Circular Dichroism of Barbituric Acid Derivatives. Influence of Solvents and Substituents upon the Cotton Effects of (*S*)-5-Alkyl-5-(2′-pentyl)barbituric Acids[1]

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Abstract: The effects of solvents and 5-alkyl substituents on the circular dichroism (CD) spectra of a number of 5-alkyl-5-(2′-pentyl)barbituric acids are reported. These compounds show three ellipticity bands in the region 200–300 nm. The bands are found at around 260, 240, and 212 nm. The solvent studies suggest that the 260- and 212-nm bands arise from a n–π^* and π–π^* transition, respectively. The intermediate band may be due to an n–σ^* transition or to a second n–π^* transition. The sign and intensity of the Cotton effects (CE) are discussed in relation to the conformation of the barbituric acid ring and the relative steric relationship between the heterocyclic ring and the 5-alkyl substituents.

The 5,5-dialkylbarbituric acids (barbiturates) are highly active molecules in biological systems, the best known of which is their sedative action in the central nervous system (CNS). Although this class of compounds has been extensively used in medical and biological studies for many years, the molecular basis of their mode of action is unknown. Barbiturates are 6-oxo derivatives of uracil, a component of the nucleic acids. This similarity may be important since barbiturates have been found to associate preferentially with adenine[2] analogous to the uracil–adenine binding in nucleic acids. The strong interaction observed between barbiturates and adenine led to the suggestion that the barbiturates exert their biological activity by specifically binding and inactivating a variety of molecules containing adenine, including coenzymes and adenosine 5′-triphosphate.[2] An important component of this interaction is the stereochemistry and conformation of the barbituric acid ring as well as the C(5) lipopylic side chains known to be necessary for CNS activity. In order to gain insight into the geometry of the barbiturates, we have conducted a detailed study of the circular dichroism (CD) properties of several 5-alkyl-5-(2′-pentyl)barbituric acid derivatives. Since a primary consideration in efforts to determine molecular stereochemistry from CD data is the nature of the electronic transition(s) which gives rise to an observed ellipticity band, we have devoted considerable effort to establishing the types of transitions exerted by these compounds. The information gained should also be helpful in determining the structure of other barbiturates such as biotransformation products.

In an earlier report we described the syntheses and absolute configuration of several (*S*)-5-alkyl-5-(2′-pentyl)barbituric acid derivatives.[3] The optical rotatory dispersion (ORD) spectra of these compounds were determined and found to show at least two Cotton effects (CE). It was noted that the ORD curve of (*S*)-5-ethyl-5-(2′-pentyl)barbituric acid (**1**) was quite different from the curve of (*S*)-5-(2′-pentyl)barbituric acid (**2**). The suggestion was put forth that these differences may be due to conformation and might be helpful in explaining the differences in biological activity of these two compounds.

In view of the biological significance of barbituric acid derivatives[4] and the current interest in the chiroptical properties of heterocyclic and biologically interesting compounds,[5] we have now investigated the ultraviolet (uv) and CD properties of several (*S*)-5-alkyl-5-(2′-pentyl)barbituric acid derivatives. All of these compounds contain the symmetrical trioxopyrimidine chromophore which can be dissymmetrically perturbed by its surroundings, thus giving rise to optically active absorption bands.

Results and Discussion

The uv, ORD, and CD curves of 5-ethyl-5-(2′-pentyl)-barbituric acid, measured from 200 to 340 nm in methanol–0.1 *N* HCl (1 : 1) are presented in Figure 1. In agreement with our earlier report based on ORD studies, the CD curve of **1** shows a low intensity CE at 257 nm and a higher ellipticity CE at 212 nm. In addition, the CD curve shows a shoulder at approximately 238 nm which is not apparent in the ORD curve. The uv spectra in the same solvent exhibits a maximum at 212 nm but shows only tail absorption in the region 240–340 nm. In our earlier report,[3] based mainly on location and relative amplitude of the CE observed in the ORD spectra, the high and low wavelength CE were attributed to a n–π^* and π–π^* transition, respectively. In order to more fully determine the nature of these electronic transitions and to establish the nature of the CE at 238 nm observed only in the CD curve, we have studied the effect of solvent and substitution on the CE spectra of several (*S*)-5-alkyl-5-(2′-pentyl)-barbituric acids.

Due to the nonbonding electron pairs of the car-

(1) This investigation was supported by Contract No. PH-43-NIGMS-65-1057 from the National Institute of General Medical Sciences, National Institutes of Health.
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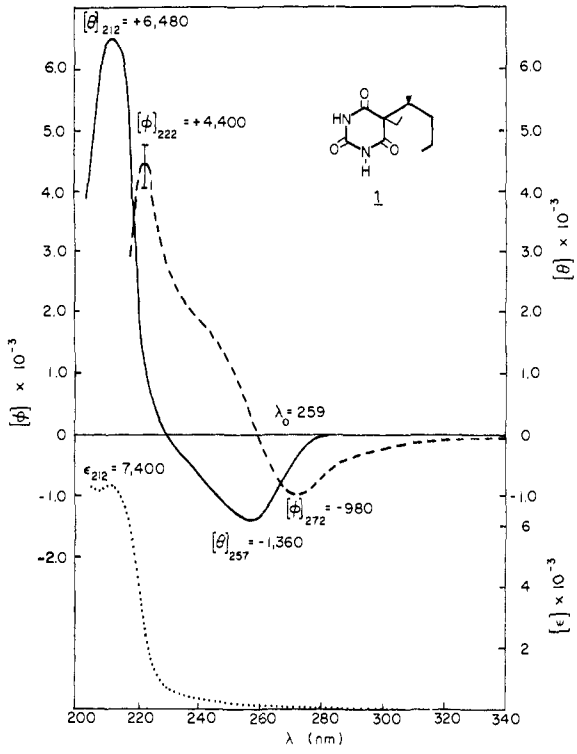

Figure 1. Ultraviolet absorption (....), ORD (----), and CD (——) spectra of (*S*)-5-ethyl-5-(2′-pentyl)barbituric acid (**1**) in 50% v/v methanol–0.1 *N* hydrochloric acid.

