SPECIAL ARTICLES

SYNTHESIS OF SUBSTANCES OF POSSIBLE PHYSIOLOGICAL ACTIVITY

THE methods developed by Fieser and Hershberg[1] for the synthesis of phenanthrene and hydrophenanthrene dicarboxylic anhydrides have been applied to the preparation (E. B. H.) of hydroxy and methoxy derivatives which are of interest for their possible oestrogenic activity. The condensation of succinic anhydride with 1-methoxynaphthalene afforded a suitable starting material for the synthesis of 9-methoxyphenanthrene-1, 2-dicarboxylic anhydride (m.p. 249–250°, corr.) by reduction, condensation of the ester with oxalic ester, cyclization and dehydrogenation. Plans to obtain the 7-substituted isomer by a similar process from the known γ-(6-methoxy-1-naphthyl)-butyric acid[2] were abandoned with the appearance of a paper by Cohen, Cook and Hewett[3] anticipating this part of our program. The 6-methoxy and the 6, 7-dimethoxy derivatives of octahydrophenanthrene-11, 12-dicarboxylic anhydride were prepared by the addition of butadiene to the unsaturated anhydrides obtained from anisol and from veratrol by condensation with succinic anhydride, reduction, ester condensation and cyclization. The ethers were demethylated after hydrogenation of the active ethylenic linkage. 6-methyl-7-hydroxyoctahydrophenanthrene-11, 12-dicarboxylic anhydride (m.p. 134.5–135.5°, corr.) was prepared similarly from γ-(3-methyl-4-methoxyphenyl)-butyric acid.[4]

As a further approach to the oestrone type of structure, the anhydride of phenanthrene-1, 2-dicarboxylic acid was converted into 1′, 3′-diketo-1, 2-cyclopentenophenanthrene (M. F. and E. B. H.) by condensation of the dimethyl ester with ethyl acetate. 1′, 3′-diketo-3, 4-cyclopentenophenanthrene (m.p. 201.4–202°, corr.) was obtained similarly.

We may report also the synthesis (M.F. and E.B.H.) of chrysene, 2, 3-dimethyl-6, 7-acechrysene (m.p. 222.6–223.1°, corr.), and 6, 7-dimethyl-3, 4-benzphenanthrene (m.p. 94.5–95°, corr.) from starting materials already described, by obvious extensions of the hydrocarbon synthesis developed by Fieser and Hershberg. The last two substances are being tested for carcinogenic activity. In connection with the latter problem 5, 10-dimethyl-1, 2-benzanthracene (m.p. 147–147.5°, corr.; picrate, m.p. 173.7–174.2°, corr.) has been synthesized for comparison with cholanthrene (M. S. N.). The method consisted in the reaction of *o*-tolylmagnesium bromide with naphthalene-1, 2-dicarboxylic anhydride to give a keto acid which yielded β-(*o*-toluyl)-naphthalene on decarboxylation, addition of the methyl Grignard reagent to the ketonic group of the keto ester, reduction of the resulting lactone by Martin's modification[4] of the Clemmensen method, cyclization to an anthrone and reduction with zinc and alkali.

By a reaction analogous to the reported Diels-Alder addition to cyclic unsaturated anhydrides, a new type of hydrophenanthrene derivative of interest in connection with the morphine problem has been made available (H. L. H.). Butadiene and 2, 3-dimethylbutadiene were successfully added to 3, 4-dihydro-1-naphthoic ester affording, after hydrolysis, 5, 8, 9, 10, 13, 14-hexahydrophenanthrene-13-carboxylic acid (morphine numbering), m.p. 137–137.5°, corr., and its 6, 7-dimethyl derivative, m.p. 162–162.5°, corr. These yielded phenanthrene and 2, 3-dimethylphenanthrene on dehydrogenation. The compounds are of significance because of the presence of a carbon-substituent in the position (C_{13}) assumed in the Gulland-Robinson formula for morphine to be occupied by the ethanamine chain. To provide a closer approach to the morphine structure a general synthesis of the required starting materials has been developed: α-keto-δ-phenylvaleric acid (m.p. 61–62°) is obtained by the acid hydrolysis of ethyl α-oxalyl-γ-phenylbutyrate and the ester is cyclized to 3, 4-dihydro-1-naphthoic acid. The 3-methoxy derivative of the hydrophenanthroic acid has been obtained and other syntheses are in progress.

The publication of the results of these and other experiments has been deferred for a time, pending the preparation for the press by one of us (L. F. F.) of the posthumous papers of the late Samuel C. Hooker.

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1 L. F. Fieser and E. B. Hershberg, *Jour. Am. Chem. Soc.*, 57: 1508, 1851, 2192 (1935).
2 A. Butenandt and G. Schramm, *Ber.*, 68: 2083, 1935.
3 A. Cohen, J. W. Cook and C. L. Hewett, *Jour. Chem. Soc.*, 52, 1936.
4 E. L. Martin, *Jour. Am. Chem. Soc.*, in press.

POTASSIUM: A BASAL FACTOR IN THE SYNDROME OF CORTICOADRENAL INSUFFICIENCY

AN increasing number of regulatory functions is now being ascribed to the adrenal cortex. These might be controlled by a number of hormones elaborated by the gland, or possibly the manifold effects of adrenal insufficiency are due to the breakdown of a single regulatory mechanism, to which the other effects are secondary.

The morbid anatomy of animals dying of adrenal insufficiency does not give any definite indications as to the cause of death; more striking changes are found in the blood chemistry during the course of the syndrome. These are, briefly, lowered sodium and