[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY AT THE UNIVERSITY OF WISCONSIN]

SOME NEW DERIVATIVES OF BARBITURIC ACID

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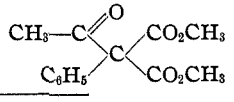
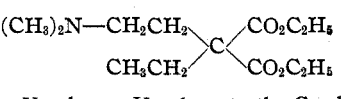
The experiments herein described were made in conjunction with attempts to prepare vinyl analogs of barbital (veronal) and phenobarbital (luminal). Carnot and Tiffeneau[2] have stated that, if the number of carbon atoms in the radicals at Position 5 in the barbituric acid nucleus exceeds eight, a decline in hypnotic effect occurs. Comparatively little importance has been attached to the unsaturated derivatives as judged by the number prepared, although they show marked hypnotic power.[3] Hence it was thought most desirable to prepare unsaturated derivatives corresponding to the most important members of the series.

The most feasible method that occurred to us involved the introduction of the halogen ethyl group into the mono-alkylated malonic ester, elimination of halogen acid either directly or indirectly, and condensation of the resulting compound with urea. Dox and Yoder[4] reported difficulty in substituting a bromo-ethyl radical into malonic ester. To avoid this we used ethylene chloro-iodide and found that the reaction could be controlled so that diethyl β-chloroethyl-ethyl-malonate was obtained in 50% yield. No halogen ethyl substitution could be made to take place when dimethyl-phenylmalonate was employed under the same conditions. This may have been due to the diminished ether solubility and different results might be obtained with diethyl phenylmalonate. The dimethyl ester was employed for the reasons given by Rising and Stieglitz,[5] these being its greater ease of condensation with urea, and the advantage of working with a solid rather than the liquid diethyl ester.

An attempt was made to prepare dimethyl phenyl-vinyl-malonate through the ketone (I) but the reduction did not proceed in the desired manner. The only product isolated beside unchanged acetyl derivative was dimethyl phenylmalonate. It is prepared in nearly calculated yield by the action of acetyl chloride on dimethyl sodio-phenylmalonate in alcohol-free ether.



I



II

[1] An abstract of a thesis submitted by Vandeveer Voorhees to the Graduate School of the University of Wisconsin in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1924.

[2] Carnot and Tiffeneau, *Compt. rend.*, **175**, 241 (1922).

[3] Wiki, *Archiv. Inter. Pharmacodynamie*, **27**, 117 (1923).

[4] Dox and Yoder, THIS JOURNAL, **45**, 1757 (1923).

[5] Rising and Stieglitz, *ibid.*, **40**, 723 (1918).

The ethylation of phenylbarbituric acid by the action of ethyl bromide on the sodium salt[6] in alcohol or aqueous solution and the action of ethyl iodide on the silver salt[7] were unsuccessful. No attempt, therefore, was made to introduce the chloro-ethyl group by the use of ethylene chloro-iodide.

Bromination of the sodium salt of phenylbarbituric acid in aqueous solution gave a monobromo derivative. The action of ethylmagnesium bromide upon this derivative results only in the recovery of phenylbarbituric acid. The melting point of phenylbarbituric acid after crystallization from hot water was found to be 263° (corr.) instead of 250° as reported in Bayer's patent.[6]

The conversion of dimethyl ethyl-chloroethyl-malonate to dimethyl ethyl-vinyl-malonate which was attempted by refluxing with freshly powdered calcium oxide in xylene and with sodium ethylate in ether resulted in the recovery of the unchanged ester. Heating in sealed tubes in ether solution with sodium ethylate resulted in the breakdown to low-boiling esters.

By heating the diethyl ethyl-chloroethyl-malonate with dimethylamine in absolute ether in a sealed tube the diethyl β-dimethylaminoethyl-ethyl-malonate (II), was obtained. Upon condensation with urea this compound gave a good yield of the corresponding barbituric acid and this was subjected to exhaustive methylation. When heated under diminished pressure at 220° the quaternary base decomposed yielding an amorphous substance which was partially soluble in alkali and which was reprecipitated by acid. Investigation of this substance has not been completed for lack of time and materials.

