*Anal.* Calcd. for $C_{15}H_{11}O_4Br$: C, 53.73; H, 3.28. Found: C, 53.68; H, 3.38.

Piper-*o*-chlorobenzoin (?).—Three and sixty-five one-hundredths grams of *o*-chlorobenzaldehyde was dissolved in 50 cc. of 50% alcohol containing 3.0 g. of potassium cyanide and the whole was boiled briskly; 3.75 g. of piperonal in saturated alcoholic solution was added at a steady rate over one and three-fourths hours. On cooling, an oil separated which was removed and sludged with ligroin. After twenty-four hours the crystalline product was filtered off and recrystallized from alcohol; yield, 50%.

Piper-*o*-chlorobenzoin forms white needles, m. p. 115°, very soluble in benzene and chloroform, moderately soluble in alcohol, ether and ligroin.

*Anal.* Calcd. for $C_{15}H_{11}O_4Cl$: C, 61.94; H, 3.78. Found: C, 61.84; H, 4.14.

## Summary

By considering the reactivity of aldehydes in the simple benzoin reaction, a method has been worked out whereby mixed benzoins may be obtained from the large majority of aromatic aldehydes. Eight new mixed benzoins have been prepared by the method.

DURHAM, NORTH CAROLINA

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

# SUBSTITUTED PHENYLETHYLBARBITURIC ACIDS[1]

BY E. W. BOUSQUET AND ROGER ADAMS

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Of the numerous 5,5-disubstituted barbituric acids that have been prepared and offered to the physician as hypnotics, the one which is of peculiar interest is the phenylethyl derivative.[2] This substance is generally accepted by the clinician as having, in addition to the usual soporific value, a specific sedative action toward epileptics, much more marked than appears in the various dialkylbarbituric acids. Phenylethylbarbituric acid (phenobarbital) is more toxic than most of the important dialkyl derivatives, though the ratio of effective dosage and toxicity is not so very different from that of barbital[3] itself. The phenylmethyl[4] and the phenylallyl[5] barbituric acids have also been prepared, but appear to be of less interest than the better-known phenylethyl derivative.

In spite of the importance of phenobarbital, derivatives containing substituents in the benzene ring, with the exception of the *p*-methoxyphenylethylbarbituric acid,[2] which was mentioned in the original patent, have never been prepared. Numerous investigators have obtained barbituric acid derivatives isomeric with phenylalkyl- or phenylallylbarbituric

[1] This communication is an abstract of a portion of a thesis submitted by E. W. Bousquet in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] German Patent 249,722, *Friedländer*, XI, 928 (1912).

[3] Nielsen, Higgins and Spruth, *J. Pharmacol.*, **26**, 271 (1925).

[4] U. S. Patent 1,025,526 (1912).

[5] U. S. Patent 1,056,793 (1912).

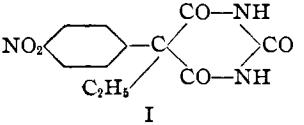
acid, such as benzylalkyl,[6] benzylallyl[7] or ethylphenethyl.[8] None, however, proved to be of any value. The dibenzyl-,[9] the 5,5-di-(*p*-hydroxyphenyl)-[10] and the 5,5-di-(3-methyl-4-hydroxyphenyl)-[10] barbituric acids have also been described and were shown to have no soporific effect.

This investigation had as its object the preparation of substituted phenylalkylbarbituric acids, in order, if possible, to obtain a compound with lower toxicity and possibly higher soporific value than phenobarbital.

The method commonly used for preparing phenylethylbarbituric acid is condensation of phenylacetic ester and oxalic ester to phenyloxalacetic ester, elimination of carbon monoxide by heating to give phenylmalonic ester, condensation with an alkyl halide to give phenylalkylmalonic esters and, finally, condensation to the corresponding barbituric acid. The application of this procedure is of questionable value on account of the difficulty of obtaining substituted phenylacetic esters, and also because such substitution products do not enter readily into the subsequent reactions. No directions were given in the original patent for preparing the *p*-methoxyphenylethylbarbituric acid but, presumably, the method just mentioned was the one used.

