RESEARCH PAPERS

THE ABSOLUTE CONFIGURATIONS OF THE α- AND β-METHYLCHOLINE ISOMERS AND THEIR ACETYL AND SUCCINYL ESTERS*

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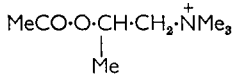
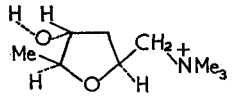
The absolute configurations of the (+)-acetyl-α- and -β-methylcholine iodides have been established, being related to D(−)-alanine hydrochloride and L(+)-lactic acid respectively. The (+)-, (−)- and racemic forms of the precursor amino-alcohols have been converted to the succinyl esters and these quaternised.

THE muscarinic activity of (+)-acetyl-β-methylcholine (I) (equiactive with acetylcholine) is about 100 times greater than that of the (−)-isomer (Major and Bonnett, 1935; Major and Cline, 1936).

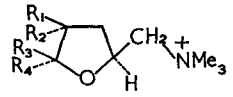


I

L(+)-Muscarine (II) (Hardegger and Lohse, 1957) is reported to be about 200 to 800 times more active than the D(−)-isomer (Gyermek and Unna, 1958).



II



III

That the spatial arrangement of the substituents on the tetrahydrofuran ring of the muscarine isomers influences their activity is clearly shown by the fact that (±)-epi- (III; $R_1 = OH$, $R_2 = R_4 = H$, $R_3 = Me$), (±)-allo- (III; $R_1 = OH$, $R_2 = R_3 = H$, $R_4 = Me$) and (±)-epiallo-muscarine (III; $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = Me$) possess only 1/300th, 1/150th and 1/100th respectively the muscarinic potency of (±)-muscarine (Gyermek and Unna, 1958; Waser, 1958).

It was of interest to establish the absolute configurations of the isomers of acetyl-α- and -β-methylcholine. This, it was considered, might allow a delineation of the stereochemical factors associated with possible receptor sites at which muscarinic activity is mediated.

* See Beckett and others (1960 and 1961) for preliminary reports of some of the present work.

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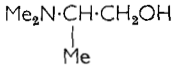
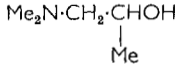
The (+)- and (−)-isomers of 2-dimethylaminopropan-1-ol (IV) and 1-dimethylaminopropan-2-ol (V) and also their racemic forms, prepared during this investigation, were converted to their succinyl esters and quaternised. These compounds were considered to be important in investigations into the stereochemical factors involved in neuromuscular blocking activity.

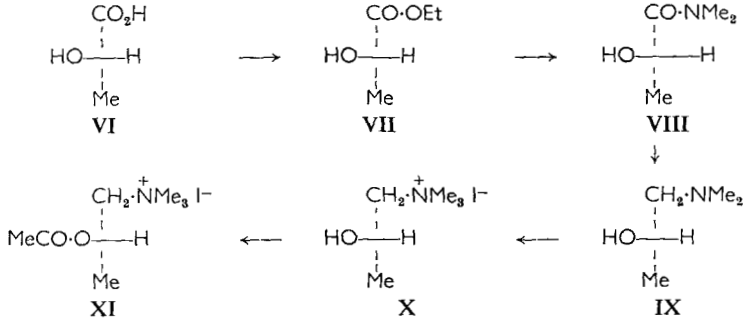


IV



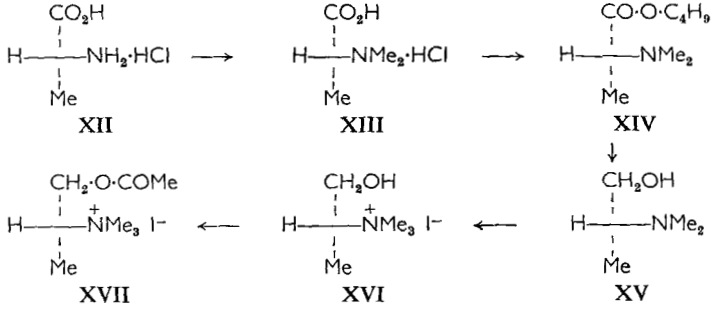
V

(+)-Acetyl-β-methylcholine (XI) was related to L(+)-lactic acid(VI) by the following stereospecific route:



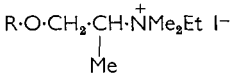
Zinc ammonium L(−)-lactate, prepared from lactic acid (VI), was converted to ethyl L(−)-lactate (VII), which on treatment with dimethylamine, followed by reduction with lithium aluminium hydride, gave L(+)-1-dimethylaminopropan-2-ol (IX), which on quaternisation with methyl iodide gave L(+)-1-dimethylaminopropan-2-ol methiodide (β-methylcholine iodide) (X). This on acetylation gave L(+)-1-dimethylaminoprop-2-yl acetate methiodide (acetyl-β-methylcholine iodide) (XI). Independently and at about the same time, Ellenbroek and van Rossum (1960) also established the absolute configuration of acetyl-β-methylcholine. The (+)- and (−)-isomers of 1-dimethylaminopropan-2-ol were prepared by resolution of the racemic alcohol using (+)-tartaric acid and α-bromo-(+)-camphor-π-sulphonic acid.

(+)-Acetyl-α-methylcholine (XVII) was related to D(−)-alanine hydrochloride (XII) by the following stereospecific route.



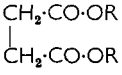
D(−)-Alanine hydrochloride (XII) was reductively methylated to give D(−)-2-dimethylaminopropionic acid hydrochloride (XIII) which on esterification with butanol gave butyl D(+)-2-dimethylaminopropionate (XIV). Reduction with lithium aluminium hydride gave D(−)-2-dimethylaminopropan-1-ol (XV), which on quaternisation with methyl iodide gave D(+)-2-dimethylaminopropan-1-ol methiodide (α-methylcholine iodide) (XVI). Acetylation with acetic anhydride gave D(+)-2-dimethylaminopropyl acetate methiodide (acetyl-α-methylcholine iodide) (XVII). L(−)-2-Dimethylaminopropyl acetate methiodide was prepared from L(+)-alanine hydrochloride by a similar synthetic route.

