Circular Dichroism of 5-Alkyl-5-(3-hydroxy-1-methylbutyl)barbituric Acids

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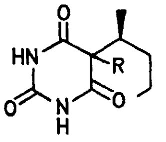
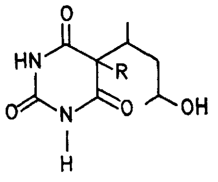
The c.d. spectra for 5-alkyl-5-(3-hydroxy-1-methylbutyl)barbituric acids (2) in trifluoroethanol show two Cotton effects in the 230—260 nm region opposite in sign from those of similar compounds lacking a side-chain 3-hydroxy-group.

We have previously reported that the c.d. curves of several (*S*)-5-alkyl-5-(1-methylbutyl)barbituric acids (1; R = alkyl) show three Cotton effects in the 200—260 nm range.[1] The two longer wavelength n–π^* Cotton effects (*ca.* 260 and *ca.* 250 nm) were of negative sign,† and the shorter wavelength π–π^* Cotton effect was positive. In the case of the unsubstituted derivative (1; R = H), the signs of all three Cotton effects were opposite from those of all the other derivatives. We now present the c.d. properties of 5-ethyl- and 5-allyl-5-(3-hydroxy-1-methylbutyl)barbituric acids (2a and b), which differ from the barbituric acids in our earlier studies[1] in possessing a polar hydroxy-group on the 1-methylbutyl side chain.



(1)



(2)a; R = Et
b; R = $CH_2{:}CH{\cdot}CH_2$

The c.d. data for the isomers of compounds (2a and b) in trifluoroethanol are summarized in the Table. In contrast to the 5-alkyl-5-(1-methylbutyl)barbituric acids previously studied,[1] the lower wavelength n–π^* transition showed a larger amplitude than the higher wavelength n–π^* transition. More importantly, the signs of the two Cotton effects of both the (1′*S*,3′*S*)- and (1′*S*,3′*R*)-isomers of (2a and b) are positive, and the (1′*R*,3′*R*)- and (1′*R*,3′*S*)-epimers show similar but negative Cotton effects. These results contrast sharply with the c.d. curves of all the (*S*)-5-alkyl-5-(1-methylbutyl)barbituric acids, which showed two negative Cotton effects in the 260—240 nm region,[1] and emphasize the extreme sensitivity of the barbituric acid derivatives to changes in molecular stereochemistry.

It is possible to rationalize these results on the basis of the chiral alkyl substituent–heterocycle stereochemistry. Yeh and Richardson calculated the n–π^* rotatory strength as a function of rotation about the C(5)–CHMePr bond.[2] According to these authors, the sign of the n–π^* band depends upon the torsion angle θ between the bonds C(5)–C(:O) and C(1′)–CH_3 when a Newman projection is viewed along the C(1′)–C(5) bond. In the case of (1′*S*)-isomers the calculations showed that for 300° > θ > 240° the rotatory strength was negative,

Observed long-wavelength maxima and molar ellipticities of 5-alkyl-5-(3-hydroxy-1-methylbutyl)barbituric acids in trifluoroethanol

Compound	Stereochemistry	λ/nm[a]	10^{-2} [θ]	λ/nm	10^{-2} [θ]
(2a)	1′*S*, 3′*R*	256	+3.4	234	+16.1
	1′*R*, 3′S	256	−3.4	234	−15.5
	1′S, 3′*S*	257	+5.3	234	+16.5
	1′*R*, 3′*R*	257	−5.3	234	−15.6
(2b)	1′*S*, 3′*R*	256	+2.9	234	+15.1
	1′*R*, 3′*S*	256	−2.9	233	−14.9
	1′*S*, 3′*S*	257	+5.3	234	+16.0
	1′*R*, 3′*R*	257	−4.6	234	−15.6

[a] This maximum appeared as a shoulder on the higher-amplitude lower-wavelength maximum.

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† We suggested previously[1] that one of the longer wavelength Cotton effects could be due to an n–π^* or an n–σ^* transition.

[1] F. I. Carroll and A. Sobti, *J. Amer. Chem. Soc.*, 1973, **95**, 8512.

