[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

1,3-Dimethyl-5-alkyl Barbituric Acids

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All of the barbituric acid derivatives which have been reported to have pronounced hypnotic activity are disubstituted in the 5-position. While the 5,5-dialkyl barbituric acids are the hypnotics most commonly encountered, certain 1,5,5-trialkyl derivatives (notably Evipan) are active, producing narcosis of short duration. Some 1,3,5,5-tetraalkyl derivatives produce a hypnotic action of very transient character.[1] This paper reports a study of a series of 1,3,5-trialkyl barbituric acids, which was undertaken to determine whether such compounds have hypnotic activity comparable to their 1,5,5-isomers, or are inactive like the 5-monoalkyl[2] and 1,5-dialkyl[3] barbituric acids.

Fischer and Dilthey[4] imply that *sym*-dialkyl ureas cannot be condensed with mono or dialkyl malonic esters. Trial showed that while a dialkyl malonic ester, ethyl diethylmalonate, does not condense with *sym*-dimethyl urea, monoalkyl malonic esters react readily, producing 1,3,5-trialkyl barbituric acids. The procedure of Biltz and Wittek,[5] in which malonic acid is condensed with alkyl ureas in the presence of acetic acid and acetic anhydride, also proved to be adaptable to the condensation of monoalkyl malonic acids with *sym*-dimethyl urea, and was used in preparing several of the trialkyl barbituric acids. The direct alkylation of 1,3-dimethyl barbituric acid with benzyl chloride produced principally 1,3-dimethyl-5,5-dibenzyl barbituric acid, together with some 1,3-dimethyl-5-benzyl barbituric acid. The latter compound was prepared easily by the reduction of 1,3-dimethyl-5-benzylidene barbituric acid.

When this investigation was started, no source of *sym*-dimethyl urea was available, and it was sought to develop a practical synthesis of 1,3-dimethyl barbituric acid from caffeine as an intermediate for the preparation of 1,3,5-trialkyl barbituric acids. The procedure of Biltz[6] for the oxidation of caffeine was modified by the substitution of sodium hypochlorite for potassium chlorate as the oxidizing agent. Subsequent reduction with stannous chloride produces tetramethyl alloxantine conveniently in any desired quantity and approximately 80% yield. The reaction of phosphorus pentachloride with tetramethyl alloxantine, which produces 1,3-dimethyl-5,5-dichloro barbituric acid,[7] proceeds smoothly in 76% yield if tetrachloroethane is used as a solvent. This sequence of reactions constitutes a highly satisfactory method for preparing 1,3-dimethyl-5,5-dichloro barbituric acid. The latter compound can be hydrogenated catalytically[8] in the presence of palladium or platinum, producing 1,3-dimethyl barbituric acid in 90% yield.

Experimental Part

1,3-Dimethyl-5-alkyl Barbituric Acids.—The monoalkyl malonic esters and acids which were employed in the synthesis of the compounds listed in Table I were prepared by standard methods. Pure *sym*-dimethyl urea was obtained from a crude commercial product[9] by distillation in vacuum and recrystallization from chloroform and ether. The trialkyl barbituric acids were prepared by one or more of the following methods.

A. Preparation from monoalkyl malonic esters.—The condensations were effected by the customary Fischer–Dilthey method.[4] Molecular equivalents of *sym*-dimethyl urea and the monoalkyl malonic esters were refluxed for twelve hours with three equivalents of concentrated alcoholic sodium ethoxide. After removal of the alcohol in vacuum, the residual salts were dissolved in water, the solutions extracted with ether to remove neutral by-products and the products precipitated with concd. hydrochloric acid. In the synthesis of 1,3,5-trimethyl barbituric acid, part of the product remained dissolved in the aqueous acid solution, and was isolated by evaporating the latter to dryness and extracting the residue with absolute alcohol.

While the monoalkyl malonic esters condensed readily with *sym*-dimethyl urea, ethyl diethyl malonate failed to condense at all under similar conditions, and was recovered unchanged.

