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N-Quaternary Compounds

Part XXVII.[1] Circular Dichroism of Chiral Pyridinium Derivatives

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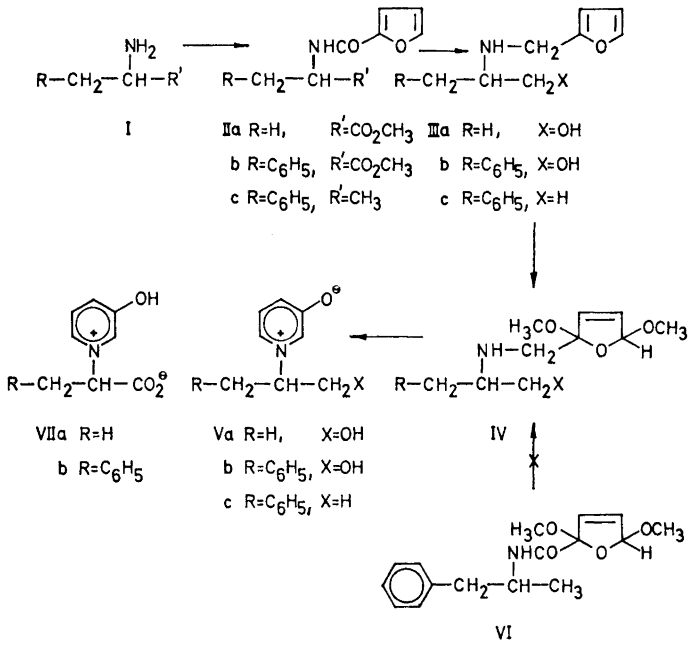
Optically active pyridinium-3-oxides have been synthesized from corresponding amino compounds with configurational retention. The oxypyridyl chromophore attached to the chiral carbon gives rise to polarized light absorption with CD maxima at about 290 nm and 205 – 215 nm.

CD curves have also been recorded for *N*-furoyl-alanine derivatives and for *N*-furfurylphenylalaninol as well as for the respective amphetamine derivatives.

Studies on polarized light absorption of α-3-hydroxypyridinium carboxylic acids have recently been reported.[2] This paper deals with polarized light absorption of the 3-hydroxypyridinium chromophore in the absence of any carboxyl function. For this purpose pyridinium derivatives with a chiral *N*-alcanol or *N*-hydrocarbon sidechain (V) have been synthesized. The previously prepared α-pyridinium acids (*e.g.* VII) were thought unsuitable as intermediates in syntheses of optically active alkanols since the acids are readily racemized.[3–5] The pyridinium alcohols were therefore prepared from furan-alaninols by procedures as used in the syntheses of analogous acids.[4] The pyridinium alcohols obtained showed good optical stability. Thus the optical rotation of Va in 6 N NaOH solution at 40° was unchanged after 8 h.

The amino acid methyl ester was acylated with furoyl chloride and both the amide and ester groups in II reduced smoothly with lithium aluminium hydride in ether. The furoyl (IIc) and furfuryl (IIIc) derivatives of (–)-amphetamine were similarly prepared. The furfurylalaninols were oxidized electrolytically in methanolic ammonium bromide at –30°C. Mainly for reasons of low solubility the amphetamine derivative (IIIc) could not be oxidized in satisfactory yield by this procedure. An alternative pathway involving acylation of amphetamine with 2,5-dimethoxy-2,5-dihydrofuroyl chloride followed by lithium aluminium hydride reduction of the amide carbonyl group (VI) failed in the reduction step because of steric hindrance.



Oxidation of *N*-furfurylamphetamine (IIIc) was finally achieved with hydrogen peroxide in 4 N HCl as found for corresponding acids.[4] Under these conditions the oxidized furan is converted without isolation to the pyridinium-hydrocarbon (Vc). Similarly the methoxylated furfuryl alcohols (IV) were converted to the respective pyridinium derivatives (Va, Vb) by heating for a short time in 4 N HCl. Higher acid concentrations led to water elimination from the *N*-side-chain. The pyridinium alcohols were isolated as phosphotungstic acid salts and obtained in crystalline state as HBr or HCl salts after ion exchange chromatography. The amphetamine (Vc) was obtained directly.

