (Found: C, 42·5; H, 8·2; N, 8·2; Cl, 41·6. $C_6H_{13}Cl_2N$ requires C, 42·3; H, 7·7; N, 8·2; Cl, 41·7%). The *picrate*, prepared directly from the hydrochloride, crystallised from benzene as pale yellow needles, m. p. 174—175° (mixed m. p. 159—168° with 3-chloro-1-methylpiperidine picrate described above) (Found: C, 39·7; H, 3·9; N, 15·2; Cl, 9·7. $C_{12}H_{15}ClN_4O_7$ requires C, 39·8; H, 4·2; N, 15·5; Cl, 9·8%).

An aqueous solution of this hydrochloride was carefully neutralised with aqueous sodium hydroxide, the liberated base was extracted with ether, the ether extract dried ($MgSO_4$), and the solvent removed *in vacuo*. Throughout the process of basification and extraction with ether the temperature was kept below 0°. The crude base gave a picrate, m. p. 174—175°, identical with the above picrate obtained directly from the hydrochloride. Pure *2-chloromethyl-1-methylpyrrolidine* was obtained as a liquid, b. p. below 0°/0·05 mm., n_D^{20} 1·4655 (Found: C, 54·0; H, 9·3; N, 10·5; Cl, 26·3. $C_6H_{12}ClN$ requires C, 54·0; H, 9·1; N, 10·5; Cl, 26·6%), $\nu_{max.}$ 8·26, 9·6, and 13·65 μ. The distilled base also gave a picrate, m. p. 174—175°, identical with that obtained from the hydrochloride.

Thermal Instability of 2-Chloromethyl-1-methylpyrrolidine and 3-Chloro-1-methylpiperidine.—Samples of 2-chloromethyl-1-methylpyrrolidine were heated at 100° for (*a*) 0·5 hr., and (*b*) 1 hr. The product obtained contained a little solid material; it was rapidly distilled at 0·1 mm. at room temperature. The proportion of 3-chloro-1-methylpiperidine in the total distillate estimated from the infrared absorptions at the 12·67, 13·18, and 13·65 μ bands was in (*a*) 45% and (*b*) 60%. When the chloropyrrolidine was heated at a lower temperature (50°) for 0·5 hr. no rearrangement occurred. 3-Chloro-1-methylpiperidine was unaffected when heated at 100° for 1 hr.

Instability of 2-Chloromethyl-1-methylpyrrolidine in Boiling Propan-2-ol.—A 5% solution of 2-chloromethyl-1-methylpyrrolidine in propan-2-ol was refluxed for 4 hr., cooled, acidified with concentrated hydrochloric acid, and evaporated to dryness *in vacuo*. The resulting hydrochloride was dissolved in water, and the liberated base extracted with ether, dried ($MgSO_4$), and distilled below 0° as described previously. The product (60%) had an infrared spectrum identical with that of authentic 3-chloro-1-methylpiperidine.

Acyl Derivatives of 2-Hydroxymethyl-1-methylpyrrolidine and 3-Hydroxy-1-methylpiperidine.—Authentic specimens of several acyl derivatives of 2-hydroxymethyl-1-methylpyrrolidine and 3-hydroxy-1-methylpiperidine for use as reference samples in the infrared absorption measurements and for thermal rearrangement studies were prepared. These were obtained by the reaction of the appropriate acid chloride (1 mol.) with the alcohol (1 mol.) in boiling benzene, and their properties are shown in Tables 1 and 2.

Thermal Rearrangement of Acyl Derivatives.—Samples of the acyl derivatives shown in

[11] Soulal, B.P. 820,503/1959.

TABLE 1. *Esters (or ether) of 2-hydroxymethyl-1-methylpyrrolidine.*

No.	Acyl	Salt	M. p. or b. p./mm.	n_D^{20}	Form and solvent	Distinguishing infrared bands (μ)
1	Ac	—	74°/11	1·4454	—	8·18, 9·7
2	,,	Picrate	110—111°	—	Platelets EtOH	—
3	Bz	—	103°/0·07	1·5215	—	7·25, 7·38, 8·03
4	,,	Picrate	176—177°	—	Needles EtAc	—
5	$CO\cdot CH_2Ph$	—	106°/0·2	1·5130		9·3, 10·05
6	,,	Picrate	91—92°	—	Needles EtOH	—
7	$CO\cdot CHPh_2$	—	—	1·5545	—	7·67, 9·27, 10·1
8	,,	Picrate	106—108°	—	Needles EtOH	—
9	$CO\cdot CPh_2\cdot OH$	—	99—101° †	—	—	8·8, 10·0, 11·45, 11·56
10	(CH_2Ph ether)	—	83°/0·02	1·5144	—	*
11	(CH_2Ph ether)	Picrate	100—102°	—	Needles EtOH	—