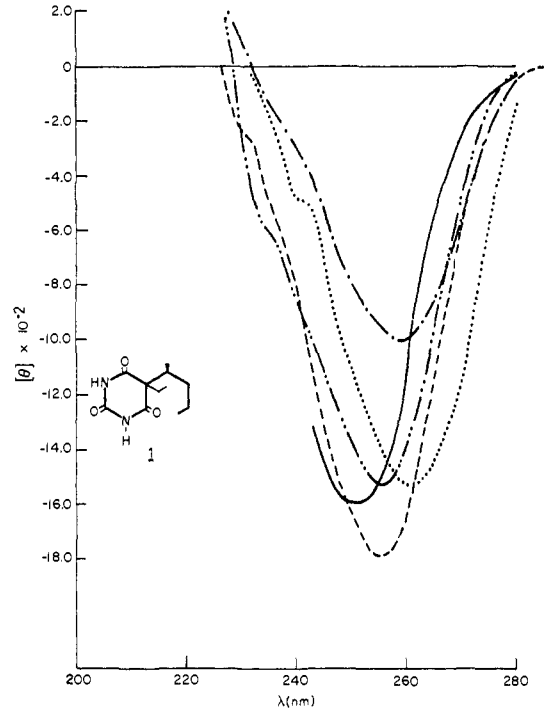

Figure 2. The CD spectra of **1** in trimethyl phosphate (...); methanol (-··-); water (-· ··-); trifluoroethanol (----); and trifluoroacetic acid (——) showing the high wavelength low amplitude negative Cotton effect.

bonyl oxygens and the nitrogen atoms of the barbituric acid ring, these compounds are capable of exhibiting n–π^* transitions. Solvent studies have been used to characterize n–π^* transitions and to distinguish them from π–π^* transitions in many cases including a number of heterocyclic systems.[6] In protonic solvents the lone pair of electrons are engaged in hydrogen bonding, and the promotion of these electrons to a π^* orbital requires energy to weaken or break the hydrogen bond in addition to the normal transition energy. This results in absorption at shorter wavelength. Thus, n–π^* transitions show blue shifts in going from nonpolar to more polar solvents. In contrast π–π^* transitions show red shifts on changing from non-hydrogen-bonding to hydrogen-bonding solvents. This results from the favorable interaction of the highly polar excited state with the solvent cage of the more polar solvents.

The CD spectra of the higher wavelength CE of **1** in trimethyl phosphate, methanol, water, trifluoroethanol, and trifluoroacetic acid are shown in Figure 2. Figure 3 shows the lower wavelength positive CE of **1** in dichloroethane, acetonitrile, and methanol. The high wavelength negative band as well as the shoulder on this band shows a blue shift with increasing solvent polarity. The low wavelength positive band shows a red shift. The same type of shifts in the positive band are also apparent in the ultraviolet spectra in acetonitrile, methanol–H_2O (1 : 1), methanol, and trifluoromethanol (see Figure 4). Note the left side of the uv curves. Here the absorption is dominated by the π–π^* absorption, and the curves show the characteristic red shift of such transitions as the polarity of the

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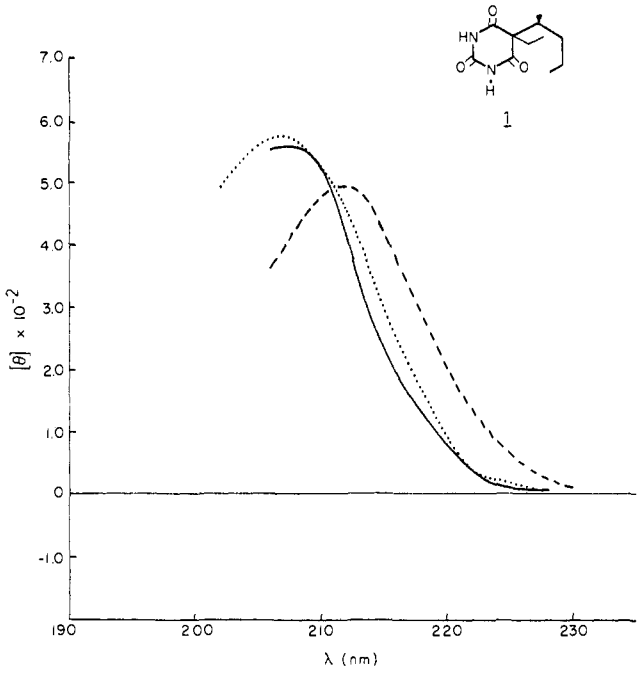


Figure 3. The CD spectra of **1** in dichloroethane (——); acetonitrile (...); and methanol (---) showing the low wavelength high amplitude positive Cotton effect.

solvent is increased. In our earlier paper the negative and positive bands were attributed to n–π^* and π–π^* transitions, respectively. The position of the CD bands and their shift with solvent polarity give added support for these assignments. The blue shift of the high wavelength shoulder suggests that the nonbonding electrons are also involved in this band.