The CD curves for V were recorded in 0.1 N HCl solution. The highest wave-length absorption band, the L_b band, at about 290 nm (Fig. 1) is optically active. Thus the alanine analogue (Va) has a positive CD maximum at 285 nm and the phenylalaninol (Vb) and its desoxy analogue (Vc) a negative maximum at 290 nm. The negative sign for this Cotton effect in the phenyl derivatives is as found for the corresponding acid (VIIb).[2] The opposite sign for the alaninol analogue (Va) led us to examine the corresponding acid (VIIa) and the Cotton effect found positive as for the alcohol (Va). All previously studied acid analogues of the L-configuration, however, have shown a negative Cotton effect at this wave-length. An explanation for the anomalous behaviour of the simple alanine derivatives should await further experimental data.

The second pyridyl band in UV occurs as a shoulder at 221 nm for Va and at 225 nm for Vb and Vc. The major absorption band is at 203 nm. The strongly negative CD maxima at 204 nm for the phenyl derivatives (Vb and Vc) correlate

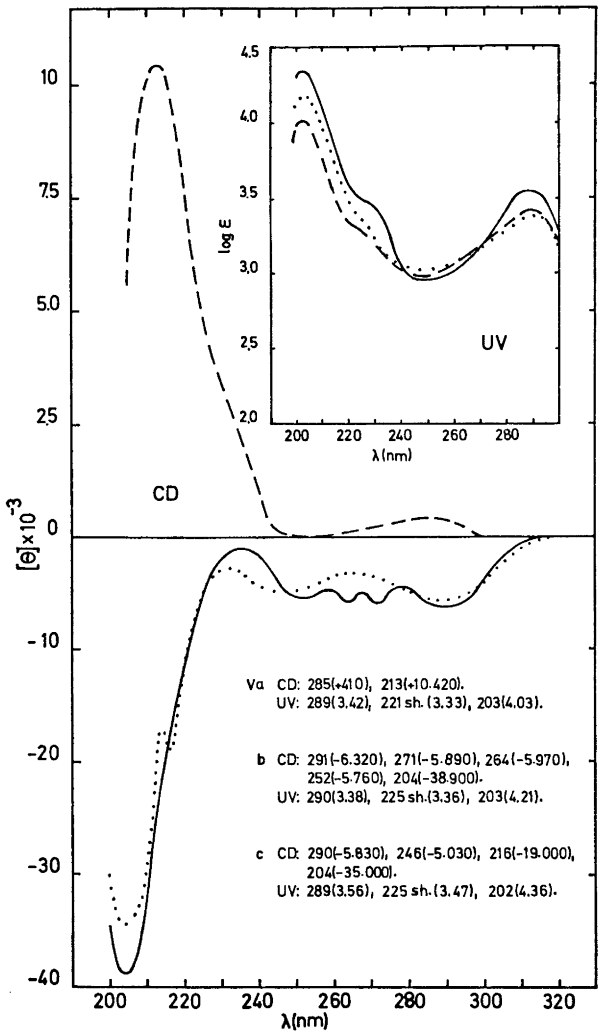


Fig. 1. CD and UV absorption of Va (– – –), Vb (———) and Vc (·····) in 0.1 N HCl.

well with this UV band while the alaninol analogue has an intermediate maximum at 213 nm. The latter corresponds closely to the optical transition in the acid (VIIa) while the phenyl alanine (VIIb) has a strong band at 224 nm not seen in the Vb but the amphetamine (Vc) has a weaker band at 216 nm.

It is thus seen that the pyridyl chromophore, depending on substituents, will show strong polarized light absorption in the lower accessible region where the carboxyl chromophore absorbs. Since the pyridyl absorption is very strong the carboxyl band may be fully hidden or its appearance strongly modified.

