lyophilized preparation obtained from Sigma Chemical Co.) to make a 4% protein solution. This concentration was used by Hansch in a correlation of protein binding with partition coefficients.[14] Both the portions of solution with and without added protein were agitated at 37° for 16 hr. The protein-containing solution was filtered through an Amicon Model 12 ultrafiltration cell fitted with a Type UM 2 Diaflo ultrafiltration membrane. Both the filtrate and the solution without protein were measured by ultraviolet absorption spectroscopy. The per cent binding to BSA was determined by the equation: % binding = $(X_1 - X_2)/X_1(100)$, wherein X_1 = OD of solution not containing protein and X_2 = OD of filtrate after ultrafiltration. The OD values were measured at wavelengths above 310 nm since some absorption due to compounds from the BSA passing through the ultrafiltration membrane was found below 310 nm.

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Analgesics. 1. Selected 5-Substituted 5-Propionoxybarbituric Acids

Julius A. Vida,*† Carlos M. Samour, Mary H. O'Dea, Theodore S. T. Wang, William R. Wilber,

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 February 6, 1974*

Several 5-substituted 5-propionoxybarbituric acids were synthesized and evaluated for analgesic activity. One compound, 5-propionoxy-5-(1-phenylethyl)barbituric acid (**29**), displayed better analgesic activity than codeine orally and had half the analgesic potency of morphine when administered subcutaneously. Compound **29** constitutes the *first example of a potent analgesic lacking a basic center* (of pK_a permitting extensive protonation at physiological pH).

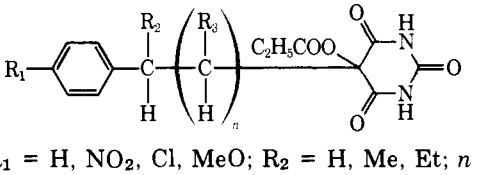
Several investigators have reported[1-3] the structural features generally found in potent analgesics; these may be summarized as follows: (1) a basic amine function, usually tertiary and limited in size; (2) a highly substituted central atom with none of its valency bonds linked to hydrogen (quarternary carbon or tertiary nitrogen); (3) an aromatic group (such as phenyl) connected to the central atom; (4) a two-carbon chain separating the central atom from the nitrogen.

During the past 15 years many potent analgesics have been described which possess structural features that deviate from the above requirements, particularly with respect to the permitted size of the basic group, and the necessity for a reevaluation of structure-activity relationships in analgesics was pointed out as early as 1959 by Eddy.[4]

However, as late as 1970 Casy[5] stated that "in spite of the continual appearance of novel structures characterized as having morphine-like actions which are reversed by antagonists such as nalorphine, no significant analgesic has been yet identified which lacks either a *basic center* (of pK_a permitting extensive protonation at physiological pH values) or *aromatic* features."

We have now synthesized a series of compounds which are characterized by the following structural features: (1) the lack of a basic center (of pK_a permitting extensive protonation at physiological pH values); (2) the lack of a central quaternary carbon atom to which a phenyl group is connected; (3) the lack of a two-carbon chain separating a central quaternary carbon atom from the nitrogen atom.

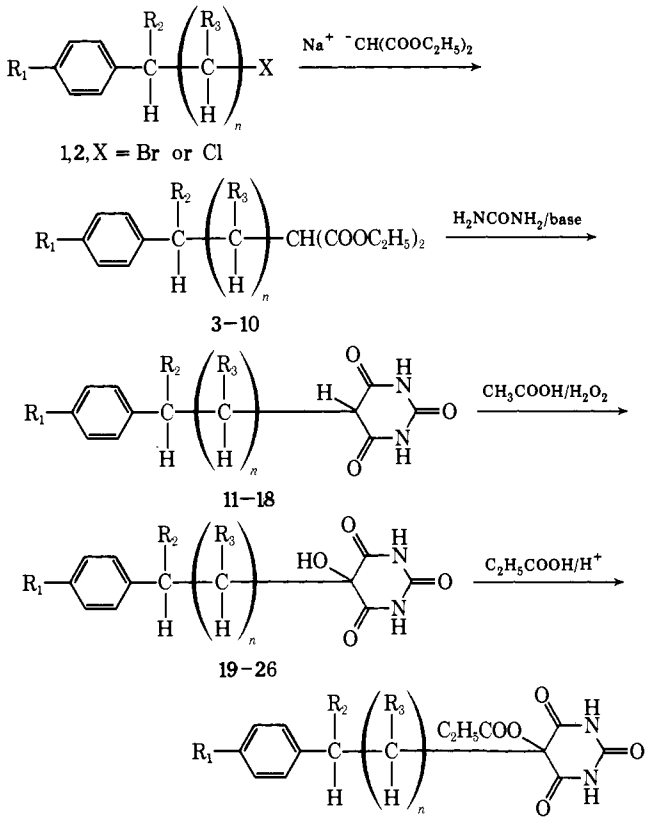
The general structure of the new class of potent analgesics is shown



