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N-Quaternary Compounds. Part XXXVIII.* Syntheses and Chiroptical Properties of Some 2-Trimethylammoniopropan-1-ols

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The CD-spectra of some dimethylamino- and trimethylammoniopropan-1-ols have been discussed in terms of conformational preferences. The CD-spectra of 1,1-*gem*-diphenyl derivatives contain, in addition to the usual aromatic absorption at 210 – 220 nm and 250 – 270 nm, a third dichroic band at 230 nm. The origin of this band is discussed.

The circular dichroic absorption of some α-trimethylammonio carboxylic acids has recently been reported upon;[2] such studies have also been extended to α-trimethylammonio aldehydes.[3] In this report we describe chiroptical data for stereochemically related hydroxy derivatives; the latter are homologues of the biologically important choline molecule.

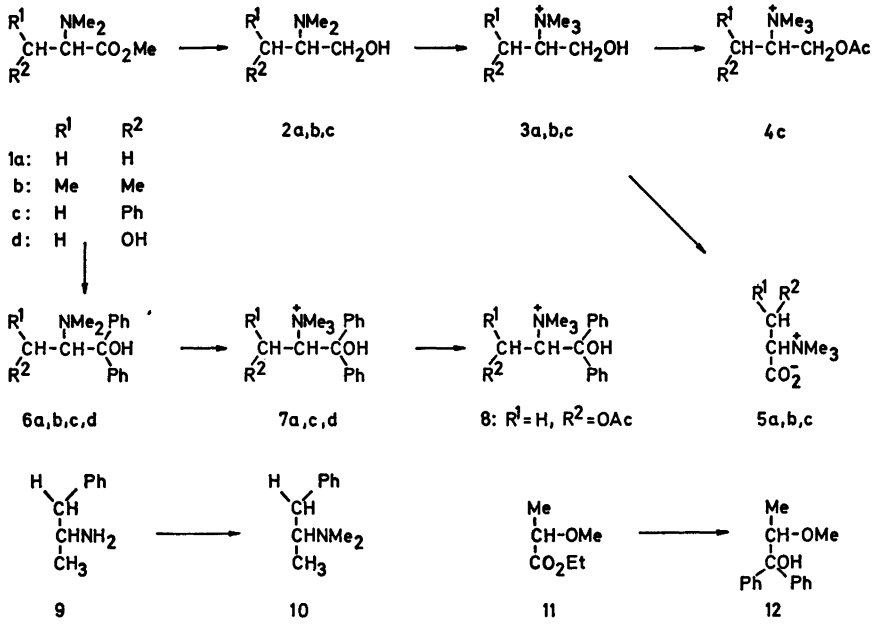
The syntheses of hydroxy analogues for the dichroic absorption studies are outlined in Scheme 1. α-Dimethylamino acids and their esters (*1*) are suitable starting materials as they are available in an enantiomerically pure form by reductive methylation of the respective optically active amino acid.[4,5] Lithium aluminium hydride reduction of (*S*)-*1* gave the alcohol (*2*) which was *N*-quaternised (*3*) by means of methyl iodide; acetylation gave the choline ester (*4c*). Acid permanganate oxidation of the aliphatic cholines (*3a*, *3b*) gave the corresponding α-trimethylammonio acids (*5a*, *5b*) with the same D-line rotation as previously found on direct quaternisation of the respective amino acids.[2] The specific rotation for the aromatic acid (*5c*) prepared from *3c*, however, was only half of that obtained after permethylation of phenylalanine.

The *gem*-diphenyl derivatives (*6*) were prepared from the esters (*S*)-*1* by treatment with phenyl lithium. The methiodides (*7a*, *7c*, *7d*) were available from the reaction of *6* with methyl iodide. The valine derivative (*6b*), however, failed to react presumably because of the added steric interference from the isopropyl group.

Quaternisation of *6d* with methyl iodide in acetic anhydride furnished the sterically less hindered mono-acetate (*8*).

