Synthesis and Alkaline Decomposition of 5-Alkyl-5-(1-methyl-3-oxobutyl)barbituric and 2-Thiobarbituric Acid Derivatives[1]

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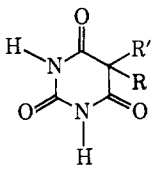
5-Ethyl- and 5-allyl-5-(1-methyl-3-oxobutyl)barbituric acids (VIIIa and VIIIb) and 5-ethyl- and 5-allyl-(1-methyl-3-oxobutyl)-2-thiobarbituric acids (VIIIc and VIIId) were synthesized. These compounds were shown to decompose *via* a reverse Michael type reaction under alkaline conditions. The decomposition of VIIIa as a function of pH was studied. The decomposition of all 4 compounds was determined at pH 10.7 and 30°. The 2 thiobarbituric acid derivatives decomposed more rapidly than their corresponding barbituric acid analogs, and the 5-allyl derivative decomposed faster than the 5-ethyl compound in each case. The significance of these results to the metabolism studies of 5-alkyl-5-(1-methylbutyl)barbituric and 2-thiobarbituric acids is discussed.

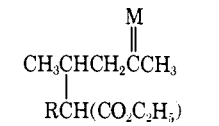
Metabolism studies of 5-ethyl- and 5-allyl-5-(1-methylbutyl)barbituric acids (I, pentobarbital, and II, secobarbital), respectively, have shown that the ω-1-C of the 5-(1-methylbutyl) side chain is the most susceptible position to metabolic oxidation.[2-6] Studies using radiolabeled I showed that over 65% of this drug is excreted as 5-ethyl-5-(3-hydroxy-1-methylbutyl)barbituric acid (III).[3,7] Similarly, the metabolism of II gives 5-allyl-5-(3-hydroxy-1-methylbutyl)barbituric acid (IV)[7] as the main biotransformation product resulting from oxidative attack on the 5-(1-methylbutyl) group of this compound.[5] In contrast, the metabolism of 5-ethyl-5-*n*-hexylbarbituric acid (V) gives, in addition to 15% of the ω-1 alcohol, 5-ethyl-5-(5-hydroxyhexyl)-barbituric acid (VI), 9% of the ω-1 ketone derivative, 5-ethyl-5-(5-oxohexyl)barbituric acid (VII).[8] The reason for the metabolic formation of an ω-1 ketone from V, but not from I and II is not known. However, it has been suggested that 5-alkyl-5-(hydroxyalkyl)barbituric acids are metabolically oxidized only when the OH group is located more than 3 C atoms away from the barbituric acid ring.[8]



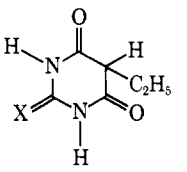
I, R = C_2H_5; R' = $C_3H_7CHCH_3$
II, R = C_3H_5; R' = $C_3H_7CHCH_3$
III, R = C_2H_5; R' = $CH_3CHOHCH_2CHCH_3$
IV, R = C_3H_5; R' = $CH_3CHOHCH_2CHCH_3$
V, R = C_2H_5; R' = C_6H_{14}
VI, R = C_2H_5; R' = $CH_3CHOHC_4H_9$
VII, R = C_2H_5; R' = $CH_3C(O)C_4H_9$

The present paper reports the syntheses and chemical stability studies of two 5,5-dialkylbarbituric acids and two 5,5-dialkyl-2-thiobarbituric acids which contain a 5-(1-methyl-3-oxobutyl) side chain. A possible explanation for the absence of these compounds in previous metabolism studies of 5,5-dialkylbarbituric and thiobarbituric acids containing a 5-(1-methylbutyl) group is presented.

