Analgesics. 2. Selected 5-Substituted 5-(1-Phenylethyl)barbituric Acids

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

Kendall Company, Lexington, Massachusetts 02173

and John F. Reinhard

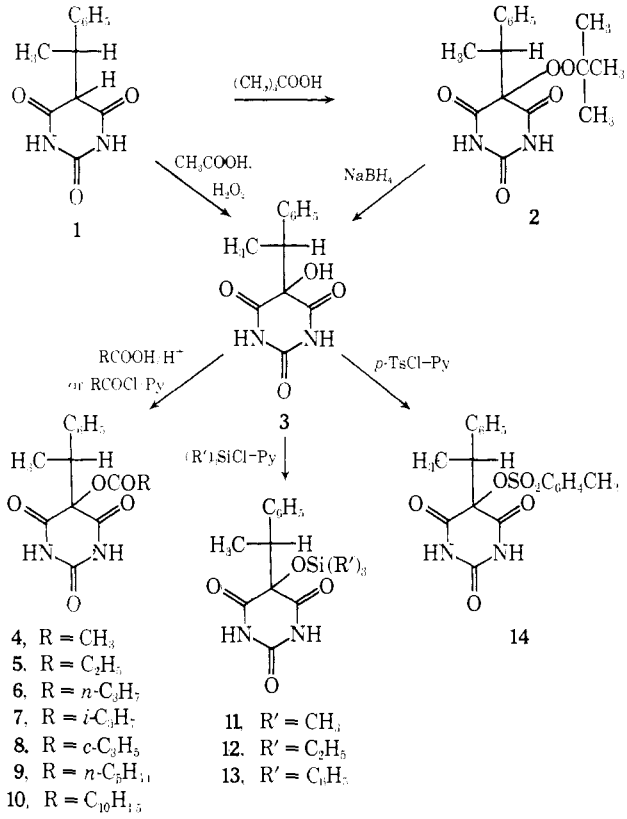
Department of Medicinal Chemistry and Pharmacology, Graduate School of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115. *Received May 20, 1974*

Several 5-substituted 5-(1-phenylethyl)barbituric acids displayed potent analgesic activity. One compound, 5-acetoxy-5-(1-phenylethyl)barbituric acid (**4**), exhibited better analgesic activity than codeine orally and had one-third the analgesic potency of morphine when administered subcutaneously. Another compound, 5-cyclopropylcarbonyloxy-5-(1-phenylethyl)barbituric acid (**8**), exhibited better analgesic activity than codeine orally and was approximately ten times as potent as morphine when administered subcutaneously. Three other compounds, compounds **6**, **7**, and **11**, also revealed better analgesic activity than codeine orally.

We reported[1] previously that 5-propionoxy-5-(1-phenylethyl)barbituric acid was a more potent analgesic than codeine orally and showed half the analgesic potency of morphine when administered subcutaneously. It was of interest, therefore, to learn whether analgesic activity would be displayed by other derivatives of 5-(1-phenylethyl)barbituric acid, such as the 5-hydroxy, 5-ethoxy, 5-tosyloxy, 5-trialkylsilyloxy, and 5-triphenylsilyloxy analogs. It was also of interest to learn how changes in the size of the acyloxy group might affect the analgesic activity of the compounds compared to that of 5-propionoxy-5-(1-phenylethyl)barbituric acid.

Chemistry. The acyloxy, trialkylsilyloxy, triphenylsilyloxy, and tosyloxy derivatives of 5-(1-phenylethyl)barbituric acid were synthesized by the following reaction sequence (Scheme I).

