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THE PREPARATION OF ETHYL PHENYLMALONATE AND OF 5-PHENYL-BETA-HYDROXYETHYLBARBITURIC ACID[1]

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In continuation of the study of the effect of the introduction of a hydroxyl group on the toxicity and therapeutic action of medicinal substances, which has been under way for some time in this Laboratory,[2] it was desired to prepare a number of barbituric acids substituted in the 5-position with phenyl and hydroxyalkyl groups.

In spite of the valuable hypnotic properties of 5-ethylphenylbarbituric acid ("Luminal") but few aryl substituted barbituric acids have been prepared. This is probably largely due to the fact that barbituric acids of this type are difficult to synthesize.

The method which has been generally applied to the synthesis of 5-phenylbarbituric acids has been as follows. Esters of phenylacetic acid have been condensed with esters of oxalic acid to produce an ester of phenyloxalylacetic acid and the latter compound decomposed by heat with loss of carbon monoxide and formation of an ester of phenylmalonic acid.[3] The latter compounds, on condensation with urea, give the desired product.

For the synthesis of Luminal a further method of preparation of the intermediate methyl ethylphenylmalonate has recently been described by Rising and Zee.[4] The procedure recommended involves the following steps: ethylation of phenylacetonitrile; condensation of the sodium salt of phenylbutyronitrile with methyl chloroformate to form methyl ethylphenylcyano-acetate; treatment of the latter substance with a methyl alcohol solution of hydrogen chloride to form the desired ester.

Inasmuch as it is our purpose to prepare a number of derivatives of phenylbarbituric acid, it appeared to us highly desirable to have a method as satisfactory as possible for the preparation of ethyl phenylmalonate, an intermediate useful for the preparation of all of them. For this reason considerable time was devoted to a study of the synthesis of this compound.

[1] This investigation was conducted in coöperation with the National Research Council Sub-Committee on Hypnotics, 1926.

[2] (a) Cretcher and Pittenger, THIS JOURNAL, **46**, 1504 (1924); (b) **47**, 2560 (1925); (c) Cretcher, Koch and Pittenger, *ibid.*, **47**, 3083 (1925).

[3] (a) W. Wislicenus, *Ber.*, **27**, 1091 (1894); (b) Rising and Stieglitz, THIS JOURNAL, **40**, 723 (1918).

[4] Rising and Zee, THIS JOURNAL, **49**, 541 (1927). Another paper by these authors has just appeared [THIS JOURNAL, **50**, 1208 (1928)] wherein they describe an improvement of their method which produces an over-all yield of 43.1% of methyl ethylphenylmalonate from phenylacetonitrile.

It was first attempted to prepare ethyl phenylmalonate by condensation of ethyl phenylacetate with ethyl carbonate. The directness of the method is the important advantage which this process would have over that in common use. The condensation was attempted, under varying conditions, in alcohol, ether and benzene, and with both sodium and sodamide. Condensation was effected only with sodium and only in ether and benzene. At best (in benzene) it was not possible to obtain a yield greater than 20%, due to the condensation of ethyl phenylacetate with itself. This is in accord with the observations of Volhard[5] and of Scheibler and Mahboub.[6]

Our attention was then directed to phenylacetonitrile as a suitable intermediate for our purpose. The sodium salt, prepared with sodium in ether, was condensed with ethyl chloroformate. The yield of ethyl phenylcyano-acetate was only 50%.

We next studied the condensation of phenylacetonitrile with ethyl carbonate. The method of Hessler[7]—sodium as condensing agent, in ether—was repeated with results closely checking those of Hessler, who obtained a yield of 55% of ethyl phenylcyano-acetate. Sodium ethylate in alcohol gave 55% and sodamide in benzene gave 30%. By far the best results were obtained with sodamide in ether, according to the method of Bodroux[8] for the condensation of benzyl cyanide with esters. For maximum yield (70%) it is necessary to follow closely the conditions given in the Experimental Part of this paper.

Inasmuch as phenylmalonic esters are not alkylated in good yield, it was thought that it might be an advantage to alkylate phenylacetonitrile before attempting the condensation to introduce the second carboxyl group. In no case, however, did we succeed in condensing a substituted benzyl cyanide with ethyl carbonate.

The conversion of phenylcyano-acetate to ethyl phenylmalonate was effected most advantageously with hydrogen chloride and alcohol according to the method of Wislicenus.[9] It is essential that the alcoholic solution of the nitrile be thoroughly saturated with hydrogen chloride, as analysis showed in one case where saturation was not complete, a nitrogen content indicating 10% of unchanged nitrile, which is practically impossible to separate from the ester owing to the fact that their boiling points are only about three degrees apart.

The ethylation of ethyl phenylmalonate was accomplished most advantageously in alcohol solution with ethyl iodide or bromide or by heating the dry sodium salt of the ester with ethyl bromide in a sealed tube at

[5] Volhard, *Ann.*, **296**, 1 (1897).

