4-Chloro-α-methyl-3-nitrobenzeneacetonitrile (22). 4-Amino-α-methylbenzeneacetonitrile[4] (**20**, 43.8 g, 0.3 mol) was dissolved in a warm solution of concentrated HCl (90 ml) and H_2O (275 ml). The stirred solution was cooled and diazotized at 0–5° by the dropwise addition of a solution of $NaNO_2$ (22.8 g, 0.33 mol) in H_2O (40 ml) during 30 min. After a further 30 min, the diazotized solution was added dropwise during 30 min to a stirred solution of CuCl (30 g, 0.3 mol) in concentrated HCl (100 ml) and H_2O (100 ml) kept at 85–90°. The mixture was stirred at this temperature for a further 30 min, cooled to room temperature, and extracted with Et_2O (3 × 150 ml). The organic solution was shaken with a saturated solution of Na_2CO_3 (100 ml) and H_2O (100 ml), then dried (Na_2SO_4), and evaporated. In this way, chloro compound **21** was obtained as a mobile brown oil (39.0 g, 79%) which was identical with an authentic sample.[2]

The oil (39.0 g, 0.236 mol) was added dropwise during 50 min to a stirred solution of fuming HNO_3 (*d* 1.5, 120 ml) kept at −5–0°. After a further 40 min at this temperature and 2.5 hr at room temperature, the solution was poured onto ice (350 g). The product was extracted with Et_2O (3 × 150 ml) and the extracts were neutralized with a saturated solution of $NaHCO_3$. The Et_2O extracts were finally washed with H_2O (100 ml), dried (Na_2SO_4), and evaporated. This gave pure **22** as a light brown gum (42.0 g, 84%) which solidified on standing: mp 36–39°. Anal. ($C_9H_7ClN_2O_2$) C, H, N.

2-(4-Chlorophenyl)-1,α-dimethyl-5-benzimidazoleacetic Acid (5). 4-Chloro-α-methyl-3-nitrobenzeneacetonitrile[2] (**22**, 19 g, 0.09 mol) was heated and stirred for 5 hr at 150° in a sealed glass vessel with 33% CH_3NH_2 in EtOH and allowed to cool overnight. The mixture was treated with 2 *N* NaOH and extracted with $CHCl_3$ (three times). The combined $CHCl_3$ solutions were dried (Na_2SO_4), filtered, and evaporated to give a product which, after chromatography on silica gel ($CHCl_3$ as eluent), yielded 4-methylamino-α-methyl-3-nitrobenzeneacetonitrile (**23**) as an orange solid (11 g, 60%): NMR ($CDCl_3$) δ 1.63 (d, 3 H), 3.04 (d, 3 H), 3.88 (q, 1 H), 6.93 (d, 1 H), 7.52 (dd, 1 H), 8.1 (m, 1 H), 8.15 (d, 1 H).

The foregoing product (11 g, 0.05 mol) with EtOH (300 ml) and 50% Pd/C (0.5 g) was hydrogenated at room temperature and pressure to give 3-amino-4-methylamino-α-methylbenzeneacetonitrile (**24**, 8.25 g, 88%) as a dark oil which was about 95% pure (TLC). The above nitrile (**24**, 2.6 g, 0.015 mol) and 4-chlorobenzaldehyde (2.12 g, 0.015 mol) were refluxed in C_6H_6 for 0.5 hr, while the theoretical amount (0.26 ml) of H_2O was collected in a Dean-Stark apparatus. The C_6H_6 solution was evaporated to dryness under reduced pressure and the residual oil heated at 100° for 15 min in AcOH (30 ml) containing lead tetraacetate (4.68 g). The brown solution was diluted with H_2O, neutralized with $NaHCO_3$ solution, and extracted with $CHCl_3$. This was dried (Na_2SO_4) and evaporated to dryness and the product was purified by chromatography (SiO_2, $CHCl_3$ eluent) to give 2-(4-chlorophenyl)-1,α-dimethyl-5-benzimidazoleacetonitrile (**25**, 3 g, 69%) as a solid: NMR [$CDCl_3$–$(CD_3)_2SO$] δ 1.09 (d, 3 H), 3.82 (s, 3 H), 4.06 (q, 1 H), 7.32–7.87 (m, 7 H).

