CCCXLVI.—*The Configuration of the Ammonium Ion. Part II. Geometrically Isomeric Quaternary Ammonium Salts derived from 4-Phenyl- and 4-Hydroxy-piperidine.*

By WILLIAM HOBSON MILLS, JOHN DAVIES PARKIN, and WILLIAM JOSEPH VICTOR WARD.

WITH the view of obtaining experimental evidence with regard to the distribution of the valencies of the nitrogen atom * in the quater-

* With regard to the stereochemistry of tervalent nitrogen I would take this opportunity to point out that the optical activity of the pyridylhydrazone of *cyclo*hexylene dithiocarbonate, which Mills and Schindler (J., 1923, **123**, 312) regarded as evidence of the non-planar distribution of the valencies of the doubly linked tervalent nitrogen atom, is capable of a different interpretation. At the time that the work was carried out we were of opinion that the dithiocarbonate was necessarily derived from the *cis*-form of the dithioglycol and our conclusions were based on this assumption. In view, however, of the remarkable investigations of Hückel and his co-workers (*Annalen*, 1925, **441**, 1; 1926, **451**, 109, 132; 1927, **453**, 163), from which it appears that *trans*-forms of the dicyclic compounds decalin, β-hydrindanone, and decahydroquinoline are not only capable of existence, but may even be more stable than the corresponding *cis*-forms, this view can no longer be upheld and I am now of opinion that the optically active hydrazone is probably to be regarded as a derivative of the *trans*-dithioglycol, and if this is the case the pyridylhydrazone is molecularly dissymmetric however the valencies of the doubly-linked nitrogen atom are disposed.—W. H. M.

nary ammonium ion Mills and Warren (J., 1925, **127**, 2507) prepared and examined some of the salts of 4-phenyl-4′-carbethoxybispiperidinium-1 : 1′-spiran. They showed that these salts could be obtained in optically active forms and pointed out that the pyramidal configuration for the ammonium ion (which might perhaps be regarded as *a priori* the more probable on the older view that the electric charge on the ion was stereochemically equivalent to the directly linked acid radical in the non-ionised salt) was thereby excluded and gave reasons for concluding that the ion consequently had the *tetrahedral* configuration (as was more probable on the electronic theory of molecular structure).

In the present communication an account is given of another and independent method of investigating the same question. Since in the ammonium ion the nitrogen atom and the four attached radicals do not lie in the same plane, it was to be anticipated that geometrical isomerism should occur among the quaternary salts of the 4-substituted piperidine bases. Such isomerism we have found does, in fact, exist and its investigation provides a means of obtaining a decision between the pyramidal and the tetrahedral configuration of the ammonium ion. For if the ammonium ion has the pyramidal configuration, then, as will be evident from Fig. 1,* every 4-substituted quaternary piperidinium salt, $RCH<^{CH_2\cdot CH_2}_{CH_2\cdot CH_2}>NR'R''X$, should be capable of existence in two geometrically isomeric forms even although the two radicals R′ and R″ attached to the nitrogen atom might be identical. Each isomeride would be a racemic compound when these radicals were different, and a simple substance when they were identical, but in spite of this, if the isomerism could be detected in the one case it should also be demonstrable in the other. If, on the other hand, the ammonium ion has the tetrahedral configuration (Fig. 2) it is evident that geometrical isomerism could only occur when the radicals R′ and R″ were different and would disappear if they became identical.

We have examined salts of five quaternary bases derived from 4-substituted piperidines, three with different radicals R′ R″ (type I), and two with identical radicals R′R′ (type II) attached to the nitrogen atom.

* The rings in this and the following diagrams are represented plane for simplicity. There is an evident difficulty in representing piperidinium salts according to the Bischoff theory of the pyramidal configuration of ammonium salts, for it involves the replacement in *cyclo*hexane of a methylene group with a valency angle of 110° or more by an ammonium residue with a valency angle of less than 90°.

The difference between the two types proved to be clearly marked. The salts of type I, formed from a tertiary base,

$$RCH\langle \begin{matrix} CH_2 \cdot CH_2 \\ CH_2 \cdot CH_2 \end{matrix} \rangle NR',$$

and an alkyl halide, R''X, all showed themselves, when subjected to fractional crystallisation, to be mixtures of pairs of isomerides. On the other hand, the salts of type II, prepared in a corresponding manner, proved to be homogeneous.