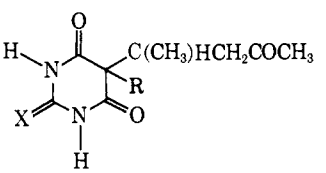
The 5-alkyl-5-(1-methyl-3-oxobutyl)barbituric acids (VIIIa and VIIIb) and corresponding 2-thiobarbituric acids (VIIIc and VIIId) were synthesized by the sequence IX → X → XI → VIII (see Experimental Section and Table I).[9,10] The protection of the keto



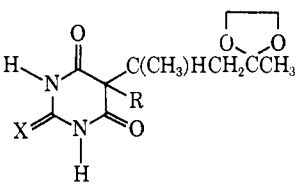
IXa, M = O; R = C_2H_5
b, M = O; R = C_3H_5
Xa, M = $O(CH_2)_2O$; R = C_2H_5
b, M = $O(CH_2)_2O$; R = C_3H_5



XIIa, X = O
b, X = S



VIIIa, R = C_2H_5; X = O
b, R = C_3H_5; X = O
c, R = C_2H_5; X = S
d, R = C_3H_5; X = S



XI

C=O of IX was an essential step. Attempts to condense IX (R = C_2H_5) with urea to give VIIIa gave 5-ethylbarbituric acid (XIIa). Uv analysis of the crude product indicated the absence of VIIIa. This result was particularly interesting since XIIa could have been formed by the decomposition of VIIIa. The compound (VIIIa) which has a 1,5-ketone barbituric acid CO relationship with H atoms on the C next to the ketone CO could easily undergo a reverse Michael type reaction to give 3-penten-2-one and the resonance-stabilized

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

(2) K. H. Palmer, M. S. Fowler, M. E. Wall, L. S. Rhodes, W. J. Waddell, and B. Baggett, *J. Pharmacol. Exp. Ther.*, **170**, 355 (1969).

(3) E. Titus and H. Weiss, *J. Biol. Chem.*, **214**, 807 (1955).

(4) E. W. Maynert and J. M. Dawson, *ibid.*, **195**, 389 (1952).

(5) W. J. Waddell, *J. Pharmacol. Exp. Ther.*, **149**, 23 (1965).

(6) H. Tsukamoto, H. Yoshimura, and H. Ide, *Chem. Pharm. Bull.*, **11**, 9 (1963).

(7) 5-Ethyl-5-(3-hydroxy-1-methylbutyl)barbituric and 5-allyl-5-(3-hydroxy-1-methylbutyl)barbituric acids are obtained as a mixture of 2 diastereoisomeric pairs.[2,5]

(8) E. W. Maynert, *J. Pharmacol. Exp. Ther.*, **150**, 476 (1965).

(9) Ide, Yoshimura, and Tsukamoto[10] have reported that VIIIb can be prepared by oxidizing IV with CrO_3 in AcOH. These authors report mp 110° for VIIIb prepared by their procedure. We find the VIIIb has mp 158–159° when prepared by the procedure reported in this paper.

(10) H. Ide, H. Yoshimura, and H. Tsukamoto, *Chem. Pharm. Bull.*, **15**, 411 (1967).

TABLE I

BARBITURIC AND 2-THIOBARBITURIC ACIDS

Compd[a]	Recrystn solvent	Mp, °C	% yield[b]	Uv pH	Uv λ_{max}, mμ	Uv $\epsilon \times 10^{-3}$	Molecular formula[c]
VIIIa	C_6H_{14}–Me_2CO	157–159	78	10.7[d]	242	10.6	$C_{11}H_{16}N_2O_4$
VIIIb	C_6H_{14}–EtOAc	158–159	91	10.7[d]	242	9.6	$C_{12}H_{16}N_2O_4$
VIIIc	C_6H_{14}–Me_2CO	140–144	60	10.7[d]	305	28.0	$C_{11}H_{16}N_2O_3S$
VIIId	C_6H_{14}–EtOAc	151–152	45	10.7[d]	306	26.4	$C_{12}H_{16}N_2O_3S$
XIa	C_6H_{14}–EtOAc	151–153	65	10.7	240	9.8	$C_{13}H_{20}N_2O_5$
XIb	C_6H_{14}–EtOAc	123–125	67[e]	10.7	240	9.1	$C_{14}H_{20}N_2O_5$
XIIa	C_6H_{14}–EtOAc	195–197[f]	70	11.4	268	19.9	$C_6H_8N_2O_3$
				10.7	268	20.1	
				9.3	268	20.0	
				7.3	268	20.8	
XIIb	C_6H_{14}–Me_2CO	165–167[g]	54	10.7	267	20.1	$C_7H_8N_2O_3$
XIIc	C_6H_{14}–EtOAc	195–196[h]	84	10.7	273	15.4	$C_6H_8N_2O_2S$
					283 (s)	14.5	
XIId	C_6H_{14}–EtOAc	135–136[i]	73	10.7	286	12.7	$C_7H_8N_2O_2S$
					272 (s)	11.7	