The CD-curves for the aromatic cholines (*S*)-*3c* and (*S*)-*4c* were almost identical; therefore only the CD-curve for the acetate (*4c*) is reproduced (Fig. 1). The multiple Cotton effect due to the phenyl group in the 250 – 270 nm region is negative while the sign for its dimethylamino precursor (*S*)-*2c* is positive (Fig. 2). For comparison it is pointed out that the dichroic absorption is positive in the desoxy-analogues (*S*)-α-methyl-β-phenethylamine (*9*), its *N*,*N*-dimethyl derivative (*10*) as well as in acid salts and in the methiode.[6] By the definition of absolute configuration the actual group arrangements around the chiral carbon in the latter corresponds to that of their (*R*)-choline analogues; thus reduction of (*S*)-phenylalaninol gives (*R*)-α-methyl-β-phenethylamine. In agreement with the published report[6] (*R*)-α-*N*,*N*-trimethyl-β-phenethylamine (*10*) has

* Part XXXVII, see Ref. 1.



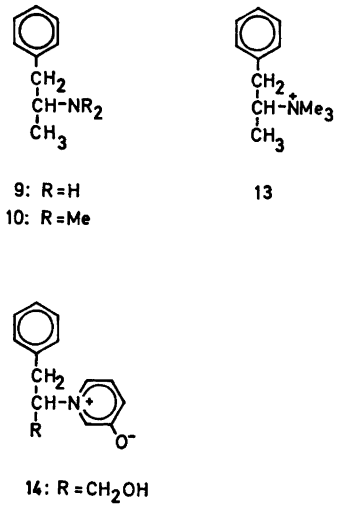
Scheme 1.

negative absorption in the 250 – 270 nm region and is thus opposite to that of its hydroxy analogue (*S*)-*2c*; *10* was prepared from (*R*)-(−)-amphetamine by reductive methylation.

A quadrant sector rule has been proposed for the prediction of the sign for the longest wavelength Cotton effect with the stereochemistry of α-phenylalkylamines. The rule has been established empirically by correlating the observed sign with preferred conformers in suitable model compounds.[7,8] The observed CD-sign for (*R*)-*10* is predicted by the rule (Fig. 2).[8] The conformational mobility in open chain structures, however, is considerable; hydroxylation such as in *2c* may well affect the conformational equilibrium which in its turn may alter the overall rotational sign. Besides the conformational aspects, the introduced hydroxy group may also directly interfere with the chiral absorption of the phenyl ring.

The considerable non-bonded interaction from the ammonium group in *3c* and *4c* is expected to favour *anti* conformational equilibria with respect to the phenyl group; this corresponds to the preferred conformational equilibrium of α-*N*,*N*-trimethyl-β-phenethylamine. The quadrant sector rule for the latter then predicts the observed longest wavelength rotation for *3c* and *4c*. Assignments of preferred conformations to be considered in the quadrant sector rule, however, are complicated by the conformational situation at the choline part of the molecule. It is known from conformational studies of choline and acetyl choline in solutions that an overwhelming predominance of the *gauche* form exists.[9] The *gauche* forms are sterically the most unfavourable but the electrostatic attraction between the cationic nitrogen atom and the oxygen atom is the more important. The conformational equilibrium, however, is sensitive to further steric interaction and α-substitution leads to increased population of *trans* forms.[10] Both *3c* and *4c* are to be regarded as α-substituted cholines and therefore probably will show little conformational preference for this part of the molecule.

A negative multiple Cotton effect in this region has also been found for the (*S*)-α-pyridinium analogue (*14*) of *3c*.[11] The strongly negative absorption for the pyridinium derivative in the 220 nm region has been reversed for the methylamino derivatives (*2c*, *3c*, *4c*). The intensity for the absorption below 220 nm is



Scheme 2.

much higher than at any other wavelength and in all cases gives the sign of the optical rotation in the visible part of the spectrum; this observation generally appears to be true.[8,12]

The CD-curves for the *gem*-diphenyl-dimethylamines (*6*) contain a negative multiple Cotton effect in the 250–270 nm region (Fig. 2). The CD-sign has been reversed in the methiodides (*7a* and *7d*) but has been retained in the phenyl analogue (*7c*). The sign for the latter is the same as in its phenylalaninol analogues (*3c* and *4c*) (Fig. 1). All the *gem*-diphenyl derivatives have strongly positive dichroic absorption at or below 220 nm. This represents the usual strong $\pi \rightarrow \pi^*$ absorption in phenyl derivatives. In addition dichroic absorption bands are present in the 230–235 nm region. The sign is negative for the dimethylamines (*6*) and is reversed for the methiodides (*7a* and *7d*). In the acetate (*8*), prepared from *7d*, the dichroic absorption is again negative and the maximum position has undergone a slight hypsochromic shift. The spectrum of the triphenyl derivative (*7c*) has no specific band seen at this wavelength. The absorption in this case, however, may well be hidden under the broad and overlapping 220 nm band (Fig. 1). The UV spectra for *6* and *7* are very similar to that of the α-methoxy analogue shown in Fig. 3; in no case was a separate UV-band detectable in the 230 nm region.