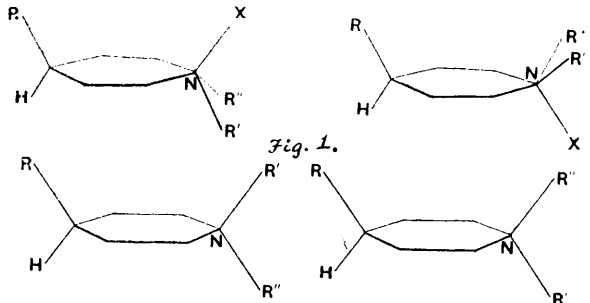


Fig. 1.

Fig. 2.

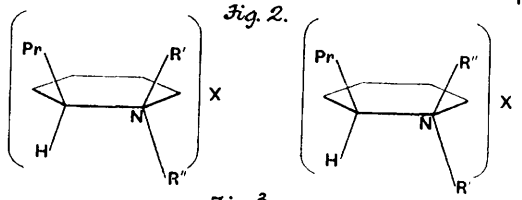
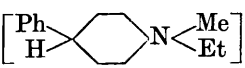
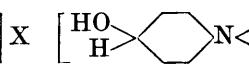
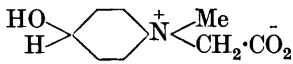


Fig. 3

The salts investigated were prepared from 4-phenylpiperidine and from 4-hydroxypiperidine. From the former compound were obtained the iodides and perchlorates of phenylmethylethylpiperidinium (I) and phenylbenzylethylpiperidinium and also phenyldiethylpiperidinium iodide and phenyldipropylpiperidinium iodide. From the latter compound the methobromides of 4-hydroxypiperidylacetic acid and of its ethyl ester (II) were prepared, as well as

(I.)  (II.) 

 (III.)

the corresponding betaine (III). Each of these salts in which two different radicals were attached to the nitrogen atom (salts of type I) was found to exist in two isomeric forms, as is shown in the following table :

Salts of type I.

Salt.	M. p. of α-isomeride.	M. p. of β-isomeride.
4-Phenyl-1-methyl-1-ethylpiperidinium iodide...	180°	140°
4-Phenyl-1-methyl-1-ethylpiperidinium perchlorate	135	159
4-Phenyl-1-benzyl-1-ethylpiperidinium iodide ...	240	210—215
4-Phenyl-1-benzyl-1-ethylpiperidinium perchlorate	208	189
Ethyl 4-hydroxy-1-piperidylacetate methobromide	221	206
Ethyl 4-hydroxy-1-piperidylacetate picrate	152—153	126
4-Hydroxy-1-piperidylacetic acid methobromide	170—172	210
4-Hydroxy-1-piperidylacetic acid methylbetaine	271—272	266—267

The salts of type II were found to consist of one form only. They had a sharp melting point and systematic fractional crystallisation gave no indication of the existence of a second modification.

Salts of type II.

	M. p.
4-Phenyl-1 : 1-diethylpiperidinium iodide	177°
4-Phenyl-1 : 1-dipropylpiperidinium iodide	190

In view of the evident possibility of the existence of geometrical isomerism in these salts and the absence, as far as can be seen, of any other cause to which the isomerism could be due, it appears safe to conclude that the isomerism exhibited by the salts of type I actually is a geometrical isomerism of the type sought for dependent on the non-planar distribution of the valencies of the ammonium nitrogen atom. This clear-cut difference between the salts of the two types therefore demonstrates that the quaternary ammonium ion has not a pyramidal configuration. It shows that the two radicals R′ and R″ attached to the nitrogen atom are unequally distant from the group R attached to the 4-carbon atom. The quaternary ammonium ion therefore cannot have the pyramidal configuration, and the valencies of the nitrogen atom in this ion must accordingly be tetrahedrally disposed.

The isomerism exhibited by the salts of type I thus corresponds closely with the *cis-trans* isomerism which occurs among the substitution derivatives of *cyclo*hexane, the relationship between the two forms of, for example, phenylmethylethylpiperidinium being represented by tridimensional formulæ such as those in Fig. 2 (R = Ph, R′ = Me, R″ = Et).