where R_1 = H, NO_2, Cl, MeO; R_2 = H, Me, Et; n = 0, 1. When n = 1, R_3 = H, Me.

†A preliminary account of this work was presented by J. A. Vida and C. M. Samour before the Medicinal Chemistry Division, 165th National Meeting of the American Chemical Society, Dallas, Texas, April 1973, Abstracts of Papers, MEDI-21.

Scheme I



R_1 = H, NO_2, Cl, CH_3O; R_2 = H, CH_3, C_2H_5; n = 0, 1; when n = 1, R_3 = H, CH_3

Chemistry. The compounds in this series were prepared as shown in Scheme I.

With the exception of two compounds the phenylalkyl halides (bromides or chlorides) used in the preparation of (phenylalkyl)malonates were available commercially. Compounds **1** and **2** were prepared by bromination of propylbenzene and *p*-nitroethylbenzene, respectively, with bromine in ultraviolet light. The (phenylalkyl)malonates were prepared from the halides by condensation reactions with diethyl sodiomalonate. The crude products were purified by distillation under reduced pressure (**3-9**) or crystallization (**10**). The (phenylalkyl)malonates (**3-10**) were converted into the 5-(phenylalkyl)barbituric acids with urea in alkaline medium. The conversion of the 5-(phenylalkyl)barbituric acids **11-18** to the corresponding 5-hydroxy-5-(phenylalkyl)barbituric acids **19-26** could best be achieved by oxidation with peracetic acid. The 5-hydroxy-5-(phenylalkyl)barbituric acids were esterified with propionic acid in the presence of strong mineral acids. Although the hydroxyl group is a tertiary one adjacent in most cases to a benzylic proton, no olefinic products of the possible elimination reaction could be isolated under the reaction conditions used.

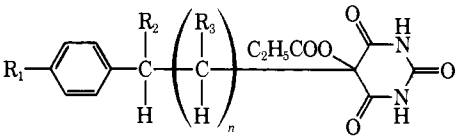
In addition to the mass spectrum, the structure of compound **29** is supported by the nmr spectrum (60 and 100 MHz) displaying a methyl signal split into a doublet by the adjacent benzylic proton. This eliminates any other possible structural assignment to compound **29**. The same type of evidence is available for all other compounds (**19-28** and **30-35**).

In the course of the condensation reaction between the malonate esters and urea, in one case, it was possible to isolate the monocarbamidomalondiamide derivative.

The monocarbamidomalondiamide derivative could be converted into the cyclic barbiturate by treatment with additional base (Scheme II).

Structure-Activity Relationship. The best analgesic activity was displayed by compound **29**. Replacement of the methyl group by either an ethyl group as in **27** or hydrogen as in **28** resulted in a decrease of analgesic activity. Insertion of another methylene group either between the phenylalkyl group and the barbituric ring as in **30** or between the phenyl and adjacent alkyl groups as in **31** caused a reduction of analgesic activity as compared to that of compound **29**. Replacement of the aromatic para hydrogen by a chloro group as in **32**, methoxy group as in **33**, or a nitro group as in **34** produced a further decrease in the analgesic potency as compared to that of the parent compound **29**.