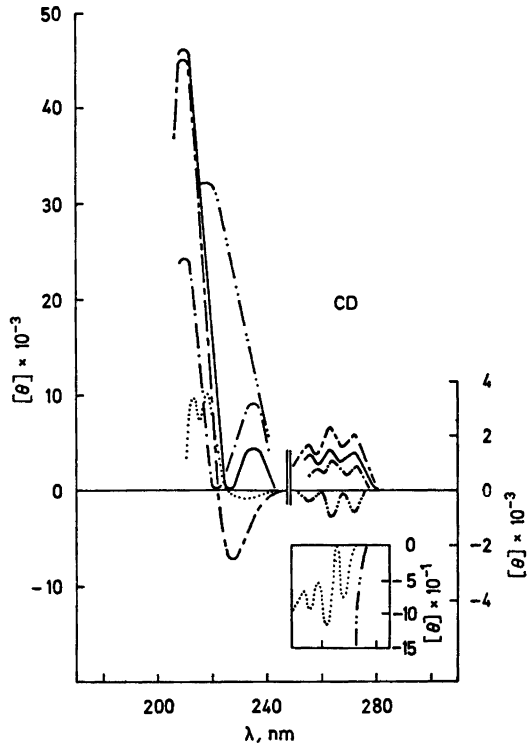


Fig. 1. CD-curves in methanol for (*S*)-3-Phenyl-2-*N*,*N*,*N*-trimethylammoniopropyl-1-acetate iodide (*4c*) · · · ; (*S*)-3-acetoxy-1,1-diphenyl-2-*N*,*N*,*N*-trimethylammoniopropan-1-ol iodide (*8*) – – – –; (*S*)-1,1-diphenyl-2-*N*,*N*,*N*-trimethylammoniopropan-1-ol iodides: (*7a*) –· – ·; (*7c*) – · · – · · and (*7d*) ———.

In the phenylalaninol derivatives (*2c*, *3c*, and *4c*) weakly dichroic bands are present in this region. These absorption bands are broad and have been shifted to about 240 nm. A common feature for these molecules is the presence of an aliphatic hydroxy group. On the other hand the spectra of a series of 1-phenyl-3-dialkylamino-propan-1-ols do not contain any aromatic dichroic absorption outside the 210–220 nm and the 250–270 nm regions.[13] The phenethylamine analogue (*10*) shows no dichroic absorption in this area nor has such absorption been reported in simple phenethylamines.[6,8] This absorption is also absent in such close analogues as the *gem*-diphenyl derivative 1,1,2-triphenylethylamine hydrochloride and in 2,3-diphenyl-1-methylpropylamine hydrochloride.[8] The hydroxy group itself does not absorb

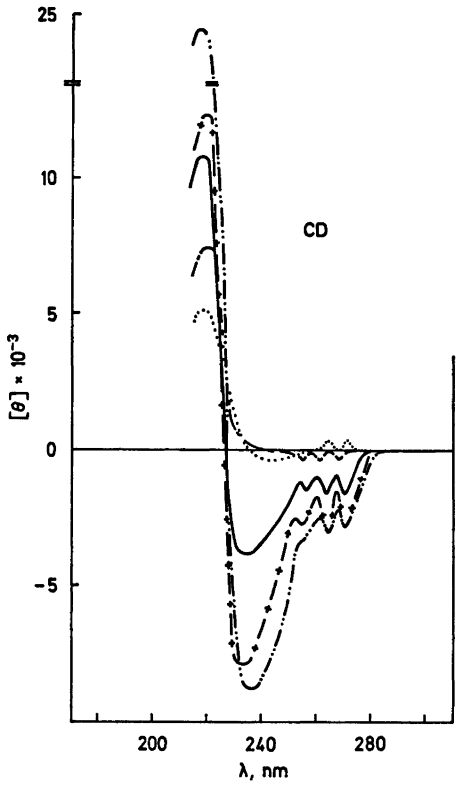


Fig. 2. CD curves in methanol for (*S*)-2-*N*,*N*-dimethylamino-3-phenylpropan-1-ol (*2c*) ····; (*R*)-α-*N*,*N*-trimethyl-β-phenethylamine (*10*) – – – –; (*S*)-1,1-diphenyl-2-*N*,*N*-dimethylaminopropan-1-ols: (*6a*) – + – +, (*6c*) – ·· – ·· and (*6d*) ———.

