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Lester Yoder

Iowa Agricultural Experiment Station

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New Intermediates for the Synthesis of Androgenic Groups¹

By LESTER YODER

A large number of compounds of steroid origin with variable androgenic activity have been described since Butenandt and Tscherning (1) first isolated androsterone in 1934. Later following the nitrogen balance experiments of Kochakian (2) with the more active androgen, testosterone, an anabolic activity was recognized as a closely associated property of androgens. Moreover this anabolic activity in some of the newer steroid androgens has now been found to deviate independently from their androgenic activity (3) (4).

These developments are of great interest not only in the production of more efficient gains in animal nutrition but also in the maintenance of a balance between sex hormones when stilbestrol is fed and of positive nitrogen balance in known hormone deficiencies of the aged (4) (5) (6).

Due to the accidental discovery of the highly potent and relatively cheap synthetic estrogen of the stilbestrol type, the problem of availability and cost is not as acute as in the supply of suitable androgens. The story of stilbestrol starts with the accidental dimerization (7) of anol to diethylstilbestrol which has the main physiological properties of the natural steroid female sex hormones. It has, however, the steroid structure with two open adjacent inner rings and not one but two of the structural groups, $-\text{COH}=\text{CH}-$, characteristic of the most active estrogens.

No similar story has developed in the area of androgens. A challenge exists for the chemist to create for androgens an analogous synthesis. If the structure of the most active steroid androgens is considered (8) it is evident that the structural group, $-\text{CO}-\text{CH}=\text{CH}-$, is predominant. It can be named the androgenic group in analogy to that group, $-\text{COH}=\text{CH}-$, of estrogenic hormones. In a totally synthetic androgen it is apparently necessary to simulate as in diethylstilbestrol the steroid contour and incorporate one or more androgenic groups. Successful syntheses of estrogens among many proposed have utilized as starting material hydrobrominated anethole (9) or p-hydroxypropiofenone (10). A total synthesis should provide for a carbonyl group in a reduced ring para to a substituent carboxyl group to provide the functional groups from which α , β

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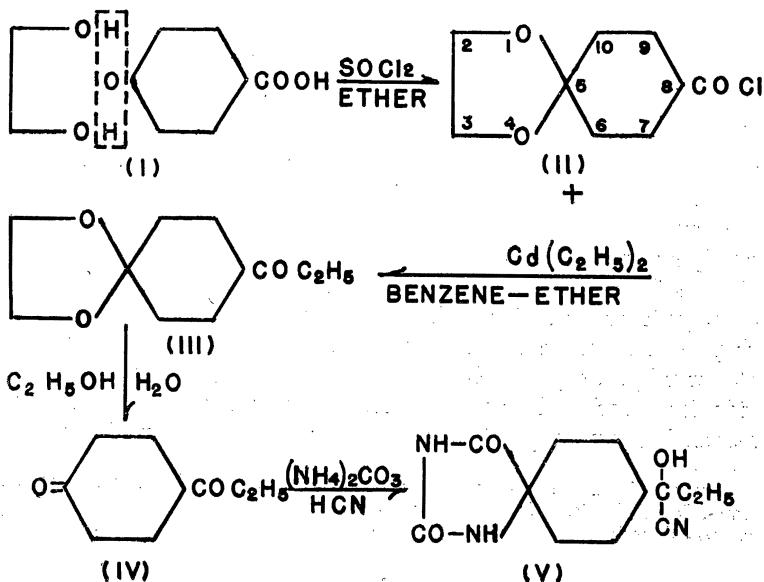
unsaturation can be introduced and in addition a substituent alkyl ketone group through which a condensation of two such molecules could be completed. Thus an appropriate starting material was found in the 4-cyclohexanone carboxylic acid of Kay and Perkin (11). The carbonyl group required preservation against subsequent reactions and this was possible by ketal formation. The carboxyl group could be converted to the propionyl group by the appropriate Grignard reagent through the acid chloride and the intermediates shown in the chart.

Another synthesis which has just now become available utilizes as starting material p-hydroxy or p-methoxypropiophenone and the new lithium-alkylamine reduction procedure of Benkeser, et al. (12). This is being investigated and should shorten the steps required to produce cheaply the necessary intermediate, 4-propionylcyclohexanone.

EXPERIMENTAL

Cyclohexanone-4-carboxylic acid was obtained in substantially the same good yields given by Kay and Perkin (11) by the sodium ethylate reaction with ethyl cyano-acetate but with the commercially available ethyl β -bromopropionate replacing the costly ethyl β -iodopropionate originally used.

1,4-Dioxaspiro[4.5]decane-8-carboxylic acid (I). — Formation of the ketal by the azeotropic distillation of a carbontetrachloride



suspension of cyclohexanone-4-carboxylic acid with ethylene glycol was accomplished by the procedure of Sulzbacher, et al. (13) even without the use of a catalyst. More than a molecular equivalent of the glycol however led to the formation of mixed esters and lower yields.

Cyclohexanone-4-carboxylic acid, 28.5 g., 0.2 mole, was treated in a 250 ml. distilling flask with 12.5 g., 0.2 mole, of ethylene glycol in 150 ml. of carbontetrachloride and slowly distilled with a piece of porous plate into an automatic separatory return receiver. The distillation was continued a few hours until 3.6 ml. of water collected in the receiver and the layer of insoluble carboxylic acid disappeared. The solvent was removed at the temperature of a boiling water bath and lowered pressure of a water aspirator. The residue then distilled at 139 to 142° at 2 mm. of pressure with a yield of 31 g. or 84 per cent.

Analysis. Calcd. for $C_9H_{14}O_4$: C, 58.06; H, 7.57.
Found C, 57.87; H, 7.38.

The cyclic ketal acid (I) has a calculated neutralization equivalent of 186. Found, 181. It readily formed the S-benzylisothiouronium salt by mixing in molar proportions the hydrochloride of the base and the sodium salt of the acid in hot absolute methanol. The crystals which separated after filtering the hot solution and cooling melted at 154°.

Analysis. Calcd. for $C_{18}H_{24}O_4SN_2$: S, 9.10; N, 7.95.
Found S, 9.22; N, 8.29.

8-Propionyl 1,4-dioxaspiro[4.5]decane(III). —The acid chloride of 1,4-dioxaspiro[4.5]decane-8-carboxylic acid (II) was prepared first by adding to a stirred solution of 18.6 g., 0.1 mole, of the acid in 150 ml. of anhydrous ether, cooled in an ice bath, 8.0 g., 0.1 mole, of anhydrous pyridine, then from a dropping funnel 12.0 g., 1.0 mole, of thionyl chloride in 50 ml. of anhydrous ether. Pyridine hydrochloride was precipitated as found for this procedure by Gerrard and Thrush (14) for carboxylic acids resistant to the action of thionyl chloride. After two hours at room