The dimethylamino and diethylamino derivatives exhibited no hypnotic properties when injected intraperitoneally in mice according to the method indicated by Dox and Yoder.[8]

Experimental Part

Diethyl β-Chloroethyl-ethyl-malonate.—Twenty g. of powdered sodium was covered with 800 cc. of dry ether and the mixture was cooled while 150 g. of diethyl ethyl-malonate was added gradually through a condenser. Then 180 g. of ethylene chloro-iodide was added and the condenser was closed by a calcium chloride tube to prevent the entrance of moisture. Gentle refluxing was maintained for four days by means of an electric hot-plate; during this time the mixture assumed a brown color with the separation of salt. The ether solution was decanted and distilled, first, to remove most of the ether, and then under diminished pressure. On redistillation through an efficient column a fraction was obtained at 131–133° (9 mm.) weighing 92 g. Without further purification, this oil was analyzed for chlorine by the Carius method.

Anal. Calcd. for $C_{11}H_{19}O_4Cl$: Cl, 14.2. Found: 13.4, 13.6.

[6] Bayer, Ger. pat. 247,952 (1912).

[7] Conrad and Guthzeit, *Ber.*, **13,** 1643 (1881); **15,** 2849 (1882).

[8] Dox and Yoder, THIS JOURNAL, **45,** 1815 (1923).

Diethyl β-Dimethylaminoethyl-ethyl-malonate.—Thirty g. of diethyl β-chloroethyl-ethyl-malonate was heated in a sealed tube at 100° with 16.2 g. of dimethylamine in 100 cc. of ether dried over sodium. After 19 hours, a sample was removed and amine formation was found to be about 25% of that calculated. The heating was continued for a total of 81 hours. Water was added and the solution acidified with hydrochloric acid. The unchanged chloro ester was extracted with ether and weighed 17 g. The amine was then liberated with sodium hydroxide and distilled under diminished pressure. Ten g. of the colorless oil was obtained, boiling at 135–136° (10 mm.).

Diethyl β-Diethylaminoethyl-ethyl-malonate.—From 25 g. of diethyl β-chloroethyl-ethyl-malonate and 25 g. of diethylamine at 100° for 24 hours there was obtained 20 g. of unchanged ester and 3.2 g. of diethylamino compound boiling at 145–152° (12 mm.).

5-β-Dimethylaminoethyl-5-ethylbarbituric Acid.—To a solution of 2.66 g. of sodium (3 atomic equivalents) in 100 cc. of absolute alcohol in a bomb tube, 4.6 g. of powdered urea (2 molecular equivalents) was added, and then 10 g. (1 equivalent) of the dimethylamino compound above described. After the mixture had been heated at 100° for eight hours the bomb contained a precipitate of carbonate. The alcohol was distilled under diminished pressure. The residue was dissolved in water and the solution acidified with hydrochloric acid. The residue of the amine hydrochloride and salt left upon evaporation to dryness was extracted with hot alcohol, from which the hydrochloride of the aminobarbituric acid crystallized as the solution cooled; yield of dry product, 8.5 g. It is a white, crystalline powder extremely soluble in water but nonhygroscopic. It melts at 246–247° in a sealed tube and possesses a bitter-sweet taste. Analysis for chlorine was effected by precipitation with silver nitrate solution.

Anal. Calcd. for $C_{10}H_{18}O_3N_3Cl$: Cl, 13.45. Found: 13.35.

The free base was prepared from the hydrochloride by shaking with the calculated amount of freshly prepared silver oxide. From 8.5 g. of the hydrochloride, 5.7 g. of the base was obtained. It crystallizes well from absolute alcohol; m. p., 171°.

5-β-Diethylaminoethyl-ethylbarbituric Acid Hydrochloride.—This compound was prepared by the procedure described above, using 0.76 g. of sodium (3 atomic equivalents), 50 cc. of absolute alcohol, 1.33 g. of urea (2 molecular equivalents) and 3.2 g. of diethyl diethylaminoethyl-ethyl-malonate. It was obtained as a white powder by crystallization from alcohol; m. p., 258–260° (sealed tube); yield, 1.7 g. Analysis for chlorine was effected by precipitation with silver nitrate solution.