The above nitrile **25** (3 g, 0.01 mol) was stirred in refluxing concentrated HCl (30 ml) for 1 hr. The mixture was poured into an excess of $NaHCO_3$ solution and filtered, the pH adjusted to pH 7 with concentrated HCl, and the product extracted with $CHCl_3$ which was dried (Na_2SO_4) and decolorized (C). The $CHCl_3$ was evaporated to yield **5** (1 g, 32%) as a buff solid: mp 225–227°; NMR [$CDCl_3$–$(CD_3)_2SO$] δ 1.54 (d, 3 H), 3.8 (s, 3 H), 3.82 (q, 1 H), 7.25 (m, 7 H). Anal. ($C_{17}H_{15}ClN_2O_2$) C, H, N.

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Analgesics. 3. Selected 1-Substituted and 1,3-Disubstituted 5-Propionoxy-5-(1-phenylethyl)barbituric Acids

Julius A. Vida,* Carlos M. Samour, Mary H. O'Dea,

Kendall Company, Lexington, Massachusetts 02173

and John F. Reinhard

Department of Medicinal Chemistry and Pharmacology, Graduate School of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115. *Received December 23, 1974*

Several 1,3-disubstituted and 1-substituted derivatives of 5-propionoxy-5-(1-phenylethyl)barbituric acid were synthesized and evaluated for analgesic activity. Three of these compounds, 1,3-bis(methoxymethyl)-5-propionoxy-5-(1-phenylethyl)barbituric acid (**2**), 1,3-dimethyl-5-propionoxy-5-(1-phenylethyl)barbituric acid (**7**), and 1-methyl-5-propionoxy-5-(1-phenylethyl)barbituric acid (**10**), exhibited better oral activity than codeine sulfate.

In previous reports[1,2] we have shown that analgesic activity is associated with a series of 5-acyloxy-5-phenylalkylbarbituric acids, and we have discussed the structure–activity relationships of these 5,5-disubstituted compounds. We have now prepared a series of 1,3-disubstituted and 1-substituted derivatives of one of the most potent compounds reported earlier, 5-propionoxy-5-(1-phenylethyl)-barbituric acid, in order to evaluate the effects of nitrogen substituents on the analgesic activity.

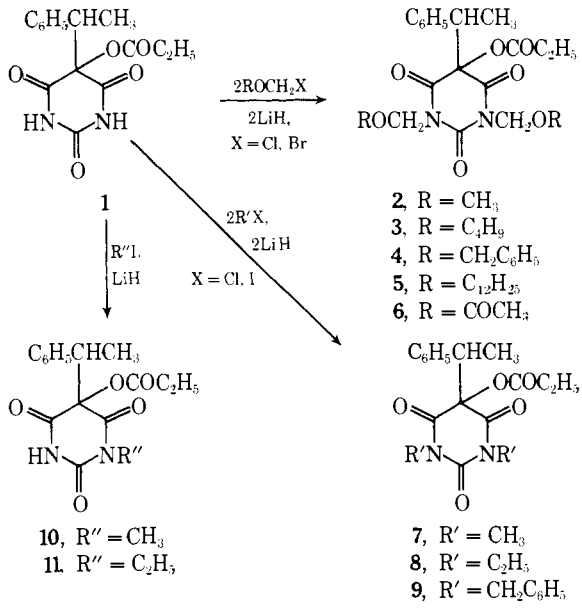
Chemistry. 1,3-Bis(alkoxymethyl)-5-propionoxy-5-(1-phenylethyl)barbituric acids (**2–5**) were prepared by alkylation of 5-propionoxy-5-(1-phenylethyl)barbituric acid (**1**) with alkyl chloromethyl ethers in the presence of 2 equiv of base. 1,3-Bis(acetoxymethyl)-5-propionoxy-5-(1-phenylethyl)barbituric acid (**6**) was prepared from **1** and bromomethyl acetate in a similar manner.