[a] A general procedure for each type of synthesis used is given in the Experimental Section. [b] Based on pure compd isolated. [c] Analyzed for C, H, N, and S when present. [d] Obtained at 0°. [e] This represents the overall yield from IXb. The ketal Xb decomposes slightly on distn. [f] E. H. Volwiler, *J. Amer. Chem. Soc.*, **47**, 2236 (1925), reported mp 193–194°. [g] M. V. Nadkarni and J. W. Jones, *J. Amer. Pharm. Ass.*, **39**, 297 (1950), reported mp 167°. [h] J. Lee, *J. Amer. Chem. Soc.*, **60**, 993 (1938), reported mp 173–174°. [i] M. Giannini, M. Fedi, and F. Russo, *Boll. Chim. Farm.*, **98**, 714 (1959), *Chem. Abstr.*, **54**, 9945 (1960), reported mp 120–122°.

anion of 5-ethylbarbituric acid.[11] That the decomposition of VIIIa is the most likely source of XIIa in the attempted preparation of VIIIa directly from IX is supported by the fact that VIIIa is converted into XIIa in high yield under strongly alkaline conditions whereas IX is relatively stable under the same conditions.

The results described above prompted us to study the decomposition of VIIIa at various pH values in order to obtain information concerning the stability of VIIIa under conditions commonly used for the isolation of the metabolites of 5,5-dialkylbarbituric acids.[2,4,5] The decomposition was followed indirectly by measuring the increase in absorbance at 268 nm due to the formation of the anion of 5-ethylbarbituric acid. The results obtained at pH 11.4, 10.7, 9.3, and 7.3 are presented in Figure 1. All the experiments were conducted at 30° with the exception of the pH 7.3 run which was conducted at 37°. These results show that VIIIa is rapidly decomposed at pH 11.4 and 10.7, is very unstable at pH 9.3, and is decomposed slowly even at physiological conditions of pH 7.3 and 37°. Therefore, the absence of VIIIa in the metabolism studies of 5-ethyl-5-(1-methylbutyl)barbituric acid (I) can be explained either by decomposition of VIIIa during the work-up of the metabolites, which commonly involves an alkaline extraction, or by the decomposition of VIIIa *in vivo*. If the former explanation is correct, one would expect to find 5-ethylbarbituric acid (XIIa) from the metabolism work-up. If the decomposition of VIIIa takes place *in vivo*, XIIa or possibly 5-ethyl-5-hydroxybarbituric acid may be expected. The isolation of ω-1 ketone metabolites in the case of V, but not in I, is reconciled in either case, since V would not be expected to undergo a reverse Michael reaction similar to VIIIa.

For comparative purposes the decompositions of VIIIa, VIIIb, VIIIc, and VIIId were studied at pH 10.7. The results obtained are shown in Figure 2. It is apparent that the 5-allyl derivatives VIIIb and VIIId are more rapidly decomposed than the corresponding 5-ethyl derivatives VIIIa and VIIIc, and that the 2-thiobarbituric acids VIIIc and VIIId decomposed at a much faster rate than the barbituric acids VIIIa and VIIIb. However, the rate of decomposition in all 4 cases is appreciable, and any attempt to find these compounds in metabolism studies would have to avoid the use of alkaline reagents in the purification procedure.[12]