The CD spectra in the high wavelength region of

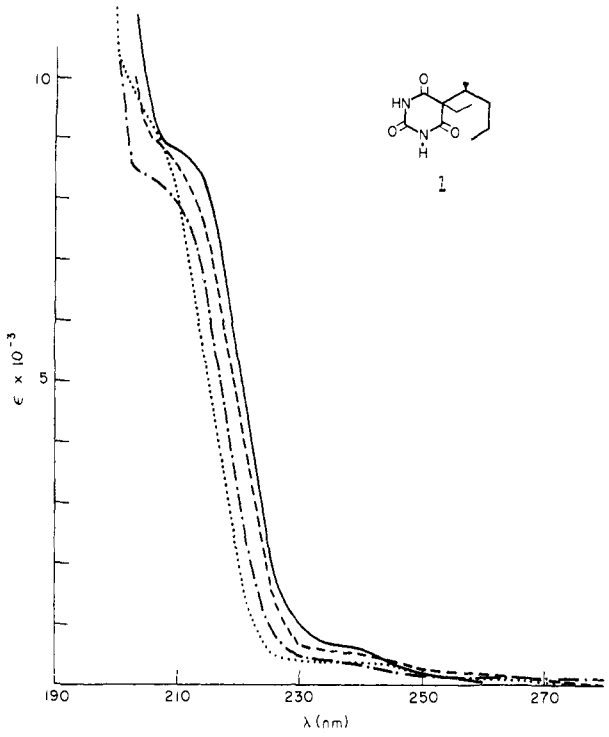


Figure 4. The uv spectra of **1** in acetonitrile (...); methanol (---); trifluoroethanol (-··-); and methanol–water (1:1) (——).

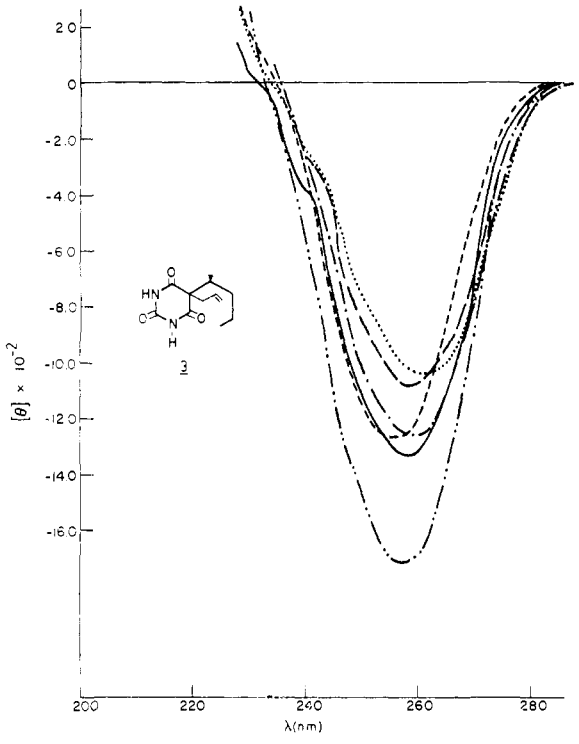


Figure 5. The CD spectra of **3** in trimethyl phosphate (...); dioxane (— —); acetonitrile (——); methanol (·-·); methanol–H_2O (1:1) (---); and trifluoroethanol (-· ·-).

(*S*)-5-allyl- (**3**), (*S*)-5-propyl-(**4**), (*S*)-5-isopropyl- (**5**), (*S*)-5-methyl-5-(2′-pentyl)barbituric acid (**6**), and (*S*)-5-(2′-pentyl)barbituric acid (**2**) are illustrated in Figures 5–9. Representative solvent effect curves are included in each figure to ensure that we are observing the same transition in each compound. It is apparent that the substituent at position 5 can have a profound effect on

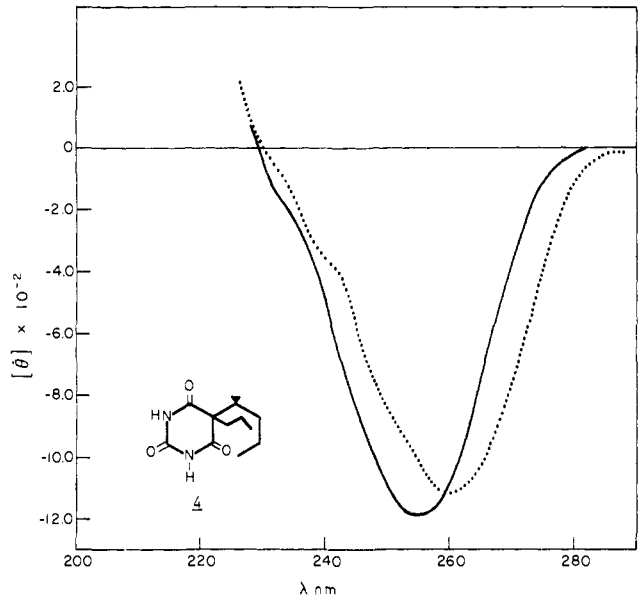


Figure 6. The CD spectra of **4** in trimethyl phosphate (...) and trifluoroethanol (——).