[2] C.-Y. Yeh and F. S. Richardson, *Theor. Chim. Acta*, 1975, **39**, 197.

whereas for *ca.* 350° or for θ within the regions 0—20° or 150—200° the computed rotatory strength was positive. If θ were in the range 240—300° for (*S*)-(1) (R = alkyl) * and 150—200° for (*S*)-(1) (R = H) and the (1′*S*)-isomers of (2a and b), a negative and a positive Cotton effect, would be expected, as was observed.† Molecular models show that θ values in the region 240—300° for (1; R = alkyl) allow maximal separation between the methyl and propyl components of the 1-methylbutyl group and the other 5-alkyl substituent R. For θ in the region 150—200° the propyl group of (1; R = H) and the CH_2·CH(OH)Me group (2) are *trans* to the other 5-alkyl substituent.

Theoretical calculations by Yeh and Richardson [2] also showed that the difference in sign of the *n*–π* Cotton effects of 5,5-dialkyl- and 5-alkyl-barbituric acids could be accounted for by chiral distortions within the trioxopyrimidine ring. Thus, the difference in sign of the *n*–π* Cotton effects between (1; R = alkyl) and (1; R = H) could depend upon the tendency of the trioxopyrimidine ring to assume various possible conformations. However, since the mode of ring puckering of 5,5-diethylbarbituric acid varies significantly among the six crystal structures reported,[3,4] Voet [5] has suggested that the distortion of the trioxopyrimidine ring is largely determined by crystal packing forces.

EXPERIMENTAL

C.d. measurements were made at ambient temperature (*ca.* 25 °C) with a Durrum-JASCO 20 ORD-CD spectropolarimeter calibrated with (+)-camphor-10-sulphonic acid (0.313° ellipticity for a 1 mg ml^{-1} solution in water; 1.0 cm cell; 290.5 nm). The cell compartment was continually purged with dry purified nitrogen. Time constants of 16 and a low scanning speed (*ca.* 100 nm h^{-1}) were used. In general, measurements were made at path lengths of 0.1 cm and a concentration of 2.0 mg ml^{-1}. The trifluoroethanol (Eastman Organic Chemicals) was distilled before use.

Several c.d. spectra were recorded at a sensitivity setting of 0.001° cm^{-1} for each compound studied. The c.d. data are expressed in terms of molar ellipticity, [θ], defined as $\psi M/10lc$, where ψ is the measured ellipticity in degrees, l is the path length in cm centimeters, c is the concentration in g ml^{-1}, and M is the molecular weight.

I.r., u.v., n.m.r., and mass spectra of all the (*S*)-5-alkyl-5-(3-hydroxy-1-methylbutyl)barbituric acids were in agreement with the assigned structures. The purity of the compounds was checked by g.l.c. analysis of the *O*-trimethylsilyl derivatives by using a Packard Becker 417 gas chromatograph equipped with a flame ionization detector. Silanized glass columns (6 ft × 1/8 in) packed with 3% SP.2250 on 100—120 mesh Supelcoport were used.

The 5-alkyl-5-(3-hydroxy-1-methylbutyl)barbituric acids were prepared as reported previously.[6]

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* This conformation is similar to the crystalline state conformation of 5-(1′,3′-dimethylbutyl)-5-ethylbarbituric acid P. H. Smit and J. A. Kanters, *Acta Cryst.*, 1974, **B30**, 784; J. M. A. Sitsen and J. A. Fieser, *Pharm. Weekblad*, 1974, **109**, 61) but different from that proposed on the basis of ^1H n.m.r. studies (G. D. Daves, jun., R. B. Bilshee, W. R. Anderson, and H. Downes, jun., *Mol. Pharmacol.*, 1975, **11**, 470).

† The positive Cotton effects of (1; R = H) and the (1′*S*)-isomers of (2) could also be accounted for if θ is *ca.* 350° or 0—20°. These possibilities [especially for (2)] seem much less likely, owing to steric interactions.

[3] B. M. Craven and E. A. Vizzini, *Acta Cryst.*, 1971, *B*27, 1917, and references cited therein.

[4] S. Kiryu, *J. Pharm. Sci.*, 1971, **60**, 699.

[5] D. Voet, *J. Amer. Chem. Soc.*, 1972, **94**, 8213.

[6] F. I. Carroll and G. N. Mitchell, *J. Medicin. Chem.*, 1975, **18**, 37.