SYNTHESIS OF 5-ACETAMIDO SUBSTITUTED BARBITURATES

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ABSTRACT

A series of 22 5-acetamido and 5-amino barbituric acids as well as corresponding thiobarbiturates and N-methylated derivatives have been prepared for hypnotic activity evaluation. From comparative studies of their infrared spectra, various frequencies have been ascribed to the acetamido and amino groups at C-5 position. S-Alkylation resulted in the formation of unstable thioethers which hydrolyzed to give corresponding barbituric acids and mercaptans.

We were interested in preparing for biological evaluation, a new series of barbituric acids in which an amino group, free or acetylated, would be attached to carbon-5. A survey of the literature showed that of the many barbituric acids prepared, only a few have an amino group in the fifth position. These new compounds which we have prepared were obtained by condensing the alkylated acetamido malonic esters with urea or thiourea in the presence of sodium ethoxide. Tables I and II give the description of the various compounds prepared.

Some of these new barbiturates were methylated with dimethyl sulphate in alkaline solution.

With barbituric acids, N-methylated compounds were obtained as expected and isolated. They were characterized by distillation with soda lime. The methylamine thus formed was identified (1). The yields of N-methylated compounds were in the range of 40–60% (Table III).

With thiobarbituric acids, methylation can occur either on the nitrogen (N-1) or on the sulphur located on C-2. When 5,5-dialkylthiobarbiturates were methylated, N-methylation along with some methylation on the sulphur atom took place. However, it has been shown by Lee (2) that "5,5-dialkyl-2-alkyl-thiobarbituric acids are unstable substances evolving a strong thiol-like odor in air". It is not surprising, then, that we isolated, after the methylation of 5-acetamido-5-phenoxypropyl-2-thiobarbituric acid, 10% of the corresponding non-methylated 2-oxygen analogue and 40% of the N-methylated thiobarbiturate. 5-Acetamido-5-isobutyl thiobarbiturate gave, similarly, 45% of 5-acetamido-5-isobutyl barbituric acid.

The substitution of the sulphur atom by oxygen in these two attempts of methylation could only be explained by the labile nature of the intermediate methyl thioether formed at carbon-2.

To confirm this, sodium pentothal was refluxed in 95% ethanol with excess allyl bromide, and benzyl chloride. In both cases pentobarbital could be isolated in 68% yield.

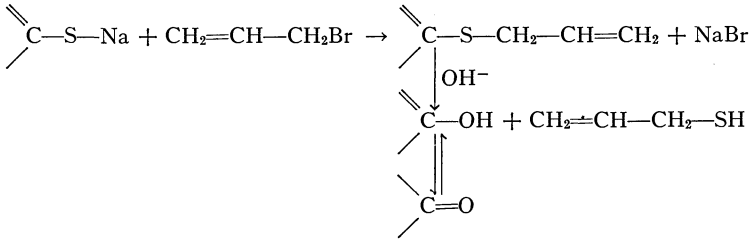
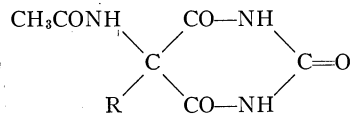


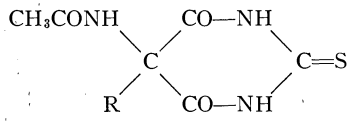
TABLE I



No. of compound	R	Yield (%)	M.p. (° C)	Cryst. solvent	Refluxing time (hours)	Formula	% N Calc.	% N Found
I	n-C_3H_7—	67	296	DMF–H_2O	18	$C_9H_{13}N_3O_4$	18.50	18.23
II	n-C_4H_9—	75	276	DMF–ethanol	6	$C_{10}H_{15}N_3O_4$	17.42	17.44
III	CH_2=CH—CH_2—	61	333 dec.	DMF–H_2O	3	$C_9H_{10}N_3O_4$	18.59	18.66
IV	CH_3>CH—CH_2— CH_3	44	318	Ethanol	5	$C_{10}H_{15}N_3O_4$	17.42	17.43
V	$C_6H_5CH_2$—	60	318	DMF–H_2O	4	$C_{13}H_{13}N_3O_4$	15.27	15.15
VI	$C_6H_5O(CH_2)_3$—	70	275	DMF–ethanol	5	$C_{15}H_{17}N_3O_5$	13.16	13.16

