The picrate is precipitated by the addition of a solution of sodium picrate to aqueous dimethylguanidine sulfate; after recrystallization from water, it melts sharply at 229–230°.[5]

Methyl Mercaptan Sodium Salt.—When methyl mercaptan is passed into a 25% solution of sodium hydroxide, absorption takes place with evolution of heat; after saturation, the solution on standing deposits flat needles which may attain a length of several centimeters. These crystals rapidly effloresce on exposure to air, apparently giving up water of crystallization. The salt is readily soluble in cold water and even more so in cold methyl alcohol. Although a boiling alkaline solution of methyl mercaptan (unlike ethyl mercaptan and its homologs) does not yield the free mercaptan in appreciable quantities to the distillate, the salt possesses a powerful odor; attempts to determine directly the percentage of water of crystallization were unsuccessful, owing to loss of substance other than moisture. When the crystals are heated above 200° decomposition sets in, sodium disulfide being formed in considerable amount.

Analyses. Subs., 0.5468: Na_2SO_4, 0.2540. Subs., 0.6584: NaCl, 0.2489. Calc. for $2CH_3SNa.9H_2O$: Na, 15.23. Calc. for $CH_3SNa.5H_2O$: Na, 14.75. Found: Na, 15.04, 14.90.

Summary

A convenient method is described for the preparation of mono- and dialkylguanidines.

A description is given of 3 crystalline salts hitherto not mentioned in the literature: methylguanidine sulfate, α,α-dimethylguanidine sulfate, and the sodium salt of methyl mercaptan.

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SOME DIALKYLBARBITURIC ACIDS WITH TERTIARY AMINO GROUPING

BY ARTHUR W. DOX AND LESTER YODER

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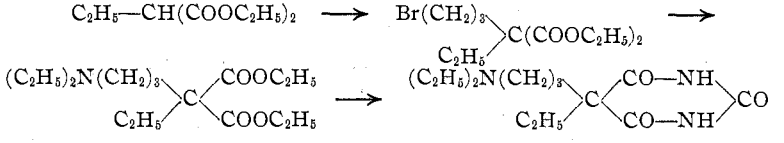
In continuation of the investigations in the barbituric acid series which have been in progress in this Laboratory during the past 2 years, it seemed worth while to prepare certain more complex derivatives for the purpose of studying their physiological activity. Previous work has shown that the dialkylbarbituric acids of the veronal type exhibit hypnotic properties over quite a range of molecular weight. Our aim was now to add to the dialkylbarbituric acid another grouping with known physiological activity, but united through a stable linkage so that the substance would not readily undergo hydrolysis and enable the two components to exert their separate activities independently. The phenomenon of "synergy," familiar to pharmacologists, has been studied rather extensively in the case of simple mixtures of physiologically active substances, but comparatively little

[5] Schenck, Ref. 2, gives the melting point as 230°. Werner and Bell, Ref. 4, give 227°.

is known concerning the effect of combining two or more such substances in a stable union.

The derivatives described in this paper may be considered as dialkyl-barbituric acids (5-ethyl-5-propyl- and 5-*iso*amyl-5-propyl-barbituric acids) with diethylamine, ethylaniline, acetanilide and phenacetin, respectively, attached to the γ-carbon of the propyl group.

The steps by which these syntheses were accomplished may be illustrated in the case of 5-ethyl-5-diethylamino-propyl-barbituric acid as follows,



