Preparation of the Hydrochlorides.—The amines were dissolved in anhydrous ethyl ether and dry hydrogen chloride was passed through the solution. White crystals precipitated; these were filtered off and washed with ether. They were recrystallized by dissolving in the least amount of absolute alcohol possible and precipitating with anhydrous ether. They are white crystalline compounds. Analyses are recorded in Table I.

Preparation of the Chloroplatinates.—The amines were dissolved in small amounts of concd. hydrochloric acid and the theoretical amount of chloroplatinic acid added. Upon stirring and scratching the glass dish, the chloroplatinates crystallized out. The chloroplatinate of the di-α-furfuryl amine crystallized in red crystals, while that of the tri-α-furfuryl amine formed orange crystals. Analyses are recorded in Table I.

Preparation of the Chloro-aurate.—The method is the same as for the chloroplatinates. Both chloro-aurates are yellow, crystalline solids.

Summary

1. The mono-, di- and tri-α-furfuryl amines have been prepared in a pure condition and their properties, as well as those of some of their salts, are reported.

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NEW DERIVATIVES OF BARBITURIC ACID

BY ARTHUR W. DOX AND EDWARD G. JONES

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Although more than sixty 5,5-dialkyl and 5,5-arylalkyl derivatives of barbituric acid, exclusive of homologs with further substitution on the nitrogen or substitution of oxygen or halogen in one or both of the alkyls, have been described, their variations in hypnotic potency and type of action are sufficient to warrant the preparation of additional members of the series as new alkyl halides become available. Among the alcohols which until very recently have not been obtainable for the preparation of halides required for such syntheses are tetrahydrofurancarbinol and *n*-amyl alcohol. The present paper describes the preparation of certain 5,5-disubstituted barbituric acids containing a tetrahydrofuranmethyl or a *n*-amyl group.

Tetrahydrofuranmethyl Bromide.—The alcohol used was a pure preparation supplied by the Miner Laboratories of Chicago. Although this alcohol, in contrast to the non-hydrogenated furancarbinol, is quite stable under ordinary conditions of light, air and moisture, it was found to be unstable to mineral acids, in the presence of which it showed a strong tendency to form tarry products. For this reason the yields of bromide obtained by treatment with hydrobromic acid, with or without sulfuric acid, or with phosphorus tribromide were small. The best yield of bromide thus far obtained was only 25%. It is not improbable that the yield might be much improved by suitable modifications of the usual methods of preparing alkyl bromides. The product was

a colorless liquid with the odor characteristic of alkyl bromides and a boiling point of 168–170° at 744 mm.

Anal. (Carius). Subs. 0.2561: AgBr, 0.2943. Calcd. for C_5H_9OBr: Br, 48.48. Found: 48.90.

Ethyl Ethyltetrahydrofuranmethylmalonate.—The ordinary malonic ester synthesis was performed, using molecular proportions of the bromide just described, ethyl ethylmalonate and sodium ethoxide in absolute alcohol. The product was a colorless, oily liquid with faint, fruity odor and boiled at 155–157° at 12 mm.

Anal. Subs., 0.1777: CO_2, 0.4104; H_2O, 0.1426. Calcd. for $C_{14}H_{24}O_5$: C, 61.76; H, 8.82. Found: C, 62.98; H, 8.98.

Ethyltetrahydrofuranmethylbarbituric Acid.—The well-known Fischer and Dilthey synthesis, whereby the ester is condensed with urea in the presence of sodium ethoxide in absolute alcohol under pressure, gave a 75% yield of the disubstituted barbituric acid, which after recrystallization from dilute alcohol melted at 190°. The melting point is very close to that of barbital (191°) but a mixed melting point of the two substances showed a depression of 41°. The substance is rather more soluble in water than barbital and crystallizes in flat needles of much the same appearance.

Anal. (Kjeldahl). Subs., 0.1765: cc. of 0.1 *N* acid, 14.92. Calcd. for $C_{11}H_{16}O_4N_2$: N, 11.67. Found: 11.80.

