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SOME DERIVATIVES OF NORMAL-BUTYL-MALONIC ACID

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The sudden transition, during very recent years, of *n*-butyl alcohol from a rare and expensive chemical curiosity to a cheap article of commerce has stimulated research, particularly along pharmaceutical lines, looking to the introduction of new products derived from butyl alcohol. Thus far such researches have been confined mainly to the preparation of homologs of well-known substances. The butyl homologs of veronal and procaine may be cited by way of illustration. At any rate, the substitution of the butyl for the ethyl group in almost any drug containing one or more ethyl groups is worth considering as a pharmaceutical possibility.

The object of this work was to prepare, for physiological tests, the butyl homolog of veronal in which only one of the two ethyl groups is replaced by butyl. For this purpose, the ethyl ester of *n*-butyl-malonic acid, first described by Adams and Marvel[1] served as the starting point and, while this material was at hand, a number of other derivatives of incidental interest were also prepared.

Experimental

***n*-Butyl-malonamide.**—Ten g. of ethyl *n*-butyl-malonate and 40 cc. of concentrated aqueous ammonia were shaken in a tightly stoppered bottle, then shaken at frequent intervals during the day. Small needle-shaped crystals began to form in about 4 hours. After 24 hours the crystals were collected and the unchanged ester was treated as before with a fresh quantity of ammonia. The total yield of amide was 3.8 g. Recrystallized from alcohol the substance formed slender hair-like needles which matted together. It was difficultly soluble in water, readily soluble in alcohol and it melted at 200°.

Analyses. Subs., 0.2, 0.2: 25.2, 25.0 cc. of 0.1 *N* NH_3. Calc. for $C_7H_{14}N_2O_2$: N, 17.72. Found: 17.64, 17.50.

***n*-Butyl-*N,N'*-dimethyl-malonamide.**—Ten g. of ethyl *n*-butyl-malonate and 50 g. of a 33% aqueous solution of methylamine were vigorously shaken. Crystal formation was noticed in about an hour; then the mass rapidly became thick with crystals. After standing overnight, the crystals were collected and washed with cold water, then with ether. Recrystallized from hot water the substance was obtained in white, glistening needles, melting at 184°. The yield was 7 g.

Analyses. Subs., 0.2, 0.2: 21.7, 21.6 cc. of 0.1 *N* NH_3. Calc. for $C_9H_{18}N_2O_2$: N, 15.05. Found: 15.19, 15.12.

***n*-Butyl-malonanilide.**—Ten g. of the ester was dissolved in 8.7 g. of aniline (2 mols.) and heated in an oil-bath at 150°. Very little reaction occurred during 8 hours' heating at this temperature. The temperature was then raised and the mixture gently refluxed under an air condenser for one hour. On cooling the solution, a solid mass of crystals was obtained. This mass was broken up and washed with ether, then recrystallized from boiling alcohol. The yield was 10 g. of white needles melting at 193°.

[1] Adams and Marvel, THIS JOURNAL, **42**, 316 (1920).

Analyses. Subs., 0.2, 0.2: 13.0, 12.9 cc. of 0.1 *N* NH_3. Calc. for $C_{19}H_{22}N_2O_2$: N, 9.03. Found: 9.10, 9.03.

n-Butyl-malono-o-toluide.—This compound was prepared by gently heating under a reflux condenser 10 g. of ethyl *n*-butyl-malonate with 10 g. of freshly distilled *o*-toluidine for 1 hour. The solid mass which formed as the solution cooled was treated as in the preceding experiment. The yield was 12 g. of white needles melting at 202°.

Analyses. Subs., 0.2, 0.2: 12.05, 11.95 cc. of 0.1 *N* NH_3. Calc. for $C_{21}H_{26}N_2O_2$: N, 8.28. Found: 8.43, 8.36.

5-n-Butyl-barbituric acid.—Eleven g. of ethyl *n*-butyl-malonate, 3.5 g. of sodium dissolved in 65 cc. of absolute alcohol, and 4.5 g. of urea were heated for 6 hours in an autoclave at 105°. The white insoluble product containing the sodium salt of *n*-butyl-barbituric acid was separated by filtration from the alcoholic mother liquor, then dissolved in water and made slightly acid with hydrochloric acid. The *n*-butyl-barbituric acid separated in white scaly crystals. These were purified by recrystallization from alcohol and then from water. The substance is more soluble in alcohol than in water, and is readily soluble in dil. alkalies. It melts at 214°.