Experimental Part

In the double alkylation of ethyl malonate it is preferable to introduce the unsubstituted alkyl first. Otherwise, the alkylene bromide tends to form a cyclic derivative in which both reactive hydrogens of the ethyl malonate are substituted.[1] Ethylene and trimethylene bromides are the only alkylene halides readily available. Attempts to introduce a β-bromo-ethyl group by treatment of the alkyl malonic ester with ethylene bromide were much less successful than the introduction of the γ-bromo-propyl group with trimethylene bromide. The latter was accordingly used throughout in these preparations. The yields, however, were smaller than those obtained in the preparation of the ordinary dialkylmalonic esters. The loss was obviously due to a side reaction in which hydrobromic acid is removed from the trimethylene bromide, giving allyl bromide which was easily recognized by its odor. By using benzene in place of alcohol, this difficulty was largely overcome, but a further loss was the formation of a considerable amount of a high-boiling product, probably a tetracarboxylic ester resulting from a reaction between 2 molecules of sodium alkylmalonic ester and 1 of trimethylene bromide. This secondary reaction was reduced to a minimum by the use of a great excess of trimethylene bromide. The alkyl-γ-bromopropyl-malonic esters then reacted readily with basic secondary amines and with the sodium salt of acyl amines to form alkyl-γ-alkylaminopropyl-malonic esters, which in turn condensed with urea with ring closure giving the desired barbituric acids with alkylamine substitution on the γ-carbon of the propyl group.

Ethyl Ethyl-γ-bromopropyl-malonate.—Twelve g. of finely divided sodium was gradually added to a cold solution of 95 g. of ethyl ethylmalonate in 250 cc. of anhydrous benzene. Practically all of the sodium dissolved with evolution of hydrogen. To the cold solution 200 g. (calc., 107 g.) of trimethylene bromide was added. The temperature of the cooling bath was gradually raised and finally the mixture was refluxed until it became neutral to litmus. The product was shaken with water to remove the sodium

[1] Dox and Yoder, THIS JOURNAL, **43**, 680, 1368, 2097 (1921).

bromide, then dried with calcium chloride and finally distilled under diminished pressure. The first portion of the distillate consisted of benzene, trimethylene bromide and ethyl ethylmalonate, then the condensation product came over between 160° and 180° at 20 mm., leaving about 8 g. of a high-boiling residue. After three fractionations, we obtained 50 g. of an oil boiling at 169–174° at 20 mm. pressure.

Analysis. Subs., 0.1780: AgBr, 0.1037. Calc. for $C_{12}H_{21}O_4Br$: Br, 25.8. Found: 24.8.

Ethyl Ethyl-γ-diethylaminopropyl-malonate.—A mixture of 50 g. of ethyl ethyl-γ-bromopropyl-malonate and 30 g. of diethylamine was gently refluxed for 2 hours on a water-bath. Diethylammonium bromide separated rapidly at first. The reaction product was shaken with a concd. solution of sodium hydroxide and the latter drawn off through a funnel. The remaining oily layer was dried with solid sodium hydroxide and distilled under diminished pressure. After two fractionations, 40 g. of a yellow oil boiling at 143–149° at 6 mm. pressure was collected.

Analyses. Subs., 0.2012, 0.2080: NH_3, 6.7, 6.9 cc. of 0.1 *N* acid. Calc. for $C_{16}H_{31}O_4N$: N, 4.65. Found: 4.66, 4.64.

5-Ethyl-5-γ-diethylaminopropyl-barbituric Acid.—A mixture of 10 g. of ethyl ethyl-γ-diethylaminopropyl-malonate, 3 g. of urea, and 40 cc. of absolute alcohol in which 2.5 g. of sodium had been dissolved, was heated in an autoclave at 108° for 7 hours. The white pasty product was made neutral to litmus by the addition of concd. hydrochloric acid, the precipitated sodium chloride removed by filtration, and the alcoholic filtrate evaporated to a sirup on the steam-bath. On the addition of sodium hydroxide solution, crystals of the barbituric acid separated, which were dried by suction and purified by recrystallization from water; yield, 3.5 g.; m. p., 165–166°. The substance is insoluble in strong alkali, ether or benzene but readily soluble in water or alcohol. It is basic and forms salts with acids.

Analyses. Subs., 0.2, 0.2: NH_3, 22.35, 22.35 cc. of 0.1 *N* acid. Calc. for $C_{13}H_{23}O_3N_3$: N, 15.61. Found: 15.64, 15.64.