Pharmacology. Analgesic Activity. All of the compounds listed in Table I exhibited analgesic activity. Compounds **27**, **28**, **30-32** were in the potency range of aminopyrine. Compound **29**, the outstanding member of the series, was in the potency range of morphine. It is noteworthy, however, that compound **29**, unlike morphine, was effective orally as well as after subcutaneous injection; moreover, its oral potency exceeded that of codeine by a wide margin. The time for the development of peak analgesic activity was 0.5 hr, suggesting rapid absorption from the gastrointestinal tract. One would judge that absorption from this site was not only rapid but substantially complete, since the peak time by this route was identical with that following subcutaneous injection. This



27, n = 0; R_1 = H; R_2 = Et
28, n = 0; R_1 = H; R_2 = H
29, n = 0; R_1 = H; R_2 = Me
30, n = 1; R_1 = H; R_2 = Me; R_3 = H
31, n = 1; R_1 = H; R_2 = H; R_3 = CH_3
32, n = 0; R_1 = Cl; R_2 = Me
33, n = 0; R_1 = MeO; R_2 = Me
34, n = 0; R_1 = NO_2; R_2 = Me

Scheme II

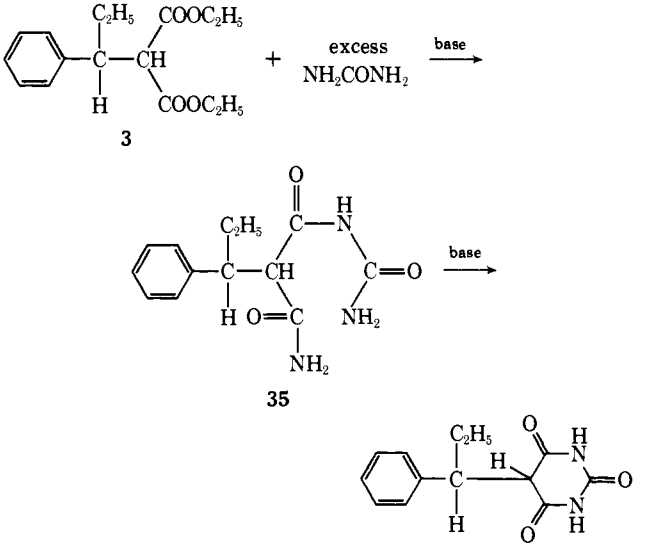


Table I. Pharmacologic Activity of Selected 5-Substituted 5-Propionoxybarbituric Acids

Compd no.	Analgesic act., ED_{50}, mg/kg	Peak time, hr	Hypnotic act., mg/kg	Acute toxicity, LD_{50}, mg/kg	CNS effects	Other
27	~200 po	0.5	Absent after 500 mg/kg po	>500 po	Stimulation	Straub tail
28	~200 po	0.5	Absent after 200 mg/kg po	>200 po <1000 po	Stimulation	Straub tail
29	>6.5 po <13.0 po 8.8 (6.3–12.1) sc	0.5	No hypnosis	70 (57.4–85.4) po	Stimulation	In writhing test, ED_{50} = ~7 mg/kg po; ED_{50} = 27 (22.0–33.2) mg/kg po; Straub tail at 25 mg/kg and above
30	>200 po <500 po	1	>1000 po	>1000 po	Decreased spontaneous movements	Alert on handling
31	~100 po ~100 sc	0.5	>1000 po >1000 sc	>1000 po	None noted	
32	>100 po <500 po	0.5	>500 po	>500 po	Stimulation	Ptosis
33	>500 po	2	>500 po	>500 po	None noted	
34	~500 po	1	>500 po	>500 po	None noted	
Morphine sulfate	4.8 (3.7–5.6) sc	0.5				
Codeine sulfate	26 (17.9–37.7) sc	0.5				
	118 (65.6–212.4) po	0.5				
Amino-pyrine	215 (134.4–344.0) po	0.5				
Acetyl-salicylic acid	500 (413.2–605.0) po	1				

compound also exhibited marked analgesic potency, in the range of morphine, in the writhing test. Compounds **33** and **34**, the weakest members of the series, were in the potency range of acetylsalicylic acid.

Hypnotic Activity. In spite of their structural relationship to the hypnotic barbiturates, it is noteworthy that not a single member of the series exhibited hypnotic activity. Indeed, CNS stimulation, rather than depression, would appear to be a major pharmacological property of the series and particularly of its most potent member (**29**).

