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N-QUATERNARY COMPOUNDS—IXL

CIRCULAR DICHROISM OF α-TRIMETHYLAMMONIO ALDEHYDES

M. GACEK and K. UNDHEIM*

Department of Chemistry, University of Oslo, Oslo 3, Norway

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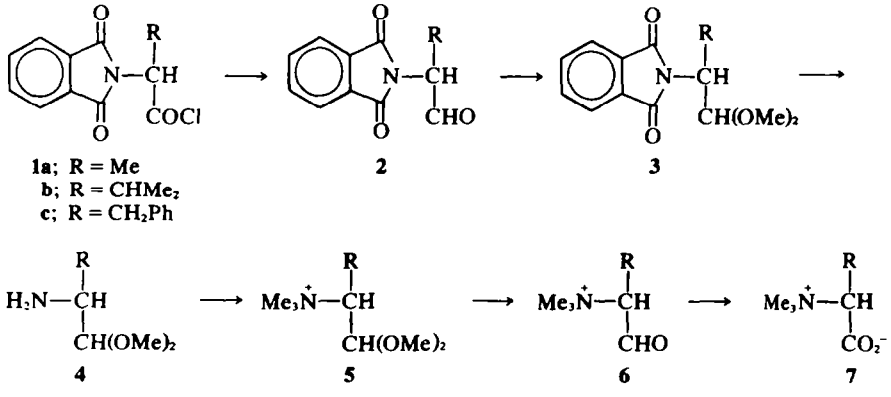
Abstract—(S)-α-Trimethylammonio aldehydes have been synthesised over several steps from corresponding amino acids. The dichroic carbonyl absorption can be rationalised in terms of the Octant Rule with the assumption of a preferred conformation. The chiroptical properties of intermediate α-phthalimido aldehydes have also been investigated.

Recently we have reported on the CD absorption of some α-trimethylammonio carboxylic acids[2] and corresponding hydroxy compounds formed by reduction of the carboxylic group;[1] the latter are analogues of the biologically important choline molecule. Cholines are biologically oxidised to the corresponding betaines; the oxidation is thought to proceed over the aldehyde as an intermediate.[3,4] For stereochemical correlations of such molecules with chiroptical data, we herein report an extension of our studies[1,2] to α-trimethylammonio aldehydes **6**.

The synthetic pathway worked out to the desired optically active ammonio aldehydes is shown in Scheme 1. N-phthaloyl protected amino acids of the L-configuration were converted into the respective acid chlorides by means of thionyl chloride.[5,6] We found it advantageous to use methylene chloride as solvent in this reaction in which case the acid chloride **1** was obtained in a crystalline and pure state. Rosenmund reduction of **1** by heating at 110° for 10 hr furnished the aldehyde **2**. A significant degree of racemisation was a possibility in the reduction due to the relatively vigorous reaction conditions. Milder and different reaction conditions were therefore thought advisable. A suitable reagent for this purpose was found in tri-t-butoxyaluminium hydride;[8] selective reduction of the acid chloride group was thus achieved in diglyme at −70°. The optical purities of the products from both methods, however, were similar suggesting insignificant racemisation.

The formyl group in **2** was protected by dimethyl acetal formation (**3**) before removal of the phthaloyl group by the usual hydrazine treatment. The low boiling α-amino dimethyl acetal (**4**) formed could be distilled without racemisation. Compound **4** was permethylated (**5**) by means of methyl iodide in methanol in the presence of magnesium oxide. Alkaline reaction conditions are to be avoided because of the ease of racemisation of **5**. Not unexpectedly, the reaction is sensitive to steric effects; the reaction rate varies with the R-substituent. Thus the isopropyl derivative (**4b**) reacted markedly more slowly than did the methyl (**4a**) and benzyl (**4c**) analogues. The isopropyl derivative (**5b**) was relatively optically stable under the reaction conditions; the permethylation was therefore allowed to proceed almost to completion. The benzyl derivative, activated by the phenyl group, was extensively racemised, the reaction was therefore stopped



SCHEME 1.

when only partially completed. Racemisation of the latter was complete after 30 hr. The methyl analogue (**5a**) showed intermediate optical stability.