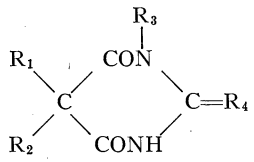
The U.V. absorption for compound VI λ_{max} = 280, 274 mμ, ϵ_{max} = 3×10^2, 3.2×10^2.

TABLE II



No. of compound	R	Yield (%)	M.p. (° C)	Cryst. solvent	Refluxing time (hours)	Formula	Nitrogen Calc.	Nitrogen Found	U.V. absorption λ_{max}(mμ)	U.V. absorption ϵ_{max} = $\times10^3$
VII	H—	65	284 dec.	Acetic acid	6	$C_6H_7N_3O_3S$	20.89	20.75	292	19
VIII	p-$OCH_3C_6H_4CH_2$—	68	237	Ethanol–H_2O	6	$C_{14}H_{15}N_3O_4S$	13.09	12.78	292	25
IX	$NCCH_2$—CH_2—	28	292	Dioxane	6	$C_9H_{10}N_4O_3S$	22.04	21.64	292	22
X	$C_6H_5CH_2$—	70	288 dec.	Ethanol	6	$C_{13}H_{13}N_3O_3S$	14.43	14.35	296, 240	26, 14
XI	CH_2=CH—CH_2—	66	244	Ethanol	3	$C_9H_{11}N_3O_3S$	17.42	17.54	292, 238	19, 12
XII	$(CH_3)_2$CH—CH_2—	60	269	Dioxane–benzene	6	$C_{10}H_{15}N_3O_3S$	16.34	16.31	294	23
XIII	$C_6H_5O(CH_2)_3$—	70	204	Ethanol	6	$C_{15}H_{17}N_3O_4S$	12.53	12.42	290, 236	27, 17

TABLE III



No. of compound	R_1	R_2	R_3	R_4	Yield (%)	M.p. (° C)	Cryst. solvent	Time	Formula	% C Calc.	% C Found	% H Calc.	% H Found	% N Calc.	% N Found	λ_{max}(mμ)	$\epsilon_{max} = \times 10^3$
XIV	CH_3CONH—	$C_6H_5CH_2$	CH_3	S	50	283	DMF–H_2O	30 min	$C_{14}H_{16}N_2O_3S$	55.00	54.50	4.90	4.52	13.77	13.70	264	18
XV	CH_3CONH	H	CH_3	S	60	251	Diox-C_6H_6	30 min	$C_7H_9N_3O_3S$	—	—	—	—	19.53	19.38	288	17
XVI	CH_3CONH	CH_2=CH—CH_2	CH_3	O	40	324	Diox-C_6H_6	30 min	$C_{10}H_{13}N_3O_4$	50.21	49.93	5.44	5.31	17.37	17.57	—	—
XVII	CH_3CONH	$C_6H_5O(CH_2)_3$—	CH_3	O	64	208	Diox-H_2O	30 min	$C_{16}H_{19}N_3O_5$	57.66	56.69	5.70	5.78	12.65	12.68	280, 274	2.6, 2.7
XVIII	CH_3CONH	$C_6H_5O(CH_2)_3$—	CH_3	S	45	233	DMF–ethanol	30 min	$C_{16}H_{19}N_3O_4S$	55.01	54.87	5.44	5.42	12.03	12.04	270	28
XIX	NH_2.HCl	C_6H_5—CH_2—	H	O	70	264	Dil. HCl	6 hr	$C_{11}H_{12}ClN_3O_3$	48.23	48.40	4.45	4.38	15.58	15.75	—	—
XX	NH_2.HCl	$C_6H_5O(CH_2)_3$—	H	O	30	262	Dil. HCl	18 hr	$C_{18}H_{16}ClN_3O_4$	49.76	49.86	5.10	4.93	13.42	13.57	280, 274	2.5, 2.8
XXI	NH_2.HCl	n-C_4H_9	H	O	45	255	Dil. HCl	16 hr	$C_8H_{14}ClN_3O_3$	40.76	40.57	5.94	5.96	17.83	17.64	—	—
XXII	NH_2	n-C_3H_7	H	O	51	207	DMF–H_2O	12 hr	$C_7H_{11}N_3O_3$	45.40	45.30	6.08	5.94	22.70	22.61	—	—

