373. *The Resolution of* α-m-*Hydroxyphenylethylmethylamine and the Preparation of* d- *and* l-*Miotine* (*Methylurethanes of* d- *and* l-α-m-*Hydroxyphenylethyldimethylamine*).

By JOSEPH MCL. MACDONALD and EDGAR STEDMAN.

THE methylurethane of α-*m*-hydroxyphenylethyldimethylamine was first prepared by Stedman and Stedman (J., 1929, 609), but attempts to resolve it were unsuccessful. Nevertheless, the racemic substance was found to possess intense miotic activity, and on this account the name miotine was suggested for it (*Amer. J. Physiol.*, 1929, **90**, 528). Since then, miotine has been shown, in common with other urethanes of the same type, to be a parasympathetic stimulant (White and Stedman, *J. Pharm. Exp. Ther.*, 1931, **41**, 259; Aeschlimann and Reinert, *ibid.*, **43**, 413), and to possess the power of inhibiting the hydrolysis of methyl butyrate and of tributyrin by liver esterase (Stedman and Stedman, *Biochem. J.*, 1931, **25**, 1147). In view of these results, the resolution of miotine has been reinvestigated.

Attempts were first made to effect the direct resolution by crystallisation of salts of this base with optically active acids. A number of acids were examined, but in no case could a crystalline salt be prepared. Consideration was therefore directed to the possibility of resolving one of the compounds utilised in the synthesis of miotine. Of these, α-*m*-hydroxyphenylethyldimethylamine appeared to be the most suitable. No greater success was, however, obtained with this substance than with miotine itself. It appeared, moreover, unlikely that better results would be secured with either α-*m*-methoxyphenylethyldimethylamine or *m*-methoxyphenylmethylcarbinol, the only remaining substances theoretically capable of resolution which are used in the preparation of miotine.

The possibility was then considered of resolving α-*m*-hydroxyphenylethylmethylamine, which, it was anticipated, would form salts with smaller solubilities than those of the corresponding tertiary base. This substance was accordingly prepared by the

interaction of α-*m*-methoxyphenylethyl bromide with methylamine, followed by demethylation of the methoxy-base by hydrobromic acid. The salts of this secondary base were, in fact, less soluble than those of the corresponding tertiary base, and it was possible to prepare a crystalline hydrogen *d*-tartrate and a hydrogen *l*-malate. Indications were, moreover, obtained, that some separation of the two enantiomorphs occurred on crystallisation of these salts, but it was evident that the difference between the solubilities of the two *d*-tartrates as well as of the two *l*-malates was so small that only small yields of the pure enantiomorphic forms of the base would be obtained after long fractionation.

Attention was next directed to the bromocamphorsulphonates. Attempts to prepare these by double decomposition between ammonium α-bromocamphor-π-sulphonate and the hydrochloride of the base in aqueous solution at first failed. By dissolving the free base in an aqueous solution of bromocamphorsulphonic acid and then removing the solvent, a sticky product was, however, obtained which could be crystallised from ethyl acetate. After recrystallisation from the same solvent, purification was completed by crystallisation from water, d-α-m-*hydroxyphenylethylmethylamine* d-α-*bromocamphor-π-sulphonate* being obtained in pure form. In view of the readiness with which this salt crystallised from water, its direct preparation from aqueous solution was re-examined, and, on using the above preparation for inoculation, crystallisation readily occurred. It was subsequently found that practically pure *dd*-salt separated without seeding from a solution of α-*m*-hydroxyphenylethylmethylamine hydrochloride in a carefully chosen volume of water on the addition of 0·5 equiv. of ammonium *d*-bromocamphorsulphonate. It is difficult to offer an adequate explanation of this result, which is in contradiction to the earlier experiments. Although it might be attributed to nuclei from the laboratory atmosphere initiating crystallisation, we suggest that the hydrochloride employed in the earlier experiments, although analytically pure, was contaminated with a minute amount of impurity which inhibited the crystallisation. This explanation is supported by the fact that the original preparation of the base, which was employed in these experiments, was not quite colourless, whereas the specimens used in the later experiments were crystallised from a different solvent and were perfectly colourless.

In view of the good yield of the d-*base* obtained in the above experiments, it was hoped that it would be possible to purify the *l*-base remaining in the mother-liquors, but repeated crystallisation of the recovered base had no effect on its purity. By converting it into its hydrochloride and recrystallising this salt, the pure

hydrochloride of the *l*-base was obtained, but the yield was too small to render this a practicable method for the purposes in view. Ammonium *l*-bromocamphorsulphonate was therefore prepared from *l*-borneol, and the pure l-α-m-*hydroxyphenylethylmethylamine* l-α-*bromocamphor*-π-*sulphonate* was obtained by the method employed in the case of the *d*-isomeride, by using the base recovered from the mother-liquors in the preparation of the latter.