Acute Toxicity. In general, the members of this series exhibited low acute toxicity, their LD_{50}'s exceeding 500 mg/kg, in line with their relatively low analgesic potency, in the range of the antipyretic analgesics. Compound **29** is the outstanding exception with an LD_{50} of 70 mg/kg. This is in line, however, with the factual association of activity and toxicity. The margin of safety (LD_{50}/ED_{50} = >5), nonetheless, would appear to be well within acceptable limits for a therapeutic agent.

Effects on the Central Nervous System. CNS stimulation appears to be a prominent pharmacological property of this series, increasing in intensity with increasing dosage. Compound **29** exerted little CNS-stimulant activity except for the Straub tail response at fully analgesic dosage, but with increasing dosage animals were overtly stimulated and in the lethal range death occurred following clonic-tonic convulsive seizures. Only a single compound (**30**) showed a decrease in spontaneous movements following massive dosage (1000 mg/kg).

Physical Dependence Capacity. Compound **29** was tested for physical dependence capacity. Based on a single dose suppression assay at a subcutaneous dose of 4.0 mg/kg, compound **29** has no physical dependence capacity.

Experimental Section

Pharmacology. All compounds were administered orally (po) or subcutaneously (sc) suspended in 10% aqueous acacia. Adult male albino mice (18–30 g, Charles River) were used throughout this study.

Analgesic activity was determined by the Eddy hot-plate method[6] 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) + 2 standard deviation units. 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. The analgesic activity by either the original Eddy procedure or its modification did not differ significantly.

In addition (in some instances), analgesic activity was determined by the writhing test of Siegmund, *et al.*[7] Briefly, a candidate compound was administered orally or subcutaneously to adult male albino mice in groups of ten. At the predetermined time of peak effect, the animals were challenged by intraperitoneal injection of phenylquinone. An analgesic response was recorded if the animals failed to show the stereotyped (writhing) response.

Acute Toxicity. The compounds were administered orally and/or subcutaneously 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 cause death in 50% of the animals (LD_{50}) was computed according to Litchfield and Wilcoxon.[8]

Effects on the Central Nervous System. 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 with the aid of a standard photoelectric cell apparatus; (b) exhibited 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 behavior of untreated controls; and (d) showed increased tonus of skeletal muscles on handling.

(2) **CNS Depression.** 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 re-

corded if the animals showed ataxic movements or other signs as reported by Swinyard, *et al.*,[9] or failed to "log roll" for at least 1 min on a rod (Rotarod)[10] rotating at 6 rpm.

Hypnotic activity 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 if the dose required to induce sleep in the animals differed significantly from the dosage required to cause death in the animals.

Physical Dependence Capacity Protocol.‡ Monkeys, physically dependent on 3.0 mg/kg of morphine sulfate administered every 6 hr, were withdrawn until abstinence signs of intermediate severity were present (12–14 hr). The coded drug was injected at this time by persons other than the observer. The monkeys were graded just prior to injection and at intervals of 0.5, 1, 2, 3, 4, 5, and 6 hr after injection. Grades were based on withdrawal intensity or opiate-like depression and side effects, if present.

Analyses and Spectra. Microanalyses were within ±0.3% of the theoretical values as performed by Galbraith Laboratories, Knoxville, Tenn. 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, Ir, nmr, uv, mass spectra, and tlc were all appropriate.

1-Bromo-1-phenylpropane (1). To propylbenzene (240 g, 2 mol) was added bromine (320 g, 2 mol) dropwise over a 2-hr period with stirring and illumination by a Westinghouse 275-W sun lamp. Illumination was continued for 5 min after the addition was complete. The obtained liquid was distilled at reduced pressure (20 mm) and the product, 1 (305 g, 85%), was collected at 90–120° and used without further purification.

α-Bromo-*p*-nitroethylbenzene (2). To *p*-nitroethylbenzene (151.16 g, 1 mol) was added bromine (176 g, 1.1 mol) dropwise over a 1-hr period, with stirring and illumination by a Westinghouse 275-W sun lamp. Stirring was continued for 1 hr. The reaction mixture was evaporated under reduced pressure at 100°, and the residue was used without purification.