1,3-Dialkyl derivatives **7–9** and 1-alkyl derivatives **10** and **11** of 5-propionoxy-5-(1-phenylethyl)barbituric acid were obtained by alkylation of **1** with alkyl halides in the presence of 2 equiv and 1 equiv of base, respectively (Scheme I). No attempts were made to separate any racemates obtained throughout this study.

Structure–Activity Relationships. The best analgesic

* Address correspondence to this author at Bristol Laboratories, Syracuse, N.Y. 13201.

Scheme I



activity was shown by 1-methyl-5-propionoxy-5-(1-phenylethyl)barbituric acid (**10**) which was equal in activity to the parent compound **1**. 1,3-Bis(methoxymethyl)-5-propionoxy-5-(1-phenylethyl)barbituric acid (**2**) also showed good activity, being only slightly less active than compound **1**. 1,3-Dimethyl-5-propionoxy-5-(1-phenylethyl)barbituric acid (**7**) exhibited approximately one-fifth the potency of compound **1**. Increasing the sizes of the 1,3-bis(alkoxymethyl)-, the 1,3-dialkyl-, or the 1-alkyl substituents caused sharp decreases in activity, along with decreased toxicity. 1,3-Bis(acetoxymethyl)-5-propionoxy-5-(1-phenylethyl)barbituric acid (**6**) also showed greatly decreased activity and toxicity compared to the parent compound.

Pharmacology. Analgesic Activity. Compounds **2–11**, listed in Table I along with the parent compound **1**, were evaluated for analgesic activity orally by the Eddy hotplate method. Compounds **2** and **10** displayed one-third to one-half the potency of subcutaneously administered morphine. Compound **7** was one-half as active as subcutaneously administered codeine. Compounds **2**, **7**, and **10** were all more potent than orally administered codeine and appear to be rapidly absorbed from the gastrointestinal tract. Compounds **3**, **4**, **6**, **8**, and **11** showed oral activity in the potency range of aminopyrine. Compounds **5** and **9** showed weak activity at doses which also produced signs of CNS toxicity.

Hypnotic Activity. The compounds in this series completely lack hypnotic activity, even at toxic doses.

Effects upon the Central Nervous System. CNS stimulation appears to be a prominent pharmacological property of this series, increasing in intensity with increasing dosage.

Acute Toxicity. In general, the less potent compounds exhibited low acute toxicity, and the more potent members of the series were correspondingly more toxic. Therapeutic indices (LD_{50}/ED_{50}), however, were generally favorable, averaging between 5 and 10, values considered within the range of safety. Clonic–tonic convulsive seizures constituted the major feature of the pattern of toxicity, with death resulting from respiratory paralysis.

Experimental Section

Pharmacology. Compounds 1–11 and aminopyrine were administered orally (po) suspended in 10% aqueous acacia. Codeine sulfate was dissolved in water for oral administration but suspended in 10% aqueous acacia for subcutaneous administration. Morphine sulfate was dissolved in water for subcutaneous administration. Adult male albino mice (18–30 g, Charles River) were used throughout this study.

Analgesic activity was determined in mice by the Eddy hotplate method[3] in which analgesic activity was recorded on the basis of significant increase in the area under the curve relating reaction time to a heat stimulus (55°) at intervals following drug administration. In addition, a modification of the Eddy procedure was employed in which an analgesic response was recorded if the reaction time to the heat stimulus following a drug equalled or exceeded the mean pretreatment response (based on ten animals per dose) + two standard deviation units. Experimental ranges were not determined for compounds exhibiting weak activity. ED_{50}'s with 95% confidence limits[4] were computed for all potent compounds exhibiting rectilinear dose–response relationships. For compounds which did not exhibit linear dose–response relationships, approximate values were assigned. Peak time for analgesic activity (by either the original Eddy procedure or its modification) was recorded as that time following drug administration at which the greatest percentage of animals exhibited an analgesic response. Analgesic potency by either the original Eddy procedure or its modification did not differ significantly.