The (+)-, (−)- and (±)-forms of 2-dimethylaminopropan-1-ol were converted to the ethiodides (XVIII; R = H) and their acetyl derivatives (XVIII; R = MeCO).

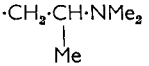


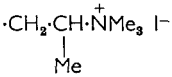
XVIII

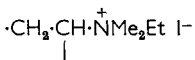
The optically active amino-alcohols were also used to prepare the succinyl esters and their quaternary derivatives of the general formula (XIX).

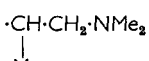


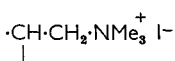
XIX

(a) R = (+)- and (−)- 

(b) R = (+)- and (−)- 

(c) R = (+)- and (−)- 

(d) R = (+)- and (−)- 

(e) R = (+)- and (−)- 

Preparation of the succinyl esters from the racemic alcohols would be expected to give a mixture of meso- and racemic forms. The presence of two distinct forms, which were considered to be the meso- and racemic forms, was established by vapour phase chromatography of the free bases. The quaternary derivatives of these esters [with the exception of compound (XIX c)] could not be separated by fractional crystallisation. The (±)-mixtures of 2-dimethylaminopropyl succinate methiodide,

1-dimethylaminoprop-2-yl succinate methiodide and 2-dimethylaminopropyl succinate ethiodide were prepared by mixing equal quantities of the optically active forms and crystallising from methanol-acetone.

An examination of the products of the interaction of the (+)- and (−)-1-dimethylaminopropan-2-ols with succinyl chloride by vapour phase chromatography indicated the presence of a mixture of two substances. On the basis of the gas chromatogram obtained with the succinate prepared from (±)-1-dimethylaminopropan-2-ol, these substances were considered to be the meso- and optically active forms. The appearance of two forms was unexpected but experiments have been carried out which have established that no racemisation or inversion of configuration of the optically active 1-dimethylaminopropan-2-ols occurred during the synthesis of their succinates. The apparent partial transformation of the optically active 1-dimethylaminoprop-2-yl succinates to the meso-form during gas chromatographic analysis is being investigated.

Experimental

Resolution of lactic acid. Lactic acid was resolved by a modification of the method of Purdie (1893) to give zinc ammonium L(−)-lactate $[\alpha]_D^{21}$ − 5·65° (*c* 8·3 in H_2O) [Purdie, 1893, quotes $[\alpha]_D$ − 6·06° (without stating concentration, solvent and temperature)].

Ethyl L(−)*-lactate.* Zinc ammonium L(−)-lactate (36 g.), $[\alpha]_D^{22}$ − 5·65° (*c* 8·3 in H_2O) was converted to lactic acid, which was then esterified with ethanol by a modification of the method Fischer and Mechel (1916) and gave ethyl L(−)-lactate (11·4 g.), b.p. 64–68° at 25 mm., $[\alpha]_D^{23}$ − 9·36° (*c* 3·16 in EtOH) [Freudenberg and Rhino, 1924, quote $[\alpha]_D^{20}$ − 10·3 to 10·5° (without stating concentration and solvent); Heilbron, 1953, quotes $[\alpha]_D^{14}$ − 10·33° (without stating concentration and solvent), b.p. 69–70° at 36 mm.].

L(+)-1-*Dimethylaminopropan-2-ol methiodide.* Ethyl L(−)-lactate (5 g.) and anhydrous dimethylamine (30 ml.) were heated in a sealed container for 1 hr. at 80° and then kept at room temperature for a further 24 hr. Excess of dimethylamine was removed by evaporation under reduced pressure and the residual oil dissolved in dry ether and reduced with lithium aluminium hydride (2 g.). After decomposition, the combined ethereal extracts were dried (anhyd. Na_2SO_4) and the ether removed by evaporation under reduced pressure. The residual liquid was distilled to give a basic fraction which contained optically active 1-dimethylaminopropan-2-ol, the specific rotation of which, based on the equivalent-weight determination, was $[\alpha]_D^{25}$ + 23·22° (*c* the equivalent of 0·9 pure L(+)-1-dimethylaminopropan-2-ol in EtOH). Treatment of an ethanolic solution with methyl iodide (2 ml.) in ethanol, followed by dropwise addition of ether, gave a solid which on crystallisation from ethanol-ether gave L(+)-1-dimethylaminopropan-2-ol methiodide m.p. 174–175°, $[\alpha]_D^{24.5}$ + 27·27° (*c* 2·2 in 90 per cent v/v EtOH) (Calc. for $C_6H_{16}INO$ equiv., 245. Found equiv., 246) [Major and Cline, 1936, quote $[\alpha]_D^{25}$ + 24·7° (without stating concentration and solvent) and m.p.

176–178° for (+)-1-dimethylaminopropan-2-ol methiodide prepared by resolution].

Resolution of 1-dimethylaminopropan-2-ol. (±)-1-Dimethylaminopropan-2-ol was resolved by the method of Major and others (1935; 1936) using (+)-tartaric acid and α-bromo-(+)-camphor-π-sulphonic acid and gave (−)-1-dimethylaminopropan-2-ol hydrogen (+)-tartrate $[\alpha]_D^{22.5}$ − 10·84° (*c* 4·9 in H_2O) [Major and Bonnett, 1935, quote $[\alpha]_D^{25}$ − 10·7° (without stating concentration and solvent)] and (+)-1-dimethylaminopropan-2-ol α-bromo-(+)-camphor-π-sulphonate, $[\alpha]_D^{24.5}$ + 80·6° (*c* 1·0 in H_2O) [Major and Bonnett, 1935, quote $[\alpha]_D$ + 83·5° (without stating solvent and temperature)].

