mixture became brown during this time. Acetone was removed by washing with water, and the oil layer was dried and fractionated, yielding 16 g. (35.6%) of methallyl chloride, b. p. 72–75°, and 22.5 g. (32%) of methallyl bromide, b. p. 92–95°.

GEORGE HERBERT JONES LABORATORY
UNIVERSITY OF CHICAGO
CHICAGO 37, ILLINOIS

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Derivatives of 1,2,3,4,5,6,7,8-Octahydroanthracene

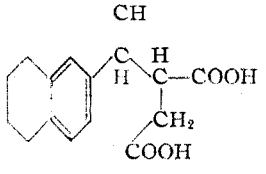
BY D. L. TURNER

It was hoped that 2-carboxy-4-keto-1-methyl-1,2,3,4,5,6,7,8-octahydrophenanthrene[1] could be prepared utilizing the Stobbe condensation.[2,3,4]

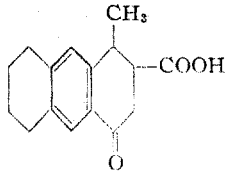
Hydrogenation of the Stobbe half-ester from 2-acetylnaphthalene using Adams catalyst in acetic acid gave a mixture containing a small quantity of I. An additional quantity of I was obtained from the mother liquor from the catalytic hydrogenation by the Raney alloy procedure,[5] which has been used for the reduction of naphthalene compounds.[6]

The Stobbe condensation with 2-acetyl-5,6,7,8-tetrahydronaphthalene gave a mixture of half-esters, which was hydrolyzed with barium hydroxide to a crystalline unsaturated acid; this was reduced by the Raney alloy procedure to the same acid obtained from 2-acetylnaphthalene.

The acid (I) underwent cyclization to give 2-carboxy-4-keto-1-methyl-1,2,3,4,5,6,7,8-octahydroanthracene (II). The carbonyl group was easily reduced to methylene, using hydrogen in the presence of palladium and perchloric acid.[7] The ultraviolet absorption spectrum of II is very similar to that of α-tetralone,[8,9] with a bathochromic shift. The direction of ring-closure was shown by dehydrogenation to 1-methylanthracene.



I



Experimenta

3-Carboxy-4-(5,6,7,8-tetrahydro-2-naphthyl)-3(?)-pentenoic Acid.—The Stobbe condensation of 310 g. of 2-acetyl-5,6,7,8-tetrahydronaphthalene with 380 g. of dimethyl succinate in the presence of potassium *t*-butoxide (from 80 g. of potassium and 1600 ml. of *t*-butyl alcohol) was carried out by the method of Johnson, Goldman and Schneider.[4] This gave 390 g. of liquid half-esters.

Part of the product (40 g.) was dissolved in 230 ml. of 95% ethanol. To this was added 87 g. of barium hydroxide octahydrate and 250 ml. of water. After refluxing for 1.5 hours, the mixture was cooled and filtered. The barium salt was decomposed with dilute hydrochloric acid and the product was taken up in ether. Evaporation of the ether gave 20 g. of crystalline acid, m. p. 176–184°. This was recrystallized from acetic acid and ethyl acetate, m. p. 184–186° (dec.).

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.96; H, 6.60.

3-Carboxy-4-(5,6,7,8-tetrahydro-2-naphthyl)-valeric Acid.—(a) The Stobbe half-esters (25 g.) from 2-acetylnaphthalene, prepared by the potassium *t*-butoxide catalyzed reaction[4] using dimethyl succinate, were dissolved in 200 ml. of acetic acid and hydrogenated over 2.0 g. of Adams catalyst starting at 3 atmospheres pressure in a Burgess–Parr hydrogenation apparatus. When the uptake of hydrogen ceased, the catalyst was filtered and the solution was distilled *in vacuo*. The residual oil was hydrolyzed by refluxing for two hours with 100 ml. of ethanol and 45 ml. of 45% potassium hydroxide. Then 100 ml. of water was added and the ethanol was removed by distillation *in vacuo*. The solution was cooled, acidified and extracted with ether. The ethereal solution was dried and distilled and the product crystallized from chloroform; it was not homogeneous. Crystallization from acetone gave 2 g., m. p. 191–194° (dec.). The acetone mother liquor was evaporated and the crystalline residue (13 g.) was dissolved in 350 ml. of 10% sodium hydroxide and reduced with 40 g. of Raney nickel–aluminum alloy.[5] This procedure gave a crystalline product, which, after recrystallization from chloroform, weighed 9 g.; m. p. 193–194° (dec.). There was no depression in m. p. when mixed with the preceding product. A sample sublimed *in vacuo* and crystallized from ether–pentane had m. p. 195–196° (gas evolution).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.24; H, 7.24.

