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

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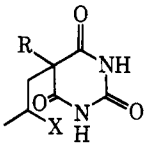
A series of acyloxybarbiturates (**13–30**) were prepared to determine if hydrolysis of the ester within the CNS would produce an active, long-acting agent. Preliminary testing indicates that these compounds retain CNS activity, but do not exhibit abnormally long action.

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 oleandomycin[4] and erythromycin.[5]

Attempts to prolong the action of meperidine, by replacement of the *N*-Me with various ester groups have also been reported[6] and the carbamate of mephenesin, gave higher and more persistent plasma levels than the parent alcohol.[7]

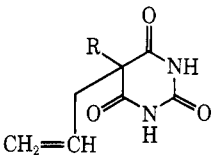
The introduction of a polar function (*i.e.*, $NH_2$, OH, $CO_2H$) into the alkyl or aryl substituent in the 5 position of the barbiturates results in compounds which are almost totally devoid of any hypnotic or anticonvulsant properties.[8] Agents such as 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**1**),[9] and 5-allyl-5-(2-aminopropyl)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.

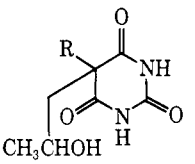
In an effort to develop barbiturates which have a



1, X = OH; R = $C_6H_5$
2, X = $NH_2$; R = $CH_2$=$CHCH_2$

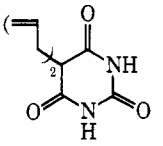
very long duration of sedative, hypnotic, or anticonvulsant action, a series of compounds were prepared which contain various ester groups on an alkyl substituent in the 5 position. The secondary alcohols, 5-isopropyl-5-(2-hydroxypropyl)barbituric acid (**4**),[11] 5-(1-methylbutyl)-5-(2-hydroxypropyl)barbituric 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 $H_2SO_4$.



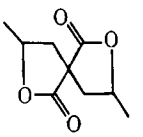


| R | | |
|---|---|---|
| **3** | $(CH_3)_2CH$ | **4** |
| **5** | $CH_3(CH_2)_2CH(CH_3)$ | **6** |
| **7** | $C_6H_5$ | **1** |
| | $CH_2$=$CHCH_2$ | **12** |

The treatment of 5,5-diallylbarbituric acid (**8**) with $H_2SO_4$ 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 $H_2SO_4$ for a short time, the mono-



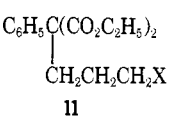
**8**



**9**

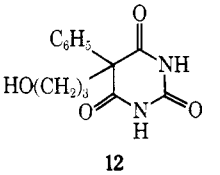
hydroxylated product, 5-allyl-5-(2-hydroxypropyl)-barbituric acid (**10**),[14] was obtained in excellent yield.

The primary alcoholic 5-phenyl-5-(3-hydroxypropyl)-barbituric acid (**12**) was prepared by the alkylation of diethyl phenylmalonate with 1,3-dibromopropane[15] 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



**12**

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

(1) Taken in part from the dissertation presented by R. A. Robinson, July 1969, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.
(2) K. Junkmann, *Arch. Exp. Pathol. Pharmakol.*, **220**, 358 (1953).
(3) J. Yamada, *Tohoku Igaku Zasshi*, **6**, 481 (1959); *Chem. Abstr.*, **54**, 10143 (1960).
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(8) W. J. Doran, "Medicinal Chemistry," Vol. IV, F. H. Blicke and R. H. Cox, Ed., Wiley, New York, N. Y., 1959, p 34.
(9) J. Gieldanowski and A. Pelazarski, *Arch. Immunol. Ter. Dosw.*, **8**, 361 (1969); *Chem. Abstr.*, **55**, 3811*b* (1961).
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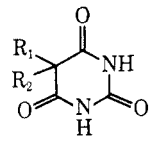
(12) E. W. Maynert and E. Washburn, *ibid.*, **75**, 700 (1953).
(13) A. J. B. Matuzak, Ph.D. Thesis, The University of Kansas, Lawrence, Kan., 1963.
(14) B. Borbanski, T. Jakobiec, and D. Prelicz, *Rocz. Chem.*, **30**, 175 (1956); *Chem. Abstr.*, **51**, 438*f* (1957).
(15) F. Salmon-Laganeur, *C. R. Acad. Sci.*, **236**, 2154 (1953).

