Tetrahedron. Vol. 29, pp. 863 to 866. Pergamon Press 1973. Printed in Great Britain

N-QUATERNARY COMPOUNDS—XXVIII
CIRCULAR DICHROISM OF α-TRIMETHYLAMMONIUM ACIDS

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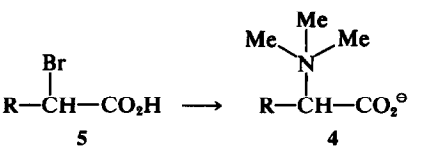
(*Received UK 7 November* 1972; *Accepted for publication* 14 *November* 1972)

Abstract—The dichroic absorption of α-trimethylammonium carboxylic acids has been compared with that of α-amino acids. The quaternary acids were synthesized by methylation of amino acids or by the Menschutkin reaction between bromo acids and trimethylamine. The stereochemical course in the Menschutkin reaction is discussed. Rate of racemisation in alkaline solution of the synthesized quaternary acids has been determined.

Optically active α-amino acids may have one or two CD-bands above 200 nm depending on the ionization state of the amino acid.[2-5] The interpretation is complicated by the contribution of an optically active transition involving the non-bonded electrons of the amino group. Protonated amino groups and carboxylate anions do not show any Cotton effect in the 230–270 nm region.[6,7] On the other hand, the amino acids at pH 1 exhibit two Cotton effects of opposite signs centered at 206–209 nm and at 244–252 nm. Both bands are explained by carboxyl n → π* transitions arising from two major conformers.[5] We decided to investigate corresponding α-trialkylammonium acids in which the lone pair on the amine nitrogen in the quaternary nitrogen is part of a chemical bond and therefore cannot interact with the carboxyl group at any pH.

A number of N-quaternary amino acids are naturally occurring.[8] The simpler ones, however, can readily be synthesized. Direct permethylation of amino acids[9,10,11] are often associated with a large degree of racemisation. We have used optically active α-dimethylamino acids, which are available from amino acids by reductive methylation,[12] in the synthesis of the N-quaternary acids 4 (Scheme 1). The dimethylamino acids of the (*S*)-configuration were esterified and then quaternized with methyl iodide in nitromethane without base addition. The bulky trimethylammonium group led to slow ester hydrolysis in acid solution. The activation energy for the hydrolysis is further dependent on the non-bonded interaction between the R-substituent and the ammonium group. (Scheme 1). Thus the alanine (**3a**) was hydrolyzed after 2·5 hr in 6N HCl while the valine and phenylalanine analogues required heating in 45% sulphuric acid for 24 hr.

Having available α-ammonium acids of known absolute configuration, we next studied the stereochemical course of the Menschutkin reaction between α-bromo acids and trimethylamine. In a previous report on the Menschutkin reaction between α-bromo acids and 3-hydroxypyridine, configurational inversion was established except when the alkylating agent is branched at the β-carbon.[13] The optical activity of the Menschutkin product decreased with reaction time. The fall in optical rotation is due to bromide ion exchange in the unreacted bromo acid caused by the bromide ions liberated in the reaction.[13] This is illustrated for the alanine (**4a**) whose specific rotations in 2N HCl were +6·6, +5·6 and +4·2° after 20, 40 and 300 min, respectively.



5 **4**

SCHEME 2

The products from the Menschutkin reaction were dextrorotary at the sodium D-line (Table 1). The compounds of the (*S*)-configuration, which were prepared directly from the respective amino acids, were also dextrorotary with the exception of the alanine (**4a**). The configurational relation-

1a: R = Me
b: R = $CHMe_2$
c: R = $CH_2C_6H_5$

2 **3** **4**

SCHEME 1

Table 1. Specific rotations at 25° in 2N HCl measured at the sodium D-line

	a	b	c
(*S*)-3	−26·5°	+18·8°	+53·4°
(*S*)-4	−20·3°	+18·9°	+51·0°
4[a]	+6·6°	+20·1°	+20·7°

[a]The Menschutkin product from (*S*)-5 (Scheme 2).

ship was also evident by comparison of the CD curves of the respective products. The curves for the products of (*S*)-configuration are reproduced in Figs 1 and 2.