Diethyl (1-Phenylpropyl)malonate (3). To a solution of sodium (46 g, 2 mol) in EtOH (750 ml) was added diethyl malonate (350 g, 2.19 mol); then compound 1 (305 g, 1.5 mol) was added over a period of 1 hr. The solution was heated at reflux for 2 hr, then cooled, and filtered to remove NaBr (220 g). The solution was acidified with AcOH (25 ml) and again filtered to remove sodium acetate. The cake was washed with Et_2O. The filtrate was evaporated and the residual liquid was distilled at 2 mm of pressure. The product, 3 (310 g, 74%), was collected at 120–150° and used without further purification.

Diethyl (1-Phenylethyl)malonate (4). To a solution of sodium (11.5 g, 0.5 mol) in EtOH (250 ml) was added diethyl malonate (80 g, 0.5 mol) and the mixture was stirred 0.5 hr. 1-Bromoethylbenzene (92.5 g, 0.5 mol) was added over a period of 1 hr and stirring was continued 16 hr at reflux. NaBr was removed by filtration and the solvent was evaporated. The resulting liquid was distilled at 5 mm of pressure. The product, 4 (119 g, 90%), was collected at 153–155°. *Anal.* ($C_{15}H_{20}O_4$) C, H.

Diethyl Benzylmalonate (5). Compound 5 was prepared from benzyl bromide (513.12 g, 3 mol) and diethyl malonate (480.51 g, 3 mol) in the same way as described for the preparation of compound 4. Obtained was 5 (80 g, 10.6%), bp 160–180° (10 mm) [lit.[11] bp 163–170° (12 mm)].

Diethyl (2-Phenylpropyl)malonate (6). Compound 6 was prepared from β-bromoisopropylbenzene (200 g, 1 mol) and diethyl malonate (160 g, 1 mol) in the same way as described for the preparation of compound 4. Obtained was 6 (125 g, 45%) collected at 140–160° at 1 mm of pressure and used without further purification.

Diethyl (1-Phenyl-2-propyl)malonate (7). Compound 7 was prepared from 2-bromo-1-phenylpropane (50 g, 0.25 mol) and diethyl malonate (40 g, 0.25 mol) in the same way as described for the preparation of compound 4. Obtained was 7 (20.4 g, 29.4%), collected at 140–160° at 2 mm of pressure and used without further purification.

‡The coded compound was submitted to the National Research Council, Committee on Problems of Drug Dependence. The tests were carried out at the University of Michigan. We are grateful to Dr. E. May for transmitting the results to us.

Diethyl (*p*-Chlorobenzyl)malonate (8). Compound 8 was prepared from *p*-chlorobenzyl chloride (126.58 g, 0.79 mol) and diethyl malonate (176 g, 1.1 mol) in the same way as described for the preparation of compound 4. Prior to distillation of the product, diethyl bis(*p*-chlorobenzyl)malonate (33 g, 10.2%) was removed by filtration. The remaining oil was distilled at 5 mm of pressure and the product, 8 (120 g, 54%), was collected at 180° [lit.[12] bp 190–192° (14 mm)]. *Anal.* ($C_{14}H_{17}O_4Cl$) C, H, Cl.

Diethyl (*p*-Methoxybenzyl)malonate (9). Compound 9 was prepared from *p*-methoxybenzyl chloride (25 g, 0.155 mol) and diethyl malonate (26 g, 0.16 mol) in the same way as described for the preparation of compound 4. Obtained was 9 (24 g, 54.5%) collected at 180–200° at 2 mm of pressure [lit.[13] bp 178–180° (3 mm)]. *Anal.* ($C_{15}H_{20}O_5$) C, H.

Diethyl (1-*p*-Nitrophenylethyl)malonate (10). Compound 10 was obtained from 2 and diethyl malonate (160 g, 1 mol) in the same way as described for the preparation of compound 4. Obtained was crude 10, a solid which was crystallized from MeOH to give pure 10 (210 g, 68%), mp 65–66.5°. *Anal.* ($C_{15}H_{19}O_6N$) C, H, N.