L(+)-1-*Dimethylaminoprop-2-yl acetate methiodide.* L(+)-1-Dimethylaminopropan-2-ol methiodide (2 g.), m.p. 177–178°, $[\alpha]_D^{24}$ + 29·7° (*c* 2·0 in 90 per cent v/v EtOH) [obtained by quaternising L(+)-1-dimethylaminopropan-2-ol (prepared by resolution) with methyl iodide] was refluxed with acetic anhydride (25 ml.) for 30 min., excess of acetic anhydride removed by distillation under reduced pressure and the syrupy residue dissolved in methanol (10 ml.). Ether was added dropwise and the salt which formed was crystallised from methanol-ether to give L(+)-1-*dimethylaminoprop-2-yl acetate methiodide* (1·9 g.), m.p. 177·5–178·5°, $[\alpha]_D^{22.5}$ + 27·0° (*c* 2·0 in 90 per cent v/v EtOH) (Found: C, 33·6; H, 6·5; N, 5·0 per cent; equiv., 286. $C_8H_{18}INO_2$ requires C, 33·5; H, 6·3; N, 4·9 per cent; equiv., 287).

D(−)-1-*Dimethylaminopropan-2-ol methiodide.* To an ethereal solution of D(−)-1-dimethylaminopropan-2-ol [prepared from (−)-1-dimethylaminopropan-2-ol hydrogen (+)-tartrate (4 g.), $[\alpha]_D^{22.5}$ − 10·84° (*c* 4·9 in H_2O)] was added methyl iodide and ethanol. The solid which separated on standing was crystallised from ethanol-ether to give D(−)-1-dimethylaminopropan-2-ol methiodide (3·2 g.), m.p. 175·5–176·5°, $[\alpha]_D^{23}$ − 29·04° (*c*. 2·0 in 90 per cent v/v EtOH) (Calc. for $C_6H_{16}INO$ equiv., 245. Found: equiv., 244) [Major and Cline, 1936, quote m.p. 176·5–177·5°, $[\alpha]_D^{25}$ − 24·7° (without stating solvent and concentration)].

D(−)-1-*Dimethylaminoprop-2-yl acetate methiodide.* D(−)-1-Dimethylaminopropan-2-ol methiodide (2·5 g.) was acetylated in the manner described for L(+)-1-dimethylaminoprop-2-yl acetate methiodide and gave D(−)-1-*dimethylaminoprop-2-yl acetate methiodide* (2·6 g.) m.p. 176–178°, $[\alpha]_D^{23}$ − 27·38° (*c* 2·0 in 90 per cent v/v EtOH) (Found: C, 33·6; H, 6·1; N, 4·6 per cent; equiv., 286. $C_8H_{18}INO_2$ requires C, 33·5; H, 6·3; N, 4·9 per cent; equiv., 287).

Resolution of alanine. Alanine was resolved by a modification of the method of Pope and Gibson (1912) to give D(−)-alanine hydrochloride, $[\alpha]_D^{20}$ − 9·72° (*c* 13·1 in H_2O)* [Bowman and Stroud, 1950, quote $[\alpha]_D^{18}$ − 9·13° (*c* 13·1 in H_2O)] and L(+)-alanine hydrochloride, m.p. 200·5–201·5°, $[\alpha]_D^{20}$ + 9·47° (*c* 13·1 in H_2O) [Merck, 1960, quotes m.p. 204° and Harper, 1956, quotes $[\alpha]_D^{20}$ + 9·5° (*c* 13·1 in H_2O)].

* These figures are in accordance with those reported by Birnbaum and others (1952) who obtained $[\alpha]_D^{25}$ + 14·4° for L-alanine and $[\alpha]_D^{25}$ − 14·3° for D-alanine (*c* 4 in 5N HCl) by an enzymic method of resolution.

D(−)-2-*Dimethylaminopropionic acid hydrochloride.* D(−)-Alanine hydrochloride was reductively methylated by the method of Bowman and Stroud (1950) and gave D(−)-2-*dimethylaminopropionic acid hydrochloride*, m.p. 117·5–119°, $[\alpha]_D^{25.5}$ − 14·47° (*c* 5·17 in H_2O) (Found: C, 38·3; H, 8·4 per cent; equiv., 154. $C_5H_{12}ClNO_2$ requires C, 39·1; H, 7·9 per cent; equiv., 154).

Butyl D(+)-2-*dimethylaminopropionate.* D(−)-2- Dimethylaminopropionic acid hydrochloride (27·1 g.) was esterified with butanol by a modification of the method of Fischer and Mechel (1916) to give *butyl* D(+)-2-*dimethylaminopropionate* (23·6 g.), b.p. 94–96° at 23 mm., $n_D^{18} = 1{\cdot}4264$, $[\alpha]_D^{24}$ + 25·1° (*c* 1·16 in EtOH) (Found: C,61·2; H, 11·0 per cent; equiv., 174. $C_9H_{19}NO_2$ requires C, 62·4; H, 11·1 per cent; equiv., 173).

D(+)-2-*Dimethylaminopropan*-1-*ol methiodide.* Butyl D(+)-2-dimethylaminopropionate (14 g.) in dry ether (75 ml.) was reduced with lithium aluminium hydride (3 g.) to give a basic oil having equiv. 138 (the calculated equivalent weight of D(−)-2-dimethylaminopropan-1-ol is 103). This oil consisted of a mixture of D(−)-2-dimethylaminopropan-1-ol and the butanol which co-distilled with the base. Correcting for the impurity, the amino-alcohol had $[\alpha]_D^{23.5}$ − 3·83° (*c* the equivalent of 2·9 pure D(−)-2-dimethylaminopropan-1-ol in EtOH) [Mitchard (personal communication), found $[\alpha]_D^{23}$ − 2·8° (*c* 3·1 in EtOH), $n_D^{20} = 1{\cdot}4373$ (Calc. for $C_5H_{13}NO$ equiv., 103. Found: equiv., 107)]. A solution of the impure amino-alcohol (0·3 g.) was treated with methyl iodide (1 ml.) and the solid which separated crystallised from ethanol-ether to give D(+)-2-*dimethylaminopropan*-1-*ol methiodide* (0·6 g.), m.p. 298·5–299·5° (decomp.), $[\alpha]_D^{22.5}$ + 4·15° (*c* 2·5 in 90 per cent v/v EtOH) (Found: C, 29·6; H, 6·6; N, 6·4 per cent; equiv., 242. $C_6H_{16}INO$ requires C, 29·4; H, 6·6; N, 5·7 per cent; equiv., 245).