The chiroptical properties are in agreement with configurational retention for the Menschutkin reaction leading to the valine (**4b**) and the phenylalanine (**4c**) analogues while the alanine (**4a**) is formed by net inversion. With the exception of α-bromo-β-phenyl-propionic acid, the stereochemical course for the reaction of the other bromo acids with trimethylamine is as found with ammonia and with 3-hydroxypyridine.[13] Trimethylamine is a more space demanding nucleophile than simple pyridines and ammonia. The additional non-bonded interaction in the transition state between the phenyl ring and the trimethylamine for S_N2 substitution increases the activation energy to the extent that the alternative S_Ni transition state is energetically favoured. (Scheme 3). This is further reflected in the relative reaction rate which is lowest for the phenyl derivative. The optical activity (Table 1) of the product **4c** is probably not a good measure for the stereospecificity of the reaction. The reason is that the reaction is relatively slow resulting in considerable racemisation of the bromo compound (**5c**) before quaternization occurs. The stereochemical importance of the non-bonded interaction between the phenyl group and the nucleophile is further illustrated in the reaction of **5c** with the less bulky dimethylamine. From the negative sodium D-line rotation the product can be assigned the (*R*)-con-

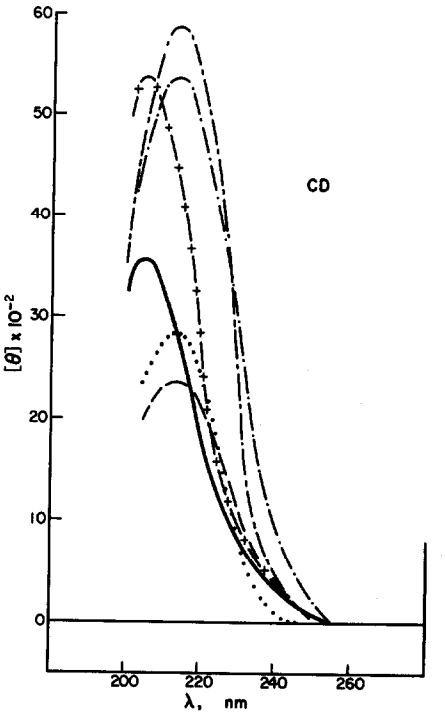
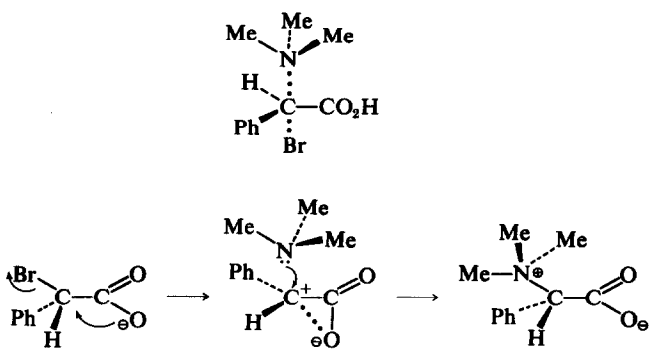


Fig 1. CD curves for the esters (*S*)-**3a** (·····) and (*S*)-**3b** (———) at pH 1, for the acids (*S*)-**4a** (— — —) and (*S*)-**4b** (—·—·—) at pH 1; for the acids (*S*)-**4a** (——) and (*S*)-**4b** (—+—) at pH 6·5.

figuration, the optical purity being of the order 30%.[15] In this case the competition between the two transition states favours the S_N2 mechanism resulting in net configurational inversion of the product.

