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N-QUATERNARY COMPOUNDS—XLIV[1]

SYNTHESIS AND CIRCULAR DICHROISM OF α-N,N-DIMETHYLAMINO AND α-N,N,N-TRIMETHYLAMMONIO KETONES

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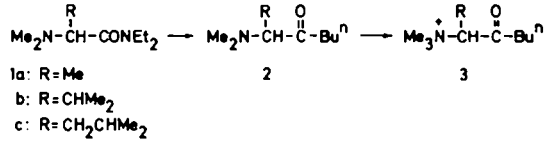
Abstract—CD spectra of acyclic α-N,N-dimethylamino ketones exhibit two absorption bands of opposite sign at *ca.* 240 and 305–315 nm. Both bands are ascribed to the same conformers. On protonation only one CD band is seen. The single CD band of α-N,N,N-trimethylammonio ketones has the same sign and almost the same wavelength maximum as the protonated amino ketones.

The study of the chiroptical properties of the ketocarbonyl group in asymmetrically perturbed cyclic systems has been fundamental in the understanding and development of ORD and CD theories.[2] Comparatively few ORD or CD studies, however, have been carried out on the non-rigid acyclic ketones.[3-7] This report describes CD investigations of some acyclic α-N,N,N-trimethylammonio and α-N,N-dimethylamino ketones as an extension of our work on α-N,N,N-trimethylammonio aldehydes.[8] Previous CD studies on acyclic amino ketones seem to be limited to a recent report which deals with the use of CD in conformational analysis of β-amino ketones.[7] Studies of α-amino ketones appear to be limited to cyclic amino ketones having fixed stereochemistry.[9-13]

The desired amino ketones were prepared according to Scheme 1. Several methods are available for the



Scheme 1.

synthesis of α-amino ketones, which are valuable intermediates in the preparation of a wide variety of heterocyclic and medicinal compounds;[3,4,14,15] α-amino ketones can also be formed enzymatically.[16] A convenient synthesis of an optically active α-amino ketone would appear to be treatment of an optically active α-amino acid amide with an organometallic reagent. With the access to amides of the (*S*)-configuration from previous work,[1] such amides (**1**) were reacted with butyllithium to yield the (*S*)-ketone **2**. The ketone formation is influenced by the steric nature of the R group in the amide which is evident from the sluggish reactivity of **1b** (R = iPr) in comparison with the reaction rates of **1a** and **1c**. CD spectra and sodium D-line rotations of the ketones were recorded soon after their preparation because of gradual racemisation on storage which was most pronounced for **2a** (R = Me). Methyl iodide was used for the alkylation. Both **2a** and **2c** were readily alkylated in cold acetone whereas **2b** (R = iPr) had to be heated in toluene.

The CD and UV spectra, as well as the dipole moments in benzene (Experimental), of the N,N-dimethylamino ketones **2** are similar. Therefore only the spectra of **2b** are reproduced in Fig. 1 but the complete

