

Synthesis of Acyloxyalkylbarbiturates as Potential Long-Acting Central Nervous System Depressants

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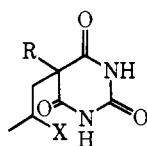
A series of acyloxybarbiturates (**13-30**) were prepared to determine if hydrolysis of the ester within the CNS would produce an active, long-acting agent. Preliminary testing indicates that these compounds retain CNS activity, but do not exhibit abnormally long action.

Esterification as a method of prolonging drug action has been used with success in the steroid hormones, such as estradiol,^{2,3} and with certain antibiotics, such as oleandomycin⁴ and erythromycin.⁵

Attempts to prolong the action of meperidine, by replacement of the *N*-Me with various ester groups have also been reported⁶ and the carbamate of mephensin, gave higher and more persistent plasma levels than the parent alcohol.⁷

The introduction of a polar function (*i.e.*, NH₂, OH, CO₂H) into the alkyl or aryl substituent in the 5 position of the barbiturates results in compounds which are almost totally devoid of any hypnotic or anticonvulsant properties.⁸ Agents such as 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**1**),⁹ and 5-allyl-5-(2-amino-propyl)barbituric acid (**2**),¹⁰ lack any significant depressant activity. However, in this laboratory it was found that esterification of a side-chain hydroxyl group produced compounds having hypnotic action.

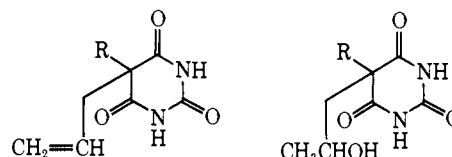
In an effort to develop barbiturates which have a



1, X = OH; R = C₆H₅
2, X = NH₂; R = CH₂=CHCH₂

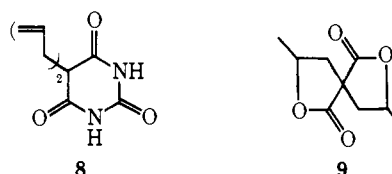
very long duration of sedative, hypnotic, or anticonvulsant action, a series of compounds were prepared which contain various ester groups on an alkyl substituent in the 5 position. The secondary alcohols, 5-isopropyl-5-(2-hydroxypropyl)barbituric acid (**4**),¹¹ 5-(1-methylbutyl)-5-(2-hydroxypropyl)barbituric acid (**6**),¹² and 5-phenyl-5-(2-hydroxypropyl)barbituric acid

(**1**),¹³ were prepared in high yield from the corresponding allylic compounds, **3**, **5**, and **7**, by hydration in the presence of H₂SO₄.



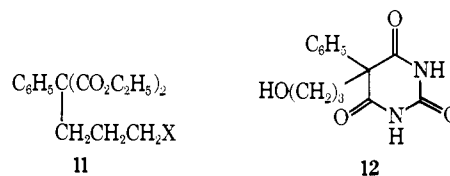
R
3 (CH₃)₂CH **4**
5 CH₃(CH₂)₂CH(CH₃) **6**
7 C₆H₅ **1**
CH₂=CHCH₂ **12**

The treatment of 5,5-diallylbarbituric acid (**8**) with H₂SO₄ at room temp for 3 hr afforded only the dilactone of bis(2-hydroxypropyl)malonic acid (**9**).¹² Reducing the reaction time to 1 hr did not change the results. When the reaction temp was lowered to 0° and **8** was allowed to react with H₂SO₄ for a short time, the mono-



hydroxylated product, 5-allyl-5-(2-hydroxypropyl)barbituric acid (**10**),¹⁴ was obtained in excellent yield.

The primary alcoholic 5-phenyl-5-(3-hydroxypropyl)barbituric acid (**12**) was prepared by the alkylation of diethyl phenylmalonate with 1,3-dibromopropane¹⁵ to give **11a** which was converted to the corresponding acetate **11b**. This was then condensed with urea in a standard barbiturate synthesis to afford **12** in moderate yield.



