ml) and heated with stirring on an oil bath. At about 130°, a vigorous evolution of gas occurred and the temperature rose to 150°. When this activity subsided, the suspension was cooled, filtered, and washed with 5 *N* hydrochloric acid. The aqueous layer was made basic and extracted with methylene chloride, and the organic phase was dried and evaporated to yield 110 mg (75%) of crystals, recrystallized from benzene to mp 134–135°; ir 5.84, 6.01, 6.14 μ; uv λ_{max} 238 (log ϵ 4.2), 320 (3.7); nmr 2.49 (s, 1 H), 3.03 (s, 1 H), 3.92 (s, 2 H), 4.0 (m, 2 H), 7.82 (s, 3 H), 6.5–8.3 (7 H), no protons exchanged with D_2O; mass spectrum major peaks *m/e* 300 (p), 243, 229.

Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.57; H, 5.25; N, 9.66.

Diazotization in aqueous nitrous acid or with isoamyl nitrite in trifluoroacetic acid led only to unchanged starting material, identified by spectra and tlc.

Registry No.—**1**, 476-28-8; **4a**, 20286-59-3; **4b** HCl, 20302-79-8; **4c**, 20286-60-6; **4c** (nitro ketone), 20286-61-7; **4c** (bromo ketone), 20286-62-8; *trans*-2-(3,4-methylenedioxyphenyl)cyclohexylamine HCl, 20302-80-1; *cis*-4-amino-5-(3,4-methylenedioxyphenyl)cyclohexene HCl, 20286-63-9; *cis*-2-(3,4-methylenedioxyphenyl)cyclohexylamine HCl, 20286-64-0; **7**, 20286-65-1; **8a**, 20286-66-2; **8a** (dibromide), 20286-67-3; **8a** (epoxide), 20286-68-4; **8b**, 20286-69-5; **9a**, 20286-70-8; **9a**, 20286-71-9; **10b**, 20286-72-0; **11a**, 20286-73-1; **11a**, 20286-74-2; **11b**, 20286-75-3; **11b**, 20286-76-4; **12b**, 20286-77-5; **12b**, 20286-78-6; **15a**, 20286-79-7; **15c**, 20287-27-8; **16**, 20286-80-0; N-(6-nitropiperonyl)-*o*-hydroxyphenethylamide, 20286-81-1; **18**, 20286-82-2; N-(*o*-hydroxy-β-styryl)-*t*-butylurethan, 20286-83-3; **19**, 20286-84-4; **20**, 20286-85-5; **23a**, 20286-86-6; **23b**, 20286-87-7; **24**, 20286-88-8; **25**, 20286-89-9; **26**, 20286-90-2; **27**, 20286-91-3.

Acknowledgment—We should like to express our deepest gratitude to the National Institutes of Health for continued and patient support of these and other studies in the synthesis of *Amaryllidaceae* alkaloids over many years.

Syntheses and Optical Rotatory Dispersion Studies of (*S*)-5-(2′-Pentyl)barbituric Acid Derivatives[1]

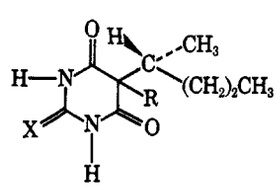
F. I. CARROLL AND R. MECK

The Chemistry and Life Sciences Laboratory, Research Triangle Institute, Research Triangle Park, North Carolina 27709

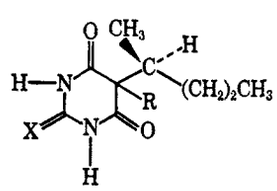
Received December 30, 1968

The syntheses of several (*S*)-5-(2′-pentyl)barbituric acid derivatives are reported and their optical properties have been investigated. Although the ultraviolet spectra of (*S*)-(−)-5-ethyl-5-(2′-pentyl)barbituric acid (IIa) shows only one maximum under the conditions studied, optical rotatory dispersion measurements have shown two Cotton effects. Some pH dependent optical rotatory dispersion studies indicate that the lower wavelength Cotton effect is the result of a $\pi-\pi^*$ transition and the higher wavelength Cotton effect is of type $n-\pi^*$. The $\pi-\pi^*$ Cotton effect is positive and the $n-\pi^*$ Cotton effect is negative. The ultraviolet spectrum of the monosubstituted barbituric acid, (*S*)-(+)-5-(2′-pentyl)barbituric acid (IIc), in acid solution showed one maximum and the optical rotatory dispersion curve in the same solvent showed a negative $\pi-\pi^*$ low wavelength and a positive $n-\pi^*$ high wavelength Cotton effect. These results show that the biologically active IIa has optical rotatory dispersion properties greatly different from those of the biologically inactive IIc. These results are discussed in relation to the differences in the structure of these two compounds.

