[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

N-Substituted Derivatives of Phenobarbital[1,2]

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A great deal of research has been devoted to the attempt to prepare soporifics of the barbituric acid series. The largest portion of this effort has been expended in substituting both hydrogens attached at the 5-C position of the nucleus by alkyl, alkenyl, aryl, and similar radicals. Also, some attention has been given to varying the radical thus attached by the introduction of halogen, hydroxyl, or carbonyl groups. In general, such modifications have produced unfavorable results, either the hypnotic activity being decreased or the toxicity increased. Somewhat surprising was the adverse effect of the carbonyl group in view of the fact that acetone and acetophenone are known to possess definite hypnotic activity.

Some attempts have been made to alter favorably the activity of 5,5-disubstituted barbiturates by further substitution through replacement of one or both hydrogen atoms attached to the nuclear nitrogen, and in some cases such alteration has been of value. Thus, for example, 1-methylphenobarbital[4] has been reported to possess a somewhat specific action toward epilepsy without the hypnotic effect produced by phenobarbital. Other N-derivatives of barbituric acids[5] are very quick-acting hypnotics with short duration of hypnosis. And, while 1-β,γ-dibromopropyl-5,5-diethylbarbituric acid[6] acts too slowly to be of use as a hypnotic, it has been employed as a sedative in the treatment of excitement and epilepsy. It is thus seen that the presence of, and variation in, groups attached to the nitrogen of the nucleus does exert an appreciable effect on the physiological activity of the barbiturate.

Few modifications of the N-substituent through introduction of halogen, hydroxyl, or carbonyl groups have been reported. Compounds containing halogen in the N-attached group have consisted mainly of N-halo-allyl or halo-propyl derivatives prepared from allyl derivatives by addition of halogen or hydrogen halide. No barbiturate containing an N-haloalkyl group of less than three C-atoms appears to have been prepared. Nor has the synthesis of derivatives having either an N-hydroxyalkyl, N-monoketonyl or N-monoacyl grouping been recorded. A few N,N-diketonyl barbiturates have been described,[7] but since these were prepared for the purpose of crystallographic study, it may be assumed that they were not tested pharmacologically. 1,3-Diacetylphenobarbital, 1,3-dipropionylphenobarbital, di-(α-bromopropionyl)-phenobarbital[8] and a few other N,N-diacylbarbiturates have been reported as having hypnotic properties, but no mention is made of N-monoacyl derivatives. The latter, because of their possibility of being rendered more soluble through formation of alkali metal salts, might be expected to be of more value.

It seemed of interest, therefore, to prepare examples of these types through appropriate N-substitution of a barbiturate of known value and importance, namely, phenobarbital. The N-derivatives of phenobarbital which we have synthesized contain hydroxyalkyl, haloalkyl, ketonyl, acyl or haloacyl groups. The reaction employed consists of the interaction of an appropriate halogen compound with a mono substituted salt of phenobarbital in an appropriate diluent or solvent.

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Experimental

1-β-Hydroxyethylphenobarbital.—To 25.4 g. (0.1 mole) of sodium phenobarbital, dried for three hours at 140°, in a 200-cc. flask fitted with stirrer and reflux condenser, was added 100 cc. (1.5 moles) of redistilled ethylene chlorohydrin, and the mixture heated to boiling while being stirred. At the end of two hours heating was discontinued, the contents of the flask cooled and filtered, and the sodium chloride (weight after drying, 5.75 g.) washed with 25 cc.

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(2) From the Ph. D. dissertation of J. J. Spurlock, June, 1940.

(3) Research Assistant, Project 19, Research Institute of The University of Texas, 1939–1940.

(4) Heyde, *Klin. Wochschr.*, **11**, 1874 (1932); through *C. A.* **27**, 779 (1933).

(5) Tabern and Volwiler, THIS JOURNAL, **58**, 1354 (1936).

(6) Houben, "Fortschritte der Heilstoffchemie," Walter de Gruyter and Co., Berlin, 1939, Vol. 3, p. 726.

(7) Hultquist and Poe, *Ind. Eng. Chem., Anal. Ed.*, **7**, 398 (1935).