5-(1-Phenylpropyl)barbituric Acid (11). Compound 35 (50 g, 0.19 mol) was added to a solution of sodium (11.5 g, 0.5 mol) in EtOH (250 ml). The mixture was heated at reflux for 20 hr and cooled, and the solvent was evaporated to near dryness. Ice water (500 ml) was added and the solution was acidified to pH 2 with HCl. After filtration, the white solid was crystallized from EtOH–H_2O (1:1, 300 ml) to give 11 (30 g, 64%), mp 181.5–183°. *Anal.* ($C_{13}H_{14}O_3N_2$) C, H, N.

5-(1-Phenylethyl)barbituric Acid (12). Sodium (2.76 g, 0.122 mol) was dissolved in EtOH (40 ml) and urea (12 g, 0.2 mol) was added. To this solution was added 4 (13.2 g, 0.05 mol) and the mixture heated at reflux for 16 hr. The cooled solution was evaporated, ice (300 g) was added, and the mixture was acidified with 2 *N* HCl to pH 1. The solid was removed by filtration, washed with H_2O, and crystallized from aqueous EtOH (150 ml, 70%) to give 12 (8.1 g, 70%), mp 218–220°. *Anal.* ($C_{12}H_{12}O_3N_2$) C, H, N.

5-Benzylbarbituric Acid (13). Compound 13 was prepared from 5 (80 g, 0.316 mol) and urea (180 g, 3 mol) in the same way as described for the preparation of compound 12. Purification was achieved by dissolving the crude product in 2 *N* NaOH and acidifying the solution with 2 *N* HCl. Precipitation was effected by saturating the solution with NaCl. The solid was collected by filtration and passed through a Dowex W-X8 cation exchange column. Recrystallization from EtOH gave 13 (20 g, 29%), mp 218–219° (lit.[14] 212.5–214°). *Anal.* ($C_{11}H_{10}O_3N_2$) C, H, N.

5-(2-Phenylpropyl)barbituric Acid (14). Compound 14 was prepared from 6 (123 g, 0.44 mol) and urea (126 g, 2.1 mol) in the same way as described for the preparation of compound 12. Obtained was 14 (65 g, 60%), mp 204–206°. *Anal.* ($C_{13}H_{14}O_3N_2$) C, H, N.

5-(1-Phenyl-2-propyl)barbituric Acid (15). Compound 15 was prepared from 7 (20.4 g, 0.077 mol) and urea (24 g, 0.4 mol) in the same way as described for the preparation of compound 12. Obtained was 15 (11 g, 61%), mp 203–206°. *Anal.* ($C_{13}H_{14}O_3N_2$) C, H, N.

5-(*p*-Chlorobenzyl)barbituric Acid (16). Compound 16 was prepared from 8 (120 g, 0.422 mol) and urea (120 g, 2 mol) in the same way as described for the preparation of compound 12. Obtained was 16 (71.5 g, 67.5%), mp 205–214°. *Anal.* ($C_{11}H_9O_3N_2Cl$) C, H, N, Cl.

5-(*p*-Methoxybenzyl)barbituric Acid (17). Compound 17 was prepared from 9 (24 g, 0.085 mol) and urea (24 g, 0.4 mol) in the same way as described for the preparation of compound 12. Obtained was 17 (15 g, 71%), mp 205–210° (lit.[15] mp 198–200°). *Anal.* ($C_{12}H_{12}O_4N_2$) C, H, N.

5-(1-*p*-Nitrophenylethyl)barbituric Acid (18). To a solution of sodium (5.5 g, 0.24 mol) in EtOH (100 ml) was added urea (25 g, 0.415 mol). To this solution was added a hot solution of 10 (31 g, 0.1 mol) in EtOH (150 ml). The mixture was stirred at reflux 5 hr, cooled, and allowed to stand 16 hr. The red precipitate was removed by filtration and dissolved in H_2O (200 ml), ice was added, and the solution was acidified to pH 2 with HCl. An oily solid formed which solidified upon stirring in an ice bath for 3 hr. The solid was removed by filtration and crystallized from MeOH. Obtained was 18 (20 g, 66%), mp 198–201°. *Anal.* ($C_{12}H_{11}O_5N_3$) C, H, N.