Analyses. Subs., 0.2, 0.2: 21.55, 21.65 cc. of 0.1 *N* NH_3. Calc. for $C_8H_{12}N_2O_3$: N, 15.22. Found: 15.09, 15.16.

5-n-Butyl-5-bromobarbituric acid.—The preceding product, like all other monoalkyl barbituric acids, is easily brominated. The calculated amount of bromine was slowly added to a solution of *n*-butyl-barbituric acid in methyl alcohol. Hydrogen bromide was evolved, and the completion of the reaction indicated by a permanent color as soon as a slight excess of bromine was present. The alcohol was carefully evaporated and the product recrystallized from water. It was obtained in white needles melting at 114°. The yield was practically quantitative.

Analysis. Subs., 0.4749: (Carius) AgBr, 0.3422. Calc. for $C_8H_{11}N_2O_3Br$: Br, 30.42. Found: 30.67.

Ethyl n-Butyl-bromomalonate.—One hundred and ninety-six g. of ethyl *n*-butyl-malonate was warmed on a steam-bath and 160 g. of bromine, containing a trace of iodine as a catalyst, was added slowly from a dropping funnel. A copious evolution of hydrogen bromide occurred. The product was distilled under diminished pressure; hydrogen bromide with some bromine and iodine passed over first. The fraction collected between 150° and 160° at 20 mm. pressure was redistilled and obtained as a colorless oil with a pleasant fruity odor. The yield was 245 g., or 89%, of a product boiling at 152–153° at 20 mm. pressure; d_{26}^{26} 1.238. At atmospheric pressure (737 mm.) the substance boiled at 252–253° with considerable decomposition into hydrogen bromide, the material in the flask rapidly becoming black.

Analysis. Subs., 0.5059: (Carius) AgBr, 0.3269. Calc. for $C_{11}H_{19}O_4Br$: Br, 27.12. Found: 27.50.

Ethyl n-Butyl-phenoxy-malonate.—To a solution of 4.6 g. of sodium in 85 cc. absolute alcohol was added 19 g. of phenol and, after the mixture was cooled, it was shaken and 60 g. of ethyl *n*-butyl-bromomalonate was added in small portions. The mixture was then gradually warmed and finally heated under a reflux condenser for 1 hour. A separation of sodium bromide occurred. After the alcohol had been distilled and the residue had been washed with water, the product was distilled *in vacuo*. The portion collected between 165° and 175° at 8 mm. pressure was redistilled, and 42 g. of a viscous oil obtained which boiled at 170–173° at 8 mm. pressure; d_{24}^{24} 1.063.

Analyses. Subs., 0.1635, 0.1553: CO_2, 0.3941, 0.3743; H_2O, 0.1222, 0.1143. Calc. for $C_{17}H_{24}O_5$: C, 66.55; H, 7.85. Found: C, 65.73, 65.73; H, 8.23, 8.18.

5-n-Butyl-5-phenoxy-barbituric acid.—Ten g. of the above ester, 2.3 g. of sodium

dissolved in 40 cc. of absolute alcohol, and 3 g. of urea were heated for 6 hours at 105°. The mixture was acidified with a slight excess of hydrochloric acid, filtered and the filtrate evaporated. On addition of water an oil was formed. This oil could not be made to crystallize until its ethereal solution had been carefully washed with water. The oil then obtained by evaporation of the ether, as it cooled, gave needle-shaped crystals. These were recrystallized from benzene containing a little alcohol. The product was 6 g. of small white needles melting at 167°. The substance has an intensely bitter taste.

Analyses. Subs., 0.2, 0.2: 14.4, 14.6 cc. of 0.1 *N* NH_3. Calc. for $C_{14}H_{16}N_2O_3$: N, 10.14. Found: 10.08, 10.22.