Although it was easy to show by fractional crystallisation that the salts of type I, as produced by the combination of tertiary base and alkyl halide, were not homogeneous, the isolation of both stereoisomerides in a state of purity from the mixtures of the two of which the crude salts consisted was not easily effected. Fractional

crystallisation brought about more or less readily the separation and isolation of the excess of the less soluble (α-) isomeride, but special methods were required to extract the pure β-isomeride from the mixture left in the mother-liquors.

The separation was most easily effected in the case of the phenylbenzylethylpiperidinium iodides. By allowing solutions of the mixed isomerides of appropriate concentration to crystallise under "aseptic" conditions, usually the α-form only separated, the β-form remaining in supersaturated solution. On then decanting the supersaturated solution and scratching, the pratically pure β-isomeride crystallised.

In the other cases the more soluble β-iodide could only be isolated through the replacement of the iodine by another acid radical which gave a less soluble salt with the β- than with the α-base. This β-salt could then be isolated in a state of purity and converted into pure β-iodide.

Thus in the case of α- and β-phenylmethylethylpiperidinium the solubilities of the perchlorates are in the inverse order of those of the iodides. The pure β-perchlorate could accordingly be isolated from the mixed perchlorates and gave on treatment with potassium iodide the pure β-iodide.

Similarly with the 4-hydroxypiperidinium salts; by fractional crystallisation of the mixed ethyl hydroxypiperidylacetate methobromides only the less soluble α-salt could be isolated. The more soluble of the two ester methobromides corresponds, however, with the less soluble of the two methylbetaines and the pure β-methylbetaine could therefore be obtained and from it the other salts of the β-series.

The stereoisomeric salts have considerable stability; no tendency to intertransformation was observed at the ordinary temperature. For example, when α-phenylmethylethylpiperidinium perchlorate was converted into iodide and then reconverted into perchlorate, pure α-perchlorate of melting point 159° was obtained. Transformation from one series to the other could, however, be brought about by heating. The change could be most easily observed with the phenylbenzylethylpiperidinium iodides. The more soluble β-iodide melts at 210—215°. If kept slightly above 215°, the molten salt resolidifies and the resolidified material is the α-isomeride, for it shows the melting point of that modification (240°, decomp.) and on conversion into perchlorate yields the pure α-perchlorate.

The relative quantities of the stereoisomeric salts produced in these additions of alkyl halides to 4-substituted tertiary piperidine bases were examined with the aid of melting point–composition curves in two of the cases investigated, namely, the addition of benzyl

chloride to phenylethylpiperidine and of ethyl bromoacetate to hydroxymethylpiperidine. In each case the quantities of the two isomerides formed were approximately in the ratio of 2 to 3. There is thus no great disproportion in the relative amounts of the two isomerides produced.

The isomerism of the quaternary ammonium salts here described is closely allied to the isomerism observed by Scholtz among the quaternary salts derived from coniine (*Ber.*, 1904, **37**, 3627; 1905, **38**, 595). Scholtz found that when an alkyl halide R'X combined with a 1-alkyl derivative of *d*-coniine, $CH_2\begin{matrix}<CH_2\text{-}CHPr\\CH_2—CH_2\end{matrix}>NR$, to form a quaternary salt the product was a mixture of two isomerides. Since the salts thus formed necessarily contained two asymmetric atoms, namely, the asymmetric carbon atom already present in the coniine and a newly formed asymmetric nitrogen atom, the isomerides were evidently the diastereoisomeric compounds (*d*C·*d*N), (*d*C·*l*N) and such isomerism should occur whatever the configuration of the quaternary ammonium nitrogen. The observations of Mills and Warren (*loc. cit.*) together with those described in the present communication show, however, that Scholtz's isomeric salts were *cis-trans* isomerides of the type indicated in Fig. 3.

Experimental.

A. Derivatives of Phenylpiperidine.

1-Alkyl Derivatives of 4-Phenylpiperidine.—4-Phenylpiperidine is shaken at the ordinary temperature with the alkyl iodide (1 mol.) and 10% aqueous sodium hydroxide (1·1 mols.). When the interaction is complete, the tertiary base (and unchanged phenylpiperidine) are extracted with ether. To remove the phenylpiperidine, the mixture is shaken with benzoyl chloride and alkali for 5—10 minutes at 50—60°. The tertiary base, and the benzoylphenylpiperidine thus formed, are taken up in ether and the former is extracted with dilute sulphuric acid from the ethereal solution. It is then isolated in the usual way, being finally purified through the crystallisation of an appropriate salt.