D(+)-2-*Dimethylaminopropyl acetate methiodide.* D(+)-2-Dimethylaminopropan-1-ol methiodide (1 g.) was refluxed for 30 min. with acetic anhydride (25 ml.), the excess of which was removed by distillation under reduced pressure. The syrupy residue was crystallised from ethanol-ether to give D(+)-2-*dimethylaminopropyl acetate methiodide* (1g.), m.p. 107–108°, $[\alpha]_D^{20.7}$ + 8·61° (*c* 5·0 in 90 per cent v/v EtOH) (Found: C, 33·2; H, 6·1; N, 5·6 per cent; equiv., 287. $C_8H_{18}INO_2$ requires C, 33·5; H, 6·3; N, 4·9 per cent; equiv., 287).

By similar procedures, L(+)-alanine hydrochloride, m.p. 200·5–201·5°, $[\alpha]_D^{20}$ + 9·47° (*c* 13·1 in H_2O)* was converted to L(+)-2-*dimethylaminopropionic acid hydrochloride*, m.p. 118·5–119·5°, $[\alpha]_D^{23.4}$ + 14·3° (*c* 5·1 in H_2O) (Found: C, 38·0; H, 8·0; N, 8·9 per cent; equiv., 151. $C_5H_{12}ClNO$ requires C, 39·1; H, 7·9; N, 9·1 per cent; equiv., 154), which on esterification gave *butyl* L(−)-2-*dimethylaminopropionate*, b.p. 91–92° at 19 mm., $n_D^{22} = 1{\cdot}4241$, $[\alpha]_D^{26}$ − 26·6° (*c* 1·1 in EtOH) (Found: C, 63·1; H, 11·6; N, 8·1 per cent; equiv., 173. $C_9H_{19}NO_2$ requires C, 62·4; H, 11·1; N, 8·1 per cent; equiv., 173). This ester on reduction gave impure L(+)-2-dimethylaminopropan-1-ol, the specific rotation of the

* *Ibid*, p. 353.

pure alcohol, on the basis of the equivalent weight, being $[\alpha]_D^{24.5}$ + 2·26° (*c* the equivalent of 2·8 pure L(+)-2-dimethylaminopropan-1-ol in EtOH) [Mitchard (personal communication), found $[\alpha]_D^{23}$ + 2·4° (*c* 3·1 in EtOH), n_D^{20} = 1·4373 (Calc. for $C_5H_{13}NO$ equiv., 103. Found: equiv., 106)] and treatment of this with methyl iodide gave L(−)-2-*dimethylaminopropan-1-ol methiodide*, m.p. 299° (decomp.), $[\alpha]_D^{24.7}$ − 4·14° (*c* 2·5 in 90 per cent v/v EtOH) (Found: C, 30·0; H, 6·5; N, 5·7 per cent; equiv., 245. $C_6H_{16}INO$ requires C, 29·4; H, 6·6; N, 5·7 per cent; equiv., 245). Acetylation of the quaternary compound gave L(−)-2-*dimethylaminopropyl acetate methiodide*, m.p. 108–109°, $[\alpha]_D^{27}$ − 9·07° (*c* 5·0 in 90 per cent v/v EtOH) (Found: C, 33·5; H, 6·1 per cent; equiv., 289. $C_8H_{18}INO_2$ requires C, 33·5; H, 6·3 per cent; equiv., 287).

(±)-1-*Dimethylaminopropan*-2-*ol methiodide*. This was prepared by the addition of methyl iodide to a solution of (±)-1-dimethylaminopropan-2-ol (3 g.) in ethanol (20 ml.). The solid which separated was crystallised from ethanol-ether and gave (±)-1-dimethylaminopropan-2-ol methiodide (6·1 g.), m.p. 158·5–159·5° (Calc. for $C_6H_{16}INO$ equiv., 245. Found: equiv., 245).

(±)-1-*Dimethylaminoprop*-2-*yl acetate methiodide*. (±)-1-Dimethylaminopropan-2-ol methiodide (3 g.) was acetylated in the manner described for L(+)-1-dimethylaminoprop-2-yl acetate methiodide and gave (±)-1-dimethylaminoprop-2-yl acetate methiodide (3·2 g.), m.p. 137·5–138·5° (Calc. for $C_8H_{18}INO_2$ equiv., 287. Found: equiv., 286) (Merck, 1960, quotes m.p. 138–139·5°).

Ethyl (±)-2-*dimethylaminopropionate*. This was prepared by a modification of the method of Karrer (1922). A solution of dimethylamine (33 per cent in EtOH) (75 g.) was added to a solution of ethyl 2-bromopropionate (50 g.) in dry ether (150 ml.) and the mixture allowed to stand overnight. The solid which separated was removed and the filtrate diluted with ether (300 ml.) and allowed to stand overnight. The ethereal liquid was washed with a solution of sodium hydroxide (6 per cent) (2 × 6 ml.), dried (anhyd. Na_2SO_4) and evaporated under reduced pressure. The residual liquid was distilled, the fraction b.p. 74–76° at 40–42 mm. (23 g.) being collected (Calc. for $C_7H_{15}NO_2$ equiv., 145. Found: equiv., 165). The high equivalent weight obtained was due to non-basic contaminant (ethanol) and the presence of the required ester was confirmed by the preparation of the *picrate*, m.p. 83° (from ethanol) (Found: C, 41·4; H, 4·7; N, 15·6 per cent; equiv., 372. $C_{13}H_{18}N_4O_9$ requires C, 41·7; H, 4·8; N, 14·9 per cent; equiv., 374).