The use of the above resolved bases for the preparation of the enantiomorphic miotines depended on the possibility of converting them into the corresponding tertiary bases without serious loss. The procedure devised by Skita and Keil (*Ber.*, 1929, **62**, 1142) appeared to be suitable for this purpose: those authors employ an aqueous solution of the hydrochloride of the base and reduce this in an atmosphere of hydrogen in the presence of formaldehyde and platinum black under an excess pressure of 3 atmospheres. This method was tried with *dl*-α-*m*-hydroxyphenylethylmethylamine, using platinum black prepared according to Willstätter and Waldschmidt-Leitz's method (*Ber.*, 1921, **54**, 113), with the modification that the pressure of hydrogen was only slightly greater than that of the atmosphere. Practically no absorption of hydrogen occurred. Since this negative result might be attributed to the fact that the hydrochloride, and not the free base, was employed, a further experiment was carried out in which a solution of the free base in methyl alcohol was used, the procedure being otherwise identical. A slow but steady absorption of hydrogen now took place until the uptake almost corresponded with the amount required theoretically. It was not, in this case, possible to isolate the tertiary base directly from the reaction mixture, but it was readily obtained in the form of its *hydrochloride*. In subsequent work, Adams's platinum oxide catalyst was found superior to Willstätter's platinum black. With this catalyst the hydrogenation takes place rapidly in methyl-alcoholic solution and the tertiary base can be readily obtained from the reaction mixture by removing the catalyst and evaporating the solution in a vacuum.

The final stage in the preparation of d- and l-*miotine*, effected by treating the resolved tertiary bases with methylcarbimide, proceeded smoothly.

EXPERIMENTAL.

dl-α-m-*Methoxyphenylethylmethylamine*, $MeO{\cdot}C_6H_4{\cdot}CHMe{\cdot}NHMe$. — This base was prepared by the action of NH_2Me on either α-*m*-methoxyphenylethyl bromide or chloride, the bromide being prep. by the method described by Stedman and Stedman (J., 1929, 609) and the chloride by adding $SOCl_2$ (24 c.c.) slowly to 41 g. of *m*-methoxyphenylmethylcarbinol. Effervescence occurred during the addition and the reaction mixture became slightly warm. After 1 hr., the product was distilled under low press. A small quantity of

$SOCl_2$ first passed over, and then α-*m*-methoxyphenylethyl chloride (35 g.) distilled as a colourless liquid, b. p. 110°/12 mm.

When preparing α-*m*-methoxyphenylethyldimethylamine, Stedman and Stedman added a solution of the bromide in C_6H_6 to an excess of $NHMe_2$ in the same solvent. This method was not applicable to the prep. of the secondary base owing to the small solubility of NH_2Me in C_6H_6. Expts. were therefore first carried out using EtOH as solvent. α-*m*-Methoxyphenylethyl bromide (prep. from 25 g. of the carbinol) was poured into 60 c.c. of a 33% solution of NH_2Me in EtOH and kept over-night. Crystals of NH_2Me,HBr separated, but on acidifying a small test portion of the solution with dil. HCl a pronounced turbidity was produced, indicating that the bromide had not all reacted. After a week, although the reaction was still apparently incomplete, the product was worked up. The solution was decanted from the NH_2Me,HBr, the latter washed with EtOH, and the combined alc. solutions acidified with HCl and the EtOH removed by steam distillation. After the bulk of the EtOH had passed over, the distillate was seen to contain a small quantity of a colourless oil. The distillation was therefore continued until this had been completely removed. The residue in the flask was then extracted with Et_2O first in acid solution and then after it had been made alk. by NaOH. After drying (Na_2SO_4), the Et_2O was evaporated from the latter extract and the product distilled under diminished press., *dl*-α-*m*-methoxyphenylethylmethylamine, b. p. 113·5—114·5°/14 mm., being obtained as a colourless oil (yield 17 g.).

The same base was similarly prepared from α-*m*-methoxyphenylethyl chloride; even after 14—15 days some non-basic material was still present. A yield of 24 g. was obtained from 35 g. of the chloride. Based on the weight of carbinol originally employed, this represents 54% of the theo., as compared with 63% when the bromide was utilised.