4-Phenyl-1-methylpiperidine was prepared from methyl iodide and phenylpiperidine by the above described method, but as the reaction is vigorous ether was used as a diluent. The base can also be prepared, as has been found by one of us and Mr. F. N. Kerr, by heating phenylpiperidine hydrochloride with formalin. It was purified by crystallisation of its perchlorate from ether–alcohol. The perchlorate forms felted needles, m. p. 106—107°, readily soluble in alcohol but sparingly in water and melting under water at about 25°. The pure *base* is a colourless liquid, m. p. 9°, b. p. 122—123°/

11 mm. (Found: C, 82·2; H, 9·8; N, 8·0. $C_{12}H_{17}N$ requires C, 82·2; H, 9·8; N, 8·0%). The *hydrochloride* (platelets from ether–alcohol) melts at 196—198° (Found: Cl, 16·6. $C_{12}H_{17}N$,HCl requires Cl, 16·75%). The picrate melts at 244° (decomp.).

4-*Phenyl*-1-*ethylpiperidine*. The reaction between ethyl iodide, phenylpiperidine, and aqueous alkali proceeds slowly in the cold, 8—10 hours' shaking being required. The tertiary *base* was purified by crystallising the perchlorate (m. p. 112°) from alcohol. It is a liquid, m. p. 11°, b. p. 137°/11 mm. (Found: C, 82·3; H, 10·1; N, 7·7. $C_{13}H_{19}N$ requires C, 82·5; H, 10·1; N, 7·4%). The *hydrochloride* has m. p. 203—205° (Found: Cl, 15·6. $C_{13}H_{19}N$,HCl requires Cl, 15·7%).

4-*Phenyl*-1-n-*propylpiperidine* was prepared by shaking *n*-propyl iodide, phenylpiperidine, and aqueous alkali together for 20 hours at room temperature, the final purification being effected through the perchlorate (m. p. 160—162·5°), which was recrystallised from ether–alcohol. The *base* is liquid at the ordinary temperature (m. p. 13°, b. p. 150°/11 mm.) (Found: C, 82·1; H, 10·5; N, 7·1. $C_{14}H_{21}N$ requires C, 82·7; H, 10·4; N, 6·9%). The *hydrochloride*, m. p. 250° (decomp.), is not very soluble in cold water (Found: Cl, 14·7. $C_{14}H_{21}N$,HCl requires Cl, 14·8%).

α-4-*Phenyl*-1-*methyl*-1-*ethylpiperidinium Iodide*.—The α-modification of this salt is most easily isolated from the mixture formed by the combination of ethyl iodide with 4-phenyl-1-methylpiperidine, the combination being brought about by boiling the base with the alkyl iodide for 2 hours.

The product, after being dissolved in alcohol and precipitated with ether, melted at 152—154°. By fractional crystallisation from ether–alcohol of the mixture of the two iodides it could be resolved into a less soluble fraction, m. p. 170°, and a more soluble fraction, m. p. 148°. Since the iodides were only slowly separated by the fractionation, they were converted into perchlorates by dissolving them in water (10 g. in 500 c.c.) at 40—50° and adding an exactly equivalent quantity of silver perchlorate in aqueous solution, a little perchloric acid being also added to promote the coagulation of the silver iodide.

The less soluble iodide fraction gave a perchlorate which, recrystallised from alcohol, yielded the pure α-perchlorate in felted needles of constant melting point 135°. On conversion of this perchlorate into iodide by dissolving it in a concentrated aqueous solution of potassium iodide, extracting the salt with chloroform, and precipitating it from the dried chloroform solution with ether, the pure α-*iodide* was obtained as colourless plates, m. p. 180—181° (Found: C, 50·7; H, 6·8; I, 38·0. $C_{14}H_{22}NI$ requires C, 50·75; H, 6·7; I, 38·3%).

It melts under water, in which it is not very soluble, dissolves readily in alcohol, and is exceedingly soluble in chloroform.