The CD curves for the (*S*)-configurational products from the N-methylation procedure are shown in Figs 1 and 2. With the carboxyl group undissociated in acid solution both the alanine (**4a**) and valine (**4b**) analogues have a single dichroic band at 213 nm (Fig 1) with the same sign as the configurationally related amino acids. No CD absorption was observed corresponding to the second CD-



SCHEME 3

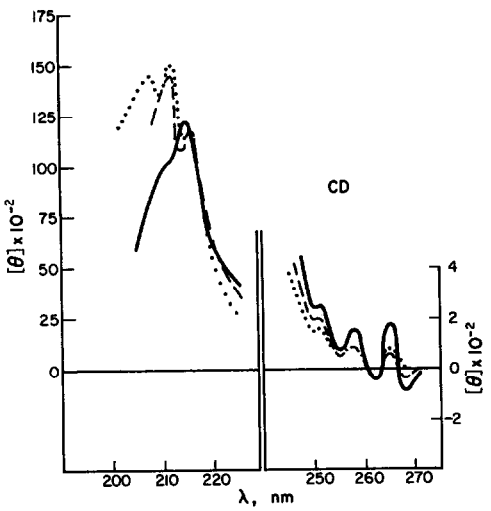
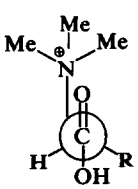


Fig 2. CD curves for the ester (*S*)-**3c** at pH 1 (——); for the acid **4c** at pH 1 (— — —) and at pH 6·5 (·····).

band in amino acids in the 235–250 nm region. The interpretation of the latter as due to n → π^* transition of the carboxyl group in a second major conformer, leads to the conclusion that the quaternary acids (**4**) exist largely in one preferred conformation. The preference for one major conformer is understandable in terms of the relative bulkiness of the trimethylammonium group. By analogy to postulations made for other α-substituted acids,[16] it is suggested in Scheme 4 that the ammonium group preferably assumes a conformation in which it becomes coplanar with the carboxyl group. In the zwitterionic form at pH 6·5, a hypsochromic shift to a single band at 205 nm has occurred in accordance with the behaviour of amino acids.[5] The respective methyl esters **3a** and **3b** have one dichroic band at 213 nm irrespective of the pH while esters of corresponding α-amino acids have an additional higher wavelength band in both acid and alkaline solution.[5]



SCHEME 4

The phenylalanine analogues **3c** and **4c** show more complex dichroic absorption. The multiple Cotton effect of the aryl group (250–270 nm) in the acid (**4c**) is unaffected by the pH change. Two dichroic bands are present at 212 and 216 nm in the spectra of both the acid **4c** and its methyl ester (**3c**) in acid solution as well as in buffer at pH 6·5. The same positional bands are seen in the spectra of the corresponding choline.[17] These CD-bands in **3c** and **4c** are therefore in part ascribed to aryl group transitions. The dissociated acid **4c** at pH 6·5 also has a third CD-band in the lower region at 208 nm which is ascribed to carboxyl n → π^* transition. The same optical transitions in the ester **3c** and the undissociated acid **4c** presumably must lead to CD-absorption which coincides with a CD-band of the aryl group and only becomes apparent after the hypsochromic shift in the ionization of the carboxyl group.

The optical stability was investigated by measuring the change in CD absorption at 235 nm in 4N NaOH at 50°. The racemisation followed first order kinetics with $k = 1{\cdot}01 \times 10^{-3}\,min^{-1}$ and $k = 1{\cdot}49 \times 10^{-3}\,min^{-1}$ for **4a** and **4c**, respectively, the half life being 686 min and 464 min, respectively. The valine analogue **4b** was only very weakly racemized under these conditions. Qualitatively the rate of deuterium exchange on the chiral carbon appeared to be similar. Corresponding α-pyridinium acids are rapidly racemized under these conditions.[18] The difference in optical stability is therefore largely attributed to the lower acidity of the chiral hydrogen in **4** which is suggested by the NMR chemical shifts in trifluoroacetic acid of the hydrogen on the chiral carbon if it is assumed that the chemical shifts can be used as a measure of the relative acidity. Thus the τ-values for **4a** (5·57 τ) **4b** (5·87 τ) and **4c** (5·50 τ) are about one unit higher[18] than for the respective α-pyridinium acids.