(8) Rosenberg, German Patent 631,097.

of ether. From the filtrate, the excess chlorohydrin was removed by distillation under diminished pressure. The clear residual gum was dissolved in 100 cc. of benzene and the solution allowed to stand for three days while crystallization proceeded slowly. The solid was filtered, thoroughly triturated with 50 cc. of benzene, filtered and dried. Thus was obtained 18.15 g. of product melting at 125–135°. Recrystallization from benzene or alcohol–water did not markedly purify this material. The dry product was triturated with three 50-cc. portions of ether, dried, and now weighed 12.7 g. but melted at 142–145°. After additional recrystallizations from dilute alcohol, the N-barbiturate derivative melted at 145.0–145.5° (cor.).

To the ether washings was added 100 cc. of petroleum ether, the solution was concentrated to about half volume, chilled and filtered, yielding 5.3 g. of phenobarbital. The yield of N-hydroxyethyl derivative, based on the net amount of phenobarbital, was 60% of the theoretical.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.85; H, 5.89; N, 10.18.

When this preparation was attempted using methanol rather than excess ethylene chlorohydrin as the reaction medium by heating for forty hours in a metal bomb at 110°, a larger quantity of phenobarbital was recovered and only 24% yield of the N-hydroxyethyl compound was obtained.

The silver salt of phenobarbital (0.1 mole) was prepared and heated with excess ethylene chlorohydrin. Although 14.3 g. of silver chloride was obtained and nearly one-half of the phenobarbital was recovered, none of the desired N-hydroxyethylphenobarbital was isolated.

1-β-Chloroethylphenobarbital.—Three grams of 1-β-hydroxyethylphenobarbital and 2.7 g. of phosphorus pentachloride were placed in a flask and warmed slightly over a steam cone, causing a vigorous evolution of hydrogen chloride and liquefaction of the contents of the flask. After no more gas was evolved, the liquid was poured onto 60 g. of cracked ice. An oil formed and later solidified. The solid was crushed, filtered, washed with a small amount of water and dried at room temperature; wt. 2.97 g.; m. p. 103–107°. After recrystallization from petroleum ether and from dilute alcohol, there remained 2.2 g. (69% yield); m. p. 112.5–113.5° (cor.).

Anal. Calcd. for $C_{14}H_{15}ClN_2O_3$: Cl, 12.03; N, 9.51. Found: Cl, 11.95; N, 9.50.

This compound was not appreciably hydrolyzed after one hour in boiling water, although the water then gave a slight test for chloride ion. A 0.5-g. sample was dissolved in 10 cc. of *N* alkali and allowed to stand for one hour; upon acidification with dilute nitric acid, a gummy material resulted which did not immediately solidify.

1-β-Bromoethylphenobarbital.—Three grams of 1-β-hydroxyethylphenobarbital and 4.4 g. of phosphorus tribromide were placed in a flask and heated in an oil-bath at 110° for ten minutes. Vigorous evolution of hydrogen bromide occurred and a clear, slightly colored solution resulted. The latter was poured into 50 cc. of alcohol, and the solution concentrated to a volume of 20 cc. over a steam cone. When 40 cc. of water was added and the mixture allowed to stand, a heavy, oily liquid at first separated; this subsequently solidified and some additional crystallization took place. The dry solid weighed 2.25 g. and melted at 112–123°. This material was boiled with four 50-cc. portions of petroleum ether and the hot solutions were decanted. The residue represented 0.34 g. of hydroxyethylphenobarbital and in addition 0.56 g. was obtained from the first filtrate. From the petroleum ether extract there was secured 1.45 g. (56% net yield) of the N-bromoethyl derivative; m. p. 125–127°. Further recrystallization from petroleum ether and from dilute alcohol resulted in the product melting at 127.5–128.5° (cor.).

Anal. Calcd. for $C_{14}H_{15}BrN_2O_3$: Br, 23.56; N, 8.26. Found: Br, 22.95; N, 8.26.

Hydroxymethylene-bis-(1-methylenephenobarbital).—For this preparation, 2.79 g. (0.1214 gram atom) of sodium was dissolved in 200 cc. of methanol, followed by 28.2 g. (0.1214 mole) of phenobarbital and 13.2 g. (0.0607 mole) of glycerol-α,γ-dibromohydrin. The solution was heated in a metal bomb at 110° for twenty hours. After removal of one-half the solvent by evaporation, 200 cc. of water was added, causing separation of a gummy solid which was dissolved in ether. This solution was first extracted with 3% sodium carbonate solution, to remove unreacted phenobarbital, and then with *N* sodium hydroxide solution followed by immediate acidification of the latter. When only a trace of material appeared upon acidification, the total material reprecipitated from the sodium hydroxide extractions was boiled with 50 cc. of distilled water, the latter being decanted while hot and this aqueous extraction being repeated three times more. The residual gum could not be induced to crystallize from any of the usual organic solvents, and on heating at 100° in a vacuum, to remove volatile material, the product became a hard, glassy solid without definite melting point. It is soluble in benzene and alcohol, insoluble in water, and moderately soluble in dilute sodium hydroxide solution. The 8.5 g. of hydroxymethylene-*bis*-(1-methylenephenobarbital) obtained represents a yield of 33%.