TABLE IV

Infrared absorptions in the range of 3400 cm^{-1} to 1450 cm^{-1}

Compound No.											
II	3375(s)	3200(s)	3100(s)	3000(m)	2875(m)	1770(s)	1740(s)	1710(s)	1645(s)	1530(s)	1460(m)
V	3375(s)	3225(m)	3125(s)	2890(m)	1750(s)	1715(s)	1660(s)	1540(s)	1500(m)	1450(m)	
VI	3400(s)	3200(sh)	3100(s)	2875(m)	1750–1710(s)	1650(s)	1600(s)	1545(s)	1500(m)	1460(s)	
XIX	3200(m)	3000(m)	2800(m)	1780(sh)	1750(s)	1720(s)	1555(m)	1545(m)	1490(m)	1450(m)	
XX	3200(s)	3010(s)	2800(s)	1780(s)	1750–1720(s)	1600(m)	1585(m)	1540(m)	1500(m)		
XXI	3200(s)	3150(s)	3100(s)	2975(s)	2800(s)	2675(m)	1760–1710(s)	1555(m)	1475(s)	1460(m)	

Hydrolysis of some 5-acetamido barbiturates with 4 *N* HCl gave the 5-amino hydrochloride barbiturates which are listed in Table III along with the N-methylated derivatives.

The hydrolysis of the 5-acetamido group to an amine hydrochloride results in the disappearance of absorptions at 3400 cm^{-1} (free N—H stretching mode), 1650 cm^{-1} (amide I band), 1365 cm^{-1} (amide II band), and 1298 cm^{-1} (amide III band) (Table IV). There is also the disappearance of the lowest of the first three carbonyl frequencies in the region 1800–1640 cm^{-1} (3). In the 5-aminohydrochloride compounds, new bands around 1585–1555 cm^{-1} and 1340 cm^{-1} are probably due to NH_3 deformation frequency and symmetric mode respectively. There is also some displacement towards lower frequencies of 3100 cm^{-1} and 2900 cm^{-1} to 3000 and 2800 cm^{-1} (VI, XX; V, XIX).

Pharmacology.—All these barbiturates (Tables I, II, and III) were tested on mice in dosage of 100 mg/kilogram, as their sodium salts. No hypnotic activity was found in any case. The replacement of an alkyl chain in position-5 by a free or acetylated amino group resulted in the loss of hypnotic activity.

EXPERIMENTAL

All the melting points reported are uncorrected and some of them depend on the rate of heating. The infrared spectra were recorded with a Beckman IR4 spectrophotometer using KBr pellets containing 0.5% by weight of sample and reported spectra are all calibrated. Ultraviolet spectra were all recorded with a Beckman DB Spectrophotometer using 95% ethanol as solvent. Analyses were performed by Dr. C. Daessle of Organic Microanalysis, Montreal.

The method used for preparing alkylated acetamido malonic esters was mainly that reported by Snyder (4) and Albertson (5) as reviewed by Cope (6). The criterion used for the completion of the reaction was its neutral reaction towards litmus. If, on vacuum evaporation, the compound solidified, it was filtered, washed with water, and dried before crystallization. However, if, on vacuum evaporation an oil was obtained, small amount of water was added and the oil extracted with benzene. The benzene solution was dried with anhydrous sodium sulphate and vacuum evaporated.