In a recent paper the preparation of some (*R*)-5-(2′-pentyl)barbituric acid derivatives (I) was reported.[2] In order to compare the optical properties, the pharmacological effects, and the metabolic fate, it was necessary to obtain the enantiomeric (*S*)-5-(2′-pentyl)barbituric acid derivatives (II) in high optical purity. The (*R*)-isomers I could be readily prepared in a high state of optical purity from commercially available (*R*)-(+)-pulegone.[2] However, the unavailability of the corresponding (*S*) isomer or other similar (*S*) derivative convertible to the (*S*)-barbituric acid derivatives II, made it necessary to seek a different synthesis of these enantiomers. Although there are two reports of the preparation of (*S*)-(−)-5-ethyl-5-(2′-pentyl)barbituric acid (IIa) in the literature, in both cases the optical purity was very low. A method reported by Kleiderer and Shonle[3] involved a displacement reaction at the asymmetric carbon atom and proved to be unsuitable for the preparation of the (*S*) isomers II in high optical purity.[4]



I



II

a, R = C_2H_5, X = O
b, R = C_2H_5, X = S
c, R = H, X = O
d, R = CH_2=$CHCH_2$—, X = O
e, R = CH_2=$CHCH_2$—, X = S

In 1966 Knabe and Philipson[5] reported the separation of racemic 5-ethyl-5-(2′-pentyl)barbituric acid (pentobarbital) into its optical antipodes *via* fractional crystallization of its diastereomeric N-methylquininium salt from a methanol and ether mixture followed by regeneration of the acid. The (*S*) isomer IIa thus obtained had $[\alpha]^{20}D$ −3.5° and was, therefore, only 28% optically pure when compared to $[\alpha]^{20}D$ 13.12° obtained for Ia.[2] Since the (*S*) isomer was reported to be the more crystalline of the two salts and easier to separate, further recrystallization of this salt should lead to optically pure IIa. Indeed, we found that IIa having $[\alpha]^{24}D$ −13.38°

(1) This research was carried out under Contract PH43-65-1057 of the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Md.

(2) C. E. Cook and C. R. Tallent, *J. Heterocycl. Chem.*, **6**, 203 (1969).

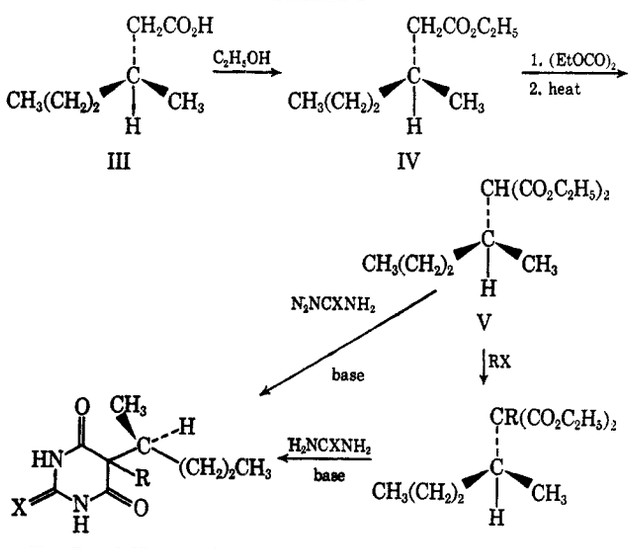
(3) E. C. Kleiderer and H. A. Shonle, *J. Amer. Chem. Soc.*, **56**, 1772 (1934).

(4) The optical purity of IIa obtained by Kleiderer and Shonle (ref 3) was 36%.