EXPERIMENTAL

The CD measurements were carried out with a Jasco Automatic Spectropolarimeter Model J-10 and a Cary 60 Spectropolarimeter in 2N HCl and phosphate buffer at pH 6·5. The cell lengths were 1 and 10 mm and the temperature 27°. The concentrations were in the range 1–2 g/l.

The racemisation studies were run in 4N NaOH at 50° in 0·5 M concentration of the α-ammonium acids using a 10 mm cell with automatic recording of the dichroic absorption at 235 mm. A plot of the logarithm of the dichroic absorption against time gave a straight line; the rate constants being $1{\cdot}01 \cdot 10^{-3}\,min^{-1}$ with half life 686 min, for **4a** and $1{\cdot}49 \cdot 10^{-3}\,min^{-1}$ with half life 465 min for **4c**. For the valine analogue (**4b**) the change in dichroic absorption after 16 hr was too small for meaningful calculations.

(S)-N,N-*Dimethylvaline methyl ester* HCl (**2b**). PCl_5 (0·06 mol) was added in three portions to (*S*)-N,N-dimethylvaline[15] (0·06 mol) in ice-cold chloroform (75 ml). The stirring was continued until most of the acid had dissolved and then for another hr at room temp. Addition of ether (300 ml) precipitated the acid chloride which after decantation of the solvent was redissolved in MeOH and left overnight. The solvent was then distilled off and the residue crystallized from acetone; yield 67%, m.p. 154–156°. (Found: C 48·74; H 9·26. Calc. for $C_8H_{17}NO_2 \cdot HCl$: C 49·09; H 9·27%); $\{\alpha\}_D^{25} = +36{\cdot}7°$ ($c = 1{\cdot}0$ in 2N HCl).

(S)-N,N-*Dimethylalanine methyl ester* (**2a**) was prepared as above in 62% yield, b.p. 42–43°/23 mm Hg;

$\{\alpha\}_D^{25} = +12{\cdot}8°$ ($c = 1{\cdot}8$ in 2N HCl). (Found: C 54·79; H 9·91. Calc. for $C_6H_{13}NO_2$: C 54·93; H 9·99%).

(S)-N,N-*Dimethylphenylalanine methyl ester* (**2c**) was also prepared[12] from the corresponding acid[15] as above.

(S)-α-*Trimethylammonium-propionic acid methyl ester chloride* (**3a**). A soln of MeI (0·04 mole) and (S)-N,N-dimethylalanine methyl ester (0·01 mol) in nitromethane (40 ml) was kept in a pressure bottle at 40° for 4 hr. The soln was then evaporated to a small volume and ether (200 ml) was added. The precipitated iodide was converted to the chloride by dissolution in water followed by addition of excess freshly prepared AgCl. The latter was added in small portions with good stirring. The insoluble material was removed by filtration and the chloride isolated by evaporation and recrystallized from MeOH/acetone; yield 72%, m.p. 191–193°. (Found: C 46·37; H 8·83. Calc. for $C_7H_{16}NO_2Cl$: C 46·27; H 8·87%).

(S)-α-*Trimethylammonium-β-methylbutyric acid methyl ester iodide* (**3b**) was prepared from **2b** as above in 70% yield, m.p. 176–178° (acetone). (Found: C 35·80; H 6·70. Calc. for $C_9H_{20}NO_2J$: C 35·89; H 6·69%).

(S)-α-*Trimethylammonium-β-phenylpropionic acid methyl ester chloride* (**3c**) was prepared from **2c** as above in 97% yield; m.p. 189° (MeOH/acetone). (Found: C 60·55; H 7·80. Calc. for $C_{13}H_{20}NO_2Cl$: C 60·59; H 7·82%).

(S)-α-*Trimethylammonium-propionic acid chloride* (**4a**). The ester **3a** (0·6 g) was completely hydrolysed by heating under reflux in 6N HCl (20 ml) for 2·5 hr. The soln was then evaporated and the residual acid crystallized from isopropanol; m.p. 205–206°. (Found: C 42·50; H 8·57; N 8·63. Calc. for $C_6H_{13}NO_2 \cdot HCl$: C 42·99; H 8·42; N 8·36%); NMR in TFA; 8·09 τ (CH_3), 6·55 τ ($\overset{+}{N}$-CH_3), 5·57τ(H^α).