The procedure first attempted in this research was to nitrate phenylethylmalonic ester and to obtain through the nitro group a variety of substituted phenylethylmalonic esters which could be condensed in the usual way to the barbituric acids. Conditions were found for nitration which gave the *p*-nitro derivative in good yields. The position of the substituting group was proved by oxidation to *p*-nitrobenzoic acid. The nitro compound was reduced to the corresponding amino and the amino, in turn, further substituted or replaced. However, proper conditions were not found for the condensation of any of the substituted phenylethylmalonic esters to the corresponding barbituric acids.

Attention was next given to the nitration of phenylethylbarbituric acid itself. A very satisfactory yield of product was obtained (I), and through this substance a series of derivatives was produced: the amino, the bromo-amino, the acetamino, the bromo-acetamino, the nitro-acetamino, the nitro-amino and the chloro. The nitro, the amino, the acetamino, the bromo-acetamino, the bromo-amino, and the chloro derivatives were kindly tested for their soporific value and toxicity by H. C. Spruth of the Abbott Laboratories, for whose help the authors are grateful. With the exception of the chloro, each was



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[6] Dox and Yoder, THIS JOURNAL, **44**, 1141 (1922); Shonle and Moment, *ibid.*, **45**, 243 (1923).

[7] Johnson and Hill, *Am. Chem. J.*, **46**, 537 (1912).

[8] Dox, THIS JOURNAL, **46**, 2843 (1924).

[9] Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

[10] Dox, THIS JOURNAL, **45**, 1811 (1923).

found to be less toxic than phenobarbital itself, but, as so frequently happens in the study of the relation between pharmacological action and chemical constitution in organic compounds, the substitution of these groups caused the hypnotic property to disappear entirely. The chloro compound possessed hypnotic power of almost the same order as the parent substance, phenobarbital, but was slightly more toxic.

## Experimental

### Preparation of the Substituted Aryl-alkyl-malonates

**Methyl Ethyl *p*-Nitrophenylethylmalonate.**—Fifteen grams of the pure methylethyl ester of phenylethylmalonic acid, b. p. 142–147° (5 mm.), was dissolved in 15 cc. of ice-cold concentrated sulfuric acid. The temperature of the ester-sulfuric acid mixture was brought down to −10° and a cold nitrating mixture consisting of 0.072 mole of fuming nitric acid (sp. gr. 1.50) in 5 cc. of concentrated sulfuric acid was added very slowly, while stirring and keeping the temperature of the reaction between −10 and 0°. Stirring was continued for two hours after the nitrating mixture had been added. The reaction mixture was added to ice-water mixture and the oily mass extracted with ether. After washing and drying, the solvent was removed and a crude yellow oil weighing 16 g. (90.4%) was obtained. Several runs using twice the molecular proportions of the above experiment gave consistent yields of 87.5% of the theoretical of purified product.

**Oxidation of Methyl Ethyl *p*-Nitrophenylethylmalonate.**—Five grams of the nitro ester was dissolved in 20 cc. of 95% alcohol and 3.5 g. of solid potassium hydroxide was added. After refluxing for two hours on the steam-bath, the alcohol was evaporated off, and a hot solution of 15 g. of potassium permanganate in 100 cc. of water was added all at once with stirring. The solution was allowed to stand for two hours and then filtered from the manganese dioxide. Upon acidification of the filtrate with concentrated hydrochloric acid, 0.5 g. of a white product precipitated. Two recrystallizations from dilute alcohol gave a product melting at 235–237° (uncorr.). Several mixed melting points containing various percentages of *p*-nitrobenzoic acid with the oxidation product showed no depression of the original melting point.