(5) J. Knabe and K. Philipson, *Arch. Pharm.* (Weinheim), **299**, 232 (1966).

could be obtained by this method. However, it was necessary to recrystallize the N-methylquininium salt twelve times from a methanol and ethyl acetate mixture in order to obtain 3% of the optically pure IIa. The low yield obtained, as well as the necessity of carrying out a separate resolution for each (S) isomer II desired, made this procedure unattractive for the preparation of reasonable amounts of a series of pure (S)-5-(2′-pentyl)-barbituric acid derivatives (II). In 1931, while engaged in a study of the Walden inversion, Levene and Marker[6] reported the preparation of (S)-(−)-3-methylhexanoic acid (III), bp 113° (17 mm), $[\alpha]^{27}D$ −2.52°. The fact that the magnitude of the reported rotation is of comparable value and opposite sign to the (R)-(+)-3-methylhexanoic acid prepared by Cook and Tallent[2] from (R)-(+)-pulegone prompted us to reinvestigate this preparation. We found that six recrystallizations of the cinchonidine salt of racemic 3-methylhexanoic acid followed by regeneration of the acid afforded III having $[\alpha]^{24}D$ −2.63°. When this acid was subjected to the reaction scheme shown in Scheme I, the optically pure 5-(2′-pentyl)barbituric acid derivatives (II) were obtained. A comparison of the $[\alpha]D$ and melting points of the (R)- and (S)-5(2′-pentyl)barbituric acid derivatives is given in Table I. Since the absolute configuration of the starting (S)-(−)-3-methylhexanoic acid (III) has been established,[7] the absolute configuration of the (S)-5-(2′-pentyl)barbituric acid derivatives (II) is known and is as represented in Scheme I. The

SCHEME I



IIa, R = C_2H_5; X = O
b, R = C_2H_5; X = S
c, R = H; X = O
d, R = CH_2=$CHCH_2$; X = O
e, R = CH_2=$CHCH_2$; X = S

identity of each compound was shown by elemental analysis, infrared, and mass spectra. As expected, the infrared and mass spectra of each derivative II were identical with those of the corresponding (R) isomer I,

(6) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **91**, 77 (1931).

(7) I. A. Holliday and N. Polgar [*J. Chem. Soc.*, 2934 (1957)] has correlated III with methyl hydrogen β-methyl glutarate, which was related to methylsuccinic acid by S. Ställberg-Slenhagen, *Arkiv Kimi, Min., Gral.*, 25A, No. 10 (1948).

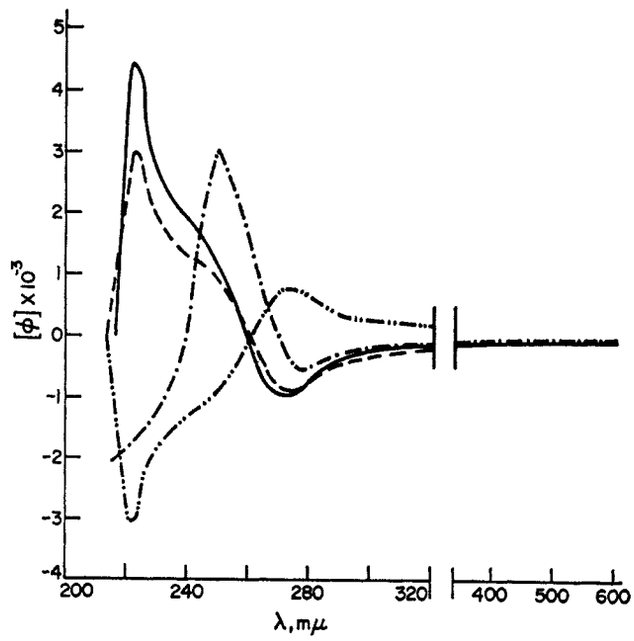


Figure 1.—Optical rotatory dispersion of (S)-(−)-5-ethyl-5-(2′-pentyl)barbituric acid (IIa) in methanol (- - - -), in 50% v/v methanol–0.1 *N* hydrochloric acid (——), in 50% v/v methanol–0.1 *N* sodium hydroxide (-·-·-), and (R)-(+)-5-ethyl-5-(2′-pentyl)barbituric acid (Ia) in methanol (-·-·-·-).

and the optical rotations were of essentially equal magnitude and of opposite sign[2] (Table I).

We have investigated the optical rotatory dispersion (ORD) of this series of optically active compounds.[8] The ORD curves of these compounds were of particular interest because of their potential application in determining the structure of metabolites which are isolated in only very small quantities. In addition, the information from the ORD studies may be of value in assigning electronic transitions to the barbituric acids. Finally, a comparison of the ORD of the active hypnotic and sedative, (S)-(−)-5-ethyl-5-(2′-pentyl)barbituric acid (IIa), and the biologically inactive (S)-(+)-5-(2′-pentyl)-barbituric acid (IIc) might reveal differences in their structure which would be helpful in explaining their biological differences.