β-4-*Phenyl*-1-*methyl*-1-*ethylpiperidinium iodide*. This modification is most easily isolated from the mixture of the two forms of the quaternary iodide which is produced by the addition of methyl iodide to phenylethylpiperidine. After completion of the combination, which proceeded with evolution of heat, the resulting crystalline cake was dissolved in a little alcohol and reprecipitated by the addition of 2—3 volumes of ether. The mixture of iodides thus obtained, m. p. 146—147·5°, was converted into perchlorate by treating it with silver perchlorate as described above. The salt which crystallised directly from the aqueous solution consisted almost entirely of the β-form and readily gave the pure β-perchlorate on crystallisation from alcohol. The β-perchlorate crystallises in plates, m. p. 159°, and is sparingly soluble in cold alcohol and very sparingly in cold water. On conversion into iodide the pure β-*iodide* was obtained. This salt crystallises in plates which liquefy in contact with cold water. It is dimorphous, the two forms melting at 140° and 146°. It always crystallises from solution in the form melting at 140°, but usually resolidifies in the form melting at 146° (Found : C, 50·75; H, 6·55; I, 38·3. $C_{14}H_{22}NI$ requires C, 50·75; H, 6·7; I, 38·3%).

The aqueous solution from which the β-perchlorate had crystallised was evaporated almost to dryness at 30—40° under diminished pressure. By fractional crystallisation from alcohol of the salt thus obtained, a further small quantity of pure β-perchlorate could be separated, but the bulk consisted of a mixture melting at 115° and crystallising unchanged from alcohol or water. This mixture, on conversion into iodide, gave a product, melting at 150°, from which, by crystallisation from ether–alcohol, an iodide of m. p. 170° was obtained and this on conversion into perchlorate gave the pure α-perchlorate identical in melting point and mixed melting point (135°) with the α-perchlorate obtained as described in the preceding section.

α- *and* β-4-*Phenyl*-1-*benzyl*-1-*ethylpiperidinium iodides*. Equivalent quantities of 4-phenyl-1-ethylpiperidine and benzyl chloride were heated at 100° for 2—3 hours. The product was dissolved in water, small quantities of unchanged material were removed by extraction with ether, and the mixed quaternary perchlorates, which are almost insoluble in water, were precipitated by adding a concentrated solution of sodium perchlorate.

From the mixture, m. p. 182°, the very sparingly soluble α-salt was obtained by extraction with alcohol. The mixed salt (20 g.) was boiled with alcohol (200 c.c.), and the solution filtered hot.

The mixture of maximum solubility, m. p. 172°, was deposited on cooling and the mother-liquor was used again to extract the undissolved salt; the process was repeated until the crystals deposited showed a melting point distinctly above 172°. The residue, which melted above 200°, was then nearly pure α-perchlorate and was recrystallised from a large volume of alcohol until it melted constantly at 208°, the melting point of the pure salt.

The β-perchlorate was obtained from the mixture of maximum solubility by a method based on its tendency to form supersaturated solutions. Alcohol was stirred with the mixture at 35—40° until practically saturated. The resulting solution was "sterilised" by heating to the boiling point and after being seeded with a few crystals of the carefully purified α-form was allowed to remain overnight, the neck of the flask being plugged with cotton wool. The α-modification then usually crystallised alone in slender needles and the decanted solution deposited the β-modification on scratching. Recrystallised from alcohol, it melted at 189°.

Mixtures of the two perchlorates have the following melting points:

% β-Form	0	20	35	50	63	75	85	100
M. p.	208°	195°	184°	172°	170°	176°	182°	189°

To convert the perchlorates into iodides, the salt (2 g.) was boiled with absolute alcohol (200 c.c.) and finely powdered potassium iodide (10 g.), and the solution filtered after 1 hour. The iodide deposited on cooling the filtrate and adding an equal volume of ether was recrystallised from aqueous alcohol containing 30—40% of water. In this manner from the α- and β-perchlorates the pure α- and β-iodides were obtained.

α-4-*Phenyl*-1-*benzyl*-1-*ethylpiperidinium iodide* crystallises in iridescent plates, m. p. 240° (decomp.) (Found: C, 58·9; H, 6·6; I, 31·2. $C_{20}H_{26}NI$ requires C, 58·9; H, 6·4; I, 31·2%), and β-4-*phenyl*-1-*benzyl*-1-*ethylpiperidinium iodide* in needles, m. p. 210—215° (Found: C, 58·8; H, 6·6; I, 31·2%).