Fig. 1 shows that the phenyl group in the alcohol (Vb) in the same way as in the acid (VIIb) [2] acts as a β-chromophore with a multiple Cotton effect in the 250 – 270 nm region. In the amphetamine derivative, however, this effect is weak as it is not apparent from the curve.

The polarized light spectra for the furoyl derivatives (II) were also recorded. The alaninol (IIa) in acid solution has positive and negative maxima at 252 and 216 nm, respectively, with associated UV bands at 255 and 215 nm. The sign of the polarized light absorption was the opposite for the aryl derivatives. The phenylalaninol (IIb) has in acid solution a negative Cotton

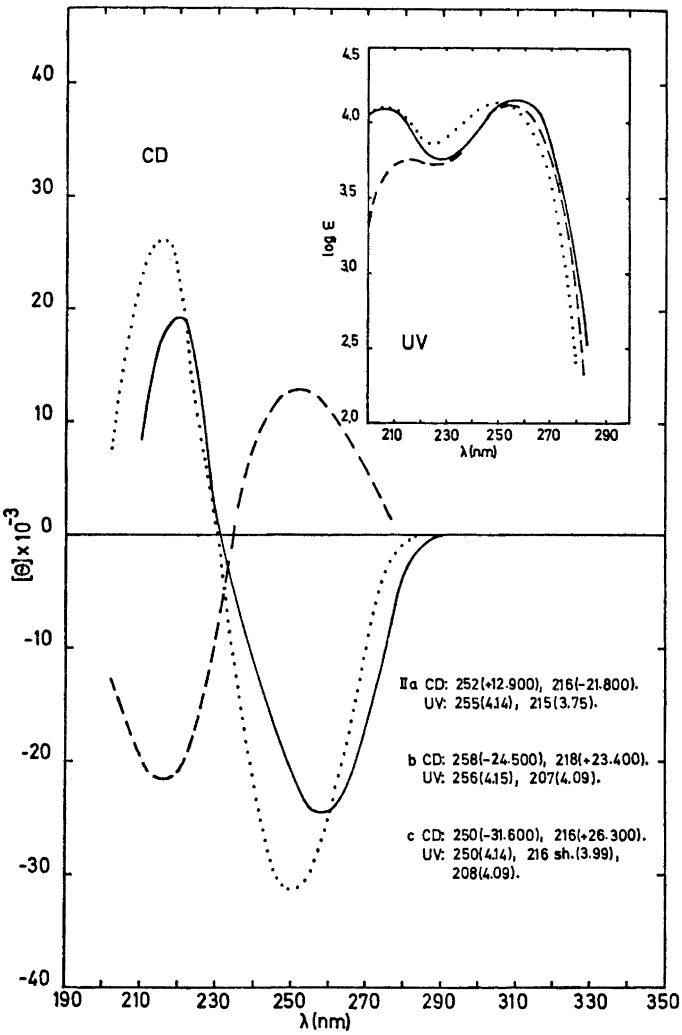


Fig. 2. CD and UV absorption of IIa (– – –) and IIb (———) in 0.1 N HCl, and of IIc (·····) in methanol.

effect at 258 nm with UV maximum at 256 nm and a positive polarized absorption band at 218 nm. The corresponding CD bands for the amphetamine (IIc), dissolved in methanol because of low water solubility, are at 250 and 216 nm with UV maximum at 250 nm and a shoulder at 216 on the band at 208 nm. The higher wavelength CD band must be associated with the furoyl chromophore which also is responsible for the lower wavelength band. Further contribution to the appearance of the latter comes from the ester carbonyls in the alaninols.