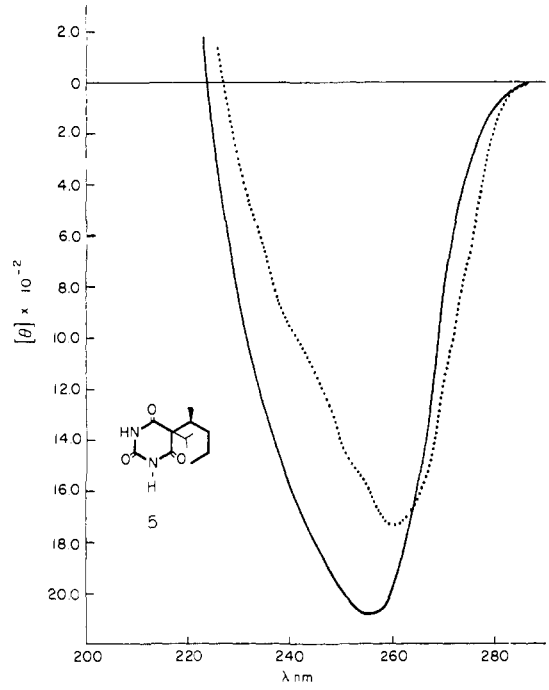


Figure 7. The CD spectra of **5** in trimethyl phosphate (. . .) and trifluoroethanol (——).

the CD curve. Whereas the CD curves of 5-allyl, 5-propyl, and 5-isopropyl compounds are all quite similar to the 5-ethyl derivative (**1**), the 5-methyl analog **6** shows two distinct CE's in the high wavelength region of approximately equal intensity. However, the most dramatic alteration of the CD spectrum of these compounds is encountered with the unsubstituted analog **2**. In complete contrast to the (*S*)-5-alkyl-5-(2′-pentyl)barbituric acids, **2** shows two positive CE's in the high wavelength region. Even though the magnitude of the observed ellipticity in individual cases varied and even the sign of the bands in one case was different, the general character of all the curves was similar. That is, the two high wavelength bands un-

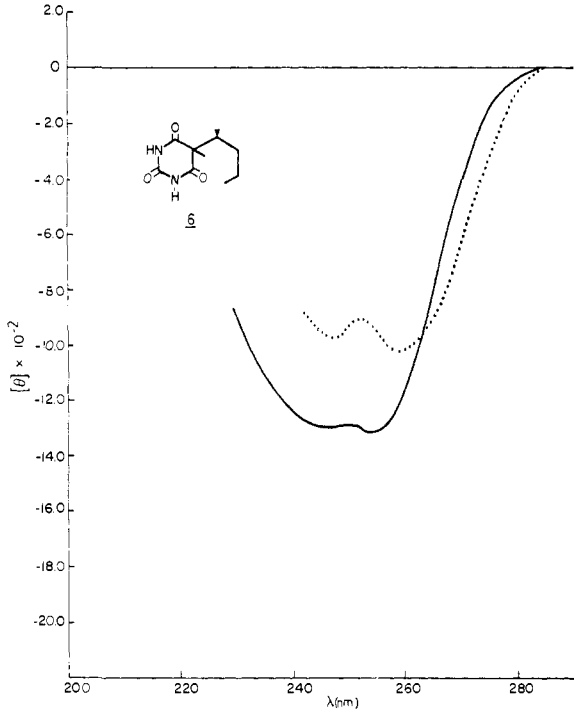


Figure 8. The CD spectra of **6** in trimethyl phosphate (. . .) and trifluoroethanol (——).

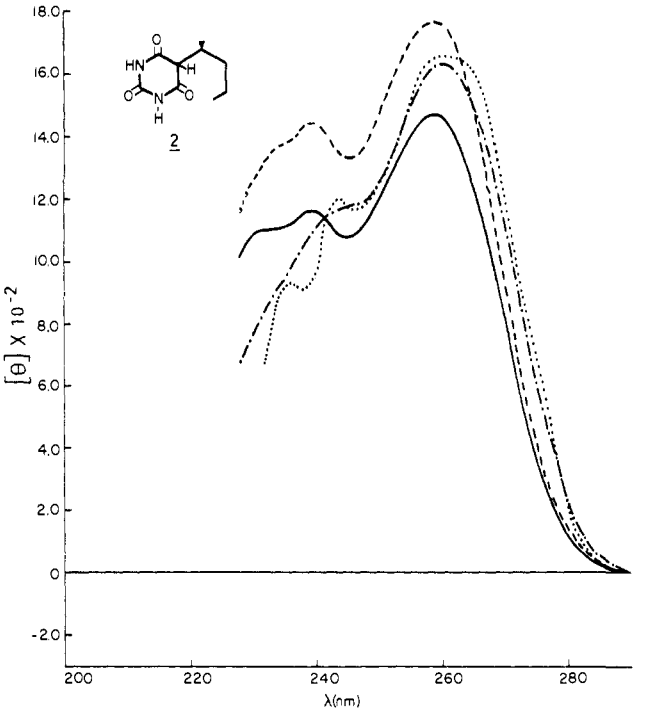
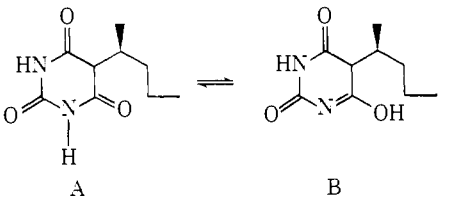


Figure 9. The CD spectra of **2** in dioxane (. . .); methanol (·-·); methanol–water (1:1) (——); and trifluoroethanol (---).

dergo a red shift on changing from polar to less polar solvents, the molar ellipticity values decrease, and the low wavelength band experiences a red shift in going from less polar to more polar solvents. These solvent studies strongly suggest that all the (*S*)-5-(2′-pentyl)-barbituric acid derivatives studied show a high wavelength n–π^* ellipticity band, a low wavelength π–π^* band, and, in addition, a third band at intermediate wavelength which is blue shifted in going from nonpolar to more polar solvents.