TABLE I



R
a, $CH_3CO$
b, $n$-$C_3H_7CO$
c, $C_6H_5CO$
d, 3,4,5-$(CH_{30})_3C_6H_2CO$
e, $p$-$NO_2C_6H_4CO$

| Compd | $R_1$ | $R_2$ $ROCH_2CH_2CH_2$ |
|---|---|---|
| Primary esters | | |
| 13 | $C_6H_5$ | a |
| 14 | $C_6H_5$ | b |
| 15 | $C_6H_5$ | c |
| 16 | $C_6H_5$ | d |
| 17 | $C_6H_5$ | e |
| Secondary esters | | $CH_3CHORCH_2$ |
| 18 | $C_6H_5$ | a |
| 19 | $C_6H_5$ | b |
| 20 | $C_6H_5$ | c |
| 21 | $C_6H_5$ | d |
| 22 | $C_6H_5$ | e |
| 23 | $CH_3(CH_2)_2CH(CH_3)$ | a |
| 24 | $CH_3(CH_2)_2CH(CH_3)$ | b |
| 25 | $CH_3(CH_2)_2CH(CH_3)$ | c |
| 26 | $CH_3(CH_2)_2CH(CH_3)$ | d |
| 27 | $CH_3(CH_2)_2CH(CH_3)$ | e |
| 28 | $i$-$C_3H_7$ | a |
| 29 | $CH_2$=$CHCH_2$ | a |
| 30 | $CH_3CHOAcCH_2$ | a |

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 $CH_2$ 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.

TABLE II

| Compd | General[a] behavior | Anti-[b] writhing | Electro-shock[c] seizure | Strych-nine[d] seizure | Metrazol[e] seizure | Intermittent[f] 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.

## Experimental Section[19]

**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 $H_2SO_4$ was allowed to stand at 25° for 3 hr. The mixt was poured into 50 ml of ice $H_2O$, and the solid material was collected, washed with $H_2O$, 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–$H_2O$)].

**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 $H_2SO_4$ (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 $H_2O$ and treated with $NaHCO_3$ (powd). Solids appeared and were filtered, and the filtrate was again treated with $NaHCO_3$. The process was repeated until no more solids were collected. The isolated material was combined, dried, and recrystd ($Me_2CO$–$CHCl_3$) to give 7.94 g (73%) of **10**, mp 166.5–168.5° [lit.[14] mp 157–158° (EtOH–$C_6H_6$)].

**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 $C_5H_5N$ and 4.50 g (0.057 mole) of $Ac_2O$ was warmed on a steam bath for 15 min and allowed to stand at 25° for 24 hr. The mixt was poured into ice $H_2O$ and acidified with 10% HCl. It was extd with $CHCl_3$, and the $CHCl_3$ exts were washed with $H_2O$ and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave an oil which was taken up in $Et_2O$. The ester crystd from either $Et_2O$ 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**) (2.60 g, 7.30 mmoles) in 50 ml of $C_5H_5N$ 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 $CHCl_3$, and the ext was washed repeatedly with 5% $NaHCO_3$ and $H_2O$ and dried ($MgSO_4$). 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 $H_2O$ and extd with $Et_2O$. The $Et_2O$ exts were washed with 5% $NaHCO_3$ and $H_2O$ and dried ($MgSO_4$). Removal of the $Et_2O$ *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

(16) H. Staudinger, *Chem. Zentralbl.*, **2**, 748 (1923).
(17) W. Kahl and Z. Chytos-Majchrowicz, *Rocz. Chem.*, **40**, 1905 (1966).
(18) J. Bojarski and W. Kahl, *ibid.*, **41**, 311 (1967).
(19) Melting points were obtained on a calibrated Thomas-Hoover Uni-Melt and are corrected. Ir data ($\mu$) were recorded on Beckman IR8 and IR10 spectrophotometers. Nmr data (ppm, $\delta$) were recorded on Varian Associates Model A-60, A-60A, and HA-100 spectrophotometers (TMS). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M Model 185, the University of Kansas. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

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 $H_2O$. The solids which sepd were collected by filtration, washed with $H_2O$, dried, and recrystd (EtOH–$Me_2CO$) 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 $CHCl_3$. The latter was washed with 5% $NaHCO_3$ and $H_2O$ and dried ($MgSO_4$). Removal of the $CHCl_3$ *in vacuo* afforded an oil which gave 1.65 g (62%) of **30**, mp 151–154° (MeCO–$CHCl_3$).