The ORD curve of IIa in methanol (Table II, Figure 1) shows a negative Cotton effect with the trough at 274 mμ. The peak occurs at 240 mμ as a shoulder on a second positive Cotton effect, the peak of which is at 223 mμ. The trough of this second Cotton effect could not be measured. As expected, the curve of IIa was the mirror image of its enantiomer Ia (Figure 1). The shape of the ORD curve of IIa in acid solution was essentially the same as that in methanol; however, the extrema of the long wavelength Cotton effect was shifted to lower wavelengths and the amplitudes of both Cotton effects were increased. In contrast the ORD curve of IIa in alkaline solution showed a bathochromic shift and showed only one peak and one trough at 250 mμ and 278 mμ, respectively. It could be argued that the two Cotton effects observed in the ORD curve of IIa in

(8) Optical rotatory dispersion were measured at the University of North Carolina at Chapel Hill as a courtesy of Dr. J. Hermans and with the help of Mr. D. J. Puett, and at Duke University as a courtesy of Dr. C. Tanford and with the help of Mr. Bob Roxby. Measurements were made with a Cary 60 spectropolarimeter at 28°. Concentration varied from *c* 0.02 to *c* 0.2. Values of molecular rotation have an accuracy of approximately 10%, except at very low wavelengths where the error is somewhat larger.

TABLE I

COMPARISON OF OPTICAL ROTATION AND MELTING POINT OF (*R*)- AND (*S*)-5-(2′-PENTYL)BARBITURIC ACID DERIVATIVES

Compound[a]	Optical rotation[b] $[\alpha]^{24}D$ (*S*) isomer	Optical rotation[b] $[\alpha]^{24}D$ (*R*) isomer[d]	Mp, °C[c] (*S*) isomer	Mp, °C[c] (*R*) isomer[d]
5-Ethyl-5-(2′-pentyl)barbituric acid (pentobarbital)	−13.19	13.12	121.5–122	122–122.5
5-Ethyl-5-(2′-pentyl)-2-thiobarbituric acid (thiopental)	−10.85	10.66	148–149	151–151.5
5-(2′-pentyl)barbituric acid	5.88	−4.8	182–182.5	182.5–183
5-Allyl-5-(2′-pentyl)barbituric acid (secobarbital)	−8.55	9.23	102.5–103.5	103–106
5-Allyl-5-(2′-pentyl)-2-thiobarbituric acid (thiamylal)	−6.53	6.68	116–116.5	117–118

[a] The name given in parentheses is the generic name of the *dl*-mixture. [b] Optical rotations were measured on a Rudolph Model 80 polarimeter at *c* 2.0 to 3.0. [c] Melting points were obtained by capillary method on sublimed samples, except for thiamylal which was purified by recrystallization from an ethyl acetate and hexane mixture. [d] Taken from ref. 2.

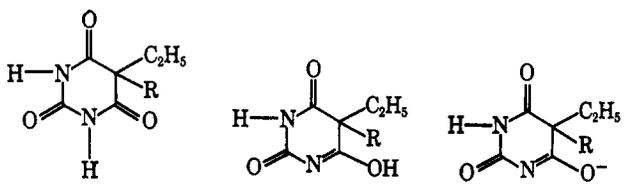
TABLE II

OPTICAL ROTATORY DISPERSION AND ULTRAVIOLET ABSORPTION DATA OF 5-(2′-PENTYL)BARBITURIC ACID DERIVATIVES

Compound	Condition	ORD λ, mμ[a]	ORD [φ][b]	vU absorption λ_{max}	vU absorption ε × 10⁻³
I	CH_3OH	320	180		
		274 P	786		
		260	0		
		240 T[c]	−1300		
		222 T	−3050		
		213.5	0		
IIa	CH_3OH	320	−200	210	9.5
		274 T	−880		
		260	0		
		240 P[c]	1300		
		223 P	3025		
		213.5	0		
IIa	pH 1.4[d]	600	−37	212	7.4
		272 T	−980		
		259	0		
		240 P[c]	1900		
		222 P	4400		
		216.5	0		
IIa	pH 12.1[e]	600	−37	240	10.0
		278 T	−540		
		269	0		
		250 P	3000		
		240	0		
		215	−2050		
IIc	CH_3OH	320	140	208[f]	8.5
		275 P	1170	268	12.1
		261.5	0		
		248 T[c]	−1150		
		223 T	0		
		15	−1200		
IIc	pH 1.4[d]	320	150	209[f]	9.1
		272.5 P	1160		
		260	0		
		245 T[c]	−1150		
		222 T	−2700		