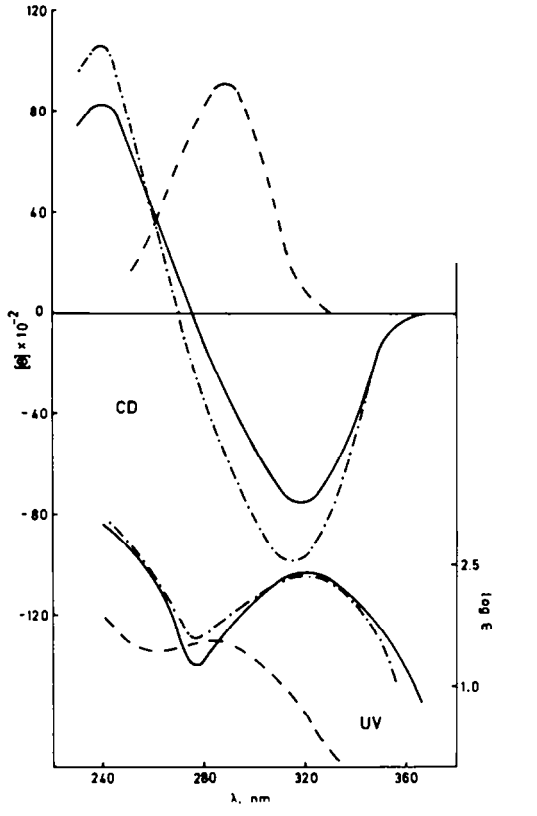


Fig. 1. CD and UV curves: (*S*) - 3 - N,N - Dimethylamino - 2 - methyl - 4 - octanone **2b** in heptane —·—, in MeOH —— and in 1N HCl— — —.

CD data for **2** are given in Table 1. The CD spectrum of **2b** recorded in heptane exhibits a negative CD absorption at 315 nm and a positive absorption at 240 nm. A similar spectrum is obtained in methanol. The long wavelength band has its correspondence in an isotropic absorption maximum at 319 nm. In aqueous HCl, where the amino group in **2** is protonated, the CD spectrum exhibits only one band corresponding to a blue shift to 289 nm of the long wavelength band with inversion of the sign of the

Table 1. Dichroic absorption; λ_{max}/nm and $\Delta\epsilon_{max}$

Solvent heptane	**2a**: 302(−0.25), 248(+0.13).† **2b**: 315(−3.30), 240(+3.55). **2c**: 304(−1.29), 238(+0.93)
Solvent MeOH	**2a**: 315(−0.05), 281(+0.06), 263(+0.04)‡ **2b**: 318(−2.53), 240(+2.76). **2c**: 304(−1.09), 238(+0.96). **3a**: 292(+1.15). **3b**: 295(+1.67). **3c**: 295(+1.36)
Solvent 1N HCl	**2b**: 289(+3.03). **2c**: 282(+1.32). **3a**: 288(+2.0).

†The maximum was not reached.
‡Minimum; the positive maximum was not reached.

dichroic absorption; similarly the UV maximum has been shifted to 285 nm. The ammonio ketones **3** in methanol [Fig. 2] also display only one CD maximum with the same positive sign as the protonated amines **2** and at about the same wavelength.

Unsubstituted ketones normally exhibit isotropic $n \rightarrow \pi^*$ absorption near 290 nm. An α-amino group causes a red shift to 300–335 nm which in part depends on the relative stereochemistry between the CO and amino group, and the shift is explained by coupling reactions between the two functional groups.[17] α-Amino ketones with fixed stereochemistry can give rise to two CD absorptions at *ca.* 220–240 nm and in the region around or above 300 nm having opposite CD signs. Both bands have been ascribed to CO $n \rightarrow \pi^*$ transitions arising through coupling reactions with the nitrogen lone pair as well as with the σ-electrons of the C–N bond.[11,13] Since α-amino ketones with fixed stereochemistry can give rise to two widely spaced CD absorptions of opposite sign, the high energy band in the CD spectra of **2** is ascribed to the same conformer or conformers which give rise to the 315 nm band. Application of the octant rule to rationalise

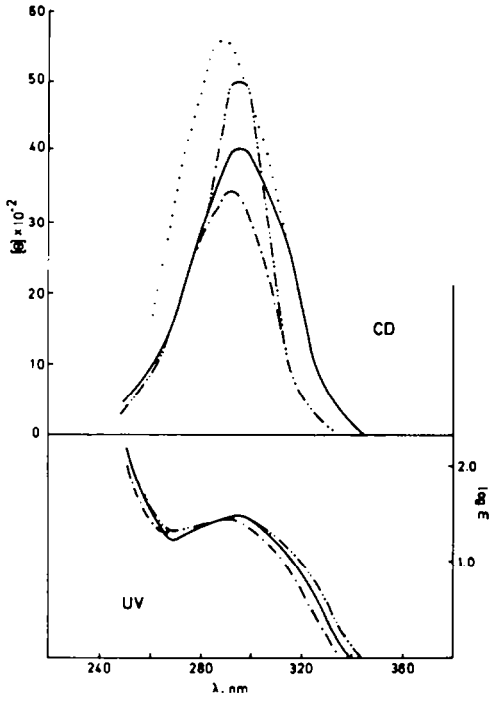
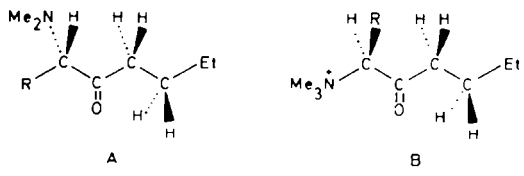