Since acetonitrile dissolves considerable quantities of NH_2Me, and does not react with the bromide, it was tried as a solvent: not only were better yields of the base obtained, but the reaction proceeded much more rapidly, as the following typical example shows. Dry NH_2Me (35 g., prepd. from its chloride) was passed into 130 g. of MeCN in a freezing mixture, and treated slowly with a solution in the same solvent of the α-*m*-methoxyphenylethyl bromide (from 64 g. of the carbinol). After 3 days the solvent was distilled off, ether added to the residue, and the NH_2Me,HBr which had separated during the evaporation of the MeCN was filtered off. The ethereal solution was then extracted with dil. HCl, the base pptd. from this extract by NaOH, and shaken out with Et_2O. There were thus obtained 52 g. (75%) of α-*m*-methoxyphenylethylmethylamine, b. p. 117—118°/15 mm. The *hydrochloride*, m. p. 152—153°, separated as colourless prisms on addition of dry Et_2O to its alc. solution (Found: Cl, 17·5. $C_{10}H_{15}ON,HCl$ requires Cl, 17·6%).

dl-α-m-*Hydroxyphenylethylmethylamine*, $HO{\cdot}C_6H_4{\cdot}CHMe{\cdot}NHMe$.—The above methoxy-compound (52 g.) was dissolved in 200 c.c. of constant-boiling HBr aq. and boiled under reflux for 6 hrs. After removal of the HBr by distillation under diminished press., the residual syrup, which frequently crystallised on standing, was dissolved in H_2O and extracted with Et_2O to remove any non-basic impurities. Preliminary expts. had shown that the phenolic base was insol. in dry Et_2O and only sparingly sol. in moist Et_2O, and was sol. in dil. aq. alkalis. Its isolation from the above solution was therefore effected by the following procedure, which utilises the fact that the base is salted out

from alk. solution by relatively high concns. of Na_2CO_3, a process which is assisted by saturating the solution with Et_2O. The solution was treated with a large excess of a hot saturated solution of Na_2CO_3, cooled, and shaken with a small quantity of Et_2O. The solid base soon separated. It was left in the refrigerator for some hours, whereupon the solid was filtered off, dried in a desiccator, extracted with hot EtOAc, and the solution filtered from a small quantity of Na_2CO_3 and cooled. *dl*-α-*m*-Hydroxyphenylethylmethylamine separated in solid form. It can be recryst. from C_6H_6 or EtOH but best from EtOAc (charcoal); it forms a felted mass of needles, m. p. 160°; yield 41 g.

The *hydrochloride*, m. p. 160°, crystallises from alcohol (Found: Cl, 18·9. $C_9H_{13}ON,HCl$ requires Cl, 18·8%).

Resolution of dl-α-m-*Hydroxyphenylethylmethylamine*.—30 G. of the racemic base were dissolved in 345 c.c. of 0·584*N*-*d*-bromocamphorsulphonic acid (Pope and Peachey, J., 1898, **73**, 895), and the H_2O removed as completely as possible by distillation under diminished press. In order to remove last traces of H_2O, the sticky brown residue was dissolved in EtOH and the solvent similarly removed, this process being repeated again with EtOH and finally with EtOAc. The residue was now dissolved in about 220 c.c. of hot EtOAc, and the solution cooled and placed in the refrigerator. After 2 days the cryst. material which had separated (46 g.; m. p. 165°) was collected. Addition of Et_2O to the mother-liquors gave a further 20 g. of the same material. Preliminary expts. had shown that further crystn. from EtOAc produced a rise in the m. p. of the product, which could then be cryst. from H_2O. In the present expt. this further crystn. from EtOAc was avoided and the two fractions were dissolved separately in hot H_2O, the first fraction (46 g.) in 150 c.c. and the second (20 g.) in 45 c.c. The two solutions were cooled and inoculated with crystals of the *d*-bromocamphorsulphonate of the base which had been obtained in the preliminary expts. After about 2 hrs. the cryst. material which had separated was filtered off, that from both batches melting at 191° (yields: 15·5 and 6·8 g. respectively). Further crystn. produced no change in the m. p., and the physical constants of the base recovered from the salt agreed with those given below for the pure *d*-base.