Acute Toxicity. The compounds were administered orally and the animals were observed for signs of toxicity over a period of several hours thereafter and again daily for a period of 1 week or until complete recovery had occurred. The number of deaths was recorded, and the dosage required to kill 50% of the animals (LD_{50}) was computed according to Litchfield and Wilcoxon.[4]

Effects on the Central Nervous System (CNS). A battery of tests was employed to determine CNS effects.

(1) **CNS stimulation** was recorded if the animals (a) exhibited increased spontaneous movements compared to untreated controls either by visual observation or by recording the actual number of movements by means of a standard photoelectric cell apparatus; (b) displayed tremors and/or convulsive seizures in response to increasing dosage; (c) were hostile, i.e., resisted handling by attempting to bite vigorously, in contrast to the relatively docile behavior of untreated controls; and (d) showed increased tonus of skeletal muscles on handling.

(2) **CNS depression** was recorded if a compound produced effects which were the opposite of those recorded in the previous section. In addition, neurological deficit was recorded if the animals showed ataxic movements or other signs as reported by Swinyard et al.[5] or failed to "log roll" for at least 1 min on a rod (Rotarod)[6] rotating at 6 rpm.

Hypnotic Activity. Sleep was determined by loss of the righting reflex. The number of mice sleeping was recorded for each dose. The compound was considered to have hypnotic activity only if the dose required to induce sleep was significantly lower than that required to cause death.

Analyses and Spectra. Microanalyses were within ±0.3% of the theoretical values as performed by Galbraith Laboratories, Knoxville, Tenn., and Atlantic Microlab, Inc., Atlanta, Ga. Melting points were obtained on a Fisher-Johns hot stage and are corrected. Ir spectra were recorded on a Perkin-Elmer 337 grating ir spectrophotometer. NMR spectra were run on Varian A-60A and HA-100 spectrometers in $(CD_3)_2SO$ with Me_4Si as internal reference. Uv spectra were recorded on a Bausch & Lomb spectronic 505 spectrophotometer. Mass spectra were determined on a Hitachi RMU-6D double-focusing spectrometer at 70 eV. Type QIF silica gel plates from Quantum Industries were used for TLC development with PhH–EtOAc mixtures. E. M. Merck 70–325 mesh silica gel (0.05–0.2 mm) pretreated with benzene (2:1, weight of silica gel–volume of benzene) was used for chromatographic separations. Ir, NMR, uv, and mass spectra and TLC were all appropriate.

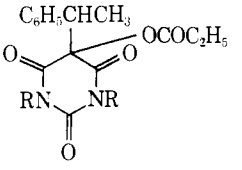
1,3-Disubstituted 5-Propionoxy-5-(1-phenylethyl)barbituric Acids (2–9). The following general procedure was used in the preparation of these compounds, shown in Table II. To a solution of 5-propionoxy-5-(1-phenylethyl)barbituric acid (1 12 g, 0.04 mol) in DMF (100 ml) was added base (0.08 mol) and the mixture was stirred 10 min at 25°. RCl (0.088 mol) was added dropwise. Stirring was continued 16 hr at the temperature shown in Table II. The cooled solution was poured into ice–H_2O (400 ml) and then extracted with EtOAc. Evaporation of the solvent gave an oily residue which was chromatographed on silica gel (300 g). Elution with C_6H_6 gave the pure products. Starting material, which remained in the column after elution of the products, could be recovered by further elution with C_6H_6–EtOAc (7:3).