Ethyl Ethyl-γ-acetanilinopropyl-malonate.—The sodium salt of acetanilide was first prepared by refluxing 9.5 g. of acetanilide in 200 cc. of anhydrous benzene with 1.6 g. of sodium. After this mixture cooled, 22 g. of ethyl ethyl-γ-bromopropyl-malonate was added and the suspension was gently heated under a reflux condenser for 12 hours. The sodium bromide was washed out with water, and the oil dried with calcium chloride and distilled. Fractionation gave 15 g. of a viscous yellow oil boiling at 244–250° at 17 mm.

Analyses. Subs., 0.2, 0.2: NH_3, 5.3, 5.4 cc. of 0.1 *N* acid. Calc. for $C_{20}H_{29}O_5N$: N, 3.85. Found: 3.71, 3.78.

5-Ethyl-5-γ-acetanilinopropyl-barbituric Acid.—To a solution of 2.5 g. of sodium in 40 cc. of absolute alcohol, 12 g. of ethyl ethyl-γ-acetanilinopropyl-malonate and 3 g. of urea were added. The mixture was heated in an autoclave at 108° for 7 hours. After neutralization with concd. hydrochloric acid the product was filtered and the filtrate evaporated to a small volume. Addition of water resulted in the separation of an oil which solidified after a time. This was recrystallized from benzene containing a little alcohol; yield, 9 g.; m. p., 180° The substance is readily soluble in alcohol, but sparingly soluble in benzene or hot water.

Analyses. Subs., 0.2, 0.2: NH_3, 18.0, 18.1 cc. of 0.1 *N* acid. Calc. for $C_{17}H_{21}O_4N_3$: N, 12.68. Found: 12.60, 12.67.

Ethyl Ethyl-γ-acetophenetidinopropyl-malonate.—Molecular proportions were used and the same procedure followed as that employed in the preparation of ethyl ethyl-γ-acetanilinopropyl-malonate, but with phenacetin in place of acetanilide. The

washed and dried oil was fractionated under diminished pressure, and the fraction boiling at 237–240° at 4 mm. was collected.

Analyses. Subs., 0.2, 0.2: NH_3, 4.7, 4.8 cc. of 0.1 *N* acid. Calc. for $C_{22}H_{33}O_6N$: N, 3.44. Found: 3.29, 3.36.

5-Ethyl-5-γ-acetophenetidinopropyl-barbituric Acid.—A solution of 13 g. of ethyl ethyl-γ-acetophenetidinopropyl-malonate and 3 g. of urea in 40 cc. of absolute alcohol containing 2.5 g. of sodium was heated in an autoclave at 108° for 7 hours. The alcoholic filtrate from the neutralized and filtered mixture was evaporated to a small volume and then diluted with water until no more oil separated. Some unchanged ester which interfered with crystallization was removed by treatment with alkali and extraction with ether. The alkaline solution was then neutralized and warmed for a short time on the steam-bath until the product began to crystallize. After recrystallization from benzene containing a small amount of alcohol, 8.8 g. of a product melting at 158–159° was obtained. The substance is very soluble in alcohol, but only sparingly soluble in benzene or hot water.

Analyses. Subs., 0.2, 0.2: NH_3, 15.9, 16.0 cc. of 0.1 *N* acid. Calc. for $C_{19}H_{25}O_5N_3$: N, 11.20. Found: 11.13, 11.20.

Ethyl *iso*Amyl-γ-bromopropyl-malonate.—A solution of 75 g. of ethyl *iso*amyl-malonate in 150 cc. of benzene was cooled and 7.7 g. of finely divided sodium was added. After the sodium had dissolved, 135 g. of trimethylene bromide was added and the mixture was heated in a bath at about 85° for 2 hours, until the reaction of the solution was neutral, when the mixture was washed, dried and distilled in a vacuum. Two fractionations gave 50 g. of a viscous oil boiling at 175–182° at 13 mm. About 25 g. of a higher-boiling residue remained in the distilling flask.

Analysis. Subs., 0.1589: AgBr, 0.0815. Calc. for $C_{15}H_{27}O_4Br$: Br, 22.7. Found: 21.8.