NMR studies of the acetals (**5**) in trifluoroacetic acid (TFA) showed that the acetal group was cleaved slowly with liberation of the formyl function. This observation was made use of in preparative work; (**5**) was heated for a short time in TFA to yield the aldehydes (**6**). The optical data for the latter suggested that the aromatic member (**6c**) was largely racemised. Further information on the relative optical purities of the products was therefore sought. For this purpose the aldehydes (**6**) were oxidised by means of acid permanganate to the corresponding carboxylic acids (**7**); the latter have previously been prepared by methylation of the respective amino acids.[2] The specific sodium D-line rotations for the oxidation products (**7**) were 50% (**7a**), 43% (**7b**) and 7% (**7c**) relative to the values previously reported.[2] Partial racemisation during the oxidation step is likely to have occurred. The major racemisation, however, is thought to have occurred during the permethylation reaction (**5**).

In view of the optical labilities of products herein discussed the emphasis will be on rotational signs and positional maxima. In fact, the extensive racemisation of **6c** made interpretation of the recorded CD-curves uncertain; further discussions of this class of compounds are therefore limited to **6a** and **6b**.

The study of the chiroptical properties in asymmetric surroundings of the keto-carbonyl group has been basic in the understanding and development of ORD and CD theories as applied to organic molecules. Little attention, however, appears to have been paid to the asymmetrically perturbed formyl group.[9-11] The saturated CO group in both ketones and aldehydes has a weak UV absorption band in the region 290–300 nm; this absorption is optically active in asymmetric surroundings. In simple Me-substituted aliphatic aldehydes the sign of the Cotton effect in this region has been found to depend on the distance between the chiral centre and the CO chromophore.[9,10] The (S)-α-trimethylammonio aldehydes (**6a** and **6b**) have the chiral centre on the α-carbon; they both display a positive dichroic absorption in acetonitrile at 298 nm (Fig 1). The nearest UV band was observed as a shoulder at 285 nm. The hypsochromic shift from the CD-maximum is presumably due to a mathematical effect arising by the addition of a weak absorption band in the CD-region to a strong UV band at a lower wavelength. In methanol and isopropanol the ellipticities of **6b** were reduced with 95% and 10% respectively in comparison with the value in acetonitrile solution. Already in isopropanol the dichroic absorption of **6a** had disappeared. These observations are attributed to the disappearance of the CO chromophore through hemiacetal formation;[12] some acetal formation is also possible. This is an equilibrium reaction and the equilibrium positions depend among other factors on the steric crowding in the adducts; the non-bonded interaction is a function of the substituents in the carbonyl compound as well as in the alcohol. The trend in the above observations is therefore as expected.