The molten β-iodide resolidifies when kept above its melting point and melts again at 240°, the melting point of the α-iodide. It was shown that the resolidified material was in fact the α-iodide by dissolving it in water and precipitating the pure α-perchlorate with sodium perchlorate.

4-*Phenyl*-1 : 1-*diethylpiperidinium iodide*. Phenylethylpiperidine was boiled with an excess of ethyl iodide for 2 hours. The resulting crystalline cake was fractionally crystallised from alcohol and ether–alcohol, but no separation could be detected, all the fractions melting at 177°, with the exception of the last, which melted at 176°, evidently on account of the presence of a trace of accidental impurity (Found:

C, 52·2; H, 7·0; I, 36·9. $C_{15}H_{24}NI$ requires C, 52·2; H, 7·0; I, 36·9%)

4-*Phenyl*-1 : 1-*di*-n-*propylpiperidinium iodide*. Phenyl-*n*-propylpiperidine was boiled under reflux for several hours with excess of *n*-propyl iodide. The resulting quaternary salt, fractionally crystallised from alcohol and alcohol–ether, showed no sign of resolution into isomeric modifications but melted constantly at 190° (Found : C, 54·7; H, 7·4; I, 34·2. $C_{17}H_{28}NI$ requires C, 54·7; H, 7·5; I, 34·0%).

We are indebted to Mr. D. Webb, of Emmanuel College, for assistance with the preparation and analysis of this and the foregoing compound.

B. Derivatives of Hydroxymethylpiperidine.

4-*Hydroxy*-1-*methylpiperidine*.—1-Methyl-4-pyridone (22·5 g.) (Lieben and Haitinger, *Monatsh.*, 1885, **6**, 300) was dissolved in boiling absolute alcohol (225 c.c.), and sliced sodium (75 g.) added as rapidly as possible. When the action had abated, absolute alcohol (750 c.c.) was added in portions of 50 c.c. After the sodium had dissolved, water was added and the mixture was distilled with steam until 1 litre of distillate had been collected. The product was then driven over with superheated steam. The aqueous distillate (2 l.), acidified with hydrochloric acid and evaporated, left a brownish residue which, crystallised from absolute alcohol, gave 4-*hydroxy*-1-*methylpiperidine hydrochloride* (20 g.) as colourless prisms, m. p. 157—158°; these were hygroscopic, very soluble in water, easily soluble in hot, and sparingly soluble in cold alcohol (Found : Cl, 23·5. $C_6H_{13}ON,HCl$ requires Cl, 23·4%). By decomposing this hydrochloride with alkali the free base (Emmert, D.R.-P. 292871) was obtained as an oil, b. p. 105°/18 mm., which we found to crystallise on keeping (m. p. 28°). The *hydrobromide* formed colourless needles, m. p. 139—140°, from alcohol (Found : Br, 40·9. $C_6H_{13}ON,HBr$ requires Br, 40·8%).

Ethyl α-4-*Hydroxy*-1-*piperidylacetate Methobromide*.—4-Hydroxy-1-methylpiperidine (12·2 g.) and ethyl bromoacetate (23·7 g.) dissolved in benzene (180 g.) reacted at room temperature with the formation of quaternary bromide, the mixture setting to a crystalline mass which was collected after 20—24 hours. The product was a mixture of the α- and β-bromides, m. p. about 204°, and the yield was practically quantitative (Found : Br, 28·2. $C_{10}H_{20}O_3NBr$ requires Br, 28·3%).

The α-modification of the salt was obtained by boiling out the product from the above quantities with absolute alcohol (90 c.c.), filtering the hot solution, and boiling the residue successively with

50 c.c. and 40 c.c. of alcohol. The residue left (6·9 g., m. p. 220°), crystallised from rectified spirit, had m. p. 221° (decomp.), which could not be raised by further treatment.