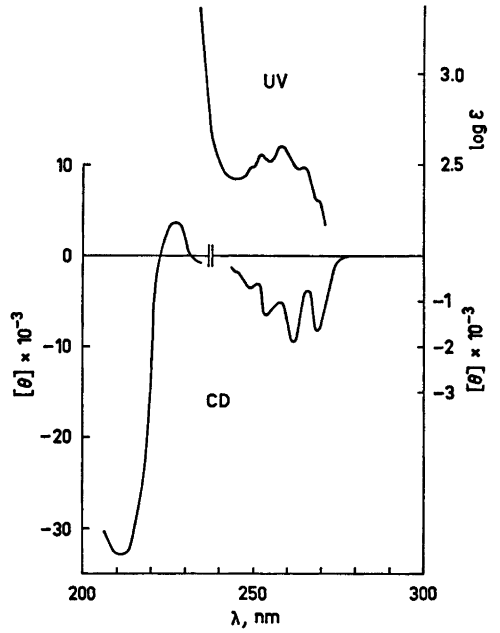


Fig. 3. CD and UV curves in methanol for (*S*)-1,1-diphenyl-2-methoxypropan-1-ol (*12*).

in this wavelength region. The amino function may be replaced by other groups; thus the α-methoxy analogue (*12*) shows dichroic absorption which relative to that of its closest analogue (*6a*) has undergone a hypsochromic shift (233→226 nm). The methoxy analogue (*12*) has the (*S*)-configuration (Scheme 1); it has the same sign for the 250 nm bands as (*S*)-*6a* but at the other maxima the signs are reversed. It is concluded that the dichroic band at about 230 nm is due to the two aromatic chromophores in the *gem*-diphenyl derivatives. The Cotton effect may be associated with some form of dipole-dipole interaction between the two aromatic chromophores. This is reminiscent of the interaction between a benzoate group and another aromatic chromophore but should split the dichroic absorption into two curves of opposite sign.[14] Inspection of the spectra shows that the other half of the band could well be hidden under the strong 210–220 nm band. A closer inspection of the spectra also shows that the intensities and the positions of the maxima varies slightly, despite the fact that the aromatic chromophore is the same. Any vicinal interaction by homoconjugation between the *gem*-phenyl groups over the two sigma bonds[8] does not alter the fact that the aromatic chromophore is the same in these derivatives. It is therefore suggested that the 230 nm band arises as a result of the dichroic absorption of a second major conformer in solution. Support for this view was sought in the studies of the effect of temperature on the 233 nm dichroic band for *6a* and *7a*. The absorption intensity was found to increase slightly with decrease in temperature while the positions of the maxima were hardly affected. The data for *6a* were: $[\theta]_{233} = -5.7 \times 10^3$ (+58 °C), $= -7.6 \times 10^3$ (+25 °C), $= -1.1 \times 10^4$ (−28 °C); for *7a*: $[\theta]_{233} = +7.4 \times 10^3$ (+62 °C), $= +9.8 \times 10^3$ (+25 °C), $+1.3 \times 10^4$ (−28 °C). The data can be interpreted in terms of changes in conforma-

tional equilibria; alteration in solvation equilibria, which may vary from compound to compound, also has to be considered.

The Cotton effects are dependent on the relative orientation of the phenyl groups with respect to one another (screwness) and in this respect the *gem*-diphenyl derivatives resemble optically active biphenyls.[15] The preferred orientation of the phenyl groups are further controlled by the group sequence through steric or electronic interaction with the other groups attached to the chiral centre. It is thus understandable that the preferred orientation of the phenyl groups will be sensitive to major alteration in the groups attached to the chiral carbon. This is illustrated by the *N*-quaternisation of *6* to the ammonium analogues (*7*); the CD-spectra are different.

EXPERIMENTAL

The CD measurements were carried out with a Jasco Automatic Spectropolarimeter Model J-10. The cell lengths were 1, 2, and 10 mm and the temperature 27 °C. The concentrations were in the range 0.2 – 0.4 g/l.

The NMR data were recorded on a 60 MHz Varian A-60A instrument.