11
a, X = Br
b, X = OAc

The esters (Table I) were all prepared from the corresponding alcohols by a number of general methods

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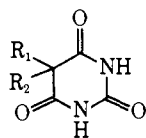
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TABLE I

Compd	R	
	R ₁	R ₂
Primary esters		ROCH ₂ CH ₂ CH ₂
13	C ₆ H ₅	a
14	C ₆ H ₅	b
15	C ₆ H ₅	c
16	C ₆ H ₅	d
17	C ₆ H ₅	e
Secondary esters		CH ₃ CHORCH ₂
18	C ₆ H ₅	a
19	C ₆ H ₅	b
20	C ₆ H ₅	c
21	C ₆ H ₅	d
22	C ₆ H ₅	e
23	CH ₃ (CH ₂) ₂ CH(CH ₃)	a
24	CH ₃ (CH ₂) ₂ CH(CH ₃)	b
25	CH ₃ (CH ₂) ₂ CH(CH ₃)	c
26	CH ₃ (CH ₂) ₂ CH(CH ₃)	d
27	CH ₃ (CH ₂) ₂ CH(CH ₃)	e
28	<i>i</i> -C ₃ H ₇	a
29	CH ₂ =CHCH ₃	a
30	CH ₃ CHOAcCH ₂	a



- a, CH₃CO
 b, *n*-C₃H₇CO
 c, C₆H₅CO
 d, 3,4,5-(CH₃)₃C₆H₂CO
 e, *p*-NO₂C₆H₄CO

TABLE II

Compd	General ^a behavior	Anti- ^b writhing	Electro- ^c shock seizure	Strych- ^d nine seizure	Metrazol ^e seizure	Intermit- ^f tent/ light stimulation
13	0/3 C	- ^g	-	-	+	
14	1/3 A	-	-	-	+	
15	1/3 A	-	-	-	+	
16	1/3 A	-	-	-	+	
17	0/3 B	-	-	-	-	
18	1/3 A	-	+	+	+	+
19	3/3 C	-	-	+	+	
20	2/3 C	-	-	-	-	
21	0/3 A	-	-	-	-	
22	0/3 C	-	-	-	-	
23	3/3 A	-	-	-	+	+
24	1/3 A	-	-	+	+	
25	0/3 A	-	-	-	-	
26	0/3 A	-	-	-	-	
27	1/3 A	-	-	+	+	
28	0/3 C	-	-	-	-	
29	0/3 A	-	-	-	+	
30	0/3 A	-	-	-	-	

^a Mouse, ip: mortality at 1 g/kg - no. tested; A = depressant; B = stimulant; C = stimulant depressant. ^b Mouse, po, 100 mg/kg. ^c Mouse, po, 200 mg/kg, 45 min. ^d Mouse, po, 200 mg/kg, 45 min. ^e Mouse, po, 200 mg/kg, 45 min. ^f *Papio papio* baboon [K. F. Killam, R. Naquet, and J. Bert, *Epilepsia*, **7**, 215 (1966)]. ^g + = active, - = inactive at dose tested.

except 5-bis(2-acetoxypropyl)barbituric acid (**30**), which could not be prepared *via* the alcohol. This ester was prepared from diallylbarbituric acid (**8**) by the addition of HBr to produce the bis(bromo) derivative.¹⁶ The ester **30** was prepared by treating the bis(bromo) compound with AgOAc.

The nmr data for **13-30** revealed a downfield shift of 0.5 to 1.0 ppm for CH₂ and CH attached to the C bearing the ester group as compared to the corresponding alcohol, thereby excluding the possibility of acylation on the pyrimidine nitrogens. Acylation of imide nitrogens in barbituric acids has been reported^{17,18} using acid chlorides in the presence of pyridine at higher temp (130-140°) than those employed in this investigation.

Biological Results.—Preliminary biological testing results of the barbiturate esters **13-30** are reported in Table II.