[6] Scheibler and Mahboub, *Ber.*, **60**, 564 (1927).

[7] Hessler, *Am. Chem. J.*, **32**, 119 (1904).

[8] Bodroux, *Compt. rend.*, **151**, 234, 1358 (1910).

[9] Wislicenus, *Ann.*, **296**, 361 (1896).

110° without a solvent. Ethylation in alcoholic solution is attended by decomposition of the ethyl phenylmalonate and production of ethyl phenylacetate.[10] It was observed that in case an excess of sodium is used decomposition may be practically complete.

Since our primary interest was not in the discovery of an improved process for making Luminal, we have not occupied ourselves to any extent with the preparation of this substance. A few experiments were conducted on condensing ethyl phenylethylmalonate with urea. The yields averaged between 30–40% and were of the same order as reported by Rising and Stieglitz from the condensation of the methyl ester with urea.[3b]

For the preparation of 5-β-hydroxyethylphenylbarbituric acid according to the method devised in this Laboratory for preparing β-hydroxyethyl compounds,[2c,11] it was necessary to prepare ethyl phenyl-β-vinyloxyethylmalonate as an intermediate. Its synthesis from ethyl phenylmalonate and β-chloro-ethylvinyl ether offered some difficulty in contrast to the ease with which ethyl vinyloxyethylmalonate is prepared from ethyl malonate.[12]

Attempts to condense the sodium salt of the ester with the chloro compound in alcohol, ether, benzene, toluene and xylene were unsuccessful. It was only upon heating the components in a sealed tube in absence of a solvent that we were able to obtain the desired product in appreciable amount.

Experimental Part

Ethyl Phenylcyano-acetate.—Three hundred grams of anhydrous ether and 42 g. of pulverized sodamide were placed in a dry two-liter three-necked, round-bottomed flask. A mercury sealed stirrer passed through the middle neck and a dropping funnel and tall reflux condenser were fitted to the side necks. During constant stirring, 117 g. of freshly distilled phenylacetonitrile was added drop by drop. A vigorous reaction ensued with evolution of ammonia. After all of the nitrile had been added, the reaction mixture was boiled in a water-bath for one-half hour. After cooling to room temperature, 150 g. of freshly distilled ethyl carbonate was added drop by drop. Replacement of the ether lost by evaporation is frequently necessary. After all of the carbonate had been added, the flask was warmed another half hour; then it was cooled in an ice-bath and treated with dilute hydrochloric acid until the aqueous layer was acid to litmus. The product was filtered and the ethereal layer separated and dried over calcium chloride.

After removal of the ether and fractionally distilling *in vacuo*, 133 g. of the desired ester was obtained, boiling (7 mm.) at 140–148° (nearly all at 145°). This is a yield of 70.3%.

A portion was further purified by redistillation. It was a colorless liquid and boiled at 165° at 19 mm.; $d_4^{20} = 1.091$.

Ethyl Phenylmalonate.—A rapid stream of dry hydrogen chloride was passed into a solution of 45 g. of ethyl phenylcyano-acetate, 65 g. of 95% alcohol and 2 g. of water. The flask was connected with a condenser and the hydrogen chloride added to saturation

[10] Wislicenus, *Ber.*, **28**, 815 (1895).

[11] Cretcher, Koch and Pittenger, THIS JOURNAL, **47**, 1173 (1925).

[12] Ref. 11, p. 1176.

of the hot solution. The reaction mixture was then cooled in an ice-bath and the cold solution saturated with hydrogen chloride. The flask was allowed to stand overnight at room temperature and on the following morning was heated one hour on a steam-bath. After cooling, sufficient water was added to dissolve the precipitated ammonium chloride; the ester was extracted with ether, washed with water and dried over calcium chloride. After removal of the ether the residual liquid was distilled. A yield of 44 g. (78.3%) of ethyl phenylmalonate was obtained at 163–166° at a pressure of 18 mm.

A portion was further purified. It was a colorless liquid and boiled at 168° (19 mm.); $d_4^{20} = 1.095$. Wislicenus[13] reported the boiling point to be 170–172° at 14 mm. He did not determine the density.

Ethyl Phenylethylmalonate.—This ester was produced most satisfactorily by the reaction of ethyl iodide or bromide with the sodium salt of ethyl phenylmalonate in boiling absolute alcohol. With ethyl iodide the yield was 61.1%. This ester boils at 170° (19 mm.); $d_4^{20} = 1.071$. The boiling point given in U. S. Patent 1,036,624 is 166° at 12 mm.

5-Phenylethylbarbituric Acid (Luminal).—Luminal was prepared as follows: 0.69 g. of sodium was dissolved in 11 g. of absolute alcohol in a glass tube and 0.9 g. of powdered urea added to the solution; 2.64 g. of ethyl phenylethylmalonate was then added. The tube was sealed and heated in an oil-bath at 115° for three hours. The tube was then cooled, opened and the contents filtered. Alcohol was removed from the filtrate by distillation *in vacuo*. The residue was dissolved in water and the unaltered ester removed by extraction with ether. The aqueous layer was acidified with a slight excess of dilute hydrochloric acid. A pure white crystalline substance was precipitated. After filtering and drying, the crude product melted at 171°. Upon recrystallization from water the melting point was 173–174°. The yield was 35% of the theoretical.