Ethyl *iso*Amyl-γ-diethylaminopropyl-malonate.—A solution of 36 g. of ethyl *iso*amyl-γ-bromopropyl-malonate in 20 g. of diethylamine was refluxed for 4 hours. A copious separation of diethylammonium bromide occurred. The mixture was washed and dried, as in the preparation of the corresponding ethyl derivative, and fractionated twice, yielding 29 g. of a thick yellow oil that boiled at 155–161° at 5 mm.

Analyses. Subs., 0.25, 0.25: NH_3, 6.7, 6.9 cc. of 0.1 *N* acid. Calc. for $C_{19}H_{37}O_4N$: N, 4.08. Found: 3.76, 3.87.

5-*iso*Amyl-5-γ-diethylaminopropyl-barbituric Acid.—A solution of 11 g. of ethyl *iso*amyl-γ-diethylaminopropyl-malonate and 3 g. of urea in 40 cc. of absolute alcohol containing 2.5 g. of sodium was heated in an autoclave at 108° for 7 hours. To the white pasty mass thus obtained, concd. hydrochloric acid was added until the reaction was neutral, the sodium chloride was removed by filtration and the alcoholic filtrate evaporated to a sirup. Upon the addition of water an oil separated which consisted largely of unchanged ester and was discarded. The aqueous solution was evaporated to crystallization and finally yielded 5 g. of a product melting at 133°. This *iso*amyl derivative is somewhat less soluble in water and more soluble in alcohol, ether or benzene than the homologous ethyl derivative described above.

Analyses. Subs., 0.2, 0.2: NH_3, 18.95, 18.90 cc. of 0.1 *N* acid. Calc. for $C_{16}H_{29}O_3N_3$: N, 13.50. Found: 13.30, 13.26.

Ethyl *iso*Amyl-γ-ethylanilinopropyl-malonate.—A mixture of 25 g. of ethyl *iso*amyl-γ-bromopropyl-malonate and 18 g. of ethylaniline was heated in an oil-bath at 160° for 4 hours. The dark, viscous oil was washed with dil. sodium hydroxide solution, then with water, dried with solid sodium hydroxide and distilled; 15 g. of a yellow oil boiling at 194–201° at 4 mm. was collected.

Analyses. Subs., 0.2, 0.2: NH_3, 5.0, 5.0 cc. of 0.1 *N* acid. Calc. for $C_{23}H_{37}O_4N$: N, 3.58. Found: 3.50, 3.50.

5-*iso*Amyl-5-γ-ethylanilinopropyl-barbituric Acid.—A solution of 10 g. of ethyl *iso*amyl-γ-ethylanilinopropyl-malonate and 2.5 g. of urea in 40 cc. of absolute alcohol containing 2 g. of sodium was heated in an autoclave at 108° for 7 hours. The product was neutralized with hydrochloric acid, the chlorides were removed by filtration and the alcoholic filtrate concentrated to a sirup. On the addition of water, an oil separated. This failed to crystallize until the impurities had been removed by extraction of the alkaline solution with ether. The oil obtained by acidifying the alkaline solution was dissolved in benzene, and the addition of ligroin then caused the product to separate gradually in needle-shaped crystals; yield, 3 g.; m. p., 135°. The substance is insoluble in water, but readily soluble in benzene, ether or alcohol.

Analyses. Subs., 0.2, 0.2: NH_3, 16.0, 16.2 cc. of 0.1 *N* acid. Calc. for $C_{26}H_{29}O_3N_3$: N, 11.69. Found: 11.20, 11.34.

Ethyl *iso*Amyl-γ-acetophenetidinopropyl-malonate.—The sodium salt of phenacetin was first prepared by refluxing a solution of 12.5 g. of phenacetin in 200 cc. of benzene with 1.6 g. of finely divided sodium. To the suspended sodium salt 24 g. of ethyl *iso*amyl-γ-bromopropyl-malonate was added, and the mixture was refluxed for several hours until it was neutral to litmus. The sodium bromide was removed with water and the oily layer dried with calcium chloride. Two fractionations under diminished pressure gave 18 g. of a viscous, yellow oil boiling at 245–250° at 4 mm.