[a] P = peak, T = trough. [b] The optical rotations are given as molar rotation, $[\phi]^{28}\lambda = [\alpha]^{28}D \times$ mol wt/100. [c] This extremum occurs as a shoulder on a lower wavelength extremum. [d] 50% v/v methanol–0.1 *N* hydrochloric acid. [e] 50% v/v methanol–0.1 *N* sodium hydroxide. [f] Shoulder on end absorption.

methanol and in acid solution result from a single electronic transition of a keto (IIaA) and enol (IIaB) form, which are converted in alkaline solution to one species, the anion (IIaC), which then shows only one Cotton effect. However, the ultraviolet spectrum of IIa in methanol or acid solution which shows only one maximum in both cases is inconsistent with this interpretation. In addition, this interpretation would indicate a $\lambda_0^{pH\ 12.1}$ 269 mμ[9] (Table II, Figure 1) for the ORD of IIa whereas the uv shows only one maximum at 240 mμ at pH 12.1. The increase in amplitude of the higher wavelength Cotton effect in going from methanol to acid solution as well as the extreme unsymmetrical character of the ORD curve of IIa in alkaline solution are also inconsistent with this interpretation. Alternatively, the two Cotton effects could result from different electronic transitions. The uv spectrum of IIa in methanol shows an absorption at 210 mμ. The position as well as the



IIaA IIaB IIaC

R = —$CH(CH_3)C_3H_7$

high intensity of this absorption suggest that it is a type $\pi-\pi^*$ transition.[10] As a result of the presence of several nonbonding, lone-pair electrons on heteroatoms (O and N), the uv spectrum of IIa would also be expected to show $n-\pi^*$ transition(s) at longer wavelengths. Although such a transition is not perceptible in the uv spectra of IIa, it would seem reasonable to attribute the long wavelength tail of the $\pi-\pi^*$ transition to a $n-\pi^*$ transition.[11] The midpoint, λ_0 213.5 mμ,[9] of the shorter wavelength Cotton effect in methanol as well as the bathochromic shift in alkaline solution, λ_0 240 mμ, agrees well with the ultraviolet maximum of IIa, $\lambda_{max}^{CH_3OH}$ 212 mμ and $\lambda_{max}^{pH\ 12.1}$ 240 mμ. Apparently this high-amplitude low wavelength Cotton effect and the strong ultraviolet absorption band are the result of the same $\pi-\pi^*$ electronic transition.[10] The second Cotton effect at λ_0 260 mμ in methanol of lower amplitude is probably due to the presence of a low intensity transition at higher wavelength even though the uv spectrum does not show a maximum in this region.[11] Because of its low intensity, its occurrence at higher wavelength than the $\pi-\pi^*$ transition, and its shift to lower wavelength in

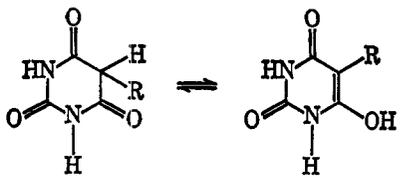
(9) λ_0 refers to the wavelength at which the rotation is zero.

(10) D. W. Turner has attributed an absorption band at 185–198 mμ in a number of cyclic imides to a $\pi-\pi^*$ transition. See D. W. Turner in "Determination of Organic Structures by Physical Methods," Vol. 2, F. C. Nachod and W. D. Philips, ed., Academic Press, New York, N. Y., 1962, Chapter 5.

(11) The ultraviolet spectrum of IIa does not show a second maximum. However, the spectrum has Σ 50–200 in methanol at 300–250 mμ and shows a very small inflection between 230 and 245 mμ.

going from alkaline to acid medium, the second transition is most likely a n–π^* type.[12,13] This interpretation of the ORD curves of IIa would be consistent with its uv spectra and the change in amplitude of the longer wavelength Cotton effect with change in pH. In addition, the extreme unsymmetrical character of the ORD curve in alkaline solution would be explained if the peak of both Cotton effects occurs at 250 mμ as this interpretation suggests.