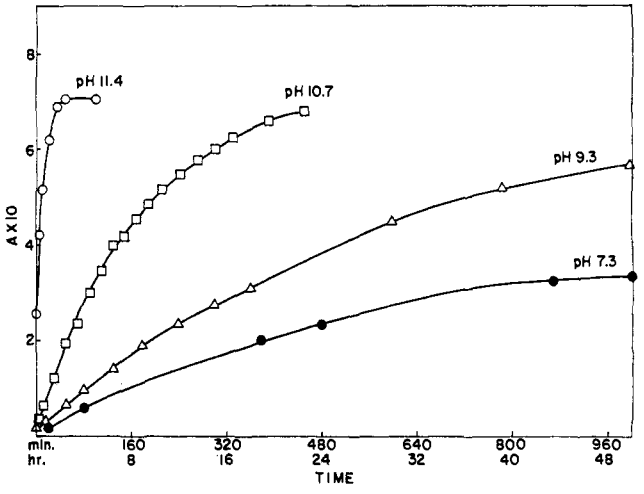


Figure 1.—Alkaline decomposition of VIIIa (initial concentration 4.17×10^{-5} *M*) to the anion of XIIa at 30° and pH 11.4, 10.7, and 9.3 and 37° at pH 7.3: ordinate, absorbance × 10 at 268 nm due to formation of anion of XIIa; abscissa, upper values in minutes for pH 11.4, 10.7, and 9.3 runs, lower values in hours for pH 7.3 run.

The uv spectral data of the barbituric acids used in this study are recorded in Table I. The ir, nmr, and mass spectra of all these compounds are in accordance with the assignments.

(11) E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.* **10**, 179 (1959).

(12) Preliminary studies by Dr. K. H. Palmer of this laboratory indicate that VIIIb and VIIIc are metabolites of II and 5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid, respectively. Ide, Yoshimura, and Tsukamoto reported that the VIIIb prepared by their procedure[9,10] had an R_f value the same as that of an unknown metabolite of rabbit administered with II.

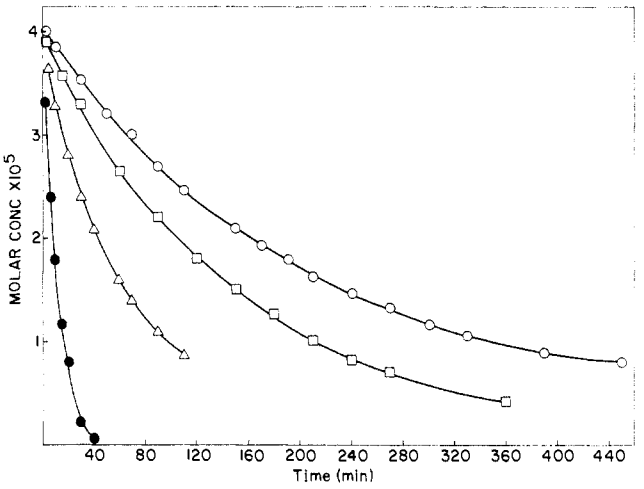


Figure 2.—Alkaline decomposition of VIIIa (○), VIIIb (□), VIIIc (△), and VIIId (●) at pH 10.7; temp 30° and initial concentration, 4.17×10^{-5} *M*. The concentrations of VIIIa and VIIIb were determined indirectly from the formations of XIIa and XIIb respectively.

Experimental Section[13]

Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. Boiling points are uncorrected. Uv spectra were measured on a Cary Model 14 spectrophotometer. Nmr spectra were recorded on a Varian Model HA-100 spectrometer (Me_4Si as internal standard). Ir spectra were measured with a Perkin-Elmer 221 spectrophotometer. Mass spectra were determined on an AEI MS-902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill. The 0.1 *M* phosphate and carbonate buffers were prepared by standard procedures.[14]

Diethyl Ethyl-(1-methyl-3-ethylenedioxybutyl)malonate (Xa).—A mixt of 15 g (0.055 mole) of diethyl ethyl-(1-methyl-3-oxobutyl)malonate,[15] 50 g (0.81 mole) of $(CH_2OH)_2$, and 0.7 g of TsOH in 200 ml of dry C_6H_6 was refluxed for 4 hr. The H_2O of ketalization was collected in a Dean–Stark trap. The reaction mixt was cooled, washed with 5% KOH and H_2O, and dried (Na_2SO_4). The solvent was removed *in vacuo* on a rotary evaporator, and the remaining liq was distd to give 12.1 g (69%) of Xa, bp 128–130° (1–2 mm), $n^{25}D$ 1.4511. *Anal.* ($C_{16}H_{28}O_6$) C, H.