1-Methyl-5-propionoxy-5-(1-phenylethyl)barbituric Acid (10). To a solution of 1 (1.5 g, 0.005 mol) in DMF (24 ml) was

Table I. Pharmacologic Activity of Selected 1-Substituted and 1,3-Disubstituted 5-Propionoxy-5-(1-phenylethyl)barbituric Acids

Compd no.	Peak time, hr	Analgesic act., ED_{50}, mg/kg po	Acute toxicity, LD_{50}, mg/kg po	CNS effects
1	0.5	>6.25 < 12.5	70 (57.4–85.4)	Stimulation, Straub tail at 25 mg/kg and above
2	1	15.6 (10.3–23.7)	>125 < 250	Stimulation, convulsions at lethal doses
3	2.5	~200	>1000	Stimulation, hyperactivity at 1000 mg/kg
4	1	~200	>1000	None noted
5	2	>400	>1000	Stimulation, hyperactivity at 400 mg/kg
6	1	~200	>1000	None noted
7	0.5	~50	>200	Stimulation, convulsions at 200 mg/kg
8	1	~200	>1000	Stimulation, hyperactivity at 1000 mg/kg
9	1	>400	>1000	Neurological deficit at 200 mg/kg
10	1	~10	>31.25 < 62.5	Stimulation, convulsions at lethal doses
11	1	~170	>1000	None noted
Morphine sulfate	0.5	4.8 (3.7–5.6) sc		
Codeine sulfate	0.5	26 (17.9–37.7) sc 118 (65.6–212.4) po		
Amino-pyrine	0.5	215 (134.4–344.0) po		

Table II. 1,3-Disubstituted 5-Propionoxy-5-(1-phenylethyl)barbituric Acids



Compd	R	Base	Temp, °C	Mp, °C	Yield, %	Formula	Analyses
2	CH_2OCH_3	LiH	25	Oil	56	$C_{19}H_{24}O_7N_2$	C, H, N
3	$CH_2OC_3H_8$	LiH	25	Oil	44.6	$C_{25}H_{36}O_7N_2$	C, H, N
4	$CH_2OCH_2C_6H_5$	LiH	25	Oil	42.3	$C_{31}H_{32}O_7N_2$	C, H, N
5	$CH_2OC_{12}H_{25}$	LiH	25	Oil	34	$C_{41}H_{68}O_7N_2$	C, H, N
6	CH_2OCOCH_3	LiH	25	Oil	49	$C_{21}H_{24}O_9N_2$	C, H, N
7	CH_3	LiH	50	83–85	57	$C_{17}H_{20}O_5N_2$	C, H, N
8	C_2H_5	LiH	50	63.5–65.5	90.5	$C_{19}H_{24}O_5N_2$	C, H, N
9	$CH_2C_6H_5$	K_2CO_3	50	133–135	37	$C_{29}H_{28}O_5N_2$	C, H, N

added LiH (44 mg, 0.0055 mol). The mixture was stirred at 60° for 0.5 hr. CH_3I (0.72 g, 0.005 mol) was added and the solution was stirred at 60° for 16 hr, then cooled to 25°, and poured into ice–H_2O (100 ml) which had been saturated with NaCl. Extraction with EtOAc, followed by evaporation of the extract, gave an oily solid which was chromatographed on silica gel (200 g). Elution with EtOAc–C_6H_6 (3:7) gave **10** (0.475 g, 30%), mp 175–177°. Anal. ($C_{16}H_{18}O_5N_2$) C, H, N. 1,3-Dimethyl-5-propionoxy-5-(1-phenylethyl)barbituric acid (**7**) and starting material were the only other identifiable products.

1-Ethyl-5-propionoxy-5-(1-phenylethyl)barbituric Acid (11). Compound 11 was obtained from 1 (12 g, 0.0395 mol) and C_2H_5I (6.3 g, 0.04 mol) in the same way as described for the preparation of compound **10**. Elution of the column (300 g of silica gel) with C_6H_6–EtOAc (19:1) gave 11 (1.9 g, 15.5%) which was crystallized from 2-propanol–H_2O (2:3). Obtained was 11, mp 125–127°. Anal. ($C_{17}H_{20}O_5N_2$) C, H, N. 1,3-Diethyl-5-propionoxy-5-(1-phenylethyl)barbituric acid (**8**) and starting material were the only other identifiable products.

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