(±)-2-*Dimethylaminopropan*-1-*ol*. A solution of the impure ethyl (±)-2-dimethylaminopropionate (100 g.) in dry ether (145 ml.) was reduced with lithium aluminium hydride (26 g.). After reduction, the combined ethereal extracts were dried (anhyd. Na_2SO_4), the ether was removed by evaporation under reduced pressure and the residual liquid distilled to give a basic fraction (33·5 g.), b.p. 54–58° at 29 mm. (Calc. for $C_5H_{13}NO$ equiv., 103. Found: equiv., 110) which was considered to consist predominantly of (±)-2-dimethylaminopropan-1-ol and a small amount of ethanol. This fraction could not be further purified

and the amino-alcohol was identified by the picrate (from ethanol) m.p. 185° [Harper (personal communication), found m.p. 185°] (Calc. for $C_{11}H_{16}N_4O_8$ equiv., 332. Found: equiv., 328) and the methiodide.

(±)-2-*Dimethylaminopropan*-1-*ol methiodide.* A solution of (±)-2-dimethylaminopropan-1-ol (3 g.) in ethanol (5 ml.) was treated with methyl iodide (4·3 g.), the mixture allowed to stand for 20 min. and then ether added dropwise. The solid which separated was crystallised from ethanol-ether to give (±)-2-dimethylaminopropan-1-ol methiodide (7·0 g.), m.p. 299–300° (decomp.) (Calc. for $C_6H_{16}INO$ equiv., 245. Found: equiv., 242) (Karrer, 1922, quotes m.p. 296°).

(±)-2-*Dimethylaminopropyl acetate methiodide.* (±)-2-Dimethylaminopropan-1-ol methiodide (1 g.) was acetylated in the manner described for L(+)-1-dimethylaminoprop-2-yl acetate methiodide and gave (±)-2-*dimethylaminopropyl acetate methiodide* (0·8 g.), m.p. 131–132° (from ethanol-ether) (Found: C, 33·6; H, 6·2; N, 4·6 per cent; equiv., 286. $C_8H_{18}INO_2$ requires C, 33·5; H, 6·3; N, 4·9 per cent; equiv., 287).

(±)-2-*Dimethylaminopropan*-1-*ol ethiodide.* (±)-2-Dimethylaminopropan-1-ol (2 g.) in ethanol (10 ml.) was mixed with ethyl iodide (3 g.), heated to 60° and kept at room temperature overnight. Excess of ethanol was removed by evaporation and the solid which formed was crystallised from ethanol-ether to give (±)-2-*dimethylaminopropan*-1-*ol ethiodide* (1·5 g.), m.p. 285–285·5° (decomp.) (Found: C, 32·8; H, 7·1; N, 5·4 per cent; equiv., 259. $C_7H_{18}INO$ requires C, 32·5; H, 7·0; N, 5·4 per cent; equiv., 259).

(±)-2-*Dimethylaminopropyl acetate ethiodide.* (±)-2-Dimethylaminopropan-1-ol ethiodide (3 g.) was heated with acetic anhydride (25 ml.) for 30 min. at 70–80°. Excess of acetic anhydride was removed by distillation under reduced pressure and the syrupy liquid dissolved in ethanol (5 ml.). Ether was added dropwise and the salt which formed was crystallised from ethanol-ether to give (±)-2-*dimethylaminopropyl acetate ethiodide* (0·9 g.), m.p. 88° (Found: C, 35·9; H, 7·0; N, 4·5 per cent; equiv., 299. $C_9H_{20}INO_2$ requires C, 35·9, H, 6·7; N, 4·7 per cent; equiv., 301).

L(−)-2-*Dimethylaminopropan*-1-*ol ethiodide.* A solution of L(+)-2-dimethylaminopropan-1-ol in ethanol (3 ml.) was treated with ethyl iodide (3g.) in the manner described for (±)-2-dimethylaminopropan-1-ol ethiodide and gave L(−)-2-*dimethylaminopropan*-1-*ol ethiodide* (1·8 g.), m.p. 279·5–280·5° (decomp.), $[\alpha]_D^{21\cdot3}$ − 2·88° (*c* 2·5 in 90 per cent v/v EtOH) (Found: C, 33·3; H, 7·1; N, 5·3 per cent; equiv., 259. $C_7H_{18}INO$ requires C, 32·5; H, 7·0; N, 5·4 per cent; equiv., 259).

L(−)-2-*Dimethylaminopropyl acetate ethiodide.* L(−)-2-Dimethylaminopropan-1-ol ethiodide (1·8 g.) was acetylated in the manner described for (±)-2-dimethylaminopropyl acetate ethiodide and gave L(−)-2-*dimethylaminopropyl acetate ethiodide* (1·8 g.), m.p. 92–93°, $[\alpha]_D^{21\cdot5}$ − 11·27° (*c* 5·0 in EtOH) (Found: C, 36·3; H, 6·7; N, 4·6 per cent; equiv., 300. $C_9H_{20}INO_2$ requires C, 35·9; H, 6·7; N, 4·6 per cent; equiv., 301).

D(+)-2-*Dimethylaminopropan*-1-*ol ethiodide.* A solution of D(−)-2-dimethylaminopropan-1-ol in ethanol (3 ml.) was treated with ethyl iodide

(4 g.) by the method described for (±)-2-dimethylaminopropan-1-ol ethiodide and gave D(+)-2-*dimethylaminopropan*-1-*ol ethiodide* (3·5 g.), m.p. 272–273° (decomp. commences at about 250°), $[\alpha]_D^{22\cdot6}$ + 2·83° (*c* 2·5 in 90 per cent v/v EtOH) (Found: C, 32·2; H, 7·1; N, 5·4 per cent; equiv., 259. $C_7H_{18}INO$ requires C, 32·5; H, 7·0; N, 5·4 per cent; equiv., 259).