In contrast to IIa, the uv spectrum of the monosubstituted barbituric acid, (*S*)-(+)-5-(2′-pentyl)barbituric acid (IIc), in methanol showed two intense absorption bands at 208 and 268 mμ (Figure 2). An analysis of the uv spectra of IIc as a function of pH as well as reference to the spectral data of other monosubstituted barbituric acids indicate that IIc exists as an equilibrium mixture of IIcA and IIcB[14] in methanol solution and in the form of IIcA at pH 1.4.[15,16]



IIcA IIcB

R = $CH(CH_3)C_3H_7$

The enol form IIcB could be considered as a 6-hydroxyuracil derivative and might be expected to show electronic transition similar to those assigned to uracil and other pyrimidines.[17] As a result one might expect the ORD curve of IIcB to be different from that of IIcA.[18] Since the ORD curves of IIc (Figure 2, Table II) in both methanol and acid solution are almost identical,[19] the curve in methanol must be due mainly to form IIcA, or the ORD properties of IIcA and IIcB, or essentially the same. The latter explanation seems less likely since the optically active 2′-pentyl side chain would be connected to the heterocyclic chromophore *via* a sp^3 bond in IIcA and a sp^2 bond in IIcB.[20] The ORD curve of IIc in acid solution shows a positive high wavelength Cotton effect with the first extremum at λ 272.5 mμ and a negative low wavelength Cotton effect with the first extremum at λ 222 mμ. Therefore, in contrast

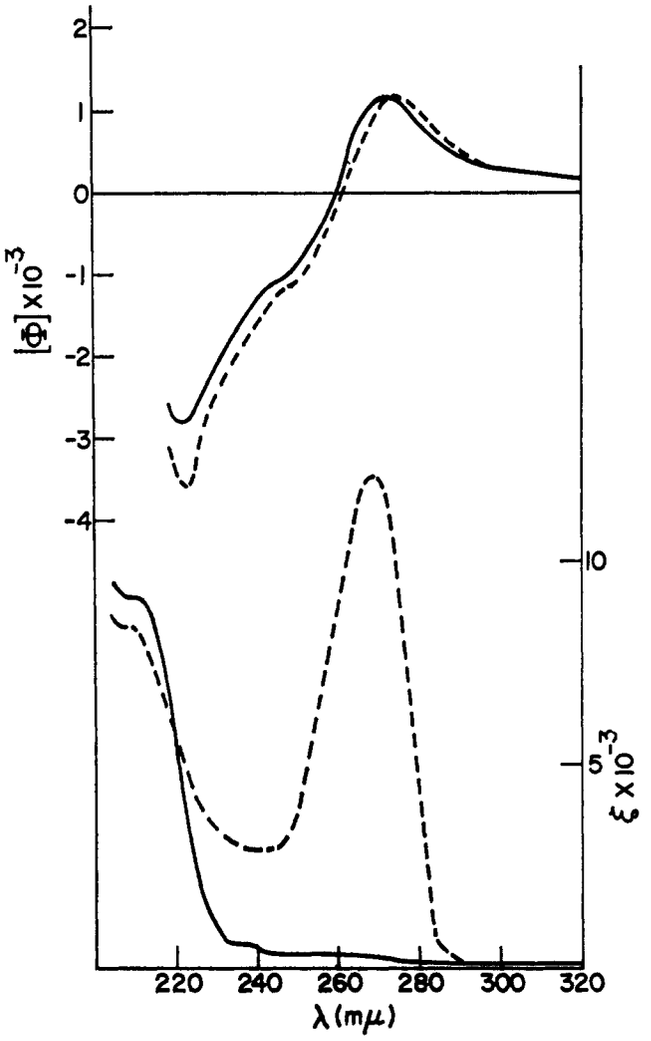


Figure 2.—Optical rotatory dispersion and absorption spectra of (*S*)-(+)-5-(2′-pentyl)barbituric acid (IIc) in methanol (- - - - -), and in 50% v-v methanol/0.1 *N* hydrochloric acid (——).

to IIa, the π–π^* Cotton effect is negative and the n–π^* Cotton effect is positive.

Since the curves of IIa and IIc in acid solution presumably result from the triketonic form IIaA and IIcA, respectively, this strikingly different rotatory behavior would indicate that the two compounds have different steric relationships between the absorption chromophore and the optically active side chain. Although the 2′-pentyl side chain would have free rotation about the 5 position of the barbituric acid ring, these differences indicate that the optically active side chain may have different preferred conformations in the two compounds. Molecular models of IIa and IIc indicate that IIa is considerably more sterically crowded than IIc and that free rotation would be considerably more difficult. This steric crowding is also evident in the uv spectrum of IIa, which shows a shift to longer wavelength relative to the spectrum of IIc, indicating increased noncoplanarity of the barbituric acid ring of IIa.[21] It is also possible that IIa and IIc have different optically active transitions or different solution characteristics. However, because of the very close similarity

(12) Since lone-pair transitions are strongly affected by changes in pH, the blue shift observed in going from the monoanion of IIa, to the neutral molecule, to the weakly protonated form, is consistent with an n–π^* transition. In a study of the ORD, CD, and uv properties of pyrimidine and purines, D. W. Miles, R. K. Robins, and H. Eyring [*Proc. Nat. Acad. Sci. U. S.*, **57**, 1138 (1967)] showed that n–π^* transitions undergo blue shifts when the pH was lowered.

