[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

The Synthesis of 5-α-Naphthyl-5-ethylbarbituric Acid

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Two types of 5-5 disubstituted barbituric acids containing the naphthyl group are possible, (1) those in which the naphthyl group is attached directly to the 5 carbon atom and (2) those in which one or more CH_2 groups are between the 5 carbon atom and the naphthyl group. The writer has already synthesized a number of the second type[1] and this paper is concerned with one of the first type, 5-α-naphthyl-5-ethylbarbituric acid.

This particular one is of interest because of its similarity to 5-phenyl-5-ethylbarbituric acid (luminal), which is widely used as a sedative and hypnotic.

The barbituric acid was prepared by the condensation of the corresponding malonic ester derivative with urea in the usual manner. Attempts to accomplish this condensation under pressure were unsuccessful and the reaction was, therefore, carried out at atmospheric pressure and with long-continued heating on the steam-bath. α-Naphthylethylmalonic ester was prepared by the alkylation of α-naphthylmalonic ester. This alkylation also required long heating on the steam-bath. α-Naphthylmalonic ester was obtained by the condensation of the methyl ester of α-naphthylacetic acid with dimethyl oxalate in a way similar to that used by Stieglitz and Rising[2] for the preparation of phenylmalonic ester, according to the following

$$(COOCH_3)_2 + C_{10}H_7CH_2COOCH_3 + NaOCH_3 \longrightarrow 2CH_3OH + CH_3OOCC(ONa)C(C_{10}H_7)COOCH_3$$

$$CH_3OOCC(ONa)C(C_{10}H_7)COOCH_3 + H_2SO_4 \longrightarrow CH_3OOCC(OH)C(C_{10}H_7)COOCH_3 + NaHSO_4$$

$$CH_3OOCC(OH)C(C_{10}H_7)COOCH_3 \text{ distilled} \longrightarrow CO + CH(C_{10}H_7)(COOCH_3)_2$$

The success of this condensation, taken together with the satisfactory method of producing α-naphthylacetic acid[3] recently reported by the writer, indicates that this may be a method generally applicable for aryl substituted barbituric acids. The investigation is being continued with the purpose of settling the question of the generality of these reactions.

Experimental Part

Preparation of α-Naphthyl-dimethylmalonate.—Four g. of sodium cut into small pieces was introduced into a 500-cc. flask fitted with a reflux condenser and containing 80 g. of dry ether. To this was added 20 g. of dimethyl oxalate, 31.5 g. of the methyl ester of α-naphthylacetic acid, and ten drops of absolute methyl alcohol. The reaction was started by heating for a few minutes on the steam-bath. Bubbles of gas (hydrogen) escaped from the mixture and a reddish-brown solid formed on the surface of the

(1) THIS JOURNAL, **55**, 2975 (1933).
(2) Stieglitz and Rising, *ibid.*, **40**, 723 (1918).
(3) *Ibid.*, **55**, 2974 (1933).

sodium, the ether solution becoming also reddish-brown in color. The reaction was allowed to continue for seventy hours. Once during this time the solid was broken up to expose any unchanged sodium. The solid was then filtered by suction and washed twice with dry ether. This solid material was reddish-brown in color and very rapidly became sticky due either to decomposition or absorption of water from the air. Cold dilute sulfuric acid was, therefore, added to it at once, whereupon a yellow oil was formed which soon crystallized. This was extracted with ether, washed with water and dried over anhydrous calcium chloride. The ether was then removed and the product distilled under reduced pressure.

Distillation.—The distillation was carried out in a Claisen distilling flask at a pressure of 5–6 mm. The pressure remained constant until a temperature of 150° was reached, when there was evidence of the giving off of gas and the pressure in the flask and receiver increased to a considerable extent. The gas given off burned with a blue flame at the outlet of the pump, indicating that it was carbon monoxide. The material in the flask became much darker in color. In a few moments the decomposition was complete and the temperature again increased. When the temperature reached 160° the product began to distil and the fraction boiling from this temperature to 173° was collected. This amounted to 13.5 g., a yield of 33%. Very little residue remained in the Claisen flask. The ester was recrystallized from 50% alcohol and separated in colorless needles which melt at 104°.

Analysis corresponded with the values calculated for α-naphthyldimethylmalonate.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.47. Found: C, 69.58; H, 5.37.