Scheme I

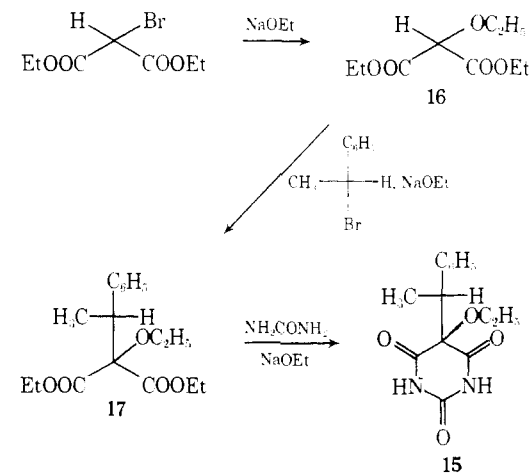


† A preliminary account of this work was presented by J. A. Vida and C. M. Samour before the Medicinal Chemistry Division at the 165th National Meeting of the American Chemical Society, Dallas, Texas, 1973, Abstracts of Papers, MEDI-21.

Oxidation of 5-(1-phenylethyl)barbituric acid (**1**) with *tert*-butyl hydroperoxide in the presence of cuprous acetate provided 5-*tert*-butylperoxy-5-(1-phenylethyl)barbituric acid (**2**). Reduction of compound **2** with sodium borohydride afforded 5-hydroxy-5-(1-phenylethyl)barbituric acid (**3**). Alternatively, as previously described,[1] compound **3** could be obtained from compound **1** by oxidation with peracetic acid. Esterification of compound **3** to produce compounds **4–10** was achieved with carboxylic acids in the presence of strong mineral acids or with acyl chlorides in the presence of pyridine. Conversion of compound **3** to 5-trialkylsilyloxy-5-(1-phenylethyl)barbituric acids, **11** and **12**, to 5-triphenylsilyloxy-5-(1-phenylethyl)barbituric acid (**13**), and to 5-tosyloxy-5-(1-phenylethyl)barbituric acid (**14**) was accomplished by treatment with *N,O*-bis(trimethylsilyl)acetamide or the appropriate trialkylsilyl, triphenylsilyl, or tosyl chloride in pyridine.

The synthesis of 5-ethoxy-5-(1-phenylethyl)barbituric acid (**15**) was accomplished from diethyl bromomalonate by reaction with sodium ethoxide followed by alkylation of the resulting diethyl ethoxymalonate (**16**) with 1-phenylethyl bromide in the presence of sodium ethoxide. The product of the alkylation reaction, diethyl ethoxy(1-phenylethyl)malonate (**17**), was converted into **15** by condensation reaction with excess urea in the presence of sodium ethoxide (Scheme II). The structures assigned to compounds **1–15** are supported by mass spectra and nmr data.

Scheme II



Structure–Activity Relationship. The best analgesic activity was displayed by the 5-acetoxy (**4**), the 5-propionoxy (**5**), and the 5-cyclopropylcarbonyloxy (**8**) derivatives of 5-(1-phenylethyl)barbituric acid. Replacement of the

Table I. Pharmacologic Activity of Selected 5-Substituted 5-(1-Phenylethyl)barbituric Acids

Compd no.	Analgesic act., ED_{50}, mg/kg	Peak time, hr	Hypnotic act., mg/kg po	Acute toxicity, LD_{50}, mg/kg po	CNS effects	Other
1	>200 po	0.5	>500	>500	None noted	
2	>200 po	0.5	No hypnosis	>200 <500	Stimulation	Straub tail, pilomotor act.
3	~200 po	1	>1000	>1000	None noted	
4	~1.5 po 13.9 (10.3–18.7) sc	0.5	>150	150 (121.9–184.5)	Stimulation	Straub tail. In writhing test, ED_{50} = ~50 mg/kg po
5	>6.25 po <12.5 po 8.8 (6.3–12.1) sc	0.5	No hypnosis	70 (57.4–85.4)	Stimulation	In writhing test, ED_{50} = ~7 mg/kg sc, ED_{50} = 27 (22.0–33.2) mg/kg po. Straub tail at 25 mg/kg and above
6	~25 po	0.5	>62.5	>62.5 <125	Stimulation	
7	>12.5 po <25 po ~25 sc	0.5	~100	~100	Stimulation	Straub tail
8	~5.0 po ~0.5 sc	0.5	No hypnosis	~50	Stimulation	Straub tail
9	>250 po	0.5	>250	>250	Stimulation	Straub tail
10	>200 po	1	>200	>200	None noted	
11	>25 < 50 po	1	>500	>400	Stimulation	Ptosis, liquid stools
12	~500 po	2	>500	>500	None noted	Delayed absorption
13	>500 po	2	>500	>500	Stimulation	
14	>500 po	0.5	>500	>500	None noted	
15	>250 po	0.5	>250	>250	None noted	
Morphine sulfate	4.8 (3.7–5.6) sc	0.5				
Codeine sulfate	26 (17.9–37.7) sc 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				