Ethyl Phenylvinyloxyethylmalonate.—After many unsuccessful attempts to prepare this ester in good yield, the following procedure was adopted: 2.3 g. of sodium was pulverized in boiling xylene. The containing tube was cooled, the xylene decanted and the sodium washed quickly with several portions of anhydrous ether. Forty g. of dry ether was added and then 23.6 g. of ethyl phenylmalonate in small portions. There was a very vigorous reaction. A calcium chloride tube was attached to the condenser and the reaction mixture allowed to stand overnight. The ether was then removed by boiling, finally under vacuum. Thirty g. of β-chloro-ethylvinyl ether was added, the tube sealed and heated at 140–145° for fourteen hours. After cooling the tube was opened, water added to dissolve the salt and the ester extracted with ether. After removal of the ether, 15.5 g. of product was obtained, boiling mostly at 189–190° at 10 mm. This is a yield of 52%.

The compound was further purified by redistillation for analytical purposes. Ethyl phenylvinyloxyethylmalonate boils at 196–197°, 17 mm. $d_4^{20} = 1.098$. It decomposes on standing in sunlight, the odor of acetaldehyde being quite strong after several weeks.

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 66.63; H, 7.24. Found: C, 66.43; H, 7.42.

5-(Phenyl-β-hydroxyethyl)-barbituric Acid (Hydroxy-Luminal).—The condensation of ethyl phenylvinyloxyethylmalonate and urea to form 5-phenylvinyloxyethylbarbituric acid was accomplished under exactly the conditions described for the preparation of Luminal. The vinyloxy compound was not isolated in pure form but converted directly into the hydroxy-Luminal by hydrolysis with acid.[2c] For purification the substance was crystallized from water. The yield of pure hydroxy-Luminal, melting at 200°, was only about 10% of the theoretical.

[13] Wislicenus, *Ber.*, **27**, 1093 (1894).

Anal. Calcd. for $C_{12}H_{12}O_4N_2$: N, 11.30. Found: N, 11.21.

5-(Phenyl-β-hydroxyethyl)-2-thiobarbituric Acid.—This compound was prepared by condensation of ethyl phenylvinyloxyethylmalonate with thiourea. The procedure was the same as that given directly above, m. p. 167°. The yield was 15%.

Anal. Calcd. for $C_{12}H_{12}O_3N_2S$: N, 10.6. Found: N, 10.9.

Phenylvinyloxyethylacetonitrile $C_6H_5CH(CH_2CH_2OCH{=}CH_2)CN$.—This nitrile was prepared by reaction of phenylacetonitrile and β-chloro-ethylvinyl ether, according to the general method devised by Bodroux and Taboury.[14] The yield was 50%. The pure compound boils at 147° (8 mm.); $d_4^{20} = 1.029$.

Anal. Calcd. for $C_{12}H_{13}ON$: N, 7.48. Found: N, 7.33.

Summary

1. A convenient method for the preparation of ethyl phenylmalonate has been described.

2. A new barbituric acid closely related to Luminal, 5-phenyl-β-hydroxyethyl-2,4,6-trioxypyrimidine, has been synthesized.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE REACTION BETWEEN THE BINARY SYSTEM, MAGNESIUM + MAGNESIUM IODIDE, AND AROMATIC ACIDS AND ACID DERIVATIVES

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The interaction of magnesium + magnesium iodide and aromatic ketones results in addition of MgI to the C=O group.[1] A similar reaction occurs with 1,2-diketones,[2] with thio-ketones[3] and apparently with quinones.[4] The MgI, the probable formation of which has been postulated, may thus be regarded as functioning like a monovalent element, as sodium. This comparison holds in reactions that are to be discussed in this communication on acids and in communications to follow, on various classes of compounds containing double and triple bonds.

Reaction of Acids with Magnesium + Magnesium Iodide.—This reaction takes place in two steps: (*a*) displacement of the acid hydrogen by MgI and (*b*) reduction of the resulting salt.

The displacement of hydrogen is best explained by the fact that there is an equilibrium reaction between MgI_2 and the organic acid. Only a small amount of HI results by virtue of this reaction; nevertheless, in the

[14] Bodroux and Taboury, *Bull. soc. chim.*, [7] **4**, 666 (1910).

[1] Gomberg and Bachmann, THIS JOURNAL, **49**, 236 (1927).

[2] Gomberg and Bachmann, *ibid.*, **49**, 2584 (1927).

[3] Schönberg and Schütz, *Ber.*, **60**, 2351 (1927).

[4] Fieser, THIS JOURNAL, **50**, 464 (1928).