(b) The pentenoic acid (30 g.) from 2-acetyltetralin was reduced by the Raney alloy procedure in 1250 ml. of 10% sodium hydroxide using 140 g. of Raney alloy. The crystalline product, m. p. 178–184°, weighed 20 g. A sample was crystallized several times from ethyl acetate and chloroform, m. p. 193–194° alone or when mixed with the acid described in (a).

4-Keto-1-methyl-1,2,3,4,5,6,7,8-octahydroanthracene-2-carboxylic Acid.—The preceding acid (17.5 g.) was refluxed with 150 ml. of acetyl chloride for two hours. The acetyl chloride was distilled but the resulting oil could not be crystallized. This anhydride was added slowly to a stirred solution of 19.8 g. of aluminum chloride in 100 ml. of nitrobenzene which was cooled to keep the temperature below 10°. The mixture was allowed to come to room temperature and after standing overnight it was hydrolyzed with ice and hydrochloric acid and steam distilled to remove nitrobenzene. The residue was taken up in ether and acids were taken out with 5% sodium carbonate. This solution was acidified and extracted with ether. Evaporation of the ether gave a gum which crystallized from nitromethane, m. p. 184–189°; weight 8 g. It was recrystallized from ether–pentane, m. p. 192–193°.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.57; H, 6.98.

The ultraviolet absorption spectrum determined with the Beckman spectrophotometer, model DU, was taken using solutions of the acid in 95% ethanol and showed maxima at 265 mμ (log ε 4.19) and 304 mμ (log ε 3.42) and minima at 235 mμ (log ε 3.35) and 294 mμ (log ε 3.33). The shape of the curve was similar to that for α-tetralone,[8,9] with very broad bands.

(1) An hypothesis to be described elsewhere suggests that this substance might exhibit the biological activity of myelokentric acid.

(2) R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 636 (1935).

(3) J. W. Cook and A. M. Robinson, *ibid.*, 505 (1938).

(4) W. S. Johnson, A. Goldman and W. P. Schneider, THIS JOURNAL, **67**, 1357 (1945).

(5) D. Papa, E. Schwenk and B. Whitman, *J. Org. Chem.*, **7**, 587 (1942).

(6) D. Papa, E. Schwenk and H. Breiger, *ibid.*, **14**, 366 (1949).

(7) K. W. Rosenmund and E. Karg, *Ber.*, **75**, 1850 (1942).

(8) P. Ramart Lucas and M. J. Hoch, *Bull. soc. chim.*, [5] **2**, 327 (1935).

(9) D. Biquard, *ibid.*, **8**, 55 (1941).

The methyl ester of this substance was made with diazomethane in ether and crystallized from ethanol, m. p. 106–107°.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.92; H, 7.43.

The semicarbazone of the acid made by the pyridine–ethanol method, was crystallized from pyridine, m. p. 270–272° (dec.).

Anal. Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71. Found: C, 64.64; H, 6.88.

1-Methyl-1,2,3,4,5,6,7,8-octahydroanthracene-2-carboxylic Acid.—The preceding acid (0.5 g.) was hydrogenated at 3 atmospheres in the presence of 0.5 g. of 10% palladium-on-Darco G-60, 1 ml. 60% perchloric acid and 40 ml. acetic acid for two hours. The catalyst was filtered, the solution was shaken with ether and water; the ether was washed free of acetic acid, dried and distilled. The product was crystallized from ethyl acetate, m. p. 218–220°.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.72; H, 8.35.

The methyl ester of this substance, made with diazomethane was crystallized from pentane, in which it is very soluble, by cooling in a Dry Ice–acetone-bath. The product had m. p. 42–43°.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.59. Found: C, 79.10; H, 8.68.

1-Methylanthracene.—The preceding acid (120 mg.) was heated at 300° with 300 mg. of palladium-on-charcoal 5% for 1.5 hours and then at 350° for 3 minutes. The product was dissolved in ether and filtered. The ether solution was washed with 5% sodium carbonate, dried and evaporated; the residue was sublimed in a high vacuum. Material subliming up to 80° was converted to the picrate and this was crystallized from ethanol, m. p. 113–115°. The hydrocarbon was obtained by passing a solution of the picrate in benzene through a column of alumina. Crystallized from pentane it melted at 77°.[10]

Acknowledgment.—I wish to thank Professor W. S. Johnson for valuable advice and Mrs. R. P. Gerhart for technical assistance. This work was aided by a grant from the American Cancer Society, recommended by the Committee on Growth of the National Research Council.