Experimental Section¹⁹

5-Phenyl-5-(2-hydroxypropyl)barbituric Acid (1).—A soln of 5.00 g (0.021 mole) of alphenal (**7**) in 50 ml of concd H₂SO₄ was allowed to stand at 25° for 3 hr. The mixt was poured into 50 ml of ice H₂O, and the solid material was collected, washed with H₂O, and dried. Compd **1** crystd (EtOH), mp 229-231° [lit.¹³ mp 224-227°], yield 5.30 g (98%).

5-(1-Methylbutyl)-5-(2-hydroxypropyl)barbituric acid (6) was prepared from 5-allyl-5-(1-methylbutyl)barbituric acid (**5**) in 60% yield by the method described above except that the reaction time was reduced to 15 min, mp 204-208° (EtOH) [lit.¹² mp 215-216° (EtOH-H₂O)].

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5-Isopropyl-5-(2-hydroxypropyl)barbituric acid (4) was prepd from 5-allyl-5-isopropylbarbituric acid (**3**) as described above with a reaction time of 15 min, in 59% yield, mp 236-238° (EtOH) [lit.¹¹ mp 221-222° (EtOH)].

5-Allyl-5-(2-hydroxypropyl)barbituric Acid (10).—A soln of 10.0 g (0.048 mole) of 5,5-diallylbarbituric acid (**8**) in 50 ml of concd H₂SO₄ (previously cooled to 0°) was stirred at 0° for 10 min, and the mixt was allowed to stand at 25°. After an additional 10 min, the reaction mixt was poured on to 50 g of crushed ice. No solids appeared, thus the soln was dild to 150 ml with H₂O and treated with NaHCO₃ (powd). Solids appeared and were filtered, and the filtrate was again treated with NaHCO₃. The process was repeated until no more solids were collected. The isolated material was combined, dried, and recrystd (Me₂CO-CHCl₃) to give 7.94 g (73%) of **10**, mp 166.5-168.5° [lit.¹⁴ mp 157-158° (EtOH-C₆H₆)].

5-Phenyl-5-(2-acetoxypropyl)barbituric Acid (18). Method A.—A soln of 5.00 g (0.019 mole) of 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**1**) in 10 ml of C₆H₅N and 4.50 g (0.057 mole) of Ac₂O was warmed on a steam bath for 15 min and allowed to stand at 25° for 24 hr. The mixt was poured into ice H₂O and acidified with 10% HCl. It was extd with CHCl₃, and the CHCl₃ exts were washed with H₂O and dried (MgSO₄). Removal of the solvent *in vacuo* gave an oil which was taken up in Et₂O. The ester crystd from either Et₂O or EtOH, yield 3.01 g (52%), mp 169-171° (EtOH).

5-Phenyl-5-[2-(3,4,5-trimethoxy)benzoyloxypropyl]barbituric Acid (21). Method B.—A soln of 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**1**) (2.00 g, 7.30 mmoles) in 50 ml of C₆H₅N was stirred and heated at 80° in the presence of 3,4,5-trimethoxybenzoyl chloride (1.90 g, 8.50 mmoles). After 18 hr, the mixt was cooled and poured into an iced soln of dil HCl. It was extd with 500 ml of CHCl₃, and the ext was washed repeatedly with 5% NaHCO₃ and H₂O and dried (MgSO₄). The soln was evapd *in vacuo* to give **21**, 2.54 g (75%), mp 246-248° (EtOH).

5-Phenyl-5-(2-butyroxypropyl)barbituric Acid (19). Method C.—A soln of 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**1**) (2.00 g, 7.62 mmoles) and butyryl chloride (0.812 g, 7.62 mmoles) in 20 ml of DMF was stirred at 100° for 3 hr. The soln was cooled and allowed to stand at 25° for an addl 8 hr. The mixt was poured into 50 ml of ice H₂O and extd with Et₂O. The Et₂O exts were washed with 5% NaHCO₃ and H₂O and dried (MgSO₄). Removal of the Et₂O *in vacuo* followed by recryst of the residue in [MeCO-petr ether (60-80°)] gave 1.86 g (75%) of **19**, mp 175-177°.