**Methyl Ethyl *p*-Aminophenylethylmalonate.**—A solution of 30 g. of methyl ethyl *p*-nitrophenylethylmalonate, b. p. 180–185° (4 mm.), in 50 cc. of 95% alcohol was reduced with hydrogen and 0.2 g. of platinum-oxide catalyst.[11] At 2–3 atm. pressure after half an hour, the theoretical amount of hydrogen had been absorbed, and the spent catalyst was filtered off and the alcohol evaporated. The resulting dark red oil amounted to 25 g. (92.7%). When pure it was a very viscous, heavy, yellow oil. Attempts to form a solid hydrochloride or benzoyl derivative were unsuccessful.

**Methyl Ethyl *p*-Acetaminophenylethylmalonate.**—Fifteen grams of the crude amino ester was slowly mixed with 17.5 g. of pure acetic anhydride. The reaction mixture was heated over the steam-bath for four hours and then distilled. The pure product was a very viscous, yellow oil. Crystallization could not be induced.

**Methyl Ethyl *p*-Hydroxyphenylethylmalonate.**—Fifteen grams of the crude amine was dissolved in a cold dilute acid mixture consisting of 20.5 g. of concentrated sulfuric acid and 15 g. of water. Twenty-eight grams of ice was then added to the sulfate. When cooled down to 0°, it was treated with a solution of 3.8 g. of sodium nitrite in 10 cc. of water, while maintaining the temperature between 0 and 5°. The diazonium mixture was then poured into a boiling solution of 35 cc. of concentrated sulfuric acid

[11] Adams and Shriner, THIS JOURNAL, **45**, 2171 (1923).

and 30 cc. of water and stirred until the evolution of gases had subsided. The black oily layer was extracted with ether and the ether extracts washed with 5% sodium hydroxide solution to take up the phenolic ester. The phenolic ester was then regenerated by treatment with dilute hydrochloric acid and extracted with ether. Six and one-half grams of a very viscous, yellow oil was obtained.

**Methyl Ethyl *p*-Methoxyphenylethylmalonate.**—Fifteen grams of freshly distilled phenolic ester was dissolved in a 20% excess of 5% sodium hydroxide solution and to this alkaline solution 8 g. of freshly distilled dimethyl sulfate was added with vigorous shaking, keeping the temperature below 60°. The reaction mixture was heated at 60–70° for an hour and when cool was extracted with ether. Ten and one-half grams of a lemon-yellow oil was obtained.

TABLE I

DERIVATIVES OF METHYL ETHYL PHENYLETHYLMALONATE

| Methyl ethyl —ethylmalonate | B. p., °C. | Analyses Calcd., % C | H | Found, % C | H |
|---|---|---|---|---|---|
| *p*-Nitrophenyl | 180–185 (4 mm.) | 56.92 | 5.80 | 56.91 | 5.71 |
| *p*-Aminophenyl | 182–185 (4 mm.) | 63.36 (N, 5.28) | 7.22 | 63.40 (N, 5.02) | 7.22 |
| *p*-Acetaminophenyl | 192–197 (3 mm.) | 62.50 | 6.89 | 62.23 | 6.82 |
| *p*-Hydroxyphenyl | 180–185 (4 mm.) | 63.12 | 6.87 | 64.13 | 6.85 |
| *p*-Methoxyphenyl | 152–156 (4 mm.) | 64.24 | 7.19 | 64.25 | 7.13 |

### Preparation of Substituted Aryl-alkylbarbituric Acids

**5-Nitrophenyl-5-ethylbarbituric Acid.**—Five grams of phenylethylbarbituric acid, m. p. 169–170°, was added to 20 cc. of ice-cold concentrated sulfuric acid. A nitrating mixture of 1.1 cc. of fuming nitric acid (sp. gr. 1.50) in 5 cc. of concentrated sulfuric acid was added slowly to the rapidly stirred mixture, while maintaining the temperature between −10 and 3°. Stirring was continued for an hour after the nitrating mixture was added. The nitration mixture was added to 300 cc. of ice-water mixture and filtered when cold. The white precipitate was washed with water until almost neutral to litmus and then dried at 100°. Two crystallizations gave 2 g. of pure material. Recrystallizations of material in the mother liquors gave average yields of 60–65% of the pure product.