As pointed out on p. 2514, this method was subsequently modified; the following is typical of the procedure finally adopted: 60 g. of the hydrochloride of the *dl*-base were mixed with 55 g. (slightly more than ½ mol.) of ammonium *d*-bromocamphorsulphonate and the mixture was dissolved in 295 c.c. of hot H_2O. The solution was cooled, and the salt commenced to separate. After being kept for 3 hrs. at room temp. with occasional shaking, the product was separated, 62 g. of cryst. material, m. p. 187—190°, being obtained. On standing in the refrigerator over-night, the mother-liquors deposited a further crop (5 g.), m. p. 182—185°, which on recrystn. from H_2O gave 4 g. of material, m. p. 188—190°. This was united with the first crop and the whole recryst. from H_2O, yielding 59 g. (79% of the theo.) of the pure bromocamphorsulphonate. d-α-m-*Hydroxyphenylethylmethylamine* d-α-*bromocamphor-π-sulphonate* crystallises from H_2O as rectangular tablets, m. p. *ca.* 193°, containing an indefinite amount of H_2O of crystn. This is lost slowly in the air and more rapidly in a vac. desiccator (Found: loss on drying in high vac. over P_2O_5, 4·7. $C_9H_{13}ON,C_{10}H_{15}O_4BrS,1\frac{1}{2}H_2O$ requires H_2O, 5·5%. Found, in dried material: C, 49·6; H, 6·0.

$C_9H_{13}ON,C_{10}H_{15}O_4BrS$

requires C, 49·3; H, 6·1%). The anhyd. salt has m. p. 197° and can be obtained directly by crystn. of the hydrated substance from EtOAc, in which it is sparingly sol. at room temp.; it is also sparingly sol. in MeOH and EtOH.

Preliminary expts. having shown that the separation of the *d*-acid salt of the *d*-base was due less to any great difference between the solubilities of the two *d*-bromocamphorsulphonates than to the greater tendency to supersaturation shown by that of the *l*-base, an attempt was made to prepare and purify the latter salt by the addition of a further $\frac{1}{2}$ mol. of ammonium *d*-bromocamphorsulphonate to the mother-liquors from the expt. described in the preceding paragraph. Although this caused the bulk of the remaining material to separate, it could not be purified by crystn.; nor could the base recovered therefrom be further purified by crystn. The latter was therefore converted into the hydrochloride, which, on recrystn. from EtOH, deposited the pure hydrochloride of the *l*-base (yield, very small). The bulk of the impure hydrochloride (23 g.) was therefore mixed with ammonium *l*-bromocamphorsulphonate (40 g.) and dissolved in 120 c.c. of hot H_2O. After 3 hrs. the cryst. salt which had separated was collected (47 g.; m. p. 192°) and recryst. from H_2O. The properties of l-α-m-*hydroxyphenylethylmethylamine* l-α-*bromocamphor-π-sulphonate* are identical with those of the corresponding *dd*-salt described above (Found : loss on drying in high vac. over P_2O_5, 3·3%. Found, in dried material : S, 6·9. $C_9H_{13}ON,C_{10}H_{15}O_4BrS$ requires S, 6·9%). Owing to the sparing solubilities of the above bromocamphorsulphonates in all ordinary solvents at room temp., their rotations were not determined. The resolution was controlled by following the m. p.'s of the various fractions during crystn. and by the rotation of the recovered bases.

d-α-m-*Hydroxyphenylethylmethylamine* was recovered from its bromocamphorsulphonate by the method described in connexion with the *dl*-base. 40 G. of the salt yielded 14 g. (87% of theo.) of the pure *d*-base, which crystallised from EtOAc in a felted mass of needles, m. p. 171°, $[\alpha]_D$ + 68·0° (*c* = 5·0 in C_5H_5N) (Found : C, 71·6; H, 8·5. $C_9H_{13}ON$ requires C, 71·5; H, 8·6%). Its *hydrochloride* crystallises from EtOH as hexagonal tablets, m. p. 201°, $[\alpha]_D$ + 20·0° (*c* = 10·0 in H_2O) (Found : Cl, 18·8. $C_9H_{13}ON,HCl$ requires Cl, 18·9%).

l-α-m-*Hydroxyphenylethylmethylamine*, when recovered from its *l*-bromocamphorsulphonate, had m. p. 171°, $[\alpha]_D$ − 68·0° (*c* = 5·0 in C_5H_5N) (Found : N, 9·1. $C_9H_{13}ON$ requires N, 9·3%), in agreement with the *d*-isomeride. Its *hydrochloride* had m. p. 201°, $[\alpha]_D$ − 20·0° (*c* = 10·0 in H_2O) (Found : Cl, 19·3%).