B. Preparation from monoalkyl malonic acids.—The synthesis of 1,3-dimethyl-5-isopropyl barbituric acid is typical. *sym*-Dimethyl urea (26.7 g.) and isopropylmalonic acid (48.3 g., 10% excess) were dissolved in 63 cc. of glacial acetic acid in a 500-cc. three-necked flask fitted with a stirrer, reflux condenser and dropping funnel. The mixture was heated to 60 to 70° and 132 cc. of acetic anhydride was added during one-half hour. The tempera-

(1) Bush and Butler, *J. Pharmacol.*, **61**, 139 (1937).

(2) Shonle and Moment, THIS JOURNAL, **45**, 243 (1923); Shonle, Keltch and Swanson, *ibid.*, **52**, 2440 (1930).

(3) Dox, *ibid.*, **46**, 1707 (1924).

(4) Fischer and Dilthey, *Ann.*, **335**, 335 (1904).

(5) Biltz and Wittek, *Ber.*, **54**, 1037 (1921).

(6) Biltz, *ibid.*, **45**, 3674 (1912).

(7) Techow, *ibid.*, **27**, 3082 (1894).

(8) Techow (ref. 7) performed this reduction with hydroiodic acid and phosphonium iodide.

(9) Supplied by the B. L. Lemke Co., New York City.

TABLE I

1,3-DIMETHYL-5-ALKYL BARBITURIC ACIDS

5-Alkyl group	M. p., °C. (uncor.)	Yield of purified products, %[g]	Recrystallization solvent	Formula	Nitrogen, % Calcd.	Found
Methyl	89.5– 90	75[a]	Benzene	$C_7H_{10}O_3N_2$	16.46	16.36
Ethyl	liquid[e]	40[a], 47[b]		$C_8H_{12}O_3N_2$	15.21	15.13
Isopropyl	108.5–109.5	67[b]	Alcohol	$C_9H_{14}O_3N_2$	14.13	14.12
Butyl	44 – 45[f]	33[b]	Ether and pentane	$C_{10}H_{16}O_3N_2$	13.20	13.13
s-Butyl	74.5– 75.5	40[b]	Alcohol and water	$C_{10}H_{16}O_3N_2$	13.20	13.14
Isoamyl	43 – 44[f]	35[a]	Ether and pentane	$C_{11}H_{18}O_3N_2$	12.38	12.33
1-Methylbutyl	55 –56.5[f]	20[b]	Alcohol and water	$C_{11}H_{18}O_3N_2$	12.38	12.41
Cyclohexyl	128.5–129	40[b]	Alcohol	$C_{12}H_{18}O_3N_2$	11.76	11.70
Benzyl	116.5–117.5	82[c], 15[d]	Alcohol	$C_{13}H_{14}O_3N_2$	11.37	11.24
Phenyl	140 –140.5	49[b]	Alcohol	$C_{12}H_{12}O_3N_2$	12.06	12.05

[a] From the monoalkyl malonic ester. [b] From the monoalkyl malonic acid. [c] By reduction of 1,3-dimethyl-5-benzylidene barbituric acid. [d] By alkylation of 1,3-dimethyl barbituric acid. [e] B. p. 130–132° (6 mm.); $n^{25}D$ 1.5012. The liquid solidified below room temperature, but could not be recrystallized successfully. [f] Purified by distillation in vacuum before crystallization occurred. [g] The low yields of the products melting below 60° were partly due to the difficulties which attended their crystallization.

ture was raised to 90° during three hours, and kept at 90° for three hours. The acetic acid and anhydride were then removed by distillation in vacuum from a water-bath, and the residue (which crystallized) was recrystallized from alcohol. The yield of product, m. p. 108–109°, was 40 g. (67%).

C. Alkylation of 1,3-dimethyl barbituric acid with benzyl chloride.—1,3-Dimethyl barbituric acid (5 g.) was dissolved in a 10% molar excess of 5% sodium hydroxide and diluted with an equal volume of alcohol. Benzyl chloride (4.9 g.) was added, and the solution was heated and stirred. After a few minutes the solution became acid to litmus. It was then made alkaline with sodium hydroxide and extracted with ether. Evaporation of the ether left a crystalline residue of 1,3-dimethyl 5,5-dibenzyl barbituric acid, which was recrystallized from alcohol; yield 3.6 g. (33%), m. p. 129.5–130°.