Syntheses: Syntheses of the esters (*1a*, *1b*, *1c*) have previously been described.[2]

(S)-N,N-Dimethylserine methyl ester (1d). (*S*)-Serine methyl ester (0.1 mol) and 35 % formalin (30 ml) were added to water (180 ml) and hydrogenated over 5 % Pd/C (5 g) for 16 h at atmospheric pressure. Conc. HCl (15 ml) was then added, the catalyst filtered off and the filtrate evaporated at reduced pressure. The residue was triturated with acetone/ether before dissolution by heating in methanol. A little undissolved material was removed by filtration before the filtrate was concentrated to about 40 ml. To this solution, cooled in an ice-bath, was added trimethylamine (12 g) in methanol (20 ml) followed by ether (400 ml). The precipitated salt was removed by filtration, the filtrate evaporated and the residue distilled to give the title compound in 51 % yield, b.p. 90 °C/11 mmHg (lit.[16] for DL-isomer gives b.p. 108 – 109 °C/25 mmHg). (Found: C 48.76; H 8.92. Calc. for $C_6H_{13}NO_3$: C 48.96; H 8.90); $[\alpha]_D = +4.0°$ ($c = 1.9$ in 2 N HCl); τ(CDCl$_3$) 7.6 (NMe), 6.3 (OMe).

(S)-2-N,N-Dimethylamino-3-methylbutan-1-ol.HI (2b). A solution of (*S*)-*N,N*-dimethylvaline methyl ester (0.023 mol) in anhydrous ether (50 ml) was added dropwise over 10 min to lithium aluminium hydride (0.048 mol) in anhydrous ether (550 mol). The reaction mixture was heated under reflux for 5 h before the excess hydride was destroyed by dropwise addition of saturated sodium sulfate solution with ice-cooling. The ether phase was washed and dried and gave on evaporation 52 % of the alcohol. This material was used in the consecutive reaction without further purification.

For analytical purposes part of this material was dissolved in 10 % HI (50 ml) and the solution filtered before evaporation. The residual material was crystallized from acetone, m.p. 135 °C. (Found: C 32.26; H 6.78. Calc. for $C_7H_{17}NO.HI$: C 32.45; H 6.61); $[\alpha]_D = +6.2°$ ($c = 1.2$ in 2 N HCl).

(S)-2-N,N-Dimethylaminopropan-1-ol.HI (2a) was synthesised from (*S*)-*N,N*-dimethylalanine methyl ester as (*2b*) above, m.p. 110 – 112 °C (acetone/ether). (Found: C 26.02; H 6.18. Calc. for $C_5H_{13}NO.HI$: C 25.98; H 6.10); $[\alpha]_D = +13.7°$ ($c = 0.7$ in 2 N HCl).

(S)-2-N,N-Dimethylamino-3-phenylpropan-1-ol (2c) was prepared in the same way from the corresponding methyl ester; properties as described.[4]

(S)-1,1-Diphenyl-2-N,N-dimethylamino-3-methylbutan-1-ol (6b). The free base of (*S*)-*N,N*-dimethylvaline methyl ester was initially prepared from its HCl-salt as follows: The salt (0.061 mol) in methanol solution (30 ml) was ice-cooled and a solution of anhydrous trimethylamine (11 g) in methanol (20 ml) added gradually with stirring. Ether (400 ml) was then added, the precipitated salt was filtered off, the filtrate was evaporated and the residual ester distilled, b.p. 84 – 85 °C/75 mmHg.

Part of the methyl ester thus obtained (0.022 mol) was dissolved in anhydrous ether and a 0.33 M solution (150 ml) of phenyl lithium in ether [17] added dropwise with stirring under N_2-atmosphere. The reaction mixture was then heated under reflux for 4 h. The cold etheral solution was extracted with 6 N HCl (6 × 15 ml), the aqueous extracts made alkaline by addition of solid sodium carbonate and the title compound extracted into chloroform. Evaporation of the washed and dried chloroform solution yielded a solid (94 %), m.p. 65 °C. This material was used in the consecutive reaction step without further purification.

For analyses part of the product was dissolved in methanol and converted to its HCl-salt by addition of 5 N HCl. Evaporation left a solid material which was recrystallized from methanol/acetone, m.p. 212 °C. (Found: C 71.36; H 8.03. Calc. for $C_{19}H_{25}NO.HCl$: C 71.33; H 8.19); $[\alpha]_D = +48.0°$ ($c = 1.1$ in 2 N HCl/MeOH (1:1)); τ (TFA) 7.0 and 6.8 (NMe), 2.4 (Ph).