cyclopropylcarbonyloxy radical by an acyl radical containing the same number of carbon atoms, such as the isobutyryl radical, as in **7**, or *n*-butyryl radical, as in **6**, resulted in decreased analgesic activity. An increase in the size of the acyloxy radical, as exemplified by the 5-*n*-hexanoyloxy (**9**) and 5-(1-adamantylcarbonyloxy) (**10**) derivatives of 5-(1-phenylethyl)barbituric acid, caused a decrease in analgesic activity compared to that of **5**. Replacement of the acyl radical by the *tert*-butylperoxy radical, as in **2**, or by the tosyl radical, as in **14**, brought about a marked reduction in the analgesic potency as compared to that of **5**. Replacement of the acyl radical, however, by the trimethylsilyl radical, as in **11**, caused only a moderate decrease in analgesic activity. The corresponding triethylsilyl (**12**) and triphenylsilyl (**13**) derivatives displayed weaker analgesic activity than that of **11**. Replacement of the acyl radical by the ethoxy radical, as in **15**, resulted in a decrease in analgesic activity compared to that of **5**. The parent compound, 5-hydroxy-5-(1-phenylethyl)barbituric acid (**3**), and its precursor, 5-(1-phenylethyl)barbituric acid (**1**), showed weak analgesic activity compared to that of compound **5**.

Pharmacology. Analgesic Activity. Unlike morphine, which is poorly absorbed from the gastrointestinal tract, compounds **1**–**15** listed in Table I exhibited analgesic activity orally by the Eddy hot-plate method.[2] The oral potencies of compounds **4** and **8** were greater than that of compound **5** and compare favorably with that of subcutaneously administered morphine. Compounds **6**, **7**, and **11** were effective orally in the potency range of subcutaneously administered codeine. Compounds **4**–**8** and **11** were all much more potent than orally administered codeine, and the short time required for peak activity indicates rapid absorption from the gut. Compound **3** has activity in the potency range of aminopyrine. The remaining compounds, **1**, **2**, **9**, **10**, and **12**–**15**, all exhibited weak analgesic activity at doses either in the potency range of aspirin or higher.

The four compounds which were most potent orally, **4**, **5**, **7**, and **8**, were also administered subcutaneously. By this route, compound **8** was more potent than compound **5** and was clearly more potent than morphine. Compound **4** appeared to be slightly less active than compound **5** but the difference was not statistically significant. Compounds **4** and **5** were approximately twice as potent as codeine by the subcutaneous route. Compound **7**, given subcutaneously, was approximately one-third as potent as compound **5** and is in the potency range of codeine.

Hypnotic Activity. The compounds in this series appear to be completely devoid of hypnotic activity, even at

toxic doses. Indeed, large doses were generally associated with CNS stimulation.

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.

Effects upon the Central Nervous System. CNS stimulation appears to be a prominent pharmacological property of this series, increasing in intensity with increasing dosage. The Straub tail response, which is typical of morphine, appeared at effective doses of the more potent compounds. Clonic-tonic convulsive seizures constituted the major feature of the pattern of toxicity, with death resulting from respiratory paralysis.