Anal. Calcd. for $C_{27}H_{28}N_4O_7$: C, 62.30; H, 5.42; N, 10.76. Found: C, 62.56; H, 5.25; N, 10.50.

1-Acetonyl- and 1,3-Diacetonyl-phenobarbital.—Thirty-seven grams (0.146 mole) of dried sodium phenobarbital was dissolved in 75 cc. of absolute methanol in a flask provided with condenser, stirrer and dropping funnel. The mixture was stirred until most of the salt had dissolved, then 20 g. (0.146 mole) of bromoacetone was added dropwise. The solution warmed slightly during the time (thirty minutes) of addition, and the mixture was slowly heated to boiling and refluxed for one hour; now the mixture was acid to litmus. The methanol was removed over a steam cone, and the residual gum was dissolved in a mixture of ether and water. The ether solution was extracted with 50-cc. portions of 3% sodium carbonate as long as immediate acidification of the alkaline extract yielded a precipitate. During this process a white crystalline solid separated in the ether layer, and upon filtration and drying weighed 9.24 g. (18% yield) and melted at 132–135°. After recrystallization from dilute alcohol, **1,3-diacetonylphenobarbital** melts at 137.5–138.0° (cor.). This compound was not decomposed by boiling with water for one hour, but 0.5 g. dissolved completely in 10 cc. of *N* alkali after about one hour; upon acidification a substance was obtained which, upon being heated, evolved a gas at about 120°.

Anal. Calcd. for $C_{18}H_{20}N_2O_5$: N, 8.14. Found: N, 8.11.

The material precipitated by acid from the sodium carbonate extraction was a heavy oil which was dissolved in ether and washed with water. The ether was removed by evaporation and the residual oil was dissolved in 50 cc. of ethyl alcohol and allowed to stand for two days in an ice-chest. The solid, which had crystallized, was filtered, washed with 15 cc. of a saturated solution of methanol in petroleum ether and dried. Thus was obtained 22.7 g. (54% yield) of material melting at 95–110°. After recrystallization from dilute alcohol, **1-acetonylphenobarbital** melts at 115–116° (cor.). It is not decomposed by boiling with water for one hour, but is slowly decomposed by contact with *N* alkali.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: N, 9.72. Found: N, 9.81.

2,4-Dinitrophenylhydrazone of 1-acetonylphenobarbital, m. p. 223.5–224.5° (cor.).

Anal. Calcd. for $C_{21}H_{20}N_6O_7$: N, 17.94. Found: N, 18.12.

1-Phenacylphenobarbital.—From interaction of 18.5 g. (0.0728 mole) of dried sodium phenobarbital and 14.5 g. (0.0728 mole) of phenacyl bromide in 100 cc. of boiling absolute methanol, after about two hours the crystalline material was filtered and shown to be **1,3-diphenacylphenobarbital.** Thus was obtained 9.1 g. (37% yield) of material melting at 155–157°, but after recrystallization from alcohol, m. p. 156.5–157.0° (cor.).[9] This compound is so sparingly soluble that it is not decomposed by boiling with water or by contact with dilute alkali at room temperature for thirty minutes.

Anal. Calcd. for $C_{28}H_{24}N_2O_5$: N, 5.98. Found: N, 5.91.

The filtrate from the reaction mixture was diluted with two volumes of water, precipitating an oil which soon solidified. The hard mass was crushed, filtered, dried, shaken with 35 cc. of ether and again filtered. The product weighed 8.95 g. (49% yield) and melted at 156–159°, but after recrystallization from dilute alcohol, **1-phenacylphenobarbital** melts at 159.5–160.0° (cor.). From the ether washings of this compound, 2.9 g. of phenobarbital was recovered.

This monoketonyl compound was not appreciably decomposed by boiling with water for one hour, but by exposure to *N* alkali at room temperature for thirty minutes, alteration occurs, and acidification yields a product softening at 60° and evolving a gas at 75–80°.

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: N, 8.00. Found: N, 8.00.