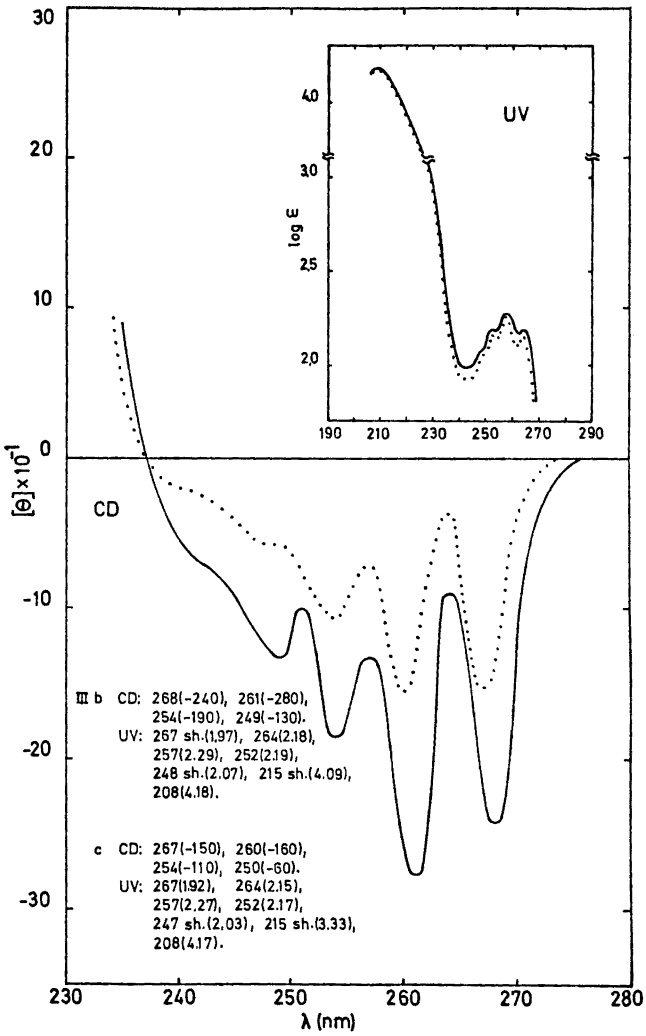


Fig. 3. CD and UV absorption of IIIb (———) and IIIc (·····) in 0.1 N HCl.

With both carbonyl groups reduced such as in *N*-furfurylalaninol (IIIa) the UV spectrum shows only the furan absorption at 215 nm. The phenylalaninol (IIIb) and the amphetamine (IIIc), however, have in acid solution a negative multiple Cotton effect at 250 – 270 nm with highly resolved UV absorption in the 245 – 270 nm region (Fig. 3). Any multiple Cotton effect from the phenyl group in the furoyl derivatives (IIb and IIc) would fall in the region for the strong furoyl absorption and is obscured because of low intensity.

Finally it is pointed out that the (–)-amphetamine and the L-phenylalanine derivatives, which have very similar CD curves throughout this series, have opposite absolute configuration, the former being (*R*) and the latter (*S*). The configurational correlation follows from the conversion of D-(+)-phenylalanine into (+)-amphetamine by full reduction of the carboxyl group.[6]

EXPERIMENTAL

The CD and UV spectra were recorded on a Jasco model J – 10 spectropolarimeter. The solvent was 0.1 N HCl, cell length 1 mm and temperature 27°C.

(S)-N-*2-Furoyl-amino acid methyl ester (II)*. The methyl ester of the amino acid hydrochloride (0.1 mol) was dissolved in water (50 ml), chloroform (220 ml) was added and the mixture cooled in an ice-bath. Magnesium oxide (0.26 mol) was added in three portions over 30 min to the ice-cold, vigorously stirred mixture. The stirring was continued for another 40 min and furoyl chloride (0.1 mol) added dropwise. After 60 min another 100 ml of chloroform were added and the mixture centrifuged at 9000 rpm. The chloroform phase was then washed with N Na_2CO_3 (50 ml), with water (2 × 30 ml) and dried over $MgSO_4$. Evaporation left a gummy material which slowly crystallized.