(13) This long wavelength Cotton effect could be due to one or more optically active transitions.

(14) Two identical structures can be drawn for form IIcB.

(15) W. J. Doran, in "Medicinal Chemistry," Vol. IV, F. F. Blicke and R. H. Cox, Ed., John Wiley & Sons, Inc., New York, N. Y., 1959, p 1.

(16) J. J. Fox and D. Shugar, *Bull. Soc. Chem. Belges.*, **61**, 44 (1952), and references cited.

(17) L. B. Clark and I. Finoco, Jr., *J. Amer. Chem. Soc.*, **87**, 11 (1965).

(18) D. W. Miles, R. K. Robins, and H. Eyring, *J. Chem. Phys.*, **57**, 1138 (1967), have correlated the ORD and CD curves of uridine and thymidine with the electronic transition of these bases and have shown that they are derived from those of benzene.

(19) This blue shift of the first extremum in going from methanol to acid solution would be expected of a n–π^* transition. The difference in rotation of the low wavelength π–π^* transition is due partly to uncertainties in measurements in this region.

(20) An examination of CPK molecular models of IIcA and IIcB shows that different heterocyclic chromophore–optically active side-chain steric relationships exist in the two forms. An ORD and CD study at various pH's may be helpful in solving this problem.

(21) D. W. Turner (ref 10) attributed a shift in the uv to longer wavelength shown by glutarimide relative to succinimide to noncoplanarity of the imide group.

in structure, this explanation seems less likely. The extreme difference of the optical rotatory properties of IIa and IIc suggest that additional ORD as well as circular dichroism (CD) and possibly magnetic circular dichroism (MCD)[22] studies of barbituric acid derivatives might be useful in explaining the biological properties of these compounds. In addition, the CD and MCD studies of II would provide additional evidence for the electronic transitions suggested in the present communication.

Experimental Section[23]

Resolution of *dl*-5-Ethyl-5(2′-pentyl)barbituric Acid (Pentobarbital).—*dl*-Pentobarbital (168 g, 0.74 mol) was converted to its N-methylquininium salt according to the method of Knabe and Philipson.[5] Twelve recrystallizations of this salt from a methanol and ethyl acetate mixture followed by regeneration of the acid from the separated N-methylquininium salt of (−)-pentobarbital gave 2.8 g (3%) of IIa purified by sublimation, mp 121–121.5°, $[\alpha]^{24}D$ −13.38° (*c* 2.38, absolute ethanol); lit.[5] mp 128°, $[\alpha]^{20}D$ −3.5° (*c* 1.83, absolute ethanol).

(*S*)-(−)-3-Methylhexanoic Acid (III).—The acid III was obtained by six recrystallizations of the cinchonidine salt from an aqueous ethanol solution according to the procedure of Levene and Marker.[6] From 415 g of *dl*-3-methylhexanoic acid, 90 g of III was obtained: bp 109–110° (13 mm), $n^{25}D$ 1.4205, $[\alpha]^{24}D$ −2.63° (neat); lit.[6] bp 113° (17 mm), $n^{25}D$ 1.4214, $[\alpha]^{27}D$ −2.52° (neat).

Ethyl (*S*)-(−)-3-Methylhexanoate (IV).—This ester was prepared according to the procedure of Levene and Marker:[6] bp 60° (7.0 mm), $[\alpha]^{23}D$ −0.40 (neat); lit.[6] bp 60° (10 mm), $[\alpha]^{27}D$ −0.42°.

(*S*)-(−)-Diethyl 2-Pentylmalonate (V).—This ester was prepared by the same procedure that Cook and Tallent[2] used to prepare the (*R*)-(+) isomer, with the exception that benzene was used in place of ether as the reaction solvent. Starting with 12 g (76.9 mmol) of ester IV, 10.2 g (57%) of V was obtained: bp 105° (2 mm), $n^{25}D$ 1.4260, $[\alpha]^{24}D$ −0.59° (neat); lit.[24] bp 103–104° (4 mm), $n^{20}D$ 1.4273 for the *dl* ester (V).

