SYNTHESIS OF STEROID COMPOUNDS AND RELATED SUBSTANCES

COMMUNICATION 38. ANALOGS OF DOISYNOLIC ACID
NOT CONTAINING A B RING

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In a previous investigation [1] we synthesized some tricyclic ketones of the types (I) and (II), which are structurally related to homoestrone with its B ring removed.

\[
\begin{align*}
(I) & \quad \begin{array}{c}
\text{O} \\
\text{CH}_3O
\end{array} \\
(II) & \quad \begin{array}{c}
\text{O} \\
\text{CH}_3O
\end{array}
\end{align*}
\]

The present paper describes further synthetic work on structural analogs of steroid hormones.

By treatment with paraform and dimethylamine hydrochloride, 4'-methoxyacetophenone (III) was converted in good yield into the hydrochloride of 3-dimethylamino-4'-methoxypropiophenone (IV)[2], which reacted with 1,3-cyclohexanedi酮 in presence of alkali with formation of the triketone (V). Attempts to cyclize
this product with the object of obtaining the oxygen-containing steroid analog (VI) were not successful, for treatment of the triketone (V) with phosphoric oxide or sulfuric acid did not yield any individual products, and treatment with boiling acetic anhydride in presence of sodium acetate gave the enol acetate (VII). When treated with alkali for a short time, this ester was hydrolyzed into the original triketone (V).

Reaction of 4'-methoxyacetophenone with acetylene by the method developed in our laboratory [3] gave the acetylenic alcohol (VIII), which was converted into the ethylenic alcohol (IX) when partially hydrogenated over a palladium catalyst. Dehydration of the ethylenic alcohol under various conditions (with the aid of potassium hydrogen sulfate, p-toluenesulfonic acid, or magnesium sulfate) was accompanied by much polymerization, and the highest yield of the diene (X) that we were able to attain was 35%. This diene readily underwent diene synthesis with maleic anhydride, and the adduct obtained (XI) was quantitatively hydrolyzed by alkali into the dicarboxylic acid (XII).

It was found that the ethylenic alcohol (IX) could be used directly in the diene condensation instead of the diene (X); dehydration of (IX) then occurred in the reaction itself. Thus, heating of the ethylenic alcohol (IX) with maleic anhydride or methacrylic acid in boiling xylene gave the corresponding adduct (XI) or (XIII) in a yield of 33% or 38%, respectively.

As in the condensation with maleic anhydride the above-mentioned dicarboxylic acid (XII) is formed as well as the adduct (XI); the total yield in this reaction attains 50%.

When boiled with aqueous-alcoholic alkali, the bicyclic ester (XIII) is converted into the acid (XIV), which we prepared also by another method. Condensation of 2-methoxy-1,3-butadiene (XXII) with methyl methacrylate and subsequent hydrolysis of the adduct (XXI) gave, as already described [4], methyl 1-methyl-4-oxo-1-cyclohexanecarboxylate (XX). Reaction of this product with p-methoxyphenyl magnesium bromide and vacuum-distillation of the reaction product gave a mixture of the above bicyclic ester (XIII) and the corresponding acid (XIV), probably formed by scission of the intermediate lactone (XVIII).

When treated with aluminum chloride in boiling xylene, the acid (XIV) was demethylated with formation of the bicyclic phenol (XV), which may be regarded as an analog of doisynolic acid (XVI) in which the B ring is missing. It must be pointed out that the previously described [5] phenolic acid (XVII), which was prepared by another method, possesses estrogenic activity.