	Found (%)				Required (%)		
No.	C	H	N	Formula	C	H	N
1	61·0	9·4	9·2	$C_8H_{15}NO_2$	61·2	9·6	8·9
2	43·2	4·7	—	$C_{14}H_{18}N_4O_9$	43·5	4·7	14·5
3	71·4	7·9	6·5	$C_{13}H_{17}NO_2$	71·2	7·8	6·4
4	51·3	4·5	12·8	$C_{19}H_{20}N_4O_9$	50·9	4·5	12·5
5	71·7	8·1	6·0	$C_{14}H_{19}NO_2$	72·1	8·2	6·0
6	52·0	4·9	11·9	$C_{20}H_{22}N_4O_9$	52·0	4·8	12·2
7	77·4	7·7	4·6	$C_{20}H_{23}NO_2$	77·7	7·5	4·5
8	58·1	4·8	10·5	$C_{26}H_{26}N_4O_9$	58·0	4·8	10·2
10	76·0	9·2	6·9	$C_{13}H_{19}NO$	76·1	9·3	6·8
11	53·6	5·0	13·3	$C_{19}H_{22}N_4O_8$	52·6	5·1	12·9

* This compound showed no bands which were absent from the piperidyl isomer (Table 2, No. 11).
† Ref. 12.

TABLE 2. *Esters (or ether) of 3-hydroxy-1-methylpiperidine.*

No.	Acyl	Salt	M. p. or b. p./mm.	n_D^{20}	Form and solvent	Distinguishing infrared bands (μ)
1	Ac	—	72°/11	1·4512	—	8·1, 8·55, 8·79, 9·4
2	,,	Picrate	122—123°	—	Needles EtOH	—
3	Bz	—	94—97°/0·05	1·5259	—	8·7, 8·8, 9·93
4	,,	Picrate	225—226°	—	Needles EtOH–EtAc	—
5	$CO\cdot CH_2Ph$	—	108°/0·4	1·5151	—	9·1, 9·4, 10·23, 11·5
6	,,	Picrate	132—133°	—	Needles EtOH–EtAc	—
7	$CO\cdot CHPh_2$	—	155—162°/0·1	1·5570	—	8·7, 9·1, 9·4, 11·5
8	,,	Picrate	128—129°	—	Needles EtOH	—
9	$CO\cdot CPh_2\cdot OH$	—	105—106° [7]	—	Platelets light petrol	7·4, 8·98
10	(CH_2Ph ether)	—	86°/0·2	1·5211	—	8·3, 8·55, 8·8, 9·15, 9·75
11	(CH_2Ph ether)	Picrate	114—115°		Needles EtAc	—

	Found (%)				Required (%)		
No.	C	H	N	Formula	C	H	N
1	61·2	9·9	9·2	$C_8H_{15}NO_2$	61·2	9·6	8·9
2	43·7	4·9	—	$C_{14}H_{18}N_4O_9$	43·5	4·7	14·5
3	71·2	7·6	6·4	$C_{13}H_{17}NO_2$	71·2	7·8	6·4
4	50·6	4·6	12·4	$C_{19}H_{20}N_4O_9$	50·9	4·5	12·5
5	71·9	8·3	6·1	$C_{14}H_{19}NO_2$	72·1	8·2	6·0
6	52·3	4·9	12·0	$C_{20}H_{22}N_4O_9$	52·0	4·8	12·2
7	77·5	7·8	4·8	$C_{20}H_{23}NO_2$	77·7	7·5	4·5
8	58·2	5·3	10·4	$C_{26}H_{26}N_4O_9$	58·0	4·8	10·4
9	73·9	7·2	4·2	$C_{20}H_{23}NO_3$	73·8	7·1	4·3
10	76·8	9·3	7·1	$C_{13}H_{19}NO$	76·1	9·3	6·8
11	52·9	5·1	13·1	$C_{19}H_{22}N_4O_8$	52·6	5·1	12·9

Table 1 were heated for (*a*) 1 hr. and (*b*) 5 hr. at 200° in an atmosphere of nitrogen. The total product was then distilled *in vacuo* and the mixture was analysed by infrared-absorption measurements. The compositions of the mixtures thus obtained are recorded in Table 3.