5,5-Bis(2-bromopropyl)barbituric Acid.—A soln of 5,5-diallylbarbituric acid (**8**) (4.00 g, 19.2 mmoles) in 20 ml of 30% HBr in glacial AcOH was placed in a glass high-pressure reaction

flask and was heated at 100° for 2 hr. The flask was cooled to 0° and opened, and the contents were poured into 50 ml of ice H₂O. The solids which sepd were collected by filtration, washed with H₂O, dried, and recrystd (EtOH-Me₂CO) to give 4.41 g (62%) of the desired compd (+ Beilstein test), mp 235–237° (lit.¹⁶ mp 237–239°).

5,5-Bis(2-acetoxypropyl)barbituric Acid (30). Method D.—To 3.00 g (8.10 mmoles) of 5,5-bis(2-bromopropyl)barbituric acid in 50 ml of glacial AcOH was added 2.75 g (16.2 mmoles) of AgOAc, and the mixt was stirred and refluxed for 2 hr. It was allowed to cool, treated with a few drops of dil HCl, and filtered. The AcOH was removed *in vacuo* to give an oil which was taken up in 100 ml of CHCl₃. The latter was washed with 5% NaHCO₃ and H₂O and dried (MgSO₄). Removal of the CHCl₃ *in vacuo* afforded an oil which gave 1.65 g (62%) of **30**, mp 151–154° (MeCO-CHCl₃).

5-Allyl-5-(2-acetoxypropyl)barbituric Acid (29). Method E.—AcCl (20 ml) and **10** (1.00 g, 4.42 mmoles) were refluxed for 1 hr, and the excess AcCl was distd. The residue was extd with 50 ml of CHCl₃. The CHCl₃ ext was washed with 5% NaHCO₃ and H₂O, dried (MgSO₄), and removed *in vacuo* to give an oil which was dissolved in C₆H₆. The acetate ester **29** was recrystd (C₆H₆), mp 140–142° (lit.¹⁴ mp 135–137°), yield 1.11 g (94%).

α-(3-Bromopropyl)phenylmalonic Acid, Diethyl Ester (11a).—A soln of diethyl phenylmalonate (56.5 g, 0.239 mole) in 50 ml of DMF was added dropwise to a stirred suspension of NaH (12.0 g, 0.250 mole) (50% in mineral oil) in 120 ml of DMF at 25° under N₂. The mixt was stirred for 1 hr and added dropwise to a stirred soln of 1,3-dibromopropane (50.5 g, 0.250 mole) in 50 ml of DMF under N₂. The mixt was stirred at 25° for 90 min and at 100° for 3 hr. Upon cooling the reaction mixt was dild with 1.2 l. of ice H₂O and extd with three 200-ml portions of petr ether (60–68°). The org exts were combined, washed with H₂O, and dried (MgSO₄), and the solvent was removed *in vacuo*. The residue was distd to afford 51.0 g (60%) of **11a**, bp 160–170° (0.3–0.3 mm) [lit.¹⁵ bp 172° (1 mm)].

α-(3-Acetoxypropyl)phenylmalonic Acid, Diethyl Ester (11b).—A soln of **11a** (35.0 g, 0.095 mole) and anhyd KOAc (18.3 g, 0.196 mole) in 159 ml of glacial AcOH was refluxed with stirring for 24 hr. The mixt was cooled, dild with 800 ml of H₂O, and extd with 4 × 200 ml of petr ether (60–68°). The org exts were combined, washed with H₂O, and dried (MgSO₄), and the solvent was removed *in vacuo*. The residue was distd to yield 24.1 g (74%) of **11b**, bp 158–165° (0.5 mm).