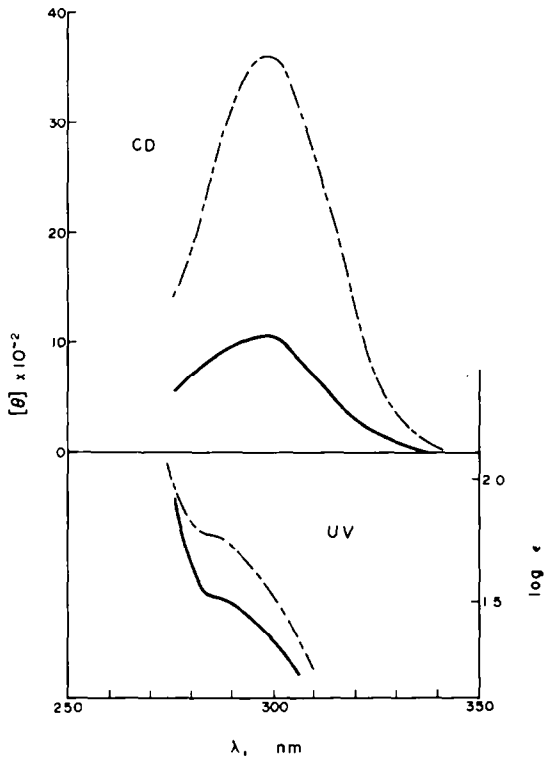


Fig 1. CD and UV curves in acetonitrile for (S) - α - trimethylammonio aldehyde iodides; **6a** ——, **6b** – – –.

It was natural to extend the CD studies of α-substituted aldehydes to the (S)-phthalimido derivatives **2** (Fig 2). Several CD bands are present in the spectra recorded in acetonitrile. A double band with negative maxima at 314–317 and 324–326 nm is ascribed to the phthalimido chromophore.[13] The assignment is supported by the presence of this band in the CD-spectra of the dimethylacetals (**3**) which were recorded in methanol (Fig 3). The electronic transitions for these bands in UV, however, were too weak to be detected. In the phthaloyl derivatives of aliphatic α-amino acids two corresponding bands are observed but these are of opposite sign; the spectrum of the phenylalanine derivative was less resolved with the highest wavelength absorption as a broad band at 280 nm.[13]

The phthalimido chromophore in **2** and **3** also gives rise to dichroic absorption at lower wavelengths. In the acetals (**3**) the absorption is positive with maximum about 280 nm, in the aldehydes (**2**) negative with maxima in the region 285–288 nm. In addition, the aliphatic aldehydes (**2**) display a positive dichroic band at 300 nm which is absent in the acetals (**3**). The positional maxima are as expected for saturated CO absorption and correspond closely to the dichroic bands in the α-trimethylammonio aldehydes (**6**); the dichroic absorption at 300 nm is therefore ascribed to the formyl group. The CO band, however, was not observed for the aromatic derivative **2c**. Presumably this absorption band positionally overlaps the stronger dic-

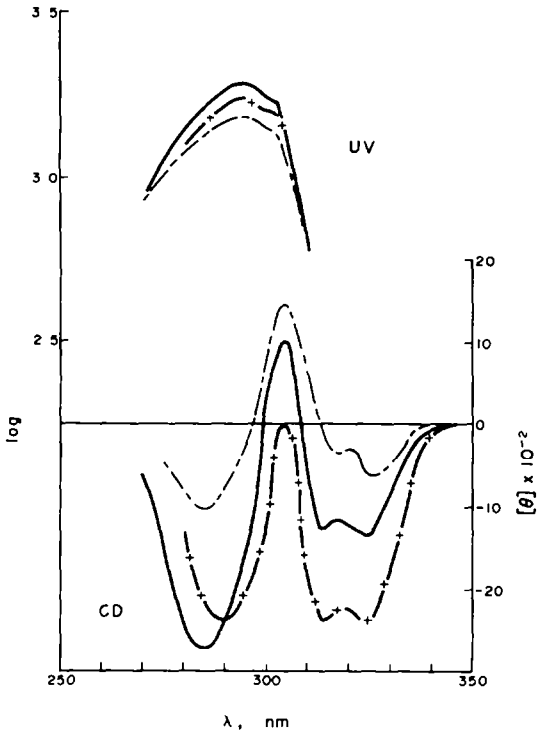


Fig 2. CD and UV curves in acetonitrile for (S) - α - phthalimido aldehydes; **2a** ———, **2b** – – – –, **2c** — + — + .