Physical Dependence Capacity. Compound 4 was tested for physical dependence capacity (ability to suppress abstinence symptoms) in withdrawn morphine-dependent monkeys. Based on a single dose suppression assay at a subcutaneous dose of 16.0 mg/kg, compound 4 revealed no physical dependence capacity. At a subcutaneous dose of 32.0 mg/kg, compound 4 caused a gradual onset of mild abstinence in nonwithdrawn morphine-dependent monkeys, suggesting that this drug may be a very weak morphine antagonist.

Experimental Section

Pharmacology. Compounds 1-15, aminopyrine, and acetylsalicylic acid were administered orally (po) or subcutaneously (sc) 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 by the Eddy hot-plate method[2] 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. Experimental ranges were not determined for compounds exhibiting weak activity. ED_{50}'s with 95% confidence limits[3] 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.

In addition, analgesic activity for two of the most active compounds, compounds 4 and 5, was confirmed by the writhing test of Siegmund, *et al.*[4] Briefly, the candidate compounds were 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 kill 50% of the animals (LD_{50}) was computed according to Litchfield and Wilcoxon.[3]

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; (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.

Physical Dependence Capacity Protocol.‡ Monkeys, physically dependent on 4.0 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, and mass spectra and tlc were all appropriate.

5-*tert*-Butylperoxy-5-(1-phenylethyl)barbituric Acid (2). Compound 1 (2.32 g, 0.01 mol),[1] *tert*-butyl peroxide (9.0 g, 0.1 mol), chlorobenzene (37 g, 0.33 mol), and cuprous acetate monohydrate (0.025 g, 120 μmol) were stirred together at 95° for 45 min. The solution was decanted and evaporated to dryness. The residue was washed with toluene and crystallized from aqueous EtOH to give 2 (1.73 g, 55%), mp 181.5-182.5°. *Anal.* ($C_{16}H_{20}O_5N_2$) C, H, N.

5-Hydroxy-5-(1-phenylethyl)barbituric Acid (3). Compound 2 (3.0 g, 0.0094 mol) was dissolved in THF (100 ml), $NaBH_4$ (6.0 g, 0.158 mol) was added, and the mixture was heated at reflux 16 hr. After cooling to 25° the solvent was evaporated. Ice (100 g) was added and the mixture was acidified to pH 1 with 2 *N* HCl. The solution was saturated with NaCl and extracted with EtOAc. The extract was evaporated to dryness and the residue was chromatographed on silica gel. Elution with EtOAc gave crude 3 (1.2 g, 45.6%) which was further purified by chromatography on silica gel. Obtained was pure 3, which was identical with the previously described[1] sample of compound 3.

5-Acetoxy-5-(1-phenylethyl)barbituric Acid (4). To a solution of H_2SO_4 (20 ml) in AcOH (200 ml) was added 3 (20 g, 0.08 mol). The mixture was stirred at 65° for 16 hr, then cooled, and poured into ice-H_2O (600 ml). To the solution was added $NaHCO_3$ until pH 7 was reached. The solution was extracted with EtOAc, the extract was evaporated to dryness, and the residue was chromatographed over silica gel. Elution with C_6H_6-EtOAc (4:1) gave a light brown solid which was crystallized from C_6H_6-hexane to give 4 (12 g, 52%), mp 228-230°. *Anal.* ($C_{14}H_{14}O_5N_2$) C, H, N.

5-Butyryloxy-5-(1-phenylethyl)barbituric Acid (6). Compound 6 was prepared from 3 (3.72 g, 0.015 mol) and butyric acid (20 ml) in the same way as described for the synthesis of compound 4. Crystallization from EtOH-Et_2O gave 6 (1.6 g, 33.6%), mp 152-155°. *Anal.* ($C_{16}H_{18}O_5N_2$) C, H, N.

5-Isobutyryloxy-5-(1-phenylethyl)barbituric Acid (7). Compound 7 was prepared from 3 (5 g, 0.02 mol) and isobutyric acid (40 ml) in the same way as described for the synthesis of compound 4. Obtained was 7 (3.4 g, 53.5%), mp 154-156°. *Anal.* ($C_{16}H_{18}O_5N_2$) C, H, N.

‡ 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.