**5-Aminophenyl-5-ethylbarbituric Acid.**—Ten grams of the nitro compound, m. p. 276–277° (uncorr.), was suspended in 125 cc. of 95% ethyl alcohol with 0.2 g. of platinum-oxide catalyst. The reduction was carried out at 40–50° at a pressure of 2–3 atm., and the theoretical amount of hydrogen was absorbed in twenty to thirty minutes.

**5-Acetaminophenyl-5-ethylbarbituric Acid.**—Nine grams of the amino compound was poured slowly into 11 g. of freshly distilled acetic anhydride, keeping the temperature below 50°. The hard, crystalline mass was heated at 70° for half an hour, after which 20 cc. of glacial acetic acid was added and the solution refluxed until a test portion with sodium nitrite solution and β-naphthol showed that acetylation was complete. The reaction was diluted with 100 cc. of water and filtered, washed and dried at 100°. Two recrystallizations gave 6 g. of pure product. It contained one molecule of water of crystallization.

**5-(Bromo-acetaminophenyl)-5-ethylbarbituric Acid.**—Two grams of the acetamino compound was brominated with 10% excess of dry bromine in 10 cc. of glacial acetic acid at 60–70°. Evolution of hydrogen bromide had ceased in an hour and the cold brominated product was precipitated by adding 50 cc. of cold water, filtered, washed and dried. Three recrystallizations gave pure material.

**5-(Nitro-acetaminophenyl)-5-ethylbarbituric Acid.**—Twenty cc. of concentrated sulfuric acid was cooled to −10° and 5 g. of acetamino compound was added with rapid stirring, keeping the temperature below 0°. A nitrating mixture containing 1.15 cc. (20% excess) of nitric acid (sp. gr. 1.42) and 5 cc. of concentrated sulfuric acid was then added, keeping the temperature between −10 and 3° during the addition. Stirring was continued for fifteen minutes after the nitrating agent had been added. The reaction mixture was poured into 150 cc. of ice water and a light yellow product separated out. The product, after two crystallizations was pure.

**5-(Bromo-aminophenyl)-5-ethylbarbituric Acid.**—Ten grams of the brominated acetamino compound was refluxed for five hours with 70 cc. of 95% alcohol and 30 cc. of 30% sulfuric acid. The alcohol was distilled off and just enough 10% sodium hydroxide solution was added to neutralize the sulfuric acid present.

**5-(Nitro-aminophenyl)-5-ethylbarbituric Acid.**—Fifteen grams of the nitrated product was refluxed for five hours with 150 cc. of 95% ethyl alcohol and 40 cc. of 20% sulfuric acid. The cold solution was filtered and 95.2% of the theoretical amount of fine yellow needles which did not melt below 320° was obtained. Purification was accomplished by taking up the product in a slight excess of cold 5% sodium hydroxide solution, filtering and precipitating by slow addition of dilute hydrochloric acid while stirring the solution rapidly. The precipitate was filtered, washed with alcohol and dried.

**5-Chlorophenyl-5-ethylbarbituric Acid.**—A solution of cuprous chloride was made by adding a mixture of 2.7 g. of sodium acid sulfite and 1.8 g. of solid sodium hydroxide in 20 cc. of water to a solution of 12.6 g. of copper sulfate and 2.3 g. of sodium chloride in 40 cc. of hot water. The white precipitate of cuprous chloride after filtration was treated with 8 cc. of concentrated hydrochloric acid and 40 cc. of water.

A diazonium salt solution was made by dissolving 10 g. of the amine in 35.5 cc. of concentrated hydrochloric acid, 20 cc. of water and 37 g. of ice. After cooling to 0°, a solution of 2.86 g. of pure sodium nitrite in 15 cc. of water was added to the amine hydrochloride. To the cuprous chloride solution was added as rapidly as possible the above diazonium salt solution, keeping the temperature between 0 and 5° for twenty minutes after addition of the solutions, when the reaction mixture was allowed to come to room temperature in the course of two hours. It was then heated to 60° for a short time.