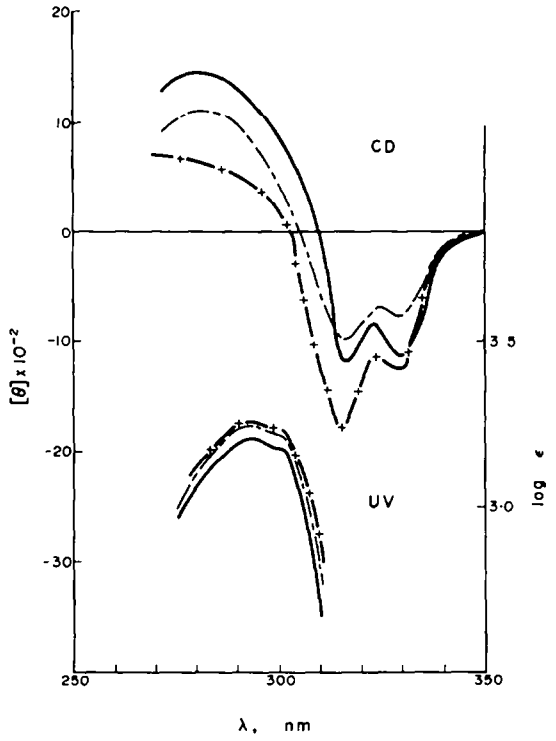


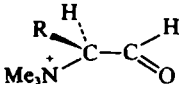
Fig 3. CD and UV curves in methanol for (S) - α - phthalimido dimethylacetals; **3a** ———, **3b** – – – –, **3c** — + — + .

hroic absorption at lower wavelength; the positional maximum of the latter is seen to have undergone a slight bathochromic shift in comparison with the aliphatic analogues (Fig 2).

The CD-curves of the aldehydes (**2**) in methanol contain no CO band at 300 nm. The CD curves are very similar to those of the acetals except for a bathochromic shift of the 281 nm band (**3**) to 291 nm; the results are in keeping with hemiacetal formation.

The $n \rightarrow \pi^*$ transition in the 245–250 nm region of the CO group in acid chlorides has recently been reported to be optically active.[14] Unfortunately the CD curves of the acid chlorides (**1**) could not be recorded in this region. In the other end of the spectrum, however, the dichroic absorption of the phthalimido chromophore has undergone a hypsochromic shift with new maxima at 294 and 304 nm. In addition the aliphatic analogues display a shoulder at 317 nm; the UV maxima were at 292 and 294 nm.

The signs of the Cotton effect of the CO group in the aldehydes (**2** and **6**) can be rationalised in terms of the Octant Rule if these molecules are assumed to adopt a preferred conformation. In amino acids and in hydroxy acids preferential conformations are assumed in which the carboxyl group is coplanar with the amino or hydroxy substituents.[15] For α-halo ketones and α-halo esters the synperiplanar conformation is the more stable while α-halo acid amides in solution prefer the antiperiplanar conformation.[16] The trimethylammonium group is bulky. In the α-trimethylammonio carboxylic acids previously studied we therefore postulated the preference for a major conformer in which the ammonium group preferably assumes a conformation in which it becomes coplanar with the carboxyl group. It is further tempting to postulate similar preferable conformations for the aldehydes (**6**) in which the ammonium group eclipses the CO oxygen (Scheme 2). Presumably electrostatic attraction between



SCHEME 2.

the quaternary N atom and the basic CO oxygen atom would add to the stabilisation of such a conformer. Analysis of this conformer according to the Octant Rule shows that the R-group falls in the far upper left octant; the rule therefore predicts the observed, positive Cotton effect. As the α-phthalimido aldehydes (**2**) also gave rise to a positive dichroic absorption for the CO group a similar conformational preference is suggested.