(*S*)-(−)-Diethyl Ethyl-2-pentylmalonate (VI, R = C_2H_5).—Using the procedure that Cook and Tallent[2] used to prepare the (*R*)-(+) isomer malonic ester V (4.8, g, 0.21 mol) gave 4.2 g (76%) of VI (R = C_2H_5): bp 115° (2 mm), $n^{25}D$ 1.4348, $[\alpha]^{23}D$ −14.84° (neat); lit.[3] bp 123–124° (10 mm), $n^{25}D$ 1.4330, $[\alpha]^{25}D$ −11.02° (neat).

(*S*)-(−)-Diethyl Allyl-2-pentylmalonate (VI, R = CH_2=$CHCH_2$—).—Using a procedure similar to that used to prepare VI (R = C_2H_5), malonic ester (V) (15 g, 65 mmol) and 3-bromopropene (23.7 g, 20 mmol) yielded 13.7 g (78%) of VI (R = CH_2=$CHCH_2$—): bp 129–130° (1.0 mm), $n^{25}D$ 1.4437, $[\alpha]^{23}D$ −16.36°; lit.[25] bp 137–140° (15 mm) for *dl* ester VI (R = CH_2=$CHCH_2$—).

(*S*)-(−)-5-Ethyl-5-(2′-pentyl)barbituric Acid (IIa).—Treatment of VI (R = C_2H_5) (3.0 g, 11.8 mmol) with urea according to the procedure that Cook and Tallent[2] used to prepare Ia gave 2.1 g (77%) of IIa.

Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.35; H, 8.10; N, 12.46.

(*S*)-(−)-5-Ethyl-5-(2′-pentyl)-2-thiobarbituric Acid (IIb).—The title compound prepared from malonic ester VI (R = C_2H_5) and thiourea[2] followed by work-up and sublimation had mp 148–149°.

Anal. Calcd for $C_{11}H_{18}N_2O_2S$: C, 54.40; H, 7.42; N, 11.54; S, 13.20. Found: C, 54.48; H, 7.57; N, 11.62; S, 13.05.

(*S*)-(+)-5-(2′-Pentyl)barbituric Acid (IIc).—Condensation of malonic ester V (0.90 g, 3.9 mmol) and urea with sodium ethoxide in ethanol[2] followed by purification and sublimation gave 0.71 g (50%) of IIc.

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.65; H, 7.23; N, 14.05.

(*S*)-(−)-5-Allyl-5-(2′-pentyl)barbituric Acid (IId).—Treatment of VI (R = CH_2=CH—CH_2) (10 g, 37.1 mmol) with urea by a procedure similar to that used to prepare IIa gave 5.7 g (65%) of IId.

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.48; H, 7.61; N, 11.76. Found: C, 60.34; H, 7.65; N, 11.83.

(*S*)-(−)-5-Allyl-5-(2′-pentyl)-2-thiobarbituric Acid (IIe).—Treatment of VI (R = CH_2=$CHCH_2$—) (2.0 g, 7.4 mmol) with thiourea by a procedure similar to that used to prepare IIb gave 0.52 g (31%) of IIe.

Anal. Calcd for $C_{12}H_{18}N_2O_2S$: C, 56.66; H, 7.13; N, 11.02; S, 12.61. Found: C, 56.62; H, 7.21; N, 10.97; S, 12.38.

Registry No.—IIa, 5767-32-8; IIb, 20224-43-5; IIc, 20224-44-6; IId, 20224-45-7; IIe, 20224-46-8.

Acknowledgment.—We take pleasure in thanking Dr. M. E. Wall, Director of this laboratory, for his kind encouragement and support of this work.

(22) See W. Voelter, R. Records, E. Bunnenburg, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 6143 (1968), for the use of MCD in an investigation of some pyrimidines.

(23) Melting points were determined using the Thomas–Hoover capillary melting point apparatus, and ultraviolet and visible spectra were measured on a Cary Model 14 spectrophotometer. Infrared spectra were measured with a Perkin-Elmer 221 spectrophotometer; samples were prepared in the form of pressed KBr disks. Mass spectra were determined on an AEI MS-902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

(24) H. A. Shonle, A. K. Kiltch, and E. E. Swanson, *J. Amer. Chem. Soc.*, **52**, 2440 (1930).

(25) K. Abe, T. Ishiraka, and Y. Tsukamoto, *J. Pharm. Soc. Jap.*, **75**, 891 (1955).