Alkylation of α-Naphthyldimethylmalonate.—Twenty-five grams of α-naphthyldimethylmalonate was added to sodium methylate solution made by dissolving 2.3 g. of sodium in 50 g. of absolute methyl alcohol. On heating over the steam-bath the ester dissolved forming a brownish colored solution. Twenty grams of ethyl iodide was then added and the mixture heated on the steam-bath with reflux for sixty hours. The methyl alcohol was then distilled from the steam-bath and the product poured into cold water, made slightly acidic with sulfuric acid, extracted with ether and dried over anhydrous calcium chloride. After distillation of the ether the product was distilled under reduced pressure, 5–6 mm. Material started distilling at 137°, the temperature rising quite rapidly; 12.5 g. of product boiling from 168–175° which crystallized slowly was secured. This ester recrystallized from 50% alcohol separated in colorless needles, melting at 109–110°. One gram additional was secured by repeated recrystallization of the low boiling fraction secured in the distillation, making the yield 48.5%.

Analysis corresponded with the values calculated for α-naphthylethyldimethylmalonate.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.06; H, 6.52.

Preparation of 5-α-Naphthyl-5-ethylbarbituric Acid.—1.3 grams (two moles) of sodium was dissolved in 75 cc. of absolute alcohol in a small flask fitted with reflux condenser, and to this was added 2.5 g. (one and one-half moles) of urea and 7.8 g. (1 mole) of α-naphthylethyldimethylmalonate. The mixture was heated on the steam-bath for six and one-half days. The alcohol was then distilled from the steam-bath, a small amount of cold water added and the mixture made acid by acetic acid in excess. Some solid and some oil (probably unchanged ester) separated as a result of this treatment. It was extracted with ether and upon evaporation of the ether, both solid and oil appeared as a residue. The oil was dissolved in benzene in the cold, leaving an almost colorless solid, which was filtered by suction and recrystallized from hot water. It separated in prismatic crystals which melted at 254–255°; 2.5 g. was secured after one recrystallization, a yield of 32.5%. Analysis corresponded with the value calculated for 5-α-naphthyl-5-ethylbarbituric acid.

Anal. Calcd. for $C_{16}H_{14}O_3N_2$: N, 9.93. Found: N, 9.86, 9.89.

Pharmacological tests of this new barbituric acid were made on white rats. For this purpose two per cent. solutions of the sodium salt of the acid were injected intraperitoneally into the test animals, which were starved for twenty-four hours previous to the injections. For each dose three to five animals were used. The minimum hypnotic dose in mg. per kg. of rat was 300 mg. The minimum anesthetic dose was 400 mg. The minimum lethal dose was 450 mg., the therapeutic index of the compound being, therefore, 1.12. On the basis of these results this barbituric acid is not as satisfactory as phenylethylbarbituric acid.

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Summary

1. The methyl ester of α-naphthylacetic acid has been condensed with dimethyl oxalate to produce α-naphthyldimethylmalonate, and this ester alkylated to form α-naphthylethyldimethylmalonate.

2. α-Naphthylethyldimethylmalonate has been condensed with urea in sodium ethylate solution to form 5-α-naphthyl-5-ethylbarbituric acid.

3. Tests have shown that this new barbituric acid possesses hypnotic properties but is not as satisfactory as 5-phenyl-5-ethylbarbituric acid.

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Studies in the Phenanthrene Series. V. 9-Acetylphenanthrene. Reduction Products of 2-, 3- and 9-Acetylphenanthrenes[1]

BY ERICH MOSETTIG AND JACOB VAN DE KAMP

Willgerodt and Albert[2] obtained by the action of acetyl chloride on phenanthrene a compound to which they assigned the formula of 9-acetylphenanthrene, basing this structure on the carbon–hydrogen analysis, formation of a phenylhydrazone and an oxime, and the chromic acid oxidation to phenanthrene-9,10-quinone. In a repetition[3] of this Friedel–Crafts reaction under the experimental conditions of Willgerodt and Albert, we obtained a mixture of 2- and 3-acetylphenanthrenes. When nitrobenzene was used as a solvent instead of carbon disulfide, the difference was only quantitative, and the 2- and 3-isomers could be isolated in a ratio of about 1:4. In spite of a careful investigation of the reaction mixture another isomer could not be detected. Neither the 2- nor the 3-ketone

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(2) Willgerodt and Albert, *J. prakt. Chem.*, [2] **84**, 383 (1911).

(3) Mosettig and van de Kamp, THIS JOURNAL, **52**, 3704 (1930).