The crude yellow product from 10 g. of the amine was washed thoroughly with 5% ammonium chloride solution, followed by water to remove all traces of insoluble copper salts; the yellow dry powder weighed 9.5 g. (83.5%) and melted with decomposition at 239–243° (uncorr.). The crude yellow powder after three recrystallizations from methyl alcohol, acetone and glacial acetic acid was pure.

TABLE II

DERIVATIVES OF PHENYLETHYLBARBITURIC ACID

| ( )-Phenyl-5-ethyl-barbituric acid | M. p., °C. (uncorr.) | Cryst. solvent | Needles | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|
| 5-Nitro- | 276–277 | 95% EtOH | White | 51.96 | 51.75 | 4.05 | 4.03 |
| 5-Amino- | 205–206 | 95% EtOH | White | 58.26 | 57.83 | 5.30 | 5.33 |
| 5-Acetamino-[a] | 147–148 | 70% EtOH | White | 54.72 | 54.53 | 5.53 | 5.68 |
| 5-Bromo-acetamino- | 291–292 | Gl. HAc | White | Br, 21.73; found, 21.57 | | | |
| 5-Nitro-acetamino- | 295–296 | 70% EtOH | Yellow | 50.27 | 48.98 | 4.22 | 4.28 |
| 5-Bromo-amino- | 253–255 | 60% EtOH | Yellow | Br, 24.57; found, 24.91 | | | |
| 5-Nitro-amino- | >320 | Rppt. NaOH | Yellow | 49.29 | 49.07 | 4.14 | 4.24 |
| 5-Chloro- | dec. 243–245 | MeOH, HAc, acetone | Tan | Cl, 13.30; found, 12.81 | | | |

[a] Calcd.: $H_2O$, 5.86. Found: $H_2O$, 5.84.

Several attempts at replacing the amino group by hydroxyl were unsuccessful and only a reddish brown dye melting with decomposition between 260–270° was isolated but not identified.

## Summary

1. 5-Phenyl-5-ethylbarbituric acid has been nitrated.

2. The following groups have been introduced into the phenyl ring through the nitro group: amino-, acetamino-, bromo-acetamino-, bromo-amino-, nitro-amino-, nitro-acetamino-, chloro-.

3. Methyl ethyl phenylethylmalonate has been nitrated and the nitro group shown to be in the para position in the benzene ring. In addition the following groups have been introduced into the phenyl ring of methyl ethyl phenylethylmalonate: 4-amino-, 4-hydroxy-, 4-acetamino-, 4-methoxy-.

4. None of the substituted phenylethylmalonates could be condensed with urea to form the corresponding barbituric acids.

5. Preliminary physiological tests which have been carried out on a majority of the 5,5-substituted phenylalkylbarbituric acids show that these compounds with the exception of the 4-chlorophenylethylbarbituric acid are inert. The sedative properties of the chloro derivative are of the same order as those of phenylethylbarbituric acid but the substance is slightly more toxic.

URBANA, ILLINOIS

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE COLLEGE OF LIBERAL ARTS, NORTHWESTERN UNIVERSITY]

# CONDENSATION PRODUCTS OF AMINO-ARSANILIC AND ARSANILIC ACIDS[1]

BY P. L. CRAMER WITH W. LEE LEWIS

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This paper is a continuation of the study[2] of condensation products of amino-arsanilic acid with 1,2-diketones to yield arsenated quinoxalines and with monocarbonyl compounds to form arsenated Schiff's bases. In the present study arsanilic acid as well as amino-arsanilic acid has been employed.

Glyoxal sodium bisulfite condenses with amino-arsanilic acid to give 6-arsono-quinoxaline-2,3-sodium bisulfite. This compound when treated with hydrochloric acid gives 6-arsono-quinoxaline, parent substance of this series.

Maltosone and lactosone, prepared according to the method of Emil

[1] This research was carried out under a grant from the Public Health Institute of Chicago. Some of the compounds are being studied for possible therapeutic value at the University of Wisconsin in the Department of Pharmacology.

[2] W. Lee Lewis, P. L. Cramer and R. S. Bly, THIS JOURNAL, **46**, 2058 (1924).