5-Cyclopropylcarbonyloxy-5-(1-phenylethyl)barbituric Acid (8). Compound **8** was prepared from **3** (3.72 g, 0.015 mol) and cyclopropanecarboxylic acid (20 g, 0.23 mol) in the same way as described for the preparation of compound **4**. Obtained was **8** (0.7 g, 14.7%), mp 114–115°. *Anal.* ($C_{16}H_{16}O_5N_2$) C, H, N.

5-*n*-Hexanoyloxy-5-(1-phenylethyl)barbituric Acid (9). To a solution of **3** (2.4 g, 0.01 mol) in pyridine (30 ml) was added hexanoyl chloride (6 g, 0.045 mol) and the mixture was stirred at 75° for 18 hr, then cooled, and poured into ice (150 g) containing HCl (30 ml). The mixture was extracted with EtOAc and the extract was evaporated to give an oil which was chromatographed on silica gel. Elution with C_6H_6–EtOAc (9:1) gave **9** (0.8 g, 23%), an oil. *Anal.* ($C_{18}H_{22}O_5N_2$) C, H, N.

5-(1-Adamantylcarbonyloxy)-5-(1-phenylethyl)barbituric Acid (10). To a mixture of 1-adamantanecarboxylic acid (3.0 g, 0.012 mol) and methanesulfonic acid (10 ml) was added **3** (2.0 g, 0.008 mol). The mixture was stirred at 85° for 0.5 hr, then cooled to 25°, and stirred for 16 hr. The solution was poured into ice–H_2O (300 ml) and the light brown precipitate was removed by filtration and chromatographed on silica gel. Elution with C_6H_6–EtOAc (9:1), followed by crystallization from acetone–hexane (1:1), gave **10** (0.15 g, 4.55%), mp 262–264°. *Anal.* ($C_{23}H_{28}O_5N_2$) C, H, N.

5-Trimethylsilyloxy-5-(1-phenylethyl)barbituric Acid (11). Procedure A. To a solution of **3** (2.5 g, 0.01 mol) in pyridine (25 ml) was added trimethylchlorosilane (1.1 g, 0.01 mol). The solution was stirred at 130° for 16 hr, then cooled, and poured into ice H_2O (200 ml) containing HCl (25 ml). The solution was extracted with EtOAc, the extract was evaporated, and the residue was chromatographed on silica gel. Elution with C_6H_6–EtOAc (4:1) provided pure **11** (1.8 g, 56%), mp 156–159°. *Anal.* ($C_{15}H_{20}O_4N_2Si$) C, H, N, Si.

Procedure B. Compound **3** (5.0 g, 0.02 mol) and *N,O*-bis(trimethylsilyl)acetamide (BSA, 6 g, 0.029 mol) were dissolved in pyridine (5 ml) and stirred 16 hr at 25° in a closed flask. Chromatography on silica gel using C_6H_6–EtOAc (19:1) gave the product which was crystallized from C_6H_6 to give **11** (2.7 g, 42%), mp 156.5–158°.

5-Triethylsilyloxy-5-(1-phenylethyl)barbituric Acid (12). Compound **12** was prepared from **3** (7.5 g, 0.03 mol) and triethylchlorosilane (5 g, 0.033 mol) in the same way as described in procedure A for the preparation of compound **11**. Obtained was **12** (2.6 g, 24%), mp 101–104°. *Anal.* ($C_{18}H_{26}O_4N_2Si$) C, H, N, Si.

5-Triphenylsilyloxy-5-(1-phenylethyl)barbituric Acid (13). Compound **13** was prepared from **3** (3.75 g, 0.015 mol) and triphenylchlorosilane (5.0 g, 0.017 mol) in the same way as described in procedure A for the preparation of compound **11**. Obtained was **13** (3.7 g, 49%), mp 270–273.5°. *Anal.* ($C_{30}H_{26}O_4N_2Si$) C, H, N, Si.