5-Hydroxy-5-(1-phenylpropyl)barbituric Acid (19). To a solution of H_2O_2 (30%, 8.5 ml) in AcOH (50 ml) was added 11 (5.0 g, 0.0203 mol). The mixture was stirred at 50° until a clear solution was obtained and then stirred 16 hr at 25°. MeOH (15 ml) and

H_2O (15 ml) were added. After standing 2 hr, the solvents were evaporated. The obtained white solid was crystallized from acetone yielding 19 (4.3 g, 83%), mp 210-212°. *Anal.* ($C_{13}H_{14}O_4N_2$) C, H, N.

5-Hydroxy-5-benzylbarbituric Acid (20). Compound 20 was prepared from 13 (3.6 g, 0.0165 mol) in the same way as described for compound 19. Obtained was 20 (2.9 g, 75%), mp 222-225° (lit.[16] mp 213-215°). *Anal.* ($C_{11}H_{10}O_4N_2$) C, H, N.

5-Hydroxy-5-(1-phenylethyl)barbituric Acid (21). Compound 21 was obtained from 12 (2.0 g, 0.0086 mol) in the same way as described for the preparation of compound 19. Obtained was 21 (1.42 g, 66%), mp 204-205°. *Anal.* ($C_{12}H_{12}O_4N_2$) C, H, N.

5-Hydroxy-5-(2-phenylpropyl)barbituric Acid (22). Compound 22 was obtained from 14 (15 g, 0.061 mol) in the same way as described for the preparation of compound 19. Obtained was 22 (10.5 g, 65.5%), mp 206-208°. *Anal.* ($C_{13}H_{14}O_4N_2$) C, H, N.

5-Hydroxy-5-(1-phenyl-2-propyl)barbituric Acid (23). To a solution of H_2O_2 (30%, 4 ml) in AcOH (40 ml) was added 15 (2.5 g, 0.01 mol). The mixture was heated at 65° until a clear solution was obtained and then stirred at 25° for 16 hr. MeOH (35 ml) and H_2O (25 ml) were added, and stirring was continued for 1 hr. The solvents were evaporated to give 23 (1.5 g, 58%), a pale yellow oil which solidified on standing. Compound 23 was used without further purification.

5-Hydroxy-5-(*p*-chlorobenzyl)barbituric Acid (24). Compound 24 was prepared from 16 (10.1 g, 0.04 mol) in the same way as described for the preparation of compound 23. Obtained was 24 (7.6 g, 71%), mp 243-245°, which was used without purification.

5-Hydroxy-5-(*p*-methoxybenzyl)barbituric Acid (25). Compound 25 was prepared from 17 (7.44 g, 0.03 mol) in the same way as described for the preparation of compound 19. Obtained was 25 (5.9 g, 74%), mp 222-223°. *Anal.* ($C_{12}H_{12}O_5N_2$) C, H, N.

5-Hydroxy-5-(1-*p*-nitrophenylethyl)barbituric Acid (26). Compound 26 was prepared from 18 (8.3 g, 0.03 mol) in the same way as described for the preparation of compound 19. Crystallization from THF gave 26 (7 g, 79.5%), mp 282-286°. *Anal.* ($C_{12}H_{11}O_6N_3$) C, H, N.

5-Propionoxy-5-(1-phenylpropyl)barbituric Acid (27). To a solution of H_2SO_4 (3.8 ml) in propionic acid (20 ml) was added 19 (2.5 g, 0.01 mol). The mixture was stirred at 65° for 16 hr, cooled, and poured over ice. $NaHCO_3$ was added until pH 7.8 was reached. The product was extracted into EtOAc and the solvent was evaporated. Chromatography on silica gel using C_6H_6-EtOAc (4:1) gave the product which was crystallized from acetone-hexane (1:1, 20 ml) to give 27 (1.4 g, 44%), mp 156-158°. *Anal.* ($C_{16}H_{18}O_5N_2$) C, H, N.

5-Propionoxy-5-benzylbarbituric Acid (28). Compound 28 was obtained from 20 (1.0 g, 0.00417 mol) in the same way as described for the preparation of compound 27. Obtained was 28 (0.7 g, 58%), mp 174.5-176°. *Anal.* ($C_{14}H_{14}O_5N_2$) C, H, N.

