THE SYNTHESIS OF CANCEROGENIC HYDROCARBONS CLOSELY RELATED TO THE STEROIDS

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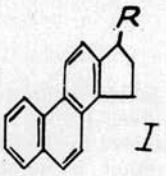
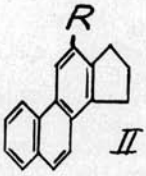
Studies of the carcinogenic activity of methylcholanthrene and cholanthrene have shown that they surpass in potency all other hydrocarbons previously investigated. From these results it might be inferred that cancerogenic hydrocarbons may arise in the living organism by the abnormal metabolism of steroids. To further elucidate this hypothesis, investigations have been planned to extend the studies of aromatic hydrocarbons related to the sterol nucleus.

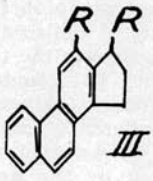
At the present we are chiefly concerned in the synthesis of a number of derivatives of 3¹-substituted-1,2-cyclopentenophenanthrenes (I), 3-substituted (II), and 3,3'-disubstituted-1,2-cyclopentenophenanthrenes (III).



I



II



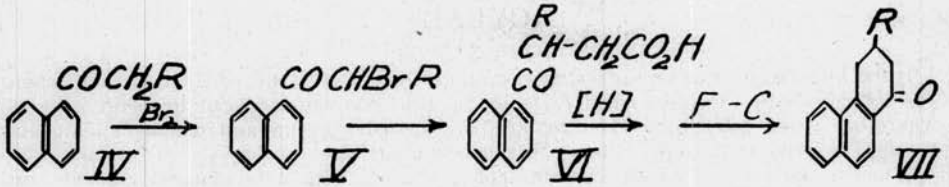
III

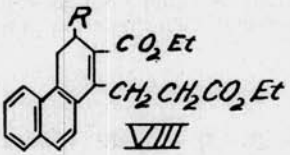
Previous syntheses of other molecules of this type have not been found practical, mainly because it is difficult to obtain the final product in sufficient quantity for complete biological assay. Therefore, it was necessary to find a good, general method which could be used for a whole series of compounds. An important intermediate for such a process is 3¹-keto-1, 2-cyclopentenophenanthrene.

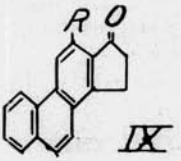
Catalytic reduction of phenanthrene, using copper-chromium oxide catalyst gives practically pure 9,10-dihydrophenanthrene.[1] This is readily acylated in the 2-position by means of an acid chloride with aluminum chloride.[2] In this way a β-bromopropionyl group was introduced into the 2-position. However, cyclyzation has been shown to go almost completely to the 3-position,[3] whereas the unhydrogenated phenanthrene nucleus, directs cyclyzation to the desired 1-position. All attempts to dehydrogenate the 2(ω-bromo) propionyl-9,10-dihydrophenanthrene or its ether derivatives lead to decomposition and polymerization, probably due to reactivity of β-substitution. Such an attack was, of necessity, finally abandoned.

At the present time two other methods of synthesis are being explored; which appear to be of a more promising nature. By the nitration of 9, 10-dihydrophenanthrene a good yield of the 2-nitro derivative can be obtained.[4] This is readily reduced to the amine either catalytically or with stannous chloride and hydrochloric acid. The resulting amine has been dehydrogenated with sulfur at 250-300° in good yield to give 2-amino-phenanthrene. An alternative method of preparation of this amine is thru the Beckmann rearrangement of the oxime of 2-acetylphenanthrene, which has been prepared in good yield by sulfur dehydrogenation of the 9, 10-dihydro derivative. The amine was then converted to the 2-bromophenanthrene by Bachman's[5] procedure. At the present time experiments are under way to prepare the 2(ω-bromo)-propionyl phenanthrene by condensation of β-bromo-propionyl chloride with either the magnesium or cadmium derivative of 2-bromophenanthrene. This product, when obtained, will be cyclysized with sulfuric acid to prepare the desired 3¹-keto-1, 2-cyclopentenophenanthrene. The keto compound can then be condensed with various Grignard reagents to give compounds of type I, above.

The second series of reactions now being studied lends itself to the preparation of compounds of type II and III. Here the starting material is α-naphthylnitrile, which is caused to condense with







aliphatic Grignard reagents to give compounds like IV. These are then treated with bromine to give α-bromo ketones (V), which are then condensed with sodio-malonic ester to give β-(1-naphthoyl)-β-alkyl propionic acids (VI). Subsequent Clemmensen reduction and ring closure gives 1-keto-3-alkyl-1,2,3,4-tetrahydrophenanthrenes[6] (VII). Condensation of VII with oxalic ester places a carbethoxy group in the 2 position and this is then followed by condensation of the ketone group with β-bromopropionic ester to give, after dehydration, the compound VIII. A Dieckmann ring closure, followed by decarboxylation should give a compound which could be readily dehydrogenated to the desired 3-alkyl-3[1]-keto-1,2-cyclopentenephenanthrene.

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