(10) Reported for 1-methylanthracene, m. p. 85–86°, picrate m. p. 113–115°; Fischer and Sapper, *J. prakt. Chem.*, [2] **83**, 203 (1911).

CHARLOTTE DRAKE CARDEZA FOUNDATION
JEFFERSON HOSPITAL
PHILADELPHIA, PENNA. RECEIVED AUGUST 26, 1949

Barbiturates Containing the 3-Methyl-2-butenyl Group

BY HENRY WALTON,[1] JOHN DOCZI AND JOHN A. KING

Because, as was stated[2] a number of years ago "the replacement of an alkyl group in 5,5-dialkylbarbituric acids by an allyl group frequently leads to an increase in effectiveness, together with a lower degree of increase in toxicity," it was of interest to determine if this therapeutic advantage was retained when the replacement was by a γ,γ-dimethylallyl group, derived from the now readily available isoprene. The present paper describes the preparation of a short series of such substances (I–VII) which are listed in Table I.

(1) National Dairy Research Laboratories Inc., Oakdale, L. I., N. Y.

(2) Volwiler, THIS JOURNAL, **47**, 2236 (1925).

It was shown by Staudinger[3] that hydrogen bromide undergoes 1,4-addition to isoprene and the structure of the resultant 3-methyl-2-butenyl bromide was proved. He also used this isoprenyl bromide to alkylate malonic ester and the thus-produced 3-methyl-2-butenylmalonic ester (VIII) was alkylated[4] with the alkyl halides suitable to give isopropyl isoprenyl malonic ester (IX) and allyl isoprenyl malonic ester (X), the latter of which was also prepared by alkylation of allyl malonic ester with isoprenyl bromide. In the present work all of these reactions were repeated and the malonic esters IX and X were condensed with urea in the Fischer–Dilthey[5] synthesis of the barbituric acids I and IV; I was also prepared by alkylation of isopropylbarbituric acid with isoprenyl bromide. Positive proof of the skeletal structure of isoprenyl malonic ester (VIII) was obtained by its condensation with urea to yield isoprenylbarbituric acid (VII) and catalytic hydrogenation of the latter to the known[2] 5-isoamylbarbituric acid. Ethyl isoprenylmalonic ester (XI), prepared from isoprenyl bromide and ethyl malonic ester, was condensed with urea to produce ethyl isoprenyl barbituric acid (V), and isopropyl isoprenyl thiobarbituric acid (VI) was obtained by the condensation of the malonic ester IX with thiourea. The two N-alkylated derivatives II and III were prepared, in the former case, by N-allylation of the barbituric acid I, and, in the latter case, by the condensation of the malonic ester IX with methylurea.

In general these substances, with the exception of II, have a rather excitatory effect on experimental animals. The oral tolerated dose of I is 100 mg./kg. mouse and the LD_{50} is approximately 200 mg./kg., with death due to convulsions. For III the tolerated dose by subcutaneous injection is around 50 mg./kg. mouse and the LD_{50} is 70 mg./kg.; by intravenous administration the LD_{50} is 12–15 mg./kg. mouse and 5–10 mg./kg. rabbit, with death due to convulsions. IV and V likewise produced spastic convulsions on injection. This reversal of the actions usually found in and associated with the ordinary barbiturates is in agreement with the recent report by Taylor and Noble[6] who described some pharmacological properties of the sodium salt of V.

We are indebted to Dr. N. Ercoli, of this Institute, for the pharmacological results herein presented and to Dr. H. M. Wuest for his suggestions concerning the problem.

Experimental

5-(3-Methyl-2-butenyl)-barbituric Acid, VII.—The following is a procedure representative of the preparation of substances I, III, IV, V, VI and VII. A mixture of

(3) Staudinger, Kreis and Schilt, *Helv. Chim. Acta*, **5**, 743 (1922).

(4) Staudinger, Muntwyler, Ruzicka and Seibt, *ibid.*, **7**, 390 (1924).

(5) Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

(6) Taylor and Noble, *Nature*, **163**, 447 (1949).