5-Tosyloxy-5-(1-phenylethyl)barbituric Acid (14). Compound **14** was prepared from **3** (2.48 g, 0.01 mol) and tosyl chloride (1.9 g, 0.01 mol) in the same way as described for the preparation of compound **9**. Obtained was **14** (1.98 g, 49%), mp 178–180°. *Anal.* ($C_{19}H_{18}O_6N_2S$) C, H, N, S.

Diethyl Ethoxymalonate (16). To a solution of sodium (4.6 g, 0.02 mol) in EtOH (300 ml) was added diethyl bromomalonate (47.8 g, 0.2 mol) and the mixture was heated at reflux for 4 hr and then cooled to 25°. NaBr (20 g, 0.196 mol) was removed by filtration and the filtrate was evaporated. The resulting liquid was distilled at 5 mm and the product **16** (28 g, 70%) was collected at 135–140°. *Anal.* ($C_9H_{16}O_5$) C, H.

Diethyl Ethoxy(1-phenylethyl)malonate (17). To a solution of sodium (2.3 g, 0.1 mol) in EtOH (100 ml) was added **16** (20.4 g, 0.1 mol). The mixture was stirred at 25° for 2 hr. 1-Bromoethylbenzene (18.5 g, 0.1 mol) was added and the mixture was stirred at reflux for 6 hr and then cooled to 25°. NaBr (9.1 g, 0.09 mol) was removed by filtration and the filtrate was evaporated. The resulting liquid was distilled at 5 mm and the product **17** (12.4 g, 40%) was collected at 175–180°.

5-Ethoxy-5-(1-phenylethyl)barbituric Acid (15). To a solution of sodium (1.38 g, 0.06 mol) in EtOH (100 ml) was added urea (3.7 g, 0.06 mol). The mixture was stirred until a clear solution was obtained. Compound **17** (6.1 g, 0.02 mol) was added dropwise and the mixture was stirred at reflux for 16 hr and then cooled to 25°. Ice–H_2O (100 ml) was added and the solution was acidified with HCl to pH 2. The precipitate was removed by filtration and washed with H_2O to give **15** (1.3 g, 24%), mp 230–233°. *Anal.* ($C_{14}H_{16}O_4N_2$) C, H, N.

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Analogs of 5'-Deoxy-5'-(methylthio)adenosine†

John A. Montgomery,* Anita T. Shortnacy, and H. Jeanette Thomas

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205.

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Twenty analogs of 5'-deoxy-5'-(methylthio)adenosine have been prepared in which the heterocyclic base, the sugar moiety, and the substituent on sulfur have all been varied. Two principal routes to these compounds were used: (1) displacement of the tosyloxy or chlorine function from $C_{5'}$ of the nucleoside or (2) preparation and reaction of the appropriate sugar with a chloropurine followed by nucleophilic displacement of the chloro group(s) from the resulting nucleosides. Only one of these nucleosides (**51**) showed a significant degree of cytotoxicity and none was active against leukemia L1210 *in vivo*.

S-Adenosyl-L-methionine (SAM), synthesized *in vivo* from adenosine triphosphate and L-methionine by ATP:L-methionine adenosyltransferase,[1] an enzyme that appears to be ubiquitous in both normal and malignant tissues, functions as a methyl group donor for transmethylations[2] and as a propylamine donor for polyamine synthesis.[3,4] In carrying out these transformations, SAM is converted to *S*-adenosyl-L-homocysteine (SAH) and 5'-deoxy-5'-(methylthio)adenosine (MTA), both of which are known to inhibit the transmethylation reactions of SAM *in vitro*.[5-7] Analogs of these compounds could interfere with the biosynthesis of SAM, with methylation by SAM, with the decarboxylation of SAM, or with the propylamine transfer from "decarboxylated SAM" to putrescine to form spermidine; either one of the latter two events would interfere with polyamine synthesis. Transfer of aminoalkyl groups other than aminopropyl would produce unnatural polyamines. Any of these postulated events could have serious consequences for proliferating cells and result in cell death. In addition, metabolism of analogs by SAM-me-

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