5-Ethyl- or 5-allyl-5-(1-methyl-3-ethylenedioxybutyl)barbituric acid (XIa and XIb) was prepared from Xa or Xb by a procedure similar to that used to prepare other 5,5-dialkylbarbituric acids.[16,17] See Table I.

5-Ethyl- or 5-Allyl-5-(1-methyl-3-oxobutyl)barbituric Acids (VIIIa and VIIIb).—A soln of 0.5 g (1.76 mmoles) of XIa or XIb in 20 ml of Me_2CO contg 0.1 g of TsOH was stirred at 25° for 3 hr. The Me_2CO was removed under reduced pressure, and the remaining residue was dissolved in Et_2O. The Et_2O soln was washed with H_2O and NaCl soln and dried (Na_2SO_4). The residue remaining after evapn of the Et_2O was recrystd from the appropriate solvent. See Table I.

5-Ethyl- or 5-Allyl-5-(1-methyl-3-oxobutyl)-2-thiobarbituric Acids (VIIIc and VIIId).—A sample of Xa or Xb was condensed with thiourea in a manner analogous to the synthesis reported for other 5,5-dialkylthiobarbituric acids.[18] Acidification of the Na salt, formed from condensation, with 4 *N* HCl effected both neutralization and removal of the ketal group to give VIIIc and VIIId.[19] See Table I.

Alkaline Stability Studies of the 5-Alkyl-5-(1-methyl-3-oxobutyl)barbituric and 2-Thiobarbituric Acids (VIII).—Each barbituric acid (VIII) was dissolved in dioxane and a 1-ml aliquot was dild to 100 ml with the appropriate 0.1 *M* carbonate or 0.1 *M* phosphate buffer. The solns were thermostated at 30° for the pH 11.4, 10.7, and 9.3 runs and at 37° for the pH 7.3 run. The uv absorbance was detd at various times. The decompn of VIIIa and VIIIb was detd indirectly by recording at various times the uv absorbance at 268 and 267 nm, respectively, due to the formation of the respective 5-alkylbarbituric acid anion.

There was considerable overlap between the absorption curves of VIIIc and XIc and between VIIId and XId at pH 10.7. However, the concn of VIIIc could be detd indirectly by recording the absorbance at 273 and 305 nm and solving for a 2-component mixt. In a similar fashion the concn of VIIId could be detd by recording the absorbance at 272 and 306 nm. The results obtained are plotted in Figures 1 and 2.

5-Alkylbarbituric and 2-Thiobarbituric Acids (XII).—The 5-alkylbarbituric (XIIa and XIIb) and 2-thiobarbituric (XIIc and XIId) acids were prepd by procedures similar to those used to prepare XIa and XIc. See Table I.

(13) Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ± 0.4% of the theoretical values.

(14) C. Long, Ed., "Biochemists' Handbook," D. Van Nostrand Co., Inc. Princeton, N. J., 1961, pp 22–42.

(15) Y. J. Dickert, P. J. Shea, and L. P. McCarty, *J. Med. Chem.*, **9**, 249 (1966).

(16) J. A. Beres, D. E. Pearson, and M. T. Bush, *ibid.*, **10**, 1078 (1967).

(17) Since IXb and Xb decomposed slightly on distn, they were both used in future synthesis without purification.

(18) G. H. Dennison, S. Wellfield, and W. Ray, U .S. Patent 2,876,225, March 3, 1959; *Chem. Abstr.*, **53**, 16,168 (1959).

(19) In the prepn of VIIId it was necessary to treat the intermediate XId with a soln of Me_2CO and TsOH to completely remove the ketal group.