**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 $CHCl_3$. The $CHCl_3$ ext was washed with 5% $NaHCO_3$ and $H_2O$, dried ($MgSO_4$), and removed *in vacuo* to give an oil which was dissolved in $C_6H_6$. The acetate ester **29** was recrystd ($C_6H_6$), 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 $N_2$. 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 $N_2$. 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 $H_2O$ and extd with three 200-ml portions of petr ether (60–68°). The org exts were combined, washed with $H_2O$, and dried ($MgSO_4$), 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 $H_2O$, and extd with 4 × 200 ml of petr ether (60–68°). The org exts were combined, washed with $H_2O$, and dried ($MgSO_4$), 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 $H_2O$ (300 ml), extd with $C_6H_6$, and acidified at 10° to congo red with 10% HCl. The crude product was washed with $H_2O$ and dried. Recryst [$Me_2CO$–petr ether (60–68°)] gave 10.2 g of **14**. Chromatog of the mother liquors on silica gel (85% $CHCl_3$–15% *i*-PrOH or 50% $CHCl_3$–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 $C_5H_5N$ (0.237 g, 3.00 mmoles) in 30 ml of dioxane was stirred at 25° for 3 hr. The rection mixt was poured onto 100 ml of ice $H_2O$ and extd with 2 × 100 ml of $Et_2O$. The org exts were combined, washed with 10% HCl and $H_2O$, and dried ($MgSO_4$). Removal of the $Et_2O$ *in vacuo* followed by cryst of the oil [$Me_2CO$–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 | $C_{15}H_{16}N_2O_5$ | A | 169–171 | $Me_2CO$–petr ether | 84 |
| 14 | $C_{17}H_{20}N_2O_5$ | F | 105–106 | $Me_2CO$–petr ether | 69 |
| 15 | $C_{20}H_{18}N_2O_5$ | F | 154–156 | $Me_2CO$–ether[c] | 62 |
| 16 | $C_{23}H_{24}N_2O_8$ | B | 157–159 | EtOH | 53 |
| 17 | $C_{20}H_{17}N_3O_7$ | B | 220–223 | EtOH | 77 |
| 18 | $C_{15}H_{16}N_2O_5$ | A | 169–171 | EtOH | 52 |
| 19 | $C_{17}H_{20}N_2O_5$ | C | 175–177 | $Me_2CO$–petr ether | 74 |
| 20 | $C_{20}H_{18}N_2O_5$ | B | 187–189 | $Me_2CO$–petr[d] ether | 54 |
| 21 | $C_{23}H_{24}N_2O_8$ | B | 246–268 | EtOH | 76 |
| 22 | $C_{20}H_{17}N_3O_7$ | B | 209–211 | $Me_2CO$–petr ether | 70 |
| 23 | $C_{14}H_{22}N_2O_5$ | A | 158–160 | EtOH–$H_2O$ | 88 |
| 24 | $C_{16}H_{26}N_2O_5$ | C | 153–156 | $Me_2CO$–petr ether | 65 |
| 25 | $C_{19}H_{24}N_2O_5$ | B | 189–192 | $Me_2CO$–petr[c] ether | 22 |
| 26 | $C_{22}H_{30}N_2O_8$ | B | 224–226 | $Me_2CO$–petr ether | 67 |
| 27 | $C_{19}H_{23}N_3O_7$ | B | 222–224 | $Me_2CO$–petr[d] ether | 22 |
| 28 | $C_{12}H_{18}N_2O_5$ | E | 151–152 | EtOH | 65 |
| 29 | $C_{12}H_{16}N_2O_5$ | E | 140–142 | $C_6H_6$ | 94 |
| 30 | $C_{14}H_{20}N_2O_7$ | D | 151–154 | $Me_2CO$–$CHCl_3$ | 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 ($CHCl_3$–EtOAc). [d] Column chromatography on Silicar CC-4 ($Et_2CO$–petr ether). [e] All compounds were anal. for C, H, N.

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