(S)-1,1-Diphenyl-2-N,N-dimethylaminopropan-1-ol (6a) was prepared from *N,N*-dimethylalanine methyl ester as above in 56 % yield; m.p. 61 °C (isoPrOH/water) [lit.[18] for DL-isomer m.p. 65 – 66 °C]. (Found: C 80.25; H 8.19. Calc. for $C_{17}H_{21}NO$: C 79.98; H 8.29); $[\alpha]_D = +54.5°$ ($c = 1.2$ in 2 N HCl); τ (CDCl$_3$), 7.9 (NMe), 2.6 (Ph).

*(S)-1,1,3-Triphenyl-2-*N,N-*dimethylaminopropan-1-ol (*6c*)* was prepared from *N,N*-dimetylphenylalanine methyl ester as above in 81 % yield. For analysis part of the product was crystallized as its HCl-salt, m.p. 209 °C (MeOH/acetone/pet. ether). (Found: C 74.96; H 7.19. Calc. for $C_{23}H_{25}NO.HCl$: C 75.09; H 7.12); $[\alpha]_D = +67.1$ ($c = 0.6$ in MeOH); τ ($CDCl_3$) 7.9 (NMe), 2.7 (Ph).

*(S)-1,1-Diphenyl-2-*N,N-*dimethylaminopropan-1,3-diol (*6d*)* was prepared as above from *N,N*-dimethylserine methyl ester in 40 % yield, m.p. 147–148 °C (isoPrOH). (Found: C 74.75; H 7.71. Calc. for $C_{17}H_{21}NO_2$: C 75.23; H 7.79); $[\alpha]_D = +11.3°$ ($c = 1.2$ in 2 N HCl/MeOH (1:1); τ ($CDCl_3$) 7.7 (NMe), 2.7 (Ph).

N-Quaternisation of the dimethylamines

A solution of the *N,N*-dimethylamino derivative (0.015 mol) and methyl iodide (0.03 mol) in nitromethane (20 ml) was kept at 40 °C in a pressure bottle for 20 h. The solution was then concentrated to about 5 ml and ether (150 ml) added. The precipitated methiodide was collected and recrystallized as described for each individual compound below.

*(S)-2-*N,N,N-*Trimethylammoniopropan-1-ol iodide (*3a*)*. Yield 50 %, m.p. 289 °C (acetone) [lit.[19] m.p. 299 °C]; $[\alpha]_D = -2.6°$ ($c = 1.1$ in 2 N HCl); τ (TFA) 6.7 (NMe).

*(S)-3-Methyl-2-*N,N,N-*trimethylammoniobutan-1-ol iodide (*3b*)*. Yield 97 %, m.p. 224–225 °C (acetone) [lit.[20] for DL-isomer 191–195 °C]; (Found: C 35.04; H 7.48. Calc. for $C_8H_{20}INO$: C 35.17; H 7.38); $[\alpha]_D = +8.6°$ ($c = 1.0$ in 2 N HCl); τ (TFA) 6.6 (NMe).

*(S)-3-Phenyl-2-*N,N,N-*trimethylammoniopropan-1-ol iodide (*3c*)* was prepared as above; properties as described.[4]

*(S)-1,1-Diphenyl-2-*N,N,N-*trimethylammoniopropan-1-ol iodide (*7a*)*. Yield 90 %, m.p. 220 °C (isoPrOH: MeOH) [lit.[18] for DL-isomer m.p. 205 °C]. (Found: C 54.09; H 6.17. Calc. for $C_{18}H_{24}INO$: C 54.38; H 6.09); $[\alpha]_D = +18.7°$ ($c = 1.1$ in 2 N HCl/MeOH (1:1); τ (TFA): 6.9 (NMe), 2.6 (Ph).

*(S)-1,1,3-Triphenyl-2-*N,N,N-*trimethylammonio-propan-1-ol iodide (*7c*)*. Yield 59 %, m.p. 138–140 °C (H_2O). (Found: C 60.40; H 5.90. Calc. for $C_{24}H_{28}INO$: C 60.89; H 5.96); $[\alpha]_D = +23.5°$ ($c = 0.6$ in MeOH); τ (TFA/$CDCl_3$) 6.9 (NMe), 2.7 (Ph).