5-Phenyl-5-(3-hydroxypropyl)barbituric Acid (12).—A soln of NaOMe was prepd by the addition of 5.52 (0.24 g-atom) of Na to 100 ml of MeOH. Urea (19.2 g, 0.132 mole) (dried at 60° *in vacuo*) was added, with stirring, to the soln. The temp of the reaction mixt was raised slowly to 50–60° and α-(3-acetoxypropyl)phenylmalonic acid, diethyl ester (**11b**) (26.9 g, 0.08 mole) was added. The reaction was stirred and refluxed for 14 hr under anhyd conditions. Upon cooling, the MeOH was removed *in vacuo* (at 60°), and the residue was dissolved in ice H₂O (300 ml), extd with C₆H₆, and acidified at 10° to congo red with 10% HCl. The crude product was washed with H₂O and dried. Recryst [Me₂CO-petr ether (60–68°)] gave 10.2 g of **14**. Chromatog of the mother liquors on silica gel (85% CHCl₃-15% *i*-PrOH or 50% CHCl₃-50% EtAc) gave an additional 4.1 g (total yield 68%), mp 155–156°.

4-Phenyl-5-(3-butyroxypropyl)barbituric Acid (14). Method F.—A soln of 5-phenyl-5-(3-hydroxypropyl)barbituric acid (**12**) (1.00 g, 3.81 mmoles), PrCOCl (0.409 g, 3.81 mmoles), and C₆H₅N

(0.237 g, 3.00 mmoles) in 30 ml of dioxane was stirred at 25° for 3 hr. The reaction mixt was poured onto 100 ml of ice H₂O and extd with 2 × 100 ml of Et₂O. The org exts were combined, washed with 10% HCl and H₂O, and dried (MgSO₄). Removal of the Et₂O *in vacuo* followed by cryst of the oil [Me₂CO-petr ether (60–68°)] gave 0.871 g (69%) of the butyryl ester **14**, mp 102–105°.

Pertinent physical data concerning the esters of the hydroxybarbiturates are included in Table III.

TABLE III

Compound ^a	Formula ^e	Esterification ^b method	Mp, °C	Recryst solvent	Yield, %
13	C ₁₅ H ₁₆ N ₂ O ₅	A	169–171	Me ₂ CO-petr ether	84
14	C ₁₇ H ₂₀ N ₂ O ₅	F	105–106	Me ₂ CO-petr ether	69
15	C ₂₀ H ₁₈ N ₂ O ₅	F	154–156	Me ₂ CO-ether ^c	62
16	C ₂₃ H ₂₄ N ₂ O ₈	B	157–159	EtOH	53
17	C ₂₀ H ₁₇ N ₃ O ₇	B	220–223	EtOH	77
18	C ₁₅ H ₁₆ N ₂ O ₅	A	169–171	EtOH	52
19	C ₁₇ H ₂₀ N ₂ O ₅	C	175–177	Me ₂ CO-petr ether	74
20	C ₂₀ H ₁₈ N ₂ O ₅	B	187–189	Me ₂ CO-petr ^d ether	54
21	C ₂₃ H ₂₄ N ₂ O ₈	B	246–268	EtOH	76
22	C ₂₀ H ₁₇ N ₃ O ₇	B	209–211	Me ₂ CO-petr ether	70
23	C ₁₄ H ₂₂ N ₂ O ₅	A	158–160	EtOH-H ₂ O	88
24	C ₁₆ H ₂₆ N ₂ O ₆	C	153–156	Me ₂ CO-petr ether	65
25	C ₁₉ H ₂₄ N ₂ O ₅	B	189–192	Me ₂ CO-petr ^c ether	22
26	C ₂₂ H ₃₀ N ₂ O ₈	B	224–226	Me ₂ CO-petr ether	67
27	C ₁₉ H ₂₃ N ₃ O ₇	B	222–224	Me ₂ CO-petr ^d ether	22
28	C ₁₂ H ₁₈ N ₂ O ₆	E	151–152	EtOH	65
29	C ₁₂ H ₁₆ N ₂ O ₅	E	140–142	C ₆ H ₆	94
30	C ₁₄ H ₂₀ N ₂ O ₇	D	151–154	Me ₂ CO-CHCl ₃	62

^a Ir and nmr data were consistent with assigned structures.

^b Refers to procedure letter in Experimental Section. ^c Column chromatography on silica gel (CHCl₃-EtOAc). ^d Column chromatography on Silicar CC-4 (Et₂CO-petr ether). ^e All compounds were anal. for C, H, N.

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