(S)-α-*Trimethylammonium-β-methylbutyric acid chloride* (**4b**). The ester **3b** (0·5 g) was hydrolysed by heating in 45% H_2SO_4 (4 ml) for 25 hr. The soln was then diluted with water (40 ml) and excess barium chloride was added. The barium sulphate was removed by centrifugation and the solution evaporated. The residue was dried *in vacuo* at 40° over KOH-pellets before dissolution in abs EtOH (30 ml). The insoluble barium chloride was removed by centrifugation and the solution evaporated. The residual material was crystallized from isopropanol; m.p. 202°. (Found: C 49·34; H 9·48; N 7·01. Calc. for $C_8H_{17}NO_2 \cdot HCl$: C 49·12; H 9·28; N 7·16%); NMR in TFA: 8·77 and 8·60τ (CH_3), 7·39τ (H^β) 6·55τ ($\overset{+}{N}$-CH_3), 5·87τ(H^α).

(S)-α-*Trimethylammonium-β-phenylpropionic acid chloride* (**4c**) was prepared from **3c** by refluxing a soln in 45% H_2SO_4 for 24 hr. The reaction was worked up as for **4b**. Recrystallization from isopropanol/acetone gave m.p. 196–198°. (Found: C 59·18; H 7·22; N 5·93. Calc. for $C_{12}H_{17}NO_2 \cdot HCl$: C 59·14; H 7·44; N 5·75%); NMR in TFA: 6·49τ ($\overset{+}{N}$-CH_3), 5·50τ (H^α), 6·6τ ($2H^\beta$), 2·59τ (C_6H_5).

Formation of α-trimethylammonium-propionic acid derivatives (**4**) *by the Menschutkin reaction.* The α-bromo acids **5a**[19], and **5b**[20], and **5c**[21] of the (*S*)-configuration were prepared by diazotisation of the corresponding (*S*)-amino acids.

A solution of the α-bromo acid (0·04 mol) in acetonitrile (40 ml) contained in a pressure bottle (250 ml) was cooled in ice-bath and anhyd trimethylamine (0·08 mole) was added. The soln was then kept at 40° for the time given below, allowed to cool and ether (250 ml) added. The white solid ppt was a mixture of the betaine and triethylamine hydrobromide. The betaine was isolated by dissolution of the mixture in water (60 ml) and gradual addition of silver acetate (0·06 mole). The ppt was filtered off, the solution freeze-dried, the residue dissolved in MeOH, insoluble material removed by filtration and the soln evaporated.

The product was converted to the hydrochloride by dissolution in conc HCl (1 ml) and evaporation followed by dissolution in water (10 ml) and evaporation. The product was then recrystallized from isopropanol. **4a**: Yield 25% after heating for 20 min; $\{\alpha\}_D^{25} = +6{\cdot}6°$ (2N HCl); (*R*)-configuration. **4b**: Yield 15% after heating for 50 min; $\{\alpha\}_D^{25} = +20{\cdot}1°$ (2N HCl); (*S*)-configuration. **4c**: Yield 10% after heating for 120 min; $\{\alpha\}_D^{25} = +20{\cdot}7°$ (2N HCl); (*S*)-configuration.

(R)-N,N-*Dimethylphenylalanine* (**1c**) was prepared by the Menschutkin reaction from (*S*)-α-bromo-β-phenylpropionic acid and dimethylamine as described for the ammonium analogues (**4**) above; m.p. 215–217°; $\{\alpha\}_D^{25} = -23{\cdot}7°$ ($c = 1{\cdot}0$ in water). The reported specific rotation for the (*S*)-isomer, $\{\alpha\}_D = +77{\cdot}1°$ (water).[15]

Acknowledgement—Part of this work was carried out at the University of Lund, Sweden, with a stipend (M.G.) from Norsk Pasteur-legat.

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