5-Propionoxy-5-(1-phenylethyl)barbituric Acid (29). Compound 29 was prepared from 21 (5 g, 0.0216 mol) in the same way as described for the preparation of compound 27. Obtained was 29 (4.54 g, 69%), mp 186-186.5°. *Anal.* ($C_{15}H_{16}O_5N_2$) C, H, N.

5-Propionoxy-5-(2-phenylpropyl)barbituric Acid (30). Compound 30 was prepared from 22 (2.5 g, 0.0096 mol) in the same way as described for the preparation of compound 27. Obtained was 30 (2.0 g, 65.5%), mp 160-162°. *Anal.* ($C_{16}H_{18}O_5N_2$) C, H, N.

5-Propionoxy-5-(1-phenyl-2-propyl)barbituric Acid (31). Compound 31 was prepared from 23 (1.5 g, 0.0058 mol) in the same way as described for the preparation of compound 27. Obtained was 31 (0.8 g, 43%), mp 123-126°. *Anal.* ($C_{16}H_{18}O_5N_2$) C, H, N.

5-Propionoxy-5-(*p*-chlorobenzyl)barbituric Acid (32). Compound 32 was prepared from 24 (7.6 g, 0.028 mol) in the same way as described for the preparation of compound 27. Crystallization from EtOAc gave 32 (6.3 g, 69.5%), mp 222-223°. *Anal.* ($C_{14}H_{13}O_5N_2Cl$) C, H, N, Cl.

5-Propionoxy-5-(*p*-methoxybenzyl)barbituric Acid (33). Compound 33 was prepared from 25 (1 g, 0.038 mol) in the same way as described for the preparation of compound 27. Crystallization from MeOH-H_2O (2:1) gave 33 (0.8 g, 66%), mp 215-219°. *Anal.* ($C_{15}H_{16}O_6N_2$) C, H, N.

5-Propionoxy-5-(1-*p*-nitrophenylethyl)barbituric Acid (34). A mixture of 26 (1.0 g, 0.0034 mol), H_2SO_4 (5 ml), methanesulfonic acid (10 ml), and propionic acid (25 ml) was stirred at 85° for 48 hr. The solution was cooled and poured into ice water (150 ml). The precipitate was removed by filtration and crystallized from EtOAc-petroleum ether (1:1). Obtained was 34 (0.71 g, 59%), mp 240-241°. *Anal.* ($C_{15}H_{15}O_7N_3$) C, H, N.

(1-Phenylpropyl)-*N*-monocarbamidomalondiamide (35). To a solution of sodium (54.8 g, 2.38 mol) in EtOH (800 ml) was added urea (240 g, 4 mol) and compound 3 (278.34 g, 1 mol). The mixture was heated at reflux 16 hr and then cooled, and a portion of the solvent was evaporated until a total volume of 1 l. was achieved. Ice water (800 ml) was added and the solution acidified with HCl to pH 2. The solid was removed by filtration, washed with water, and crystallized from EtOH. Obtained was 35 (218 g, 83%), mp 188-189°. *Anal.* ($C_{13}H_{17}O_3N_3$) C, H, N.

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Benzamidopiperidines. 2. Heterocyclic Compounds Related to Indoramin

John L. Archibald* and Gerald A. Benke

John Wyeth and Brother Limited, Taplow, Maidenhead, Berkshire, England.

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The synthesis and biological properties of some heterocyclic compounds related to indoramin are described. These are derivatives of 4-benzamidopiperidine with a side chain linking the piperidine to a heterocyclic ring. A clear separation between antihypertensive and hypotensive activities is noted among these compounds. None are as potent as indoramin in either hypotensive or antihypertensive tests.

The synthesis and hypotensive activity of benzamidopiperidylethylindoles were first described in 1968.[1] A more detailed study was published in 1971[2] in which structure-activity relationships were extensively investigated in indolylalkyl derivatives of benzamidopiperidines with particular emphasis on modifications of the amide moiety. No compound was found to be clearly superior to the parent 3-[2-(4-benzamidopiperid-1-yl)ethyl]indole (indoram-