EXPERIMENTAL

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

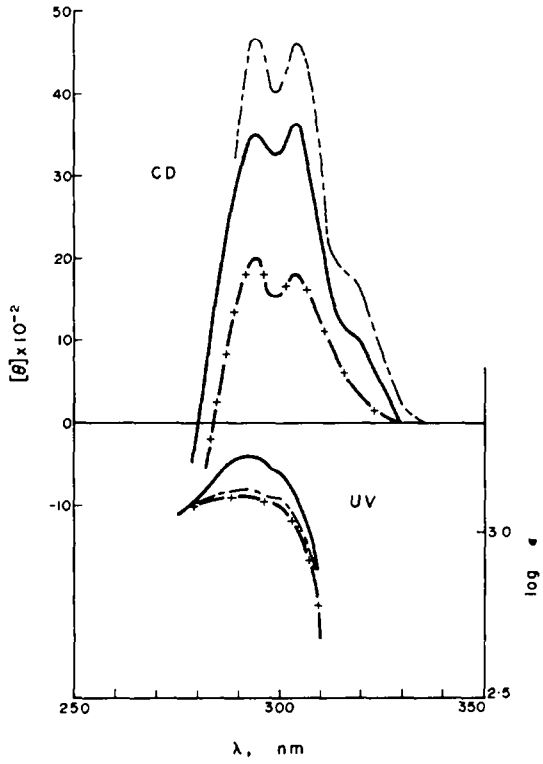


Fig 4. CD and UV curves in acetonitrile for (S) - α - phthalimido acid chlorides; **1a** ———, **1b** — — —, **1c** — + — + .

The NMR spectra were recorded with a Varian A-60A instrument.

(S)-N-*Phthaloylvalyl chloride* (**1b**). (S)-N-Phthaloylvaline[17] (0·1 mol) and thionyl chloride (60 ml) in methylene chloride (300 ml) were heated together at 50° for 3 hr in an oil bath. A little ppt was removed from the cold mixture and the filtrate evaporated at reduced pressure. Benzene (100 ml) was then added and the evaporation repeated. The residual solid was recrystallised from light petroleum; yield 88%, m.p. 121–122°. (Found: C, 58·96; H, 4·59. Calc. for $C_{13}H_{12}ClNO_3$: C, 58·78; H, 4·55%); $[\alpha]_D = -101°$ (c = 1·5 in benzene); τ($CDCl_3$) 8·8 and 9·1 (Me), 7·2 (CH–Me_2), 5·2 (N–CH).

(S)-N-*Phthaloylalanyl chloride* (**1a**),[6] from (S)-N-phthaloylalanine in 87% yield, m.p. 52–53° (light petroleum) [lit.[6] m.p. 38°]; $[\alpha]_D = -33·8°$ (c = 0·8 in benzene); τ($CDCl_3$) 8·2 (Me), 4·8 (N–CH).

(S)-N-*Phthaloylphenylalanyl chloride* (**1c**),[5] from (S)-N-phthaloylphenylalanine in 97% yield, m.p. 82° (benzene/light petroleum) [Lit.[5] m.p. 82–83°C]; $[\alpha]_D = -200°$ (c = 1·4 in benzene); τ($CDCl_3$) 6·4 (CH_2), 4·7 (N–CH), 2·9 (Ph).

(S)-2-*Phthalimidopropionaldehyde* (**2a**). (S)-N-Phthaloylalanyl chloride (0·05 mol) was dissolved in diglyme (100 ml) and the soln cooled to −70°. A soln of lithium tri-t-butoxyaluminium hydride,[8] prepared from LAH (0·055 mol) and t-BuOH (0·165 mol) in diglyme (60 ml), was then added dropwise under N_2 and with vigorous stirring. The reaction vessel was removed from the cooling bath when the addition was completed and the stirring continued at room temp for about 1 hr and the mixture poured onto ice (200 g). The mixture was next acidified using 6N HCl, extracted with chloroform, and the chloroform washed, dried and evaporated. The residual solid was recrystallised from benzene/light petroleum; yield 67%, m.p. 107–108°C [Lit.[7] m.p. 112°C]. (Found: C, 64·81; H, 4·45. Calc. for $C_{11}H_9NO_3$: C, 65·02; H, 4·47%); $[\alpha]_D = -29·0°$ (c = 2·1 in benzene); τ($CDCl_3$) 8·4 (Me), 5·3 (N–CH), 0·3 (CHO).