D(+)-2-*Dimethylaminopropyl acetate ethiodide.* D(+)-2-Dimethylaminopropan-1-ol ethiodide (1·9 g.) was acetylated by the method described for (±)-2-dimethylaminopropyl acetate ethiodide and gave D(+)-2-*dimethylaminopropyl acetate ethiodide* (2·0 g.), m.p. 90–91°, $[\alpha]_D^{25\cdot6}$ + 11·39° (*c* 5·0 in EtOH) (Found: C, 35·6; H, 7·0; N, 4·4 per cent; equiv., 303. $C_9H_{20}INO_2$ requires C, 35·9; H, 6·7; N, 4·7 per cent; equiv., 301).

L(−)-2-*Dimethylaminopropyl succinate methiodide.* L(+)-2-Dimethylaminopropan-1-ol (3·3 g.) was converted to the hydrochloride and heated with succinyl chloride (2·6 g.) in chloroform saturated with dry hydrogen chloride (20 ml.) at 90–100° for 6 hr. The chloroform was removed by distillation under reduced pressure and excess of succinyl chloride decomposed with iced water (1 ml.). The residue was made strongly alkaline with saturated sodium hydroxide solution and excess of anhydrous sodium carbonate added. The mass was extracted with ether (5 × 100 ml.) and the combined ethereal extracts dried (anhyd. Na_2SO_4). The ether was removed by evaporation under reduced pressure and the residual liquid distilled to give a basic fraction (3·5 g.), b.p. 108–146° at 0·3–0·7 mm., $n_D^{23\cdot5}$ = 1·4508, which contained optically active 2-dimethylaminopropyl succinate (Calc. for $C_{14}H_{28}N_2O_4$ equiv., 144. Found: equiv., 157). The specific rotation based on the equivalent weight was $[\alpha]_D^{25}$ − 3·35° (*c* the equivalent of 5·1 pure L(−)-2-dimethylaminopropyl succinate in EtOH). A solution of this liquid (3·2 g.) in acetone (20 ml.) was treated with methyl iodide (4 ml.) and the solid obtained crystallised from methanol-acetone to give L(−)-2-*dimethylaminopropyl succinate methiodide* (3·9 g.), m.p. 201·5–202·5° (decomp.), $[\alpha]_D^{27\cdot6}$ − 7·32° (*c* 5·0 in MeOH) (Found: C, 33·2; H, 6·1; N, 4·9 per cent; equiv., 287. $C_{16}H_{34}I_2N_2O_4$ requires C, 33·6; H, 6·0; N, 4·9 per cent; equiv., 286).

L(−)-2-*Dimethylaminopropyl succinate ethiodide.* A solution of L(−)-2-dimethylaminopropyl succinate (2·9 g.) in ethanol (3 ml.) was treated with ethyl iodide (4 g.) and the mixture kept overnight at room temperature. The solid which separated was crystallised from methanol-acetone to give L(−)-2-*dimethylaminopropyl succinate ethiodide* (2·3 g.), m.p. 159·5–160·5°, $[\alpha]_D^{23\cdot5}$ − 10·08° (*c* 5·0 in MeOH) (Found: C, 36·4; H, 6·5; N, 4·8 per cent; equiv., 298. $C_{18}H_{38}I_2N_2O_4$ requires C, 36·0; H, 6·4; N, 4·7 per cent; equiv., 300).

D(+)-2-*Dimethylaminopropyl succinate methiodide.* D(−)-2-Dimethylaminopropan-1-ol (3 g.) was converted to D(+)-2-dimethylaminopropyl succinate by the method described for L(−)-2-dimethylaminopropyl succinate methiodide. The distillate (2·3 g.) was contaminated with non-basic material and had an equivalent weight of 194. The equivalent

weight of D(+)-2-dimethylaminopropyl succinate is 144 and on the basis of this the specific rotation of the D(+)-2-dimethylaminopropyl succinate obtained was $[\alpha]_D^{25}$ + 3·42° (*c* the equivalent of 5·1 pure D(+)-2-dimethylaminopropyl succinate in EtOH). A solution of this (2·2 g.) in acetone (20 ml.) was treated with methyl iodide (2 ml.) and the solid obtained was crystallised from methanol-acetone to give D(+)-2-*dimethylaminopropyl succinate methiodide* (2·3 g.), m.p. 200·5–201° (decomp.), $[\alpha]_D^{24.5}$ + 7·23° (*c* 5·0 in MeOH) (Found: C, 33·9; H, 6·0; N, 5·2 per cent; equiv., 285. $C_{16}H_{34}I_2N_2O_4$ requires C, 33·6; H, 6·0; N, 4·9 per cent; equiv., 286).

D(+)-2-*Dimethylaminopropyl succinate ethiodide.* D(+)-2-Dimethylaminopropyl succinate (2·8 g.) was treated with ethyl iodide (4·0 g.) and gave D(+)-2-*dimethylaminopropyl succinate ethiodide* (2·8 g.), m.p. 159·5–160·5°, $[\alpha]_D^{24.5}$ + 9·6° (*c* 5·0 in MeOH) (Found: C, 36·2; H, 6·5; N, 4·5 per cent; equiv., 300. $C_{18}H_{38}I_2N_2O_4$ requires C, 36·0; H 6·4; N, 4·7 per cent; equiv., 300).

2-*Dimethylaminopropyl succinate methiodide.* (±)-2-Dimethylaminopropan-1-ol (3 g.) was converted to the hydrochloride and esterified with succinyl chloride by the method described for L(−)-2-dimethylaminopropyl succinate methiodide. A basic liquid (2 g.) was obtained on distillation, b.p. 134–138° at 0·28 mm. (Calc. for $C_{14}H_{28}N_2O_4$ equiv., 144. Found: equiv., 160), consisting mainly of 2-dimethylaminopropyl succinate, identified by the *perchlorate*, m.p. 126·5–128·5° (from acetic acid) (Found: C, 33·7; H, 6·0; N, 6·0 per cent. $C_{14}H_{30}Cl_2N_2O_{12}$ requires C, 34·4; H, 6·2; N, 5·7 per cent). It appeared likely that the basic material was a mixture of *meso-* and racemic forms. This was established by a gas chromatographic analysis (Column: silicone fluid and Daltolac; length, 6 ft.; temperature, 215°; katharometer temperature, 154°; bridge current, 130 mA; carrier gas, N_2; flow rate, 2·2 litres/hr.; pressure: inlet, 496 mm. Hg; outlet, 70 mm. Hg). The chromatogram showed two separate, well-defined peaks of different magnitude indicating the presence of distinct compounds in unequal proportions. Quaternisation of the basic liquid (1·9 g.) in acetone (10 ml.) with methyl iodide (2ml.) gave 2-dimethylaminopropyl succinate methiodide (2·7 g.), m.p. 212–213° (decomp.) (Calc. for $C_{16}H_{34}I_2N_2O_4$ equiv., 286. Found: equiv., 284) (Rosnati, 1951, quotes m.p. 213–215°). This material was considered to consist of a mixture of the *meso-* and racemic forms of the compound which could not be separated by crystallisation.