1-*p*-Bromophenacylphenobarbital.—Prepared, by the same procedure as the phenacyl analog, from 12.7 g. of sodium phenobarbital, 13.9 g. of *p*-bromophenacyl bromide and 70 cc. of methanol with heating for three and one-half hours. Here, about 2.5 g. of phenobarbital was recovered, 9.55 g. (39% yield) of product melting at 163.0–163.5° (cor.)[10] was obtained, and 5.4 g. (32% yield) of **1-*p*-bromophenacylphenobarbital** melting at 149.0–149.5° (cor.).

Anal. Calcd. for $C_{20}H_{17}BrN_2O_4$: Br, 18.62; N, 6.53. Found: Br, 18.59; N, 6.58.

1-*p*-Phenylphenacylphenobarbital.—A solution of 14 g. of sodium phenobarbital and 15.13 g. of *p*-phenylphenacyl bromide in 100 cc. of methanol was refluxed for six hours. There separated a heavy oil which set to a stiff gum on cooling. Extraction with alkali and acidification yielded 11.5 g. of solid melting at 160–180°. Two 25-cc. portions of ether leached out 3.1 g. of phenobarbital. Upon recrystallization from dilute alcohol, there was obtained 7.8 g. (44% yield) of **1-*p*-phenylphenacylphenobarbital** melting at 195.5–196.0° (cor.).

Anal. Calcd. for $C_{26}H_{22}N_2O_4$: N, 6.57. Found: N, 6.62.

The material not extracted by the alkali, and presumably 1,3-di-(*p*-phenylphenacyl)-phenobarbital, was recovered as an oil upon evaporating the ether solution, and later set to a glass-like solid.

1-Propionyl- and 1,3-Dipropionyl-phenobarbital.—Sixteen and fifteen-hundredths grams (0.0477 mole) of silver phenobarbital was placed in a flask provided with a sealed-stirrer, and a reflux condenser fitted with a drying tube. Seventy-five cubic centimeters of anhydrous benzene was added, followed by 4.85 g. (0.0525 mole) of propionyl chloride, a slight heat effect being noted. After refluxing the mixture for fourteen hours, about one-half of the benzene was distilled off, the residue left in a dark place for two days, after which 50 cc. of benzene was added, the suspension transferred to a centrifuge cell and centrifuged. The clear solution was decanted, 50 cc. of benzene was added with stirring to the solid residue, and the centrifugation and decantation were repeated. After washing the residue four times with portions of a few cubic centimeters of hot alcohol, 6.65 g. of silver chloride was obtained, the calculated quantity obtainable being 6.84 g. The alcohol solution was evaporated almost to dryness and water added, causing the precipitation of 3.55 g. of phenobarbital.

The benzene solution from the centrifuging process was evaporated to about 60 cc. and 100 cc. of petroleum ether added, causing separation of a white solid. Crystallization continued for about two days, at the end of which time 7.75 g. of material, in fractions melting 80–145°, was obtained. From the first fraction, 0.75 g. of phenobarbital was recovered. The benzene-soluble fractions were combined and recrystallized from benzene–petroleum ether and from ether–petroleum ether. Thus there was obtained 3.65 g. (net yield 43%) of **1-propionylphenobarbital,** m. p. 96.0–96.5° (cor.).

Half a gram of this material was dissolved in 10 cc. of *N* sodium hydroxide solution and allowed to stand for fifteen minutes at room temperature. This solution was acidified, the precipitate was filtered, washed with water and dried. Thus 0.35 g. of impure phenobarbital, m. p. 150–160°, was recovered. After heating 0.50 g. of the 1-propionyl derivative with water at 100° for three hours, there was recovered 0.40 g. of material softening at 90° and melting finally at 160°.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: N, 9.72. Found: N, 9.75.

After evaporating to dryness the liquor from the recrystallization of 1-propionylphenobarbital, 1.7 g. of material

(9) Hultquist and Poe, ref. 7, reported that 1,3-diphenacylphenobarbital was obtained as an oily liquid which could not be induced to crystallize.

(10) Hultquist and Poe, ref. 7, report the melting point of 1,3-di-(*p*-bromophenacyl)-phenobarbital to be 164° (uncor.).

was obtained. When purified by recrystallization from dilute alcohol, **1,3-dipropionylphenobarbital** melts at 108–109°. This derivative behaves similarly to the monopropionyl compound toward boiling water or alkaline solution.