It could be argued that the intermediate band results from an enol form B. This band could also result from



A B

association. However, since the shape and intensity of CD spectra of **1** does not change when measured in 50% v/v methanol–water, 50% v/v methanol–concentrated hydrochloric acid, and 50% v/v methanol–0.1 *N* hydrochloric acid over the concentration range 0.2 to 2.1 mg/l., neither of these suggestions seems likely. In addition, the CD curve shown in Figure 10 of (*S*)-5-ethyl-1,3-dimethyl-5-(2′-pentyl)barbituric acid (**7**), which is incapable of enolization and probably association, shows two negative long wavelength CE at λ 257–258 and 243–245.5 nm. It is also particularly interesting that neither of the ellipticity bands of **7** shows appreciable shifts with changing solvent polarity. This indicates that solvent interaction with the nitrogen atom *via* its attached hydrogen must be occurring in the compounds **1**–**6**. Since the 1,3-dimethyl derivative **7** still shows the intermediate CD band and since this band in the spectra of **1** is unaffected by changes in pH or concentration, we conclude that it is due to a new optically active transition. In support of this suggestion the uv spectra of **1** (Figure 4) in all the solvents examined shows a small inflection between 230 and 245 nm.

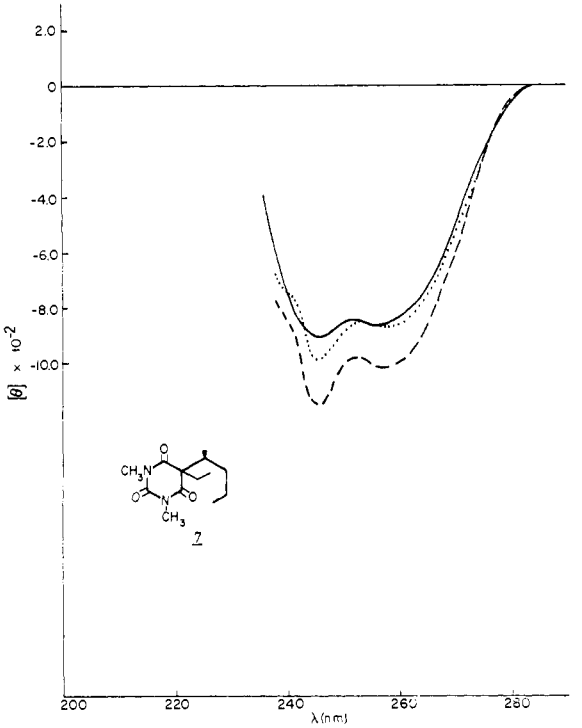


Figure 10. The CD spectra of **7** in trimethyl phosphate (. . .); acetonitrile (---); and methanol (——).

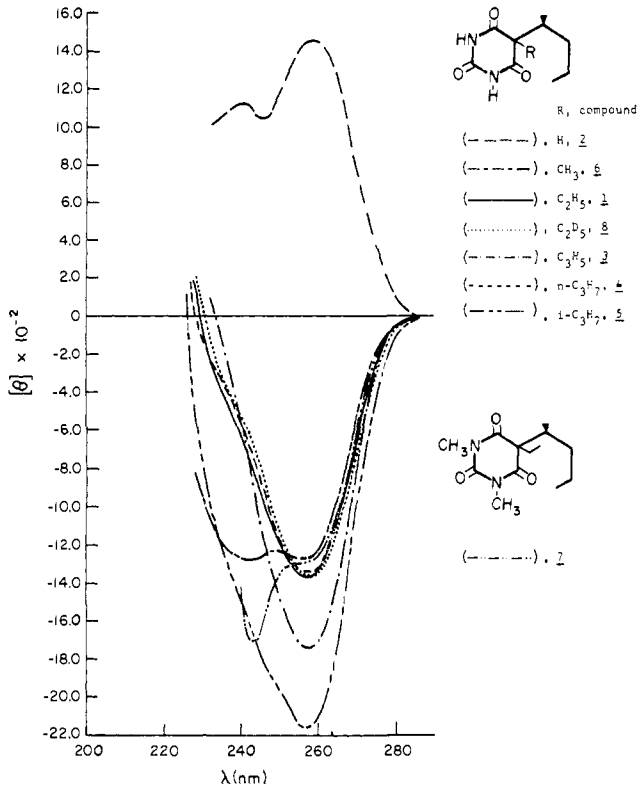


Figure 11. The CD spectra of **1–8** in 50% v/v methanol–0.1 *N* hydrochloric acid.

In some cases, amides,[7,8] lactams,[9,10] and other molecules which contain one or more –CON< [11,12] groups have been found to show three optically active CD bands similar to the (*S*)-5-(2′-pentyl)barbituric acids in this study. The high and low wavelength bands have been shown to be due to n–π^* and π–π^* transitions, respectively. In some cases the intermediate band is due to association;[10] in others it is apparently due to a new n–σ^* transition.[7–9,12] Since the heterocyclic ring of the (*S*)-5-(2′-pentyl)barbituric acids we have studied contain three –CON< groups, the intermediate band we have observed may be due to a n–σ^* transition. This band could also be due to a second n–π^* transition. However, since both a n–σ^* and a n–π^* transition would show a blue shift in going from nonpolar to more polar solvents, solvent studies are not useful in distinguishing between the two types of transitions. Additional studies involving magnetic circular dichroism may be able to establish the nature of the intermediate transition.