(S)-2-*Phthalimido*-3-*methylbutyraldehyde* (**2b**), from **1b** in 60% yield. The product was not isolated in a crystalline state; τ($CDCl_3$) 8·8 and 9·1 (Me), 7·3 (CH–Me_2), 5·6 (N–CH), 0·2 (CHO).

For elemental analysis its semicarbazone was prepared, m.p. 197–199° (MeOH) [Lit.[18] m.p. 223°C]; (Found: C, 58·60; H, 5·48: Calc. for $C_{14}H_{16}N_4O_3$: C, 58·32; H, 5·59%); $[\alpha]_D = +21·1°$ (c = 0·4 in HOAc).

(S)-2-*Phthalimido*-3-*phenylpropionaldehyde* (**2c**), from **1c** in 50% yield, m.p. 113°C (benzene/light petroleum). (Found: C, 73·34; H, 4·58. Calc. for $C_{17}H_{13}NO_3$: C, 73·10; H, 4·69%); $[\alpha]_D = -207°$ (c = 0·5 in benzene); τ($CDCl_3$) 6·5 and 6·6 (CH_2), 5·0 (N–CH), 2·9 (Ph), 0·3 (CHO).

(S)-2-*Phthalimidopropionaldehyde dimethyl acetal* (**3a**). (S)-2-Phthalimidopropionaldehyde (0·04 mol) was dissolved in the minimum amount of MeOH before addition of methyl orthoformate (0·044 mol) and ammonium chloride (200 mg). The resultant soln was left at room temp for 6 days before evaporation at reduced pressure. The residual organic material was extracted into ether (100 ml) and the etheral soln extracted with $NaHSO_3$aq. The ether soln was next washed, dried and evaporated. The residual oily material crystallised slowly when left in the cold. It was recrystallised by dissolution in (i-Pr)$_2$O/light petroleum and crystallisation at −30°; yield 76%, m.p. 49–51°. (Found: C, 62·45; H, 6·06. Calc. for $C_{13}H_{15}NO_4$: C, 62·65; H, 6·06%); $[\alpha]_D = -17·0°$ (c = 1·5 in MeOH); τ($CDCl_3$) 8·5 (Me), 6·6 and 6·8 (OMe), 5·6 (N–CH), 5·0 (CHO_2).

(S)-2-*Phthalimido*-3-*methylbutyraldehyde dimethyl acetal* (**3b**), from **2b** as above. The residual oil, after evaporation of the ether soln, was distilled to give the pure title compound in 46% yield, b.p. 132–134°/0·05 mmHg. The oily distillate slowly crystallised in the cold, m.p. 52–54°. (Found: C, 65·40; H, 6·96. Calc. for $C_{15}H_{19}NO_4$: C, 64·96; H, 6·90%); $[\alpha]_D = -21·8°$ (c = 1·1 in MeOH); τ($CDCl_3$) 9·0 and 9·1 (Me), 7·6 (CHMe_2), 6·6 and 6·8 (OMe), 5·9 (N–CH), 4·8 (CHO_2).

(S)-2-Phthalimido-3-phenylpropionaldehyde dimethyl acetal (**3c**), from **2c** as above; purified by distillation at 190–192°/0·1 mmHg in 65% yield. (Found: C, 70·20; H, 5·98. Calc. for $C_{19}H_{19}NO_4$: C, 70·13; H, 5·89%), $[\alpha]_D = -155°$ (c = 1·4 in MeOH); τ($CDCl_3$) 6·5 and 6·7 (OMe), 5·4 (N–CH), 4·8 (CHO_2), 2·9 (Ph).