Anal. Calcd. for $C_{20}H_{20}O_3N_2$: N, 8.33. Found: N, 8.25.

Acidification of the alkaline solution precipitated 1,3-dimethyl-5-benzyl barbituric acid, which was recrystallized from alcohol; yield 1.2 g. (15%), m. p. 116.5–117.5°.

Reduction of 1,3-dimethyl 5-benzylidene barbituric acid[10] (13.5 g.) in 400 cc. of acetone with hydrogen in the presence of palladinized charcoal gave 11.1 g. (82%) of 1,3-dimethyl-5-benzyl barbituric acid.

The properties of the 1,3,5-trialkyl barbituric acids and other details of their preparation are recorded in Table I. The sodium salts were prepared for pharmacological testing by treatment with an equivalent quantity of sodium ethoxide in alcohol solution, and were crystallized by cooling or adding ether.

Tetramethyl Alloxantine.—In a three-liter three-necked flask equipped with a mechanical stirrer, thermometer and dropping funnel was placed 200 g. of anhydrous caffeine. A mixture of 245 cc. of concd. hydrochloric acid and 100 cc. of water was added with stirring, followed by 500 cc. of water, and the mixture was stirred until all of the caffeine was in solution. The flask was immersed in an ice-bath and 750 cc. of commercial sodium hypochlorite solution (laundry bleach, 15–16% available chlorine) was added slowly with stirring so that the temperature remained at 36 to 40°. A precipitate which formed during the addition gradually went back into solution, but usually it was necessary to add an additional 50 to 150 cc. of sodium hypochlorite to complete the solution. The last portions were added slowly, and the addition was stopped as soon as the solution became clear. The addition required 1.2 to 1.5 hours.

In order to avoid serious loss of material, it was necessary to reduce the dimethyl alloxan formed in the above oxidation immediately. A solution of 100 g. of stannous chloride ($SnCl_2 \cdot 2H_2O$) in 75 cc. of concd. hydrochloric acid and 75 cc. of water was added rapidly with stirring. After five minutes the stirrer was stopped and the mixture (containing a heavy precipitate of tetramethyl alloxantine) was allowed to stand for two hours. The precipitate was then filtered with suction, removed from the funnel and boiled with 250 cc. of water, cooled and again filtered. The tetramethyl alloxantine obtained on drying varied from white to light pink in color; yield 143 g. (81%).

1,3-Dimethyl-5,5-dichlorobarbituric Acid.—Tetramethyl alloxantine (100 g.), phosphorus pentachloride (200 g.) and *sym*-tetrachloroethane (250 cc.) were placed in a 1-liter three-necked flask attached by cork stoppers to a stirrer and reflux condenser. The mixture was heated in an oil-bath at 155 to 165° for fifty to eighty-five minutes, until the vigorous evolution of hydrogen chloride ceased. The mixture was then cooled and the solvent (and phosphorus oxychloride) removed by distillation in vacuum from a hot water-bath. The residue was dissolved in 600 cc. of alcohol and filtered through glass wool. The crude product obtained on cooling and by concentration of the mother liquor weighed 103 g.; recrystallization from alcohol gave 101 g. (76%) of pure 1,3-dimethyl-5,5-dichlorobarbituric acid, m. p. 157–158°.

1,3-Dimethyl Barbituric Acid.—1,3-Dimethyl-5,5-dichlorobarbituric acid (76 g.) was dissolved in 400 cc. of acetone, boiled with Norit and filtered to remove any traces of catalytic poisons. Palladinized charcoal catalyst (2 g., containing 0.2 g. of palladium)[11] was added, and the solution was shaken with hydrogen at a pressure of 1 to 2 at-

(10) Akabori, *Ber.*, **66**, 139 (1933).