5-*n*-Butyl-5-ethyl-barbituric acid.—Ethyl ethylbutyl-malonate has been prepared by Raper[2] by treating ethyl ethyl-malonate with *n*-butyl iodide and sodium ethylate. In our preparation the two alkyl groups were introduced in the reverse order, *i. e.*, by treatment of ethyl *n*-butyl-malonate with ethyl bromide and sodium ethylate. The product boiled at 243–245° at 755 mm. pressure. 12.2 g. of this ester, 3.5 g. of sodium dissolved in 65 cc. of absolute alcohol, and 4.5 g. of urea were heated for 6 hours at 105°. After acidifying the alcoholic mixture and filtering the solution, the filtrate was evaporated and cooled. Upon addition of water, an oil separated. This was treated with a dilute solution of sodium hydroxide and extracted with ether to remove any unchanged ester which interfered with crystallization. The alkaline solution was then acidified and the crystals thus obtained were recrystallized from dilute alcohol. The yield was 9 g. of a substance melting at 125°. It was sparingly soluble in water, and readily soluble in alcohol and in dil. alkali.

Analyses. Subs., 0.2, 0.2: 18.75, 18.60 cc. of 0.1 *N* NH_3. Calc. for $C_{10}H_{16}N_2O_3$: N, 13.29. Found: 13.13, 13.02.

Physiological Properties

The butylphenoxy-barbituric acid described above is analogous in structure to the dialkyl-barbituric acids, except that the phenyl group is linked to the pyrimidine ring through an oxygen atom. It might be expected, therefore, to possess hypnotic properties. However, it was found to be practically inert. One g. administered to a dog caused only very slight muscular incoördination. In this connection we tested also the lower homolog, ethylphenoxy-barbituric acid, which will be described in another paper. This substance represents the powerful hypnotic, "luminal," with an oxygen atom inserted between the phenyl group and the pyrimidine ring. This also was inert.

n-Butyl-ethyl-barbituric acid, on the other hand, proved to be a strong hypnotic. Preliminary experiments on mice showed the effective dose to be 0.075 mg. per g. and the toxic dose 0.2 mg. per g. of body weight. These figures represent about $^1/_3$ the corresponding doses of veronal. The substitution of a butyl for one of the ethyl groups in veronal has, therefore, resulted in an increase in the intensity of physiological action.

Summary

From the ethyl ester of *n*-butyl-malonic acid a number of new deriva-

[2] Raper, *J. Chem. Soc.*, 91, 1837 (1907).

tives have been prepared. Of chief interest among these is 5-*n*-butyl-5-ethyl-barbituric acid which is a powerful hypnotic. Curiously enough, the substitution of a phenoxyl group for either of the alkyls in this substance destroys its physiological activity.

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DETECTION OF THYMINE IN THE PRESENCE OF SUGAR

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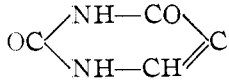
In a recent paper in THIS JOURNAL, Johnson and Baudisch[1] have described a new test for the detection of the pyrimidine, thymine,



which is specific and much more sensitive than any method hitherto suggested. Johnson and Baudisch showed that on treatment with ferrous sulfate and sodium hydrogen carbonate in the presence of air, thymine is oxidized to urea, pyruvic acid, acetol and possibly formic acid. Uracil and cytosine also give urea when treated in a like manner, but only thymine is capable of giving acetol and pyruvic acid by virtue of the methyl group in the 5 position of the pyrimidine ring. In the absence of sugar, the formation of pyruvic acid, or acetol, and urea by this oxidation is sufficient to prove the presence of thymine. Inasmuch as one of these oxidation products, namely acetol, also arises in the distillation of the simpler carbohydrates with sodium hydrogen carbonate,[2] the acetol test cannot be applied for thymine in the presence of sugar. Since sugar is present in the nucleic acid molecule, it is important to have a reaction to detect small quantities of thymine in the presence of sugar.

For the detection of urea, acetol and pyruvic acid after the oxidation of thymine, the precipitated ferric hydroxide is filtered off and the filtrate distilled. The distillate, which contains the acetol, has a sweet smell and reduces an ammoniacal solution of silver nitrate. Acetol can be identified in small quantities by the use of the test first discovered by Baudisch[3] and discussed in another paper.[2] This procedure involves heating the distillate with *o*-amino-benzaldehyde in alkaline solution with the consequent production, by condensation with acetol, of 3-oxyquinaldine. This compound is readily identified by its characteristic blue fluorescence in sodium hydrogen carbonate solution.

[1] Johnson and Baudisch, THIS JOURNAL, **43**, 2670 (1921). Baudisch and Johnson, *Ber.*, **55**, 18 (1921).

[2] Baudisch and Deuel, THIS JOURNAL, **44**, 1585 (1922).

[3] Baudisch, *Biochem. Z.*, **89**, 279 (1918).