2-*Dimethylaminopropyl succinate ethiodide.* A solution of 2-dimethylaminopropyl succinate (2 g.) in ethanol (3 ml.) was treated with ethyl iodide (4 g.) and allowed to stand at room temperature overnight. The solid which separated was crystallised from methanol-acetone to give a crystalline solid (2·5 g.), m.p. 176°. Further recrystallisation from methanol-acetone gave meso-2-*dimethylaminopropyl succinate ethiodide*, m.p. 189·5–190° (after 5 recrystallisations) (Found: C, 36·2; H, 6·4; N, 4·9 per cent; equiv., 299. $C_{18}H_{38}I_2N_2O_4$ requires C, 36·0; H, 6·4; N, 4·7 per cent; equiv., 300). From the mother liquor, a crystalline solid was obtained, m.p. 169·5–170° (Found: C, 36·2; H, 6·5; N, 4·6 per

cent; equiv., 300. $C_{18}H_{38}I_2N_2O_4$ requires C, 36·0; H, 6·4; N, 4·7 per cent; equiv., 300) and was assumed to consist essentially of racemic 2-dimethylaminopropyl succinate ethiodide.

1-*Dimethylaminoprop*-2-*yl succinate methiodide.* (±)-1-Dimethylaminopropan-2-ol (3 g.) was converted to the hydrochloride and esterified with succinyl chloride by the method described for L(−)-2-dimethylaminopropyl succinate methiodide. A basic liquid (2 g.), b.p. 145–185° at 1·3–1·5 mm., containing 1-dimethylaminoprop-2-yl succinate as *meso*- and racemic forms was obtained. This liquid was subjected to gas-chromatographic analysis (Column: silicone elastomer 10 per cent on alkali-treated Celite; length, 6 ft.; temperature, 165°; bridge current, 130 mA; carrier gas, N_2; flow rate, 2 litres/hr.; pressure: inlet, 518 mm. Hg; outlet, 24 mm. Hg). The chromatogram showed two well-defined peaks (the first being the smaller; retention times, 7·0 min. and 37 min. respectively) indicating the presence of two forms of 1-dimethylaminoprop-2-yl succinate in a ratio of about 1 : 5·5 (preliminary experiments suggest that the *meso*-form is present in the greater amount). The basic liquid was quaternised with methyl iodide (2 g.) to give a solid which on crystallisation from methanol gave 1-dimethylaminoprop-2-yl succinate methiodide (2 g.), m.p. 234·5–235·5° (decomp.) (Calc. for $C_{16}H_{34}I_2N_2O_4$ equiv., 286. Found: equiv. 289) [Rosnati, 1951, quotes m.p. 235°; Vanderhaeghe and Derudder, 1952, quote m.p. 224–226° (decomp.)]. This compound was assumed to be a mixture of *meso*- and racemic forms, the former predominating.

D-(−)-1-*Dimethylaminoprop*-2-*yl succinate methiodide.* (−)-1-Dimethylaminopropan-2-ol hydrogen (+)-tartrate (9 g.), $[\alpha]_D^{22.5}$ − 10·84° (*c* 4·9 in H_2O) was converted to (−)-1-dimethylaminopropan-2-ol hydrochloride and esterified with succinyl chloride by the method described for L(−)-2-dimethylaminopropyl succinate methiodide. A basic liquid (2·6 g.), b.p. 102–121° at 0·5–0·6 mm. (contaminated with non-basic material) was obtained (Calc. for $C_{14}H_{28}N_2O_4$ equiv., 144. Found: equiv., 175) having $[\alpha]_D^{24}$ − 12·5° (*c* the equivalent of 1·7 pure base in EtOH) calculated on the basis of the equivalent weight. A solution of the basic liquid (1 g.) in acetone (20 ml.) was treated with methyl iodide (2 ml.) and the solid which separated was crystallised from methanol-acetone to give *D*-(−)-1-*dimethylaminoprop*-2-*yl succinate methiodide* (1·6 g.), m.p. 246–247° (decomp.), $[\alpha]_D^{25}$ − 20·7° (*c* 2·0 in 90 per cent v/v MeOH) (Found: C, 33·7; H, 6·3; N, 4·9 per cent; equiv., 288. $C_{16}H_{34}I_2N_2O_4$ requires C, 33·6; H, 6·0; N, 4·9 per cent; equiv., 286).

L(+)-1-*Dimethylaminoprop*-2-*yl succinate methiodide.* (+)-1-Dimethylaminopropan-2-ol α-bromo-(+)-camphor-π-sulphonate (16·2 g.), $[\alpha]_D^{23}$ + 81·0° (*c* 1·0 in H_2O) was converted to (+)-1-dimethylaminopropan-2-ol hydrochloride and esterified with succinyl chloride. A basic liquid (1·7 g.) was obtained on distillation, b.p. 102–112° at 0·6–0·8 mm. (Calc. for $C_{14}H_{28}N_2O_4$ equiv., 144. Found equiv., 179), having $[\alpha]_D^{24}$ + 12·5° (*c* the equivalent of 1·75 pure base in EtOH) calculated on the basis of the equivalent weight. A solution of the basic liquid in acetone was treated with methyl iodide and the solid which separated

was crystallised from methanol-acetone to give L-(+)-1-*dimethylaminoprop-2-yl succinate methiodide* (1·8 g.), m.p. 246–247° (decomp.), $[\alpha]_D^{25}$ + 20·3° (*c* 2·0 in 90 per cent v/v MeOH) (Found: C, 33·8; H, 6·1; N, 4·7 per cent; equiv., 288. $C_{16}H_{34}I_2N_2O_4$ requires C, 33·6; H, 6·0; N, 4·9 per cent; equiv., 286).