For the preparation of barbiturates, 1 mole of the alkylated acetamido malonic ester was refluxed with 2 moles of sodium dissolved in absolute ethanol and 1.5 mole of urea. The condenser carried a $CaCl_2$ tube. The amount of absolute alcohol was so adjusted that the reaction mixture always retained enough fluid to be refluxed and stirred. After the reaction was completed, the mixture was cooled and vacuum evaporated. The semisolid was brought into solution by adding water and the mixture was acidified with 10% HCl to precipitate the barbiturate.

Methylation with dimethyl sulphate consisted in dissolving 5 g of the barbituric acid in 75 ml of 4% NaOH solution and then adding an equimolar amount of dimethyl sulphate. The mixture was stirred at room temperature for 0.5 hour and then acidified with cold 10% HCl.

Hydrolysis of acetamido group was performed with 4 *N* HCl. The complete dissolution of the compound indicated completion of the reaction. The reaction mixture was filtered, evaporated, and crystallized from a minimum amount of dilute HCl.

Attempted S-Alkylation of 5-Ethyl-5-(1-methylbutyl)-2-thiobarbituric Acid

Sodium pentothal, 5 g (0.021 mole), was dissolved in ethyl alcohol (150 ml, 95%), and allyl bromide (15 ml, excess) was added to it. The mixture was refluxed for 3 hours and then evaporated. The solid residue was extracted with benzene and repeatedly crystallized from benzene – petrol ether (b.p. 35–75°) (six times) to yield 3.5 g of pentobarbital m.p. 130.5° (lit. 131°). An easier way to purify the compound is by adsorption chromatography on alumina (B.D.H.) using as eluant benzene – ethyl acetate (1:1 mixture) or ethyl acetate alone. The pentobarbital thus obtained gave negative Lassaigne's test for sulphur and gave superimposable ultraviolet and infrared spectra with an authentic sample obtained from commercial Nembutal by precipitation with dilute HCl and crystallization from benzene – petrol ether mixture. It also showed no depression in mixed melting point determination. Mol. wt. (Rast) 235 (theory, 226). Anal. Calc. for $C_{11}H_{18}N_2O_3$ (226): C, 58.40; H, 7.97; N, 12.39. Found: C, 58.64; H, 8.16; N, 12.40.

Similarly sodium pentothal, 1 g (0.004 mole), on refluxing with benzyl chloride (3 ml, excess), in ethyl alcohol (30 ml, 95%) for 16 hours, and vacuum evaporation gave 0.5 g of pentobarbital. The characteristic smell of benzyl mercaptan and allyl mercaptan in the above case was noted but no efforts were made to isolate them. The characterization of the pentobarbital was done according to the method described in the case of allyl bromide.

Preparation of 5-Acetamido-5-isobutylbarbituric Acid (IV) from 5-Acetamido-5-isobutyl-2-thiobarbituric Acid (XII)

To a solution of 5.2 g (0.02 mole) of XII in 75 ml of 4% caustic soda solution was added 2.52 g (0.02 mole) of dimethyl sulphate. The mixture was stirred at room temperature for half an hour and then acidified with 10% HCl. If the mixture was kept in the refrigerator overnight, 2 g of the crystals of IV were obtained. Crystallization from dioxane–H_2O gave the analytical sample, m.p. 318°. Lassaigne's test for sulphur was negative. Anal. Calc. for $C_{10}H_{15}N_3O_4$ (241): C, 49.79; H, 6.22; N, 17.42. Found: C, 49.85; H, 6.07; N, 17.38. Mixed melting point with the sample prepared by condensation of urea and 5-acetamido-5-isobutyl malonic ester showed no depression. The two compounds also gave identical infrared spectra.

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