	M.p. °C	Yield %	Molecular formula	Found			Calc.		
				C	H	N	C	H	N
IIa	45 – 46	60	$C_9H_{11}NO_4$	54.74	5.62	7.07	54.81	5.62	7.10
IIb	73 – 74	86	$C_{15}H_{15}NO_4$	65.82	5.25	5.13	65.91	5.53	5.12

IIa was recrystallized from isopropyl ether and IIb from 2-propanol/water or water. IIa: $[\alpha]_D$ –2.7° (*c* 1.1 in 2 N HCl); +37.3° (*c* 1.2 in $CHCl_3$). IIb: $[\alpha]_D$ –67.0° (*c* 0.3 in 6 N HCl); +80.5° (*c* 1.3 in $CHCl_3$).

(R)-N-*2-Furoyl-amphetamine (IIc)*. The title compound was prepared as above from (*R*)-amphetamine, $[\alpha]_D^{20}$ –33° (neat), and furoyl chloride; yield 82 % and m.p. 102 – 103°C after recrystallization from 2-propanol/H_2O. (Found: C 73.21; H 6.65; N 6.05. Calc. for $C_{14}H_{15}NO_2$: C 73.33; H 6.59; N 6.11). $[\alpha]_D$ –105° (*c* 0.9 in MeOH).

(S)-N-*Furfurylalaninols (IIIa, IIIb)*. The finely ground *N*-2-furoyl-amino acid methyl ester (0.02 mol) was added over 10 min under anhydrous conditions to $LiAlH_4$ (0.06 mol) in anhydrous ether (300 ml) under stirring. The stirred reaction mixture was heated under reflux for 5 h, excess $LiAlH_4$ destroyed by addition of ethyl acetate (20 ml, the mixture filtered, the solid residue triturated twice with ether (50 ml), the combined ether phases washed with water (2 × 15 ml, saturated salt solution), dried over $MgSO_4$, evaporated and the residue distilled.

	B.p. °C/mmHg	M.p. °C	Yield %	Molecular formula	Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
IIIa	86–90/0.2	32–34	49	$C_8H_{13}NO_2$	61.36	8.50	9.10	61.90	8.44	9.02
IIIb		81	78	$C_{14}H_{17}NO_2$	72.34	7.25	6.03	72.69	7.41	6.05

IIIa was recrystallized from isopropyl ether/hexane; IIIb from isopropyl ether. IIIa: $[\alpha]_D$ +21.2° (*c* 1.3 in 2 N HCl), +45 (*c* 1.4 in $CHCl_3$). IIIb: $[\alpha]_D$ −15.0° (*c* 0.6 in 2 N HCl), −14.3° (*c* 1.7 in $CHCl_3$).

(R)-N-*Furfurylamphetamine (IIIc)*. The title compound was prepared by lithium aluminium hydride reduction in tetrahydrofuran of the corresponding amide as above, yield 71 %, b.p. 113–114°C/0.8 mmHg. (Found: C 78.11; H 7.77; N 6.28. Calc. for $C_{14}H_{17}NO$: C 78.11; H 7.96; N 6.50.) $[\alpha]_D$ +24.9° (*c* 1·4 in 0.1 N HCl).

The synthesis of the (*S*)-isomer from furfural and amphetamine has previously been described.[7]

N-*(2,5-Dimethoxy-2,5-dihydrofurfuryl)alaninols (IVa, IVb)*. Ammonium bromide (5.0 g) was dissolved in methanol (230 ml), the *N*-furfurylalaninol (0.03 mol) added, the solution cooled to −30°C and electrolyzed at this temperature using 3 A. Two and a half times the theoretical number of coulombs were used. Methanolic sodium methoxide (20 ml, from 1.2 g of sodium) was then added, the mixture evaporated, the residue extracted with ether (150 ml), the ether solution washed with water (2 × 15 ml), dried and evaporated. The residual oil could be distilled but was used as such in the next step.