Ethyl *n*-Amylmalonate.—The *n*-amyl bromide required for this synthesis has already been described in the literature. We prepared it from *n*-amyl alcohol supplied by the Sharples Solvents Corporation, using the hydrobromic–sulfuric acid method and collecting the fraction boiling at 127–131°. The malonic ester synthesis was performed in the usual way. Disregarding intermediate fractions which were not subjected to further fractionation, we obtained a yield of 62% of ethyl *n*-amylmalonate boiling at 134–136° at 14 mm. The ester is a colorless, oily liquid with a faint, fruity odor.

Anal. Subs., 0.2115: CO_2, 0.4812; H_2O, 0.1822. Calcd. for $C_{12}H_{22}O_4$: C, 62.6; H, 9.5. Found: C, 62.05; H, 9.64.

***n*-Amylmalonamide.**—Like most mono-alkylated malonic esters where the alkyl is primary, the above ester forms an amide when shaken for several days with an excess of concentrated aqueous ammonia. The amide crystallizes from dilute alcohol in very small needles which mat together on the filter into a felt. It is practically insoluble in water and in ether, readily soluble in alcohol and melts at 206°.

Anal. (Kjeldahl). Subs., 0.1799: cc. of 0.1 *N* acid, 20.70. Calcd. for $C_8H_{16}O_2N_2$: N, 16.28. Found: 16.11.

***n*-Amylchloromalonamide.**—This derivative was of particular interest to the writers because it represents the missing member in an homologous series on which some interesting observations had been made on sweet and bitter taste.[1] *n*-Amylmalonamide was dissolved in glacial acetic acid and a slow current of chlorine passed in until the solvent had taken on a yellow color. The solvent was then removed by distillation under diminished pressure and the residue treated with water. The white crystals which separated were then washed with water and recrystallized from dilute alcohol. The product resembles in appearance the non-chlorinated amide, but melts at 134–135° and has an intensely sweet taste. A 0.005% aqueous solution showed the same degree of sweetness as a 2% sucrose solution.

Anal. (Carius). Subs., 0.1841: AgCl, 0.1286. (Kjeldahl.) Subs., 0.1793, 0.1949: cc. of 0.1 *N* acid, 17.21, 18.81. Calcd. for $C_8H_{15}O_2N_2Cl$: Cl, 17.19; N, 13.56. Found: Cl, 17.27; N, 13.44, 13.51.

[1] Dox and Houston, THIS JOURNAL, **46**, 1278 (1924).

In one preparation in which chlorine was passed in for several hours the product melted at 106° and contained 22.25% of chlorine. Evidently a partial chlorination of the α-carbon of the amyl group had also occurred. The product had, however, approximately the same degree of sweetness as the pure substance on which the correct analysis was obtained.

n-Amylbarbituric Acid.—This was prepared by condensation of ethyl *n*-amylmalonate with urea in the presence of sodium ethoxide. After recrystallization from dilute alcohol it was obtained in flat, needle-shaped crystals melting at 215°.

Anal. Subs., 0.2027, 0.2086: cc. of 0.1 *N* acid, 20.52, 21.05. Calcd. for $C_9H_{14}O_3N_2$: N, 14.19. Found: 14.17, 14.13.

Ethyl Di-*n*-Amylmalonate.—From the higher boiling residue remaining from the preparation of ethyl *n*-amylmalonate described above, a small amount of a fraction boiling at 158–161° at 11 mm. was collected. This was a fairly pure di-amyl derivative as shown by analysis and by the preparation of the corresponding barbituric acid described below.

Anal. Subs., 0.2423: CO_2, 0.5948; H_2O, 0.2277. Calcd. for $C_{17}H_{32}O_4$: C, 68.00; H, 10.67. Found: C, 66.95; H, 10.51.

Di-*n*-Amylbarbituric Acid.—The usual method of condensing the ester with urea was employed. The free acid separated first as an oil which gradually solidified. After several recrystallizations from dilute alcohol it showed a constant melting point of 118°.

Anal. (Dumas). Subs., 0.1529: N_2, 15.5 cc. at 27° and 740 mm. Calcd. for $C_{24}H_{24}O_3N_2$: N, 10.47. Found: 10.89.