Reactions between 3-Chloro-1-methylpiperidine and Nucleophiles.—(a) *Benzilic acid.* A

[12] Doyle, Mehta, Sach, and Pearson, *J.*, 1958, 4458.

solution of 3-chloro-1-methylpiperidine (4·7 g., 1 mol.) and benzilic acid (8 g., 1 mol.) in propan-2-ol (100 ml.) was refluxed for 21 hr. and concentrated to *ca.* 30 ml. *in vacuo*. After 12 hr. at 0° the hydrochloride (8·1 g., 64%), m. p. 184—189°, that had separated was filtered off; it was dissolved in a small amount of water and the solution made alkaline with aqueous sodium

TABLE 3. *Composition * of the mixture formed by heating the esters* (VI) *at* 200°.

R	Time of heating (hr.)	Product (%) VII	VI	R	Time of heating (hr.)	Product (%) VII	VI
Ac	5	0	100	$CO{\cdot}CH_2Ph$	1	36	64
					5	69	31
Bz	1	68	32				
	5	84	16	$CO{\cdot}CHPh_2$	1	69	31
					5	91	9

* The composition was determined by infrared absorption measurement; for the acetate and benzoate at 8·8 μ, and for the phenylacetate and diphenylacetate at 9·4 μ.

hydroxide. The liberated oily base was extracted with ether, dried ($MgSO_4$), and recovered *in vacuo* as a gum (7 g.) which gave 2-(αα-diphenylglycolloyloxymethyl)-1-methylpyrrolidine as needles from heptane (m. p. and mixed [12] m. p. 105—106°). The infrared spectrum of the original gum in the 8·8 μ region indicated that it was a mixture of the pyrrolidyl and piperidyl esters in the ratio of *ca.* 7 : 3.

The heptane liquors from the crystallisation were then evaporated to a gum which on treatment with methanolic hydrogen chloride yielded a crystalline hydrochloride. This with aqueous sodium hydroxide was converted into 3-(αα-diphenylglycolloyloxy)-1-methylpiperidine, m. p. and mixed m. p. 99—101° (from heptane). A mixture of the isomeric products melted at 86—95°.

When this experiment was repeated with 2-chloromethyl-1-methylpyrrolidine instead of the chloropiperidine the resulting low-melting solid (89% yield) was found to contain the pyrrolidyl and piperidyl esters in the ratio of 3 : 2.

(b) *Sodium benzilate in propan-2-ol.* The previous experiment was repeated with sodium benzilate (8·8 g., 1 mol.) in place of the free acid. After 6 hours' refluxing the sodium chloride was separated and the filtrate evaporated to dryness *in vacuo*. The low-melting residue was triturated with dry ether and filtered to remove traces of inorganic material, and the solvent together with unchanged chloropiperidine were evaporated at 100° (bath)/0·05 mm.; the low-melting product (10·2 g., 89%) was found by infrared measurement to be a mixture of the previously described pyrrolidyl and piperidyl esters in the ratio of *ca.* 7 : 3.

(c) *Sodium benzilate in ethanol.* A solution of sodium benzilate (7·5 g., 1 mol.) in dry ethanol (50 ml.) was added during 4 hr. to a stirred boiling solution of the chloropiperidine (4·8 g., 1·2 mol.) in dry ethanol (50 ml.). Then the mixture was refluxed for 4 hr. and treated as described in experiment (b), to give a low-melting product found by infrared measurement to contain the pyrrolidyl and piperidyl esters in the ratio of *ca.* 3 : 2.

(d) *As* (c), *but inverse addition.* A solution of the chloropiperidine (4 g., 1 mol.) in ethanol (50 ml.) was slowly added to a boiling solution of sodium benzilate (9 g., 1·2 mol.) in ethanol (50 ml.). The product was found to be a mixture of pyrrolidyl and piperidyl esters in the ratio of *ca.* 7 : 3.