(S)-2-*Aminopropionaldehyde dimethyl acetal* (**4a**). A soln of (S)-2-phthalimidopropionaldehyde dimethyl acetal (0·036 mol) and hydrazine hydrate (0·042 mol) in abs EtOH (110 ml) was heated under reflux and stirring for 40 min. The mixture was next kept in an ice-bath before the precipitated phthaloyl hydrazide was removed by filtration. The filtrate was evaporated at reduced pressure and the residue triturated with methylene chloride (150 ml). Evaporation and distillation of the residue yielded the title compound with b.p. 56–58°/40 mmHg, yield 58%. (Found: C, 50·46; H, 11·09. Calc. for $C_5H_{13}NO_2$: C, 50·42, H, 11·00%); $[\alpha]_D = +3·7°$ (c = 1·7 in MeOH); τ($CDCl_3$) 8·9 (Me), 7·0 (N–CH), 6·5 and 6·6 (O–Me), 6·0 (CHO_2).

(S)-2-*Amino*-3-*methylbutyraldehyde dimethyl acetal* (**4b**), from **3b** as above by heating with hydrazine hydrate for 5 hr; yield 48%, b.p. 76–78°/45 mmHg. (Found: C, 57·45; H, 11·25. Calc. for $C_7H_{17}NO_2$: C, 57·12; H, 11·64%); $[\alpha]_D = +7·6°$ (c = 2·0 in MeOH); τ($CDCl_3$) 9·0 and 9·1 (Me), 8·2 (CH–Me_2), 7·4 (N–CH), 6·6 (OMe), 5·9 (CHO_2).

(S)-2-*Amino*-3-*phenylpropionaldehyde dimethyl acetal* (**4c**), from **3c** as above by heating with hydrazine hydrate for 40 min; yield 61%, b.p. 94–95°/0·1 mmHg. (Found: C, 67·85; H, 8·90. Calc. for $C_{11}H_{17}NO_2$: C, 67·68; H, 8·78%); $[\alpha]_D = -27·2°$ (c = 1·6 in

MeOH); τ(CDCl₃) 7·1 and 7·5 (CH_2), 6·6 (OMe), 5·9 (CHO_2); 2·8 (Ph).

(S)-2-N,N,N-*Trimethylammoniopropionaldehyde dimethyl acetal iodide* (**5a**). A mixture of (S)-2-aminopropionaldehyde dimethyl acetal (0·01 mol), MgO (0·05 mol) and MeI (0·05 mole) in MeOH (40 ml) was stirred at room temp for 18 hr. The insoluble material was then removed by filtration, the filtrate evaporated at reduced pressure and the residue triturated several times with ether before recrystallisation from acetone/EtOH; yield 30%, m.p. 224–225°. (Found: C, 33·28; H, 6·91. Calc. for $C_8H_{20}INO_2$: C, 33·22; H, 6·97%); $[\alpha]_D = -21·5°$ (c = 1·5 in H_2O); τ(D_2O) 6·8 (N–Me), 6·4 (OMe), 5·0 (CHO_2).

(S)-2-N,N,N-*Trimethylammonio-3-methylbutyraldehyde dimethyl acetal iodide* (**5b**), from **4b** as above, yield 66% after 4 days, m.p. 215–217° (i-PrOH). (Found: C, 37·51; H, 7·37. Calc. for $C_{10}H_{24}INO_2$: C, 37·86; H, 7·62%); $[\alpha]_D = +1·2°$ (c = 1·2 in H_2O); τ(D_2O) 6·7 (N–Me), 6·4 and 6·45 (OMe), 5·2 (CHO_2).

(S)-2-N,N,N-*Trimethylammonio-3-phenylpropionaldehyde dimethyl acetal iodide* (**5c**), from **4c** as above; yield 27% after 18 hr, m.p. 130–131° (acetone/ether). (Found: C, 46·29; H, 6·63. Calc. for $C_{14}H_{24}INO_2$: C, 46·04; H, 6·62%); $[\alpha]_D = +2·2°$ (c = 1·3 in N HOAc); τ6·7 (N–Me), 6·5 and 6·55 (O–Me); 5·2 (CHO_2).