d- *and* l-α-m-*Hydroxyphenylethyldimethylamine*, $HO{\cdot}C_6H_4{\cdot}CHMe{\cdot}NMe_2$.— Details of the preliminary expts. on the methylation process are recorded on p. 2515. The following typical example illustrates the method finally adopted : 5 g. of *d*-α-*m*-hydroxyphenylethylmethylamine were dissolved in 30 c.c. of hot MeOH and 3 c.c. of formalin were added. The mixture was then cooled and introduced into the hydrogenation chamber of the apparatus, which was of the type described by Hess (*Ber.*, 1913, **46**, 3120). After the apparatus had been swept out with H, 0·1 g. of PtO_2 catalyst was washed with MeOH into the upper and smaller chamber, and, after reduction, transferred to the adjoining chamber containing the reaction mixture. The apparatus was now shaken, and a rapid and steady absorption of H occurred : 700 c.c. in the first 40 mins., a further 50 c.c. in the next 15 mins.; absorption then became very slow and experience had shown that the best product was

obtained if the process was stopped at this stage although the theo. vol. (810 c.c.) had not been absorbed. The catalyst was therefore filtered off, and the MeOH evaporated on a water-bath. The syrupy residue was dried in a vac. desiccator, and solidified in 12 hrs. (yield 5·2 g.). This impure product was crystallised from a small vol. of EtOH, and 3·8 g. of material were obtained, a further 0·5 g. being recovered from the alc. mother-liquors in the form of hydrochloride. d-α-m-*Hydroxyphenylethyldimethylamine* crystallises from C_6H_6 in square tablets, m. p. 116°, $[\alpha]_D$ + 55·8° (*c* = 5·0 in EtOH) (Found: C, 72·6; H, 9·2. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·1%). The *hydrochloride* crystallised on the addition of Et_2O to its solution in EtOH in aggregates of tablets, m. p. 161°, $[\alpha]_D$ + 15·2° (*c* = 10 in H_2O) (Found: Cl, 17·9. $C_{10}H_{15}ON,HCl$ requires Cl, 17·6%).

l-α-m-*Hydroxyphenylethyldimethylamine*, m. p. 116°, $[\alpha]_D$ − 55·8° (*c* = 5·0 in EtOH) (Found: N, 8·2. $C_{10}H_{15}ON$ requires N, 8·5%), was prepared from the corresponding secondary base under the same conditions as were used for the *d*-isomeride. Its *hydrochloride*, m. p. 161°, $[\alpha]_D$ − 15·0° (*c* = 10 in H_2O) (Found: Cl, 17·7%), agrees in properties with that of the *d*-base.

Preparation of d- *and* l-*Miotine* (*Methylurethanes of* d- *and* l-α-m-*Hydroxyphenylethyldimethylamine*), $NHMe{\cdot}CO_2{\cdot}C_6H_4{\cdot}CHMe{\cdot}NMe_2$.—4 G. of *d*- (or *l*-) tertiary base were treated with about 4 c.c. of freshly prep. CO:NMe, the mixture being kept cool. The base dissolved slowly, and after about 10 mins. a cryst. product commenced to separate. The reaction mixture was kept over-night at room temp., and the excess of CO:NMe was then removed under diminished press. The residue was dissolved in warm Et_2O and the solution filtered from a small quantity of brown material. On evaporation of the Et_2O, a colourless solid was obtained (yield 4·5 g.). The *methylurethane* of *d*-α-*m*-hydroxyphenylethyldimethylamine crystallises from Et_2O, in which it is fairly sol., in flat prisms, m. p. 85°, $[\alpha]_D$ + 37·0° (*c* = 10 in EtOH) (Found: C, 64·7; H, 8·2. $C_{12}H_{18}O_2N_2$ requires C, 64·9; H, 8·1%).

The *methylurethane* of the *l*-base, m. p. 85°, $[\alpha]_D$ − 35·7° (*c* = 10 in EtOH) (Found: N, 12·3. $C_{12}H_{18}O_2N_2$ requires N, 12·6%), crystallises similarly.

The *hydrochloride* of the *d*-methylurethane, m. p. 167° (efferv. after sintering at about 160°; slow heating), $[\alpha]_D$ + 10·6° (*c* = 10 in H_2O) (Found: Cl, 13·5. $C_{12}H_{18}O_2N_2,HCl$ requires Cl, 13·7%), crystallises from EtOH in the form of tablets; and the *hydrochloride* of the methylurethane of the *l*-base has m. p. 167° (efferv.), $[\alpha]_D$ − 10·2° (*c* = 10 in H_2O) (Found: Cl, 13·7%).

Part of the expense of this investigation has been met by grants from the Earl of Moray Research Fund of this University.

DEPARTMENT OF MEDICAL CHEMISTRY,
UNIVERSITY OF EDINBURGH. [*Received, July 15th*, 1932.]