(11) Hartung, THIS JOURNAL, **50**, 3372 (1928).

mospheres and a temperature of 50° until absorption of hydrogen stopped. The catalyst was removed by filtration and the solvent distilled from the filtrate in vacuum. The residue was recrystallized twice from benzene. The yield of pure 1,3-dimethyl barbituric acid, m. p. 122–123°, was 39 g. Concentration of the mother liquors gave an additional 8.3 g. of pure material; total yield 47.3 g. (90%). The reduction is exothermic, and will go to completion without heating. It is completed more rapidly (in four to ten hours) if the temperature is maintained at about 50°.

Platinum may also be used as a catalyst for the reduction, but is less convenient because the acetone used as a solvent is also partly reduced, and absorption of hydrogen continues after the dehalogenation is complete.

1,3-Dimethyl barbituric acid was also prepared from ethyl malonate and *sym*-dimethyl urea in the presence of alcoholic sodium ethoxide in 37% yield. The most convenient preparation is the condensation of malonic acid with dimethyl urea described by Biltz and Wittek.[5]

Pharmacological Data.—We are indebted to Dr. Paul A. Mattis and Mr. Albert Latven of the Medical Research Division of Sharp and Dohme, Inc., for the pharmacological testing of the 1,3-dimethyl-5-alkyl barbituric acids. The results are summarized in Table II. All of the compounds except the 5-isoamyl, phenyl, and cyclohexyl derivatives produced hypersensitivity in mice, as evidenced by tremors or convulsions which occurred when the animals were touched. The isoamyl and phenyl derivatives induced a lethargic condition in the mice, while the cyclohexyl compound produced no noteworthy symptoms other than typical barbiturate ataxia. Only the 1-methylbutyl and cyclohexyl compounds produced narcosis from which the animals recovered, and the anesthetic doses of these two compounds closely approximated the lethal doses. It may thus be concluded that barbiturates must be disubstituted in the 5-position in order to possess distinct hypnotic properties, irrespective of substitution on the nitrogen atoms in the 1 and 3-positions.

TABLE II

1,3-DIMETHYL-5-ALKYL BARBITURIC ACIDS. RESULTS OF PHARMACOLOGICAL TESTS IN WHITE MICE[a]

5-Alkyl group	AD 50, mg./kg.	LD 50, mg./kg.
Methyl		3500
Ethyl		1600
Isopropyl		1800
Butyl		1000
s-Butyl		1000
Isoamyl		525
1-Methylbutyl	400	450
Cyclohexyl	425	525
Benzyl		1000
Phenyl		3000

[a] The method of testing and the meaning of symbols are described in THIS JOURNAL, **61**, 96 (1939).

Summary

Methods for preparing 1,3-dimethyl-5-alkyl barbituric acids have been investigated, and ten such compounds have been prepared. Their pharmacological behavior has been studied.

Practical methods have been developed for the sequence of reactions: caffeine → tetramethyl alloxantine → 1,3-dimethyl 5,5-dichlorobarbituric acid → 1,3-dimethyl barbituric acid.

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Hydrogen Exchange Reactions of Aromatic Tertiary Amines

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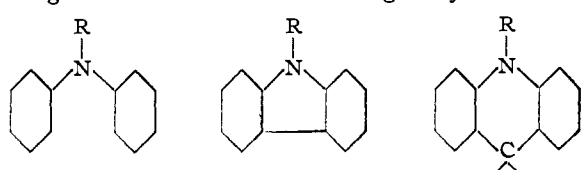
It was shown previously[1] that the acid catalyzed exchange of the ortho and para hydrogen atoms in aromatic tertiary amines is in general more or less suppressed by a substituent in one of the ortho positions. This was interpreted as primarily a steric effect and it was predicted on the same grounds that the reactivity of 1-dimethylaminonaphthalene in hydrogen exchange would be adversely affected by substituents in the 8 position. Such effects have now been observed for three substances of this type.

Further studies of the exchange reactions of heterocyclic tertiary amines have furnished results in which the role of the steric factor is not clear. Whereas previously the activating effect of an amino nitrogen on the ortho and para hydrogen atoms was found to be greatly increased



I II III

R = methyl, phenyl

(1) Brown, Widiger and Letang, THIS JOURNAL, 61, 2597 (1939).