Equal parts of the (+)- and (−)-forms of the quaternary succinyl esters were crystallised from methanol-acetone. In this way the following were prepared: (±)-1-dimethylaminoprop-2-yl succinate methiodide, m.p. 253·5–254·5° (decomp.); (±)-2-dimethylaminopropyl succinate methiodide, m.p. 195–196° (decomp.); (±)-2-dimethylaminopropyl succinate ethiodide, m.p. 160–161°.

Gas-chromatographic analysis of the succinates of the (±), (+) *and* (−)-1-*dimethylaminopropan-2-ols.* To ascertain which of the two peaks, observed in the gas chromatographic analysis of 1-dimethylaminoprop-2-yl succinate, was associated with the racemic form, equal quantities (0·2 g.) of the optically active forms were mixed and subjected to gas-chromatographic analysis (conditions as described under 1-dimethylaminoprop-2-yl succinate methiodide). Two peaks of approximately equal magnitude were obtained having retention times of 7 and 30 min. respectively. This suggested the possible contamination of the optically active forms with the meso-form. The (+)- and (−)-1-dimethylaminoprop-2-yl succinates were also subjected to gas chromatographic analysis under the same conditions and in each case two peaks of approximately equal magnitude were obtained, retention times being 8 and 38 min. and 8 and 32 min. respectively.

The origin of the meso-form in the optically active 1-*dimethylaminoprop-2-yl succinates.* The gas-chromatographic analyses suggested that the formation of the meso form arose either during the interaction of the optically active 1-dimethylaminopropan-2-ols with succinyl chloride or on the chromatographic column during the gas-chromatographic analysis. The following experiments served to establish that the formation of the meso-1-dimethylaminoprop-2-yl succinate did not take place during the preparation of the succinates from the optically active amino-alcohols:

1. A solution of (+)-1-dimethylaminopropan-2-ol α-bromo-(+)-camphor-π-sulphonate (4·5 g.), $[\alpha]_D^{23}$ + 80·1° (*c* 1·0 in H_2O) in water was made alkaline with a saturated solution of sodium hydroxide (10 ml.), excess anhydrous sodium carbonate added and the solid mass extracted with ether (5 × 100 ml.). The ethereal extracts were dried (anhyd. Na_2SO_4), treated with methyl iodide (5 ml.) and the solid which separated was crystallised from ethanol-ether to give L-(+)-1-dimethylaminopropan-2-ol methiodide (2·4 g.), m.p. 177–178°, $[\alpha]_D^{24}$ + 29·7° (*c* 2·0 in 90 per cent v/v EtOH) (Calc. for $C_6H_{16}INO$ equiv., 245. Found: equiv., 244).

2. An ethereal extract of (+)-1-dimethylaminopropan-2-ol, prepared from the α-bromo-(+)-camphor-π-sulphonate (1·2 g.), was shaken with dilute hydrochloric acid (2 × 10 ml.) and the aqueous layer evaporated to dryness under reduced pressure. The residue was dissolved in water

(1 ml.), the solution made alkaline with a saturated solution of sodium hydroxide (1 ml.), excess anhydrous sodium carbonate added and the solid mass extracted with ether (5 × 50 ml.). The ethereal extracts were dried (anhyd. Na_2SO_4), treated with a solution of methyl iodide (1 ml.) in ethanol (10 ml.) and the solid which separated crystallised from ethanol-ether to give L-(+)-1-dimethylaminopropan-2-ol methiodide (0·6 g.), m.p. 178–179°, $[\alpha]_D^{20}$ + 28·9° (*c* 2·0 in 90 per cent v/v EtOH) (Calc. for $C_6H_{16}INO$ equiv., 245. Found: equiv., 244).

3. A solution of (+)-1-dimethylaminoprop-2-yl succinate methiodide (0·6 g.), m.p. 246–247° (decomp.), $[\alpha]_D^{23}$ + 21·0° (*c* 2·0 in 90 per cent v/v MeOH) in water (40 ml.) was boiled under reflux for 1hr., cooled, and passed through a basic ion-exchange column (Amberlite IRA-400, OH). The basic eluate was evaporated under reduced pressure to about 3 ml. and acidified with a solution of hydriodic acid (55 per cent w/v) (1·5 ml.) in ethanol (30 ml.). The solution was evaporated to dryness and the solid crystallised from ethanol-ether to give L-(+)-1-dimethylaminopropan-2-ol methiodide (0·4 g.), m.p. 179–180°, $[\alpha]_D^{23}$ + 28·5° (*c* 2·0 in 90 per cent v/v EtOH) (Calc. for $C_6H_{16}INO$ equiv., 245. Found: equiv., 245).

4. To confirm that the optical activity of L-(+)-1-dimethylaminopropan-2-ol methiodide was unaffected by passage through the ion-exchange column, a solution of L-(+)-1-dimethylaminopropan-2-ol methiodide (0·6 g.), m.p. 178–179°, $[\alpha]_D^{20}$ + 28·9° (*c* 2·0 in 90 per cent v/v EtOH), in water (40 ml.) was passed through the ion-exchange column and the basic eluate worked up as previously described to give L-(+)-1-dimethylaminopropan-2-ol methiodide (0·5 g.), m.p. 178–179°, $[\alpha]_D^{22.5}$ + 28·6° (*c* 2·0 in 90 per cent v/v EtOH) (Calc. for $C_6H_{16}INO$ equiv., 245. Found: equiv., 246).

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