*(S)-1,1-Diphenyl-2-*N,N,N-*trimethylammoniopropane-1,3-diol iodide (*7d*)*. Yield 74 %, m.p. 192 °C (isoPrOH/Ether). (Found: C 51.90; H 5.76. Calc. for $C_{18}H_{24}INO_2$: C 52.31; H 5.85; $[\alpha]_D = +39.7°$ ($c = 1.1$ in 2 N HCl/MeOH (1:1); τ (TFA) 6.7 (NMe).

*(S)-3-Phenyl-2-*N,N,N-*trimethylammoniopropyl-1-acetate iodide (*4c*)*. (*S*)-2-*N,N*-Dimethylamino-3-phenylpropan-1-ol (0.0035 mol) and methyl iodide (0.007 mol) in acetic anhydride (40 ml) were heated in a pressure bottle at 80 °C for 4 h. The solution was then evaporated at reduced pressure almost to dryness and the product precipitated by ether (200 ml) addition; yield 97 %, m.p. 238 °C (EtOH); (Found: C; 46.17; H 6.05. Calc. for $C_{14}H_{22}INO_2$: C 46.29 H 6.10); $[\alpha]_D = +18.5°$ ($c = 1.0$ in 2 N HCl); τ (TFA) 7.7 (MeCO), 6.5 (NMe), 2.6 (Ph); (KBr) 1721 cm^{-1} (CO).

*(S)-3-Acetoxy-1,1-diphenyl-2-*N,N,N-*trimethylammoniopropan-1-ol iodide (*8*)* was prepared as (*4c*) above from (*6d*); yield 74 %, m.p. 203 °C (EtOH); (Found: C 52.55; H 5.48. Calc. for $C_{20}H_{26}INO_3$: C 52.76; H 5.75); $[\alpha]_D = +25.1°$ ($c = 1.1$ in 2 N HCl/MeOH (1:1); τ (TFA) 7.8 (MeCO), 6.7 (NMe), 2.6 (Ph); (KBr) 1745 cm^{-1} (CO).

(*S*)-*N,N,N*-Trimethylammoniopropionic acids (5)

The *N*-quaternary amino-alcohol (*3*) (0.001 mol) and potassium permanganate (0.002 mol) were added to 4 N H_2SO_4 (20 ml) and the resultant solution kept at 60 °C for 40 min. An aqueous solution of barium chloride was added dropwise to the cold reaction mixture to remove the sulfate ions. The reaction mixture was further worked up as previously described; properties: (*5a*), m.p. 202–204 °C; $[\alpha]_D = -19.5°$ (2 N HCl), lit.[2] −20.3°; (*5b*), m.p. 196–199 °C; $[\alpha]_D = +18.7°$ (2 N HCl), lit.[2] +18.9°; (*5c*), m.p. 192–194 °C; $[\alpha]_D = +27.5°$ (2 N HCl), lit.[2] +51.0°.

*(R)-α-*N,N-*Trimethyl-β-phenethylamine (*10*)*. L-Amphetamine (0.05 mol) in a solution of methanol (75 ml), water (30 ml) and 35 % formaline (40 ml) was hydrogenated at atmospheric pressure over 5 % Pd/C (5 g) until the hydrogen uptake had ceased. The catalyst was then removed by filtration, conc. HCl (5 ml) added and the solution evaporated to dryness at reduced pressure. The residual material was redissolved in methanol (20 ml) containing triethylamine (6 ml) and the solution poured into ether (200 ml). The precipitate was removed by filtration and the filtrate evaporated and the residual material distilled; b.p. 88 °C/9 mmHg [lit.[21] b.p. 72–74 °C/2.5 mmHg], yield 47 %. (Found: C 81.21; H 10.60. Calc. for $C_{11}H_{17}N$: C 80.95; H 10.50); $[\alpha]_D = +7.8°$ ($c = 2.6$ in MeOH).

*(S)-1,1-Diphenyl-2-methoxypropan-1-ol (*12*)* was prepared according to the procedure described for (*6*) above by treatment of ethyl L(−)-α-methoxy-lactate[22] with phenyl lithium in ether; yield 40 %, m.p. 72 °C (pet. ether) (Found: C 79.55; H 7.48. Calc. for $C_{16}H_{18}O_2$: C 79.31; H 7.49); $[\alpha]_D = -91°$ ($c = 1.4$ in MeOH); τ ($CDCl_3$) 9.0 (Me), 6.7 (OMe), 5.8 (CH), 2.8 (Ph).

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