Fig. 2. CD and UV curves in MeOH: (*S*) - 2 - N,N,N - Trimethylammonio - 3 - heptanone iodide **3a** —·—, (*S*) - 3 - N,N,N - trimethylammonio - 2 - methyl - 4 - octanone iodide **3b** —··— and (*S*) - 4 - N,N,N - trimethylammonio - 2 - methyl - 5 - nonanone iodide **3c**. — CD curve of **3a** in 1N HCl ····.



Scheme 2.

the negative sign of the long wavelength CD band requires preferential conformational arrangements in which the R group approaches synperiplanar positions with respect to the CO group which is in accordance with the preference of ketones for the stretched carbon chain (Scheme 2, **A**).

On protonation of α-amino ketones of fixed stereochemistry the high energy transition disappears and the red shift is decreased.[11,13] In the same way the low wavelength CD band for the amino ketones **2** in HCl is absent and the long wavelength band has undergone a blue shift to 289 nm. The inversion of the CD sign indicates a different conformational distribution. The CD sign is the same as that of the ammonio ketones **3**. In the case of the latter the positive dichroic absorption can be rationalised in terms of the octant rule by the assumption of a preference for conformations in which the bulky trimethylammonio group eclipses the CO oxygen (Scheme 2, **B**). Dipolar attraction between the ammonium nitrogen and the basic CO oxygen may help to stabilise such conformers. The explanation is the same as that invoked to rationalise the positive dichroic absorption of corresponding (*S*)-N,N,N-trimethylammonio aldehydes.[8] In the case of the protonated amino ketones **2** the positive dichroic absorption is rationalised by similar conformational preferences perhaps stabilised by intramolecular H-bonding between the protonated amino group and the CO oxygen.

EXPERIMENTAL

CD curves were recorded with Jasco Automatic Spectropolarimeter Model J-10. The cell lengths were 0.1–10 mm and the temperature 27°. UV spectra were recorded on a Carry-14 spectrophotometer.

Dipole moments. Dielectric constants were measured[1] at 25°C in a Weilheimer Dipolmeter DM 01 on four different solutions of each compound. The concentrations were in the range 35–140 mg in 35 g of benzene. No correction for atomic polarisation was made in the calculation of the dipole moments. Dipole moments: 2.64D (2a), 2.61D (2b) and 2.62D (2c).

(S)-2-N,N-*Dimethylamino*-3-*heptanone* (**2a**). n-BuLi soln (15% in hexane, 30 ml) was diluted with ether (150 ml; N_2-atmosphere) and the soln cooled in an ice-bath while an ethereal soln (100 ml) of (*S*) - α - N,N - dimethylamino - N',N' - diethylpropionamide[1] (0.064 mole) was added dropwise (10 min). The flask was then removed from the ice-bath, the mixture allowed to reach room temp. while the stirring was continued, and finally the mixture was heated under reflux for 4 hr. Sat Na_2SO_4 aq (2.5 ml) was added dropwise to the stirred, cold mixture placed in an ice-bath. The organic phase was collected, washed with iced water (2 × 10 ml) and dried ($MgSO_4$) before evaporation and the residual material distilled: b.p. 76–78°C/12 mmHg, yield 71%; $[\alpha]_D = -6.7°$ (c = 1.2 in iPrOH). The compound racemises easily, even on storage in the refrigerator. (Found: C, 68.46; H, 12.28. Calc. for $C_9H_{19}NO$: C, 68.74; H, 12.18%); NMR (60 MHz, $CDCl_3$): δ 2.24 (N-Me), 3.06 (N-CH).