Anal. Calcd. for $C_{12}H_{22}O_3N_3Cl$: Cl, 12.20. Found: 12.30.

Dimethyl Phenyl-acetyl-malonate.—Six g. (1.3 atomic equivalent) of powdered sodium was covered with 150 cc. of dry ether and to this was gradually added 40 g. (1 molecular equivalent) of dimethyl phenyl-malonate. After standing for two days protected from moisture, and being shaken occasionally, the product was treated with 20 g. of acetyl chloride (1.3 equivalent). A vigorous reaction took place, after which the mixture was allowed to stand for some time and occasionally shaken with water. The ether layer was separated and dried over sodium sulfate. By distillation there were obtained 3 g. of unchanged ester and 40 g. of acetyl derivative; the latter distilled at 168–175° (13 mm.). The product crystallized in plates melting at 69°.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.40; H, 5.60. Found: C, 62.16; H, 5.61.

The compound is quite stable toward acid and may be recovered unchanged after heating with concd. hydrochloric acid. Toward alkali, however, it is very sensitive, sodium carbonate solution being sufficient to remove the acetyl group with regeneration of dimethyl phenyl-malonate. Dimethyl phenylmalonate may be prepared in this way in a very high state of purity.

The acetyl derivative was dissolved in alcohol to which water was added until precipitation became imminent. The solution was then warmed and phenylhydrazine hydrochloride solution was added. After several hours the test-tube was filled with a mush of fine needles that were separated and recrystallized from alcohol; m. p., 126–127°. Kept in a stoppered tube, the phenylhydrazone decomposed after several months.

Anal. Calcd. for $C_{19}H_{20}O_4N_2$: C, 67.1; H, 5.88; N, 8.24. Found: C, 66.6; H, 5.83; N, 8.43.

Phenyl-bromobarbituric Acid.—Three g. of phenylbarbituric acid was dissolved in just enough sodium hydroxide solution to give a clear solution of about 25 cc. Saturated bromine water was then added while the mixture was stirred until a marked yellow color persisted. After a few minutes the bromo derivative rapidly separated as a coarsely crystalline substance. This when dried dissolved completely in warm alcohol (20 cc.), the unbrominated acid being almost insoluble in alcohol. On diluting this solution with about two volumes of water the bromo derivative separated as a white, crystalline solid; yield, 2.7 g. The substance melts at 214°, after which a slow decomposition takes place.

An alcoholic solution of the bromo derivative was acidified with hydrochloric acid and the mixture shaken a short time with zinc dust. A substance separated which was dissolved by diluting and boiling; it was filtered hot, crystallized on cooling, and was identified as phenylbarbituric acid.

Anal. Calcd. for $C_{10}H_7O_3N_2Br$: Br, 28.3. Found: Br, 28.2.

Ethylene Iodide.—Five hundred g. of iodine was placed in a quart bottle attached to a motor-driven shaking device. About 500 cc. of water was added and then 130 g. of chlorine (calcd. for ICl: 138 g.) was passed in. After the mixture had cooled somewhat, ethylene was admitted from a cylinder under slight pressure, the bottle being vigorously shaken at the same time. Rapid absorption took place and the temperature rose to about 50°. After three to four hours the rate of absorption fell off rapidly. The pressure was increased to 50 mm. of mercury and the shaking continued for two hours longer when absorption had practically ceased. After the mixture had stood overnight, 4 g. of sodium bisulfite was added to discharge the brown color of iodine. The crystals of ethylene iodide were filtered off with suction and washed with a little alcohol; yield, 220 g. The filtrate was distilled through a fractionating column, the pressure being controlled so as to not heat the material above 60–70°. The yield of ethylene chloride was 44 g. and that of ethylene chloro-iodide 190 g. By recrystallization of the residue from benzene enough ethylene iodide was obtained to increase the yield to 300 g. Ethylene iodide is best kept in a dark place in an atmosphere of ethylene.

Summary

1. A method is described for the synthesis of β-amino-alkyl derivatives of barbituric acid.

2. A method is described for preparing ethylene iodide rapidly and in quantity.

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