Ethyl α-4-hydroxy-1-piperidylacetate methobromide forms colourless prisms very soluble in water and sparingly soluble in alcohol (Found: C, 42·7; H, 7·1; Br, 28·3. $C_{10}H_{20}O_3NBr$ requires C, 42·6; H, 7·1; Br, 28·3%). The *picrate* forms yellow needles, m. p. 152—153°, moderately easily soluble in alcohol or water (Found: N, 13·1. $C_{16}H_{22}O_{10}N_4$ requires N, 13·0%).

α-Methylbetaine of 4-Hydroxypiperidylacetic Acid.—An aqueous suspension of freshly prepared silver oxide was gradually added to ethyl α-4-hydroxypiperidylacetate methobromide until the brown colour of the oxide persisted. The filtrate from the silver bromide was evaporated, finally over sulphuric acid in a vacuum, and the residue was dissolved in hot alcohol, a little brown insoluble matter being removed by filtration. On cooling, the betaine was deposited as pearly leaflets, m. p. 271—272°, moderately easily soluble in alcohol and easily soluble in water (Found: C, 55·2; H, 8·4. $C_8H_{15}O_3N$ requires C, 55·4; H, 8·7%).

α-4-Hydroxypiperidylacetic Acid Methobromide.—The above described betaine was converted into the corresponding methobromide by dissolving it in a slight excess of hydrobromic acid and evaporating the solution on the water-bath under diminished pressure. The residue, crystallised from alcohol, gave the *methobromide* as colourless prisms, m. p. 170—172° (Found: Br, 31·2. $C_8H_{16}O_3NBr$ requires Br, 31·5%).

If the betaine is dissolved in less hydrobromic acid, a *basic salt* is obtained containing two molecules of betaine to one molecule of hydrogen bromide. It crystallised from alcohol in clusters of fine, radiating needles, m. p. 215—218° (decomp.) (Found: Br, 18·9. $C_{16}H_{31}O_6N_2Br$ requires Br, 18·7%). Similar compounds were obtained by Krüger from pyridine betaine (*J. pr. Chem.*, 1891, **43**, 289). The substance probably has the constitution

$$\bar{Br}\left[C_5H_9(OH)\overset{+}{N}<\begin{matrix}Me & Me\\ CH_2\cdot\bar{C}O_2 & \end{matrix}>\overset{+}{N}C_5H_9\cdot OH\right]\begin{matrix}\\ \\ CH_2\cdot CO_2H\end{matrix}$$

the dotted line representing an electro-valency.

β-Methylbetaine of 4-Hydroxypiperidylacetic Acid.—The filtrate from the first extraction with alcohol of crude ethyl hydroxypiperidylacetate methobromide (p. 2622) was evaporated and the residue (11·5 g.) was converted into betaine with silver oxide. The resulting mixture of the two betaines was extracted with cold alcohol (15 c.c.), which removed most of the more soluble α-compound; the residue, crystallised from rectified spirit, gave the pure *β-methyl-*

betaine as small, beautifully formed prisms, m. p. 266—267° (decomp.), sparingly soluble in alcohol, easily soluble in water. The crystals contain one molecule of water of crystallisation which is lost at 100° (Found : C, 50·2; H, 9·1; H_2O, 9·4. $C_8H_{15}O_3N,H_2O$ requires C, 50·2; H, 9·0; H_2O, 9·4%. Found for the anhydrous compound : C, 55·6; H, 8·7. $C_8H_{15}O_3N$ requires C, 55·4; H, 8·7%). The hydrated and the anhydrous substance showed the same melting point : a mixture with the α-betaine melted at 249—251°.

β-4-*Hydroxypiperidylacetic acid methobromide* was prepared by treating the corresponding betaine with hydrobromic acid in the manner described for the α-modification; it crystallised from alcohol in prisms, m. p. 210° (decomp.) (Found : Br, 31·5. $C_8H_{16}O_3NBr$ requires Br, 31·5%). A *basic salt* corresponding with that formed from the α-betaine could be isolated by using less hydrobromic acid. It formed colourless needles, m. p. 220—221° (decomp.), from alcohol (Found : C, 44·7; H, 7·2; Br, 18·9. $C_{16}H_{31}O_6N_2Br$ requires C, 44·9; H, 7·3; Br, 18·7%).