(e) *Sodium acetate.* A solution of 3-chloro-1-methylpiperidine (26·7 g., 1 mol.) and anhydrous sodium acetate (17 g., 1 mol.) in dry propan-2-ol (50 ml.) was refluxed for 6 hr. and then cooled. Isolation as before gave a liquid (26·4 g., 84%), b. p. 74—76°/11 mm., n_D^{20} 1·4473. The infrared absorption at 8·79 μ showed this to be a mixture of 2-acetoxymethyl-1-methylpyrrolidine and 3-acetoxy-1-methylpiperidine in the ratio of 3 : 1.

(f) *Sodium benzyl oxide.* Sodium (0·7 g., 1 atomic equiv.) was dissolved in benzyl alcohol (30 ml.) and, after the solution had been cooled to 30°, 3-chloro-1-methylpiperidine (4 g., 1 mol.) was added. The mixture was heated for 4 hr. at 100°, cooled, and shaken with 5N-hydrochloric acid (70 ml.) and ether (70 ml.). The acid extract was made alkaline with aqueous sodium hydroxide, the liberated base extracted into ether and dried ($MgSO_4$), and the solvent evaporated. The residual oil on distillation *in vacuo* gave 2-*benzyloxymethyl*-1-*methylpyrrolidine* (3·6 g., 53%), b. p. 74°/0·06 mm., n_D^{20} 1·5156. The picrate was undepressed in m. p. (99—

101°) by authentic *2-benzyloxymethyl-1-methylpyrrolidine picrate* and their infrared spectra were identical.

Authentic samples of *2-benzyloxymethyl-1-methylpyrrolidine* and *3-benzyloxy-1-methylpiperidine* required as reference compounds were obtained by the method of Paul and Tchelitcheff [6] and their properties are recorded in Tables 1 and 2.

(g) *Sodium cyanide.* The procedure of Paul and Tchelitcheff [6] was followed to give *2-cyanomethyl-1-methylpyrrolidine* (61%), b. p. 92—96°/17 mm., n_D^{20} 1·4622, $\nu_{max.}$ 7·36, 8·25, 9·55, and 10·15 μ. The *picrate* crystallised from 90% aqueous ethanol as yellow needles, m. p. 182—183° (Found: C, 43·9; H, 4·6; N, 20·2. $C_{13}H_{15}N_5O_7$ requires C, 44·2; H, 4·3; N, 19·8%). The mixed m. p. with 3-cyano-1-methylpiperidine picrate (see below) was 167—171°.

(h) *Sodium hydroxide.* The 3-chloro-1-methylpiperidine was refluxed with an excess of 10% aqueous sodium hydroxide for 2 hr. After cooling, the mixture was extracted with ether, the extracts were dried ($MgSO_4$), and the solvent was evaporated. The residue was distilled, to give 2-hydroxy-1-methylpyrolidine (31%), b. p. 74—77°/18 mm. (picrate, m. p. and mixed m. p. 169—173°).

3-Cyano-1-methylpiperidine.[13]—Ethyl 1-methylpiperidine-3-carboxylate [14] was converted into 1-methylpiperidine-3-carboxyamide with concentrated aqueous ammonia. The crude amide was then refluxed with thionyl chloride for 3 hr. and after removal of the excess of thionyl chloride the residual 3-cyano-1-methylpiperidine was obtained as a liquid, b. p. 86°/10 mm., $\nu_{max.}$ 7·27, 8·33, 9·17, and 11·82 μ. The *picrate* crystallised from acetic acid as yellow needles, m. p. 186—187° (Found: C, 44·2; H, 4·6; N, 19·9. $C_{13}H_{15}N_5O_7$ requires C, 44·2; H, 4·3; N, 19·8%).

2-2′-Hydroxyethyl-1-methylpyrrolidine.—2-Cyanomethyl-1-methylpyrrolidine was converted by ethanolic hydrogen chloride into *ethyl 1-methyl-2-pyrrolidylacetate* (62%), b. p. 94—97°/17—18 mm., n_D^{20} 1·4484. This on reduction with lithium aluminium hydride in ether gave *2-2′-hydroxyethyl-1-methylpyrrolidine* (68%), b. p. 74°/1·5 mm., n_D^{20} 1·4735. The infrared spectrum of this alcohol was identical with that of an authentic specimen.[12] The tri-iodophenylurethane had m. p. and mixed m. p. 177° (decomp.).

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[14] Feldkamp, *J. Amer. Chem. Soc.*, 1952, **74**, 3831.