Ethyl *n*-Amylethylmalonate.—This was prepared from ethyl ethylmalonate, *n*-amyl bromide and sodium ethoxide in absolute alcohol. Without attempting to work up intermediate fractions, the yield of pure product was 56%. The ester boils at 139–141° at 14 mm.

Anal. Subs., 0.2080: CO_2, 0.4922; H_2O, 0.1874. Calcd. for $C_{14}H_{26}O_4$: C, 65.12; H, 10.08. Found: C, 64.54; H, 10.08.

***n*-Amylethylbarbituric Acid.**—This acid was obtained in 93% yield by condensation of the above ester with urea by means of sodium ethoxide in absolute alcohol under pressure. The sodium salt is soluble in alcohol, and when the solution is acidified the free acid separates first as an oil which gradually solidifies to well defined crystals. After recrystallization from dilute alcohol the melting point was 135°.

Anal. (Dumas). Subs., 0.2174: 23.6 cc. of N_2 at 24° and 751 mm. Calcd. for $C_{11}H_{18}O_3N_2$: N, 12.39. Found: 12.03.

The three disubstituted barbituric acids described above were subjected to preliminary tests for hypnotic action by administering the sodium salts intraperitoneally to white mice. The di-*n*-amyl derivative was found to be practically inert, the ethyltetrahydrofuranmethyl derivative showed some hypnotic action when given in sufficiently large doses, whereas the *n*-amylethyl derivative appeared to be a very effective hypnotic with a potency several times that of barbital. The *n*-amylethyl derivative now completes the series of homologous 5,5-ethyl-*n*-alkylbarbituric acids in which the *n*-alkyl is methyl to *n*-heptyl, inclusive. The physiological tests were performed by Dr. A. M. Hjort of the Dartmouth Medical School, who will report more in detail elsewhere.

Summary

New 5,5-disubstituted barbituric acids described in this paper are the ethyl-*n*-amyl, the di-*n*-amyl and the ethyltetrahydrofuranmethyl derivatives. The first of these is an effective hypnotic with several times the potency of barbital. *n*-Amylchloromalonamide, prepared from one of the intermediates, is remarkable for its intensely sweet taste, which is estimated to be about 400 times as powerful as that of ordinary sugar.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

THE ACTION OF BROMINE ON BETA-PHENYL BENZALACETOPHENONE

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For reasons that need not be specially considered here, it became desirable to secure an unsaturated ketone which has bromine in the α-position and which is too highly substituted to combine readily with other substances. It was decided, therefore, to study anew the action of bromine on β-phenyl benzalacetophenone.

Dilthey and Last[1] seem to be the first to try the action of bromine on this particular ketone and surprisingly enough they stated that no addition took place. The action of chlorine gave them a substance which they thought was a condensation product between the dichloride of phenyl benzalacetophenone and the unchanged ketone. This substance was not analyzed and was not investigated further.

Vorländer, Osterburg and Meye,[2] studying the action of bromine on this same ketone (obtained by the same method employed by Dilthey and Last), observed an evolution of hydrogen bromide and after repeated crystallizations from alcohol obtained a product which when slowly heated melted at 121° and when heated rapidly melted at 165°. This product gave them a percentage of bromine corresponding to α-bromo-β-phenyl benzalacetophenone. An attempt to remove the bromine atom by potassium hydroxide solutions failed and the substance was not further investigated.

Moureau, Dufraisse and Mackall,[3] who had obtained β-phenyl benzalacetophenone by isomerization of triphenylethinyl carbinol, studied the action of bromine on that ketone in their endeavor to identify it.

They found that, upon exposure to light, the chloroform solution of the ketone gave with bromine a colorless compound which melted at 130–

[1] Dilthey and Last, *J. prakt. Chem.*, **94**, 50 (1916).

[2] Vorländer, Osterburg and Meye, *Ber.*, **56**, 1136 (1923).

[3] Moureau, Dufraisse and Mackall, *Bull. soc. chim.*, (4) **33**, 937 (1923).