In order to find a relationship between the magnitude (and possibly the sign) of the two longer wavelength CE's and the geometry of the (*S*)-5-(2′-pentyl)barbituric acid derivatives, we have obtained the CD curves of **1–7** and 5-(ethyl-d_5)-5-(2′-pentyl)barbituric acid (**8**)[13] in the same solvent system (0.1 *N* HCl–CH_3OH, 1:1). The results obtained are shown in Figure 11.

The λ_{max} and magnitude of the long wavelength band (~258 nm) are almost identical in all the (*S*)-5-alkyl-5-(2′-pentyl)barbituric acids. In the case of **3** and **5** which have a 5-allyl and 5-isopropyl substituent, respectively, the intensity of the band is increased. In contrast, the intermediate band (230–244 nm) is extremely sensitive to changes in the 5-alkyl substituent. In the case of 5-ethyl-1,3-dimethyl-5-(2′-pentyl)barbituric acid (**7**), the intermediate band at λ_{max} 238 is more intense than the long wavelength band, whereas, it is only barely detectable in **3** (R = allyl). In the 5-methyl derivative **6**, the two bands have approximately the same intensity, and with **1** (R = C_2H_5), **4** (R = *n*-C_3H_7), and **8** (R = C_2D_5) the band appears as a low intensity shoulder on the long wavelength band. One explanation for this change in the intensity of the intermediate CE with various 5-alkyl and *N*-alkyl substituents is that the barbituric acid ring is not rigid and that the conformation of the ring is dependent on the substituent. In support of this, Gartland and Craven have studied the X-ray crystal structure of several 5,5-dialkylbarbituric acids and concluded that at least in the solid state, the ring shows a significant degree of puckering.[14]

In the unsubstituted (*S*)-5-(2′-pentyl)barbituric acid (**2**) the long wavelength band is about 15% more intense than the intermediate band; however, even more important in this example is the fact that the sign of both CE's is opposite to those observed for the (*S*)-5-alkyl-5-(2′-pentyl)barbituric acids. This observation creates a problem in attempts to correlate the sign of the CD curves with the absolute configuration. However, the change in sign does indicate that the relative geometry between the 5-alkyl side chains and the NHCO group controls the sign of the n–π^* CE observed. In the case of some lactams and diketopiperizines, Urry[11b] has shown that the sign of the CE is dominated by two opposing terms which are distance dependent. It might be that the 5-alkyl group of the 5-alkyl-5-(2′-pentyl)barbituric acid is close to the –NHCO– groups of the barbituric acid ring and thus changes the sign of the transition.

Summary

Several (*S*)-5-alkyl-5-(2′-pentyl)barbituric acids have been prepared. The compounds show a negative ellipticity band at 250–262 nm, which is blue shifted upon going from nonpolar solvents to solvents with higher polarity, which probably arises from an n–π^* transition. A second positive ellipticity band centered at 208–212 nm red shifts with increasing solvent polarity and is probably due to a π–π^* transition. The spectra of the compounds also show a third band at intermediate wavelength, which is not due to enolization or association. This band red shifts with decreasing solvent polarity; it may be due to a n–σ^* transition or to a second n–π^* transition. The magnitude of the intermediate band is extremely sensitive to changes in the 5-alkyl group indicating that the conformation of the heterocyclic ring, the 5-alkyl substituents, or both are changing as one of the 5-alkyl groups is varied.

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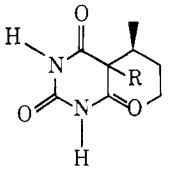
(13) (*S*)-5-(Ethyl-d_5)-5-(2′-pentyl)barbituric acid was prepared from ethyl-d_5 iodide having a minimum isotopic purity of 98%.
(14) G. L. Gartland and B. M. Craven, *Acta Crystallogr., Sect. B*, **27**, 1909 (1971).

Table I. Observed Maxima and Molar Ellipticities of (*S*)-5-Alkyl-5-(2′-pentyl)barbituric Acids