Ethyl β-4-*Hydroxypiperidylacetate Methochloride.*—The β-betaine (1 g.) was covered with absolute alcohol (10 c.c.) and dry hydrogen chloride was passed in, with cooling, to saturation; the betaine then gradually dissolved. After standing a day, the mixture was evaporated in a vacuum over sulphuric acid and solid sodium hydroxide; the residue, recrystallised from alcohol, gave the pure *ester methochloride* (0·93 g.) as rosettes of leaflets, m. p. 206° (decomp.) (Found : Cl, 14·9. $C_{10}H_{10}O_3NCl$ requires Cl, 14·9%).

The corresponding *picrate* was prepared from the chloride by double decomposition with sodium picrate; it formed golden-yellow needles, m. p. 126°, from water (Found : N, 13·0. $C_{16}H_{22}O_{10}N_4$ requires N, 13·0%). The pure β-picrate could not be obtained from the mixed picrates formed by the action of sodium picrate on the more soluble fractions of the original ester methobromide. Crystallisation from several different solvents gave only a mixture of unchanged m. p. 118—120·5°.

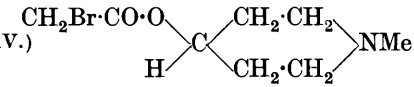
Ethyl β-4-*Hydroxypiperidylacetate Methobromide.*—The β-betaine (2 g.) and 9% alcoholic hydrogen bromide (30 c.c.) were allowed to stand over-night and then refluxed gently for 8 hours. The solid slowly dissolved on heating and, on cooling, the *ester methobromide* (2·2 g.; m. p. 205°) was deposited. After crystallisation from alcohol, in which it was moderately easily soluble, the pure compound of m. p. 206° was obtained (Found : C, 42·6; H, 7·2; Br, 28·1. $C_{10}H_{20}O_3NBr$ requires C, 42·6; H, 7·1; Br, 28·3%).

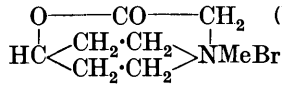
A series of mixtures of the α- and β-ester methobromides was prepared and the following melting points were observed :

% α-Salt.	M. p.	% α-Salt.	M. p.
0·0	206°	51·8	205°
13·1	205	69·7	208
26·1	203·8	81·0	211
33·4	203·5	89·0	214·3
41·9	203·8	100	221

A curve plotted from these data indicates that the two salts form a continuous series of solid solutions. The analytically pure mixture of the α- and β-bromides formed by the addition of ethyl bromoacetate to hydroxymethylpiperidine melted at 204°. This indicates that it contained either 22% or 42% of the α-salt, but the amount of α-salt isolated decides for the latter figure.

4-*Bromoacetoxy*-1-*methylpiperidine* (IV). It seemed not impossible that it might prove practicable to determine the configurations of the α- and β-series by relating compounds belonging to the one or the other to the lactone (V).

(IV.) 

 (V.)

As neither the α- nor the β-methobromide of hydroxypiperidylacetic acid showed any tendency to lactonise on heating, 4-bromoacetoxy-1-methylpiperidine was prepared as a possible source of the lactone. A solution of 4-hydroxy-1-methylpiperidine (5·1 g.) in benzene (100 c.c.) was dropped with mechanical stirring during ¼ hour into bromoacetyl bromide (9 g.), and the mixture kept overnight. The benzene was decanted from the product, the hydrobromide of the required base, which had been deposited as a gum on the sides of the flask; this gum crystallised from alcohol in clusters of minute, radiating needles, m. p. 172°, very soluble in water and sparingly soluble in alcohol [Found: C, 30·3; H, 4·9; Br (ionic), 25·2. $C_8H_{15}O_2NBr_2$ requires C, 30·3; H, 4·8; Br (ionic), 25·2%]. We were unable to prepare the required lactone from the free base corresponding with this hydrobromide. Heated in benzene solution, it gave an amorphous solid, containing 2% too little bromine for the lactone, which was probably an impure polymeride. Heated in alcohol, it gave a mixture of the α- and β-methobromides of ethyl hydroxypiperidylacetate, indicating that alcoholysis of the bromoacetyl group had occurred followed by recombination of the products, hydroxymethylpiperidine and ethyl bromoacetate. That this lactone could not be prepared is not surprising, as its formation would involve the production of a tricyclic compound containing two 7-membered rings.

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UNIVERSITY CHEMICAL LABORATORY,
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