Anal. Calcd. for $C_{18}H_{20}N_2O_5$: N, 8.14. Found: N, 8.23.

1-Bromodiethylacetylphenobarbital.—Twenty-one grams of silver phenobarbital and 75 cc. of anhydrous toluene were mixed, 16 g. of bromodiethylacetyl bromide[11] was added and the well-stirred mixture was maintained at boiling temperature for eight hours. The material was allowed to stand at room temperature for three days before the precipitate was filtered and washed twice with 25-cc. portions of benzene. The solid was washed four times by decantation with ether, then was filtered and washed with ether. The residual silver bromide weighed 11.4 g. (11.64 g. theoretically obtainable). The ether washings yielded phenobarbital of which, after recrystallization from benzene, 5.25 g. was recovered.

The filtrate from the reaction mixture was evaporated, under diminished pressure, to a gum which dissolved in 60 cc. of dry ether and was diluted with 150 cc. of petroleum ether. Spontaneous evaporation of the solvents during three days caused crystallization. The solid was filtered, and boiled with four separate 100-cc. portions of petroleum ether, permitting recovery of 1.25 g. of phenobarbital. The petroleum ether extracts yielded 9.27 g. (net yield 67%) of product melting at 132–136°. After recrystallization from dilute alcohol, **1-bromodiethylacetylphenobarbital** melts at 141–142° (cor.). This compound could be dissolved in *N* alkali and be reprecipitated unchanged by acidification after an hour.

Anal. Calcd. for $C_{18}H_{21}BrN_2O_4$: Br, 19.53; N, 6.85. Found: Br, 19.50; N, 6.97.

Through the courtesy of Eli Lilly and Company, eight of these derivatives of phenobarbital have received preliminary testing for anticonvulsant activity and the results are tabulated.

(11) Auwers, *Ann.*, **439**, 141 (1924).

Compound	Approximate M.H.D. in rats by mouth[a]	Approximate comparative anti-convulsant value,[b] %
[Diphenylhydantoin]	No action	100
[5-Ethyl-5-phenylhydantoin]	200	100
1-Propionylphenobarbital	...	125
1,3-Dipropionylphenobarbital	...	102
1-β-Hydroxyethylphenobarbital	1000	51
1-β-Chloroethylphenobarbital	200	90
1-β-Bromoethylphenobarbital	400	34
1-*p*-Phenylphenacylphenobarbital	No action	22
1-Phenacylphenobarbital	No action	None
1-*p*-Bromophenacylphenobarbital	No action	None

[a] 100–1000 mg. per kg.

[b] Equivalent doses of 50 mg. per kg.

Parke, Davis and Company have tested 1-bromodiethylacetylphenobarbital and found it to be toxic in doses of 260 mg. per kg. by stomach tube in rats; the compound exhibits definite activity as an anticonvulsant.

Summary

1. By interaction of the mono-sodium or silver salt of phenobarbital with an appropriate halogen compound, N-derivatives of phenobarbital have been prepared containing an hydroxyalkyl, haloalkyl, ketonyl, acyl, or haloacyl group.

2. In addition to ten mono-substituted derivatives, in three instances, 1,3-disubstituted phenobarbitals were obtained.

3. None of the new phenobarbital derivatives possess hypnotic power, but several exhibit strong anticonvulsant activity.

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Chemistry of Vitamin B_6. IV. Reactions in Solutions at Elevated Temperatures

BY STANTON A. HARRIS

In testing the preparation of sterile solutions of vitamin B_6 base, Dr. J. Rosin and Mr. H. Mack[1] observed the precipitation of insoluble material when 10% aqueous solutions were heated at 120° for thirty minutes. Investigation has shown that this partially crystalline product is the result of a polymerization reaction of vitamin B_6 with the loss of water, and the steps in the determination of the reaction mechanism are now described. Short periods of heating produced crystalline material which could be recrystallized for purification. The longer periods of heating produced amorphous gelatinous material which was quite insoluble. Analyses were in agreement with the formula $C_{16}H_{20}N_2O_5$ for the crystalline product. This formula corresponds to the product of the interaction of two molecules of vitamin B_6 with the elimination on one molecule of water.

Harris, Webb and Folkers[2] have shown that vitamin B_6 exhibits the following tautomerism in acid (I), neutral (II), and basic (III) water solutions. The polymerization reaction has been

(1) Control Division, Merck & Co. Inc.

(2) Harris, Webb and Folkers, THIS JOURNAL, **62**, 3198 (1940).