(R)-N-*(2,5-Dimethoxy-2,5-dihydrofuroyl)amphetamine (VI)*. (−)-Amphetamine (8.10 g, 0.06 mol) was dissolved in a mixture of benzene (40 ml) and water (10 ml), magnesium oxide (2.4 g, 0.06 mol) added, the mixture cooled in ice-bath and a benzene solution (20 ml) of 2,5-dimethoxy-2,5-dihydrofuroyl chloride, prepared from 0.06 mol of the sodium salt of the acid with oxalyl chloride,[8] added dropwise over 80 min with vigorous stirring. The benzene phase was separated, washed with a little N sodium carbonate and water, dried over magnesium sulphate, evaporated and the residue distilled. The title compound was collected at 162–164°C/0.15 mmHg; yield 4.90 g (28 %). (Found: C 65.55; H 7.20; N 4.83. Calc. for $C_{16}H_{21}NO_4$: C 65.98; H 7.27; N 4.81.) $[\alpha]_D$ = −5.7° (*c* 1.4 in $CHCl_3$).

(S)-N-*(1-Hydroxy-2-propyl)pyridinium-3-oxide (Va) and* (S)-N-*(1-hydroxy-3-phenyl-2-propyl)pyridinium-3-oxide (Vb)*. A solution of the *N*-(2,5-dimethoxy-2,5-dihydrofurfuryl)alaninol (0.02 mol) in 4 N HCl (30 ml) was heated under reflux for 40 min. Water (90 ml) was then added, any insoluble material filtered off and aqueous phosphotungstic acid (25 %) added dropwise until no more precipitate was formed. The precipitate was collected using a centrifuge (9000 rpm), washed with water and centrifuged again. The phosphotungstic acid salt was dried at 40°C before dissolution in acetone (140 ml), any insoluble material filtered off and methanol (80 ml) and water (140 ml) added. Barium acetate solution (8 %) in methanol/water (3:2) was added dropwise in slight excess, the mixture stirred for 2 h, the precipitate removed by centrifugation, the supernatant concentrated to 100 ml under reduced pressure, excess barium ions precipitated through dropwise addition of 4 N sulphuric acid and the precipitate again removed by centrifugation. The solution was then passed through a column of IRA–400 (AcO^-), the column washed with 0.01–0.1 N HOAc or water and the combined eluates freeze-dried. The residual solid, the title compound, was dissolved in 10–12 drops of 32 % HCl or 48 % HBr. The respective salts slowly crystallized out from the solution on standing at 0–4°C. The analytical samples were recrystallized from EtOH/EtOAc.

	M.p. °C	Yield %	Molecular formula	Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
Va	139–141	41	$C_8H_{11}NO_2.HCl$	50.56	6.54	7.35	50.67	6.38	7.39
Vb	166–167	52	$C_{14}H_{15}NO_2.HBr$	53.90	5.26	4.50	54.20	5.20	4.51

Va: $[\alpha]_D$ +20.8° (*c* 1.0 in 0.1 N HCl). Vb: $[\alpha]_D$ −121° (*c* 1.0 in 0.1 N HCl).

(R)-N-(*1-Phenyl-2-propyl*)*pyridinium-3-oxide (Vc)*. 30 % Hydrogen peroxide (3.36 g) was added dropwise to an ice-cold stirred solution of *N*-furfurylamphetamin (3.22 g, 0.015 mol) in 4 N HCl (40 ml). After 2 h in the cold the solution was heated under reflux for 20 min, allowed to cool, pH brought to 8 with potassium carbonate, extracted with ether, the aqueous solution brought to about pH 3 and evaporated. The dried residue was extracted with boiling ethanol (4 × 30 ml), the ethanol treated with charcoal (1 g) under heating, filtered and evaporated. The solid residue (2.0 g) was dissolved in 3 drops of concentrated HCl. After a few days in the cold a crystalline mass had been formed. The crystalline solid was recovered by filtration and recrystallized from acetone: yield 1.0 g (27 %), m.p. 110–112°C. (Found: C 67.64; H 6.51; N 5.55. Calc. for $C_{14}H_{15}NO.HCl$: C 67.33; H 6.46; N 5.61.) $[\alpha]_D$ −129° (*c* 0.5 in 0.1 H NCl).

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