Solvent	R	λ_{nm}	$[\theta] \times 10^{-2}$	λ_{nm}[a]	$[\theta] \times 10^{-2}$	λ_{nm}	$[\theta] \times 10^{-2}$
Dioxane	H	261	+16.5	244	+12.1	209	−34.7
Acetonitrile	H	260	+14.2	242.5	+11.2	207	−32.3
Methanol	H	260	+16.3	245 (S)	+11.8	210	−28.0
Methanol–H_2O (1:1)	H	259	+14.7	239.5	+11.6		
Trifluoromethanol	H	259	+17.6	239.5	+14.4		
50% v/v methanol–0.1 *N* HCl	H	258.5	+14.6	239.5	+11.3		
Trimethyl phosphate	CH_3	259	−10.2	247.5	−9.7		
Trifluoroethanol	CH_3	253.5	−13.2	246.5	−13.0		
50% v/v methanol–0.1 *N* HCl	CH_3	256	−12.7	243	−12.8	212	+42.4
Trimethyl phosphate	C_2H_5	262	−15.4	241.5 (S)	−4.9		
Dioxane	C_2H_5	258.5	−8.8	240.5 (S)	−2.8		
Dichloroethane	C_2H_5	257.5	−11.8	240 (S)	−4.8	208	+55.3
Acetonitrile	C_2H_5	257.5	−10.1	242 (S)	−3.5	207	+56.8
Methanol	C_2H_5	257	−13.6	238 (S)	−2.3	212	+50.5
Methanol–H_2O (1:1)	C_2H_5	257	−13.9	237 (S)	−4.5	212	+64.0
Water	C_2H_5	255.5	−15.3	236 (S)	−6.0		
Trifluoroethanol	C_2H_5	255	−17.9	230 (S)	−2.4		
Trifluoroacetic acid	C_2H_5	250	−16.0				
50% v/v methanol–0.1 *N* HCl	C_2H_5	257	−13.6	235	−3.87	212	+64.2
Trimethyl phosphate	C_3H_5	261	−10.4	240 (S)	−2.44		
Dioxane	C_3H_5	259	−10.9	239 (S)	−2.95		
Acetonitrile	C_3H_5	258	−13.4	240 (S)	−3.90	209	+63.7
Methanol	C_3H_5	259	−12.6			212	+57.7
Methanol–H_2O (1:1)	C_3H_5	257	−17.8				
Trifluoroethanol	C_3H_5	255	−12.7			212	+50.9
50% v/v methanol–0.1 *N* HCl	C_3H_5	257.5	−17.5	239 (S)		212.5	+66.0
Trimethyl phosphate	*n*-C_3H_7	260	−11.2	240 (S)	−3.76		
Trifluoroethanol	*n*-C_3H_7	255	−12.0	233.5	−1.90		
50% v/v methanol–0.1 *N* HCl	*n*-C_3H_7	258	−13.4	233.5	+2.4	211	+57.5
Trimethyl phosphate	*i*-C_3H_7	260	−17.3	243 (S)	−10.5		
Trifluoroethanol	*i*-C_3H_7	255	−20.8	232 (S)	−10.1		
50% v/v methanol–0.1 *N* HCl	*i*-C_3H_7	257	−21.7	236 (S)	−12.1	211	+63.0
Trimethyl phosphate	C_2H_5[b]	258	−8.68	245.5	−9.86		
Acetonitrile	C_2H_5[b]	257	−10.1	245.5	−11.5		
Methanol	C_2H_5[b]	257	−8.64	245.5	−9.06	223	+45.6
50% v/v methanol–0.1 *N* HCl	C_2H_5[b]	256	−13.0	243	−17.2		
50% v/v methanol–0.1 *N* HCl	C_2D_5	258	−13.5	235	−3.89	212	+60.7

[a] (S) represents shoulder. [b] This compound also has 1,3-dimethyl substituents.

The CD spectrum of the monosubstituted derivative (*S*)-5-(2′-pentyl)barbituric acid is similar in character to the (*S*)-5-alkyl-5-(2′-pentyl)barbituric acids; however, the individual ellipticity bands have opposite signs. The conformational relationship between the 5-alkyl substituent and the heterocyclic ring is apparently different in the 5-alkyl-5-(2′-pentyl)barbituric acids and the monosubstituted 5-(2′-pentyl)barbituric acid.

Experimental Section

Circular dichroism measurements were made at ambient temperatures (~25°) with a Durrum-Jasco Model-20 ORD-CD spectropolarimeter calibrated with *d*-10-camphorsulfonic acid (0.313° ellipticity for a 1 mg/ml solution in water using a 1.0-cm cell at 290.5 nm). The cell compartment was continually purged with dry purified nitrogen. Time constants of 4 and 16 and a low scanning speed (~100 nm/hr) were used. In general, measurements were made at path lengths ranging from 0.01 to 0.1 cm and for concentrations ranging from 2.0 to 4.0 mg/ml. In studies on the effect of concentration, path lengths up to 1.0 cm were used. Special precautions were taken to assure that the CD bands in regions of strong absorption and weak ellipticity (below ~220 nm for the (*S*)-5-(2′-pentyl)barbituric acids) were real.

Several CD spectra were recorded at a sensitivity setting of 1.0 mdeg/cm for every compound studied. The CD spectra are expressed in terms of molar ellipticity, $[\theta]$, in deg l./(mol cm), defined by

$$[\theta] = \frac{\Psi M}{10lc}$$

where Ψ is the measured ellipticity in degrees, l is the path length in centimeters, c is the concentration in grams per milliliter, and M is the molecular weight. The results obtained are summarized in Figures 1–11 and Table I.

Ultraviolet absorption spectra were obtained on a Cary Model 14 spectrophotometer using silica cells of 0.1- and 1.0-cm path length.

Solvents. Distilled water, spectroquality dioxane, dichloroethane, and acetonitrile from Matheson Coleman and Bell and spectrograde methanol from Fisher Scientific Co. were used without further purification. Trifluoroethanol (Eastman Organic Chemicals), trimethyl phosphate (Aldrich Chemical Co.), and trifluoroacetic acid (Matheson Coleman and Bell) were distilled before use.

General. Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. Ir spectra were measured with a Perkin-Elmer 221 spectrophotometer. Nmr spectra were recorded on a Varian Model HA-100 spectrometer using tetramethylsilane as an internal standard. All observed rotations at the sodium D line were determined with a Perkin-Elmer Model 141 polarimeter (1-dm cell). Mass spectra were determined on an AEI-MS 902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

The ir, uv, nmr, and mass spectra of all the (*S*)-5-alkyl-5-(2′-pentyl)barbituric acids were in agreement with the assigned struc-

tures. The purity of the compounds was checked by glc analysis using a Varian Aerograph Model 2100-2 gas chromatograph equipped with a flame ionization detector. Glass columns (6 ft × 1/8 in.) packed with 3.8% SE-30 or 3.8% OV-17 on 100–120 mesh Chromosorb W (AWS) were used.

(*S*)-5-Methyl-5-(2′-pentyl)barbituric Acid (6). The title compound prepared by a procedure previously reported for similar (*S*)-5-alkyl-5-(2′-pentyl)barbituric acids[3] was recrystallized from ethyl acetate and sublimed, mp 181–182.5°.

Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.49; H, 7.59; N, 13.19. Found: C, 56.68; H, 7.55; N, 13.33.

(*S*)-5-(Ethyl-d_5)-(2′-pentyl)barbituric Acid (8). The title compound prepared by a procedure previously reported for similar (*S*)-5-alkyl-5-(2′-pentyl)barbituric acids[3] was recrystallized from a mixture of ethyl acetate and hexane and sublimated: mp 122–123° (lit.[3] mp 121.5–122°) for the nonlabeled compound; mass spectrum (70 ev) *m/e* 231 for molecular ion.

(*S*)-5-Isopropyl-5-(2′-pentyl)barbituric Acid (5). The title compound prepared by a procedure previously reported for similar (*S*)-5-alkyl-5-(2′-pentyl)barbituric acid[3] was obtained as an oil. It was purified by chromatography on silica gel using chloroform and chloroform–ethyl acetate mixtures as the eluent. The pure product fractions were combined, concentrated on a rotary evaporator, recrystallized from an ethyl acetate and hexane mixture, and sublimed, mp 130–131°.

Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.88; H, 8.39; N, 11.66. Found: C, 59.71; H, 8.48; N, 11.86.

(*S*)-5-*n*-Propyl-5-(2′-pentyl)barbituric Acid (4). To a suspension of 0.10 g of prereduced platinum oxide in 10 ml of ethanol was added a solution of 0.57 g (2 mmol) of **3** in 10 ml of ethanol. The solution was kept under an atmosphere of hydrogen until hydrogen ceased to be absorbed. The catalyst was removed by filtration and washed well with ethanol. The solid obtained after concentration of the filtrate was recrystallized from a mixture of methylene chloride and hexane and sublimed to give 0.32 g (69%) of **4**, mp 99–100°.

Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 60.21; H, 8.59; N, 11.72.

(*S*)-5-Ethyl-1,3-dimethyl-5-(2′-pentyl)barbituric Acid (7). To 1.0 g (4.44 mmol) of **1** in 20 ml of methanol was added an ethereal solution of diazomethane, which contained excess diazomethane, and the mixture was stirred overnight at 25°. The excess diazomethane was destroyed by the addition of a few drops of acetic acid, and the mixture was concentrated to an oil. The oil was dissolved in benzene and chromatographed on silica gel using first benzene, then 3% acetone in benzene, as the eluent. The pure product fractions (by glc analysis) were combined and concentrated by freeze drying to give 0.68 g (61%) of **7** as a viscous oil.

Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.41; H, 8.71; N, 10.86.

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Molecular Orbital Studies of Thyroid Hormone Analogs

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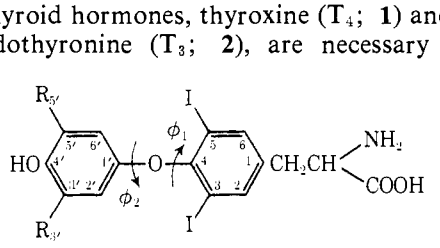
Abstract: Molecular orbital calculations on thyroxine analogs indicate that the minimum energy conformation for 3,5-disubstituted compounds is an important structural feature determining biological activity. The proximal conformation of T_3 is predicted to be very slightly (0.2 kcal/mol) more stable than the distal. The representation of the valence electrons of Cl, Br, and I with 2s- and 2p-like atomic orbitals appears to give a reasonably satisfactory representation of the electronic structure of these halogen compounds.

The thyroid hormones, thyroxine (T_4; **1**) and 3,5,3′-triiodothyronine (T_3; **2**), are necessary for the



1, $R_{5'} = R_{3'} = I$

2, $R_{5'} = I$; $R_{3'} = H$

maintenance of normal growth and metabolism in a variety of organisms.[2a] Since their isolation and structure elucidation in the first half of this century, many theories regarding their mechanism of action have been proposed.[2b–d] Also, because of the rather simple nature of their structure much work has been done on structural analogs of the hormones and, therefore, much is known about the structural features necessary for activity. However, no theory has yet evolved which ties together this detailed understanding of the structural requirements for hormone activity and those biochemical events governed by the hormones. It was thought that a molecular orbital study comparing the endogeneous hormones and a highly active methylene-bridged analog, 3,5-diiodo-4-(4′-hydroxy-3′-iodobenzyl)-DL-phenylalanine (MB-T_3), with less active analogs, 3,5-diiodo-4-(3′-iodo-4′-aminophenoxy)-DL-phenylalanine (4′-NH_2) and 3,5,3′-trimethyl-L-thyronine (Me_3), might reveal characteristics of the structural features which would lead to deductions regarding the functional role of the hormones.

We may summarize from earlier studies and from recent investigations that for a significant level of thyroid hormone activity in mammals the following struc-

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