(S)-2-N,N,N-*Trimethylammoniopropionaldehyde iodide* (**6a**). A soln of (S)-2-N,N,N-trimethylammoniopropionaldehyde dimethyl acetal iodide (0·003 mol) in trifluoroacetic acid (6 ml) was heated at 55° for 2 hr and then evaporated at reduced pressure. The residue was triturated with ether/EtOAc and the solid recrystallised from acetone-ether; yield 37%, m.p. 200–202°. (Found: C, 29·37; H, 5·70. Calc. for $C_6H_{14}INO$: C, 29·64; H, 5·80%); $[\alpha]_D = -8·0°$ (c = 1·2 in 0·1 N HCl); τ(TFA) 8·2 (Me), 6·6 (N–Me), 5·3 (N–CH), 0·4 (CHO); γ_{max} (KBr) 1715 cm^{-1} (C=O).

(S)-2-N,N,N-*Trimethylammonio-3-methylbutyraldehyde iodide* (**6b**), from **5b** as above; yield 63%, m.p. 169–171°C (acetone). (Found: C, 35·35; H, 6·66. Calc. for $C_8H_{18}INO$: C, 35·44; H, 6·69%); $[\alpha]_D = +36·9°$ (c = 1·0 in 0·1 N HCl); τ(TFA) 8·4 and 8·7 (Me), 6·6 (N–Me), 5·5 (N–CH), 0·2 (CHO); γ_{max} (KBr) 1715 cm^{-1} (C=O).

(S)-2-N,N,N-*Trimethylammonio-3-phenylpropionaldehyde iodide* (**6c**), from **5c** as above. The residue, after evaporation of the trifluoroacetic acid, was dissolved in AcOH (1 ml) and Ac_2O (7 ml) and ether (25 ml) added in small portions. In this way the title compound crystallised out from the soln. After collection and washing of the solid with ether the yield was 50%, m.p. 160–162°. (Found: C, 44·88, H, 5·61. Calc. for $C_{12}H_{18}INO$: C, 45·15; H, 5·64%); $[\alpha]_{546}^{35}$ = +3·8° (c = 0·8 in 9N HOAc); τ(TFA) 6·5 (N–Me), 5·0 (N–CH), 2·4 (Ph), 0·2 (CHO); γ_{max}(KBr) 1720 cm^{-1} (C=O).

(S)-2-N,N,N-*Trimethylammoniopropionate* (**7a**).[2] (S)-2-N,N,N-Trimethylammoniopropionaldehyde iodide (0·001 mol) was dissolved in 2 M H_2SO_4 (20 ml) and $KMnO_4$ (0·001 mol) added. The mixture was stirred at room temp for a few hr (4–7) until TLC (silica gel GF; MeOH: conc NH_3 = 3:1) showed the oxidation to be complete. The mixture was then centrifuged and the sulphate ions removed by dropwise addition of $BaCl_2$aq. The further isolation procedure has previously been described.[2]

The title compound thus prepared had specific rotation $[\alpha]_D = -10·5°$ (c = 0·7 in 2N HCl); direct methylation of the amino acid gave $[\alpha]_D = -20·3°$.[2]

(S)-2-N,N,N-*Trimethylammonio-3-methylbutyrate* (**7b**)[2] from **6b**; $[\alpha]_D = +8·1°$ (c = 1·2 in 2N HCl); by direct methylation of amino acid $[\alpha]_D = +18·9°$.[2]

(S)-2-N,N,N-*Trimethylammonio-3-phenylpropionate* (**7c**)[2] from **6c**; $[\alpha]_D = +3·7°$ (c = 1·1 2N HCl); by direct methylation of amino acid $[\alpha]_D = +51·0°$.[2]

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