(S) - 3 - N,N - *Dimethylamino* - 2 - *methyl* - 4 - *octanone* (**2b**) was prepared as above from (*S*) - α - N,N - dimethylamino - N',N' - diethyl - β - methylbutyramide[1] in 47% yield; b.p. 100–102°C/15 mmHg; $[\alpha]_D = -99°$ (c = 1.3 in iPrOH). (Found: C,

70.93; H, 12.42. Calc. for $C_{11}H_{23}NO$: C, 71.30; H, 12.51%); NMR (60 MHz, $CDCl_3$): δ 2.31 (N-Me), 2.76 (N-CH).

(S) - 4 - N,N - *Dimethylamino* - 2 - *methyl* - 5 - *nonanone* (**2c**) was prepared as above from (*S*) - α - N,N - dimethylamino - N',N' - diethyl - γ - valeramide[1] in 69% yield; b.p. 100-102°C/12 mmHg; $[\alpha]_D = -38°$ (c = 1.8 in iPrOH). (Found: C, 72.40; H, 12.38. Calc. for $C_{12}H_{25}NO$: C, 72.31; H, 12.64%); NMR (60 MHz, $CDCl_3$): δ 2.23 (N-Me), 3.10 (N-CH).

(S) - 2 - N,N,N - *Trimethylammonio* - 3 - *heptanone iodide* (**3a**). A soln of (S) - 2 - N,N - dimethylamino - 3 - heptanone (0.006 mol) and MeI (0.018 mol) in acetone (10 ml) was left at room temp for 24 hr. The precipitated ammonium salt was then collected and washed well with ether; yield 73%, m.p. 187–189° (iPrOH); $[\alpha]_D = +15°$ (c = 1.3 in 0.1N HCl). (Found: C, 40.22; H, 7.49. Calc. for $C_{10}H_{22}INO$: C, 40.13; H, 7.41%); NMR (60 MHz, TFA): δ 3.38 (N-Me), 4.71 (N-CH); IR (KBr) cm $^{-1}$: 1710 (C=O).

(S) - 3 - N,N,N - *Trimethylammonio* - 2 - *methyl* - 4 - *octanone iodide* (**3b**). A soln of (*S*) - 3 - N,N - dimethylamino - 2 - methyl - 4 - octanone (0.006 mol) and MeI (0.018 mol) in toluene (10 ml) was heated under reflux for 4 hr. The residue, after evaporation of the solvent, was crystallised from iPrOH: Et_2O; yield 19%, m.p. 145–147°; $[\alpha]_D = +32°$ (c = 1.4 in 0.1N HCl). (Found: C, 43.67; H, 7.98. Calc. for $C_{12}H_{26}INO$: C, 44.03; H, 8.01%); NMR (60 MHz, TFA): δ 3.4 (N-Me); 4.55 (N-CH); IR (KBr) cm $^{-1}$: 1720 (C=O).

(S) - 4 - N,N,N - *Trimethylammonio* - 2 - *methyl* - 5 - *nonanone iodide* (**3c**). A soln of (*S*) - 4 - N,N - dimethylammonio - 2 - methyl - 5 - nonanone (0.006 mol) and MeI (0.018 mol) in acetone (10 ml) was left at room temp. for 24 hr. The soln was then poured slowly into ether (200 ml) with stirring and the precipitated ammonium salt collected and recrystallised from iPrOH: Et_2O; yield 63%, m.p. 110–112°; $[\alpha]_D = +27°$ (c = 1.4 in 0.1N HCl). (Found: C, 45.56; H, 8.42. Calc. for $C_{13}H_{28}INO$: C, 45.76; H, 8.27%); NMR (60 MHz, TFA): δ 3.33 (N-Me), 4.45 (N-CH); IR (KBr) cm $^{-1}$: 1720 (C=O).

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