The Synthesis and Pharmacological Activity of 5-Ethyl-5-(3-hydroxy-1-methylbutyl)barbituric Acid[1]

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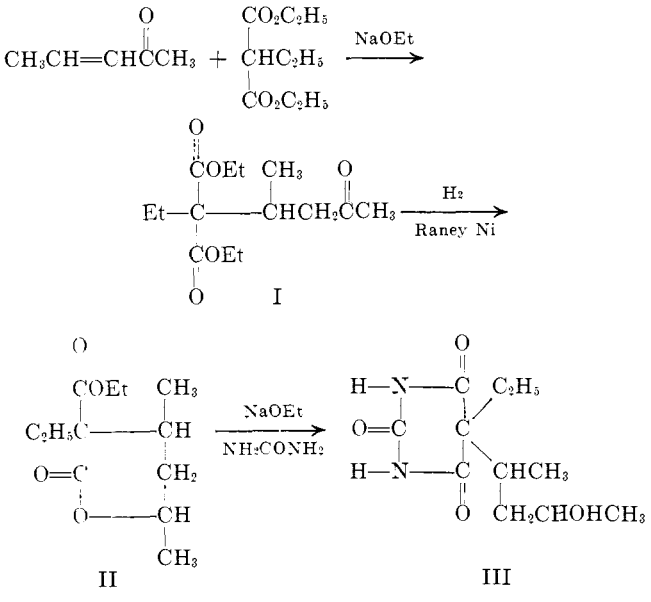
The anesthetic, pentobarbital, is excreted chiefly as 5-ethyl-5-(3-hydroxy-1-methylbutyl)barbituric acid[2a] (III). Studies using pentobarbital-2-C^{14} show that over 70% of the drug is hydroxylated.[2b] It has been stated that these metabolic products have no pharmacological activity.[3] With the synthesis (Scheme I) of adequate quantities of material, the pharmacological properties of III have been reinvestigated.

SCHEME I



Pharmacological Data.—Female, Swiss–Webster mice were treated with the test compounds suspended in 1% Methocel and administered orally by stomach tube. Two hours after drug administration, the animals were tested by the maximal electroshock method of Toman, Swinyard, and Goodman.[4] Diphenylhydantoin at a dose of 10 mg/kg was found to be more effective than III at a dose of 500 mg/kg in protecting against the tonic extensor component of convulsions.

By intraperitoneal administration of III as a 1% Methocel suspension, the ED_{38} in the maximal electroshock test was found to be 310 (252–381) mg/kg. No indication of anesthesia or ataxia was noted even in doses of 1 g/kg.

It is concluded from these experiments that III has a very weak anticonvulsant activity and no anesthetic properties. It is doubtful if any of the action of pentobarbital can be ascribed to accumulations of the metabolite.

(1) Inquiries should be sent to the E. C. Britton Research Laboratory.

(2) (a) E. W. Maynert and H. B. van Dyke, *J. Pharmacol. Exptl. Therap.*, **98**, 184 (1950); E. W. Maynert and J. M. Dawson, *J. Biol. Chem.*, **195**, 389 (1952); (b) E. Titus and H. Weiss, *ibid.*, **214**, 807 (1955).

(3) R. T. Williams, "Detoxification Mechanisms," John Wiley and Sons, Inc., New York, N. Y., 1959, p 600.

(4) J. E. P. Toman, E. A. Swinyard, and L. S. Goodman, *J. Neurophysiol.*, **9**, 231 (1946).

Experimental Section

Diethyl Ethyl(1-methyl-3-oxobutyl)malonate (I).—Diethyl ethylmalonate (188 g, 1.0 mole) was added to a stirred solution of sodium (1.3 g, 0.056 g-atom) in 150 ml of dry ethanol at 25°. 3-Penten-2-one (67.2 g, 0.8 mole), prepared by the method of Alexander and Coraor,[5] was added at 10° over a 1-hr period. The mixture was stirred at 10° for 2.5 hr, then neutralized with acetic acid. It was added to 300 ml of water, and the oil layer was separated. The aqueous layer was extracted with two 50-ml portions of ether. The ether extract and the oil layer were combined, and the solvent was removed by distillation. The residue was distilled to yield I (193 g, 88.7%), bp 102–103° (0.5 mm), $n^{25}D$ 1.4440. The product assayed 98% by glc. Infrared and nmr spectra were consistent with the assigned structure.

Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.8; H, 8.85. Found: C, 61.7; H, 8.91.

Ethyl Ethyl(3-hydroxy-1-methylbutyl)malonate δ-Lactone (II).—A solution of I (29.5 g, 0.11 mole) in 100 ml of absolute ethanol was reduced with Raney Ni at 3 atm of H_2. The solution was filtered and the solvent removed by distillation. Distillation of the residue gave II (20 g, 79%), bp 102° (0.1 mm), $n^{25}D$ 1.4560. Infrared and nmr spectra were consistent with the assigned structure. Purity was 98% by glc.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.2; H, 8.77. Found: C, 62.9; H, 8.81.

5-Ethyl-5-(3-hydroxy-1-methylbutyl)barbituric Acid (III).—Urea (15 g, 0.25 mole) was added to a stirred solution of sodium (5.75 g, 0.25 g-atom) in 150 ml of dry ethanol. This was stirred to solution at 40°, and then II (19 g, 0.09 mole) was added over a 30-min period. The solution was then refluxed for 40 hr. The solvent was removed at 20 mm until the pot temperature reached 50°. The residue was dissolved in 200 ml of water at 5–10° and extracted with two 50-ml portions of ether. The aqueous solution was neutralized to a pH of 6.0 with 5 *N* HCl and the dissolved ether was removed under reduced pressure. The solution was cooled and filtered to give III (10.9 g, 51.2%), mp 170–175°. The crude product was recrystallized from water to give 6.7 g of III, mp 187–188° (uncor). Infrared and nmr spectra were consistent with the assigned structure.

Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 54.5; H, 7.45; N, 11.58. Found: C, 54.7; H, 7.43; N, 11.26.

Samples of III were compared with material extracted from the urine of a cat anesthetized with pentobarbital. The urine was acidified to pH 6.4 and extracted with ethyl acetate. Samples were chromatographed on Whatman No. 1 paper with 1-butanol saturated with 1% ammonia as the descending solvent. The chromatograms were sprayed with a 0.1% saturated solution of cobalt acetate in pyridine. The barbiturate derivatives gave a dull purple color with this reagent. The R_f of the synthetic material in this system was 0.80 which compares favorably with the material (R_f 0.78) extracted from the urine.

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(5) E. R. Alexander and G. R. Coraor, *J. Am. Chem. Soc.*, **73**, 2721 (1951).

The Synthesis of 3-Fluoroestra-1,3,5(10)-trienes

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The substituent at the 3-position of the steroidal estrogens plays an important role in the pharmacological activities of these compounds. A vast improvement in the ratio of the hypocholesterolemic and geno-