Analyses. Subs., 0.2, 0.2: NH_3, 4.4, 4.3 cc. of 0.1 *N* acid. Calc. for $C_{25}H_{39}O_6N$: N, 3.12. Found: 3.08, 3.01.

5-*iso*Amyl-5-γ-acetophenetidinopropyl-barbituric Acid.—A solution of 10 g. of ethyl *iso*amyl-γ-acetophenetidinopropyl-malonate and 2.5 g. of urea in 40 cc. of absolute alcohol containing 2 g. of sodium was heated in an autoclave at 108° for 7 hours. The product was neutralized and filtered as usual and evaporated to a sirup. The addition of water resulted in the separation of the barbituric acid in small crystals. These were dried and recrystallized from benzene containing a little alcohol; yield, 5 g.; m. p., 155°. The substance is practically insoluble in hot water, slightly soluble in benzene, and readily soluble in alcohol. The acetyl group is not easily split off. After successive treatment with hot alkali and concd. hydrochloric acid the original substance was recovered.

Analyses. Subs., 0.1, 0.1: NH_3, 7.2, 7.3 cc. of 0.1 *N* acid. Calc. for $C_{22}H_{31}O_5N_3$: N, 10.07. Found: 10.08, 10.22.

Physiological Properties

The barbituric acids described above have a bitter taste similar to that of veronal. Some were tested physiologically by oral administration to dogs, others by intraperitoneal injection of the alkali solution into white mice. Only the possibility of sedative action was considered in these preliminary tests. The following results recorded by way of illustration are typical.

Barbituric acid	Dose G.	Wt. of dog Kg.	Effect
Ethyl-γ-acetophenetidinopropyl-.....	2	16	slight drowsiness
Ethyl-γ-diethylaminopropyl-.....	2	15	none
*iso*Amyl-γ-acetophenetidinopropyl-.....	1.8	15	none

It will be noted from the foregoing descriptions that the basic diethylamino derivatives are soluble in water but insoluble in neutral organic

solvents other than alcohol. The distribution coefficient is, therefore, less than unity. On the other hand, the neutral derivatives are practically insoluble in water. In the case of the phenacetin derivatives a possible antagonistic action of the two components was shown to be negligible. A mixture of 1 g. of dipropylbarbituric acid with 0.8 g. of phenacetin produced a very pronounced hypnotic effect on a dog of 18 kg. The explanation of the lack of hypnotic properties of these complex barbituric acids is, we believe, in some cases their insolubility which prevents absorption and their stability which precludes the possibility of hydrolysis at the point of union of the two components, and in others, the reversal of the distribution coefficient. Similarly, the intraperitoneal injection of the sodium salts into mice in doses twice as large as the effective dose of veronal produced no noteworthy symptoms, except in the case of 5-*iso*amyl-5-γ-diethylaminopropyl-barbituric acid which appeared to be toxic without preliminary sedative action. Even when the substance is administered as the sodium salt, we have reason to believe that the actual absorption takes place in the form of the free acid, and is too slow to produce any noteworthy effect. This explanation is in harmony with the Overton-Meyer theory of narcosis, according to which a substance must have a certain distribution coefficient between the two solvents water and fat (or lipoids) in order to exert hypnotic action. This of course applies strictly only to the synthetic hypnotics, none of which appear to exert any specific action upon the higher brain centers. By increasing the complexity of the dialkylbarbituric acids the solubility in water is reduced to a minimum beyond which absorption is too slow to result in the phenomenon of hypnosis, or if a strongly basic grouping has been introduced, the distribution coefficient becomes less than unity.

Summary

A number of ethyl dialkylmalonates have been prepared in which one alkyl is ethyl or *iso*amyl and the other *n*-propyl with substitution of a tertiary amino group on the γ-carbon. From these esters the corresponding barbituric acids have been prepared. The latter, when tested physiologically, failed to show the hypnotic effect characteristic of the simple dialkylbarbituric acids. This inactivity is attributed in some instances to insolubility and consequent failure of absorption, in others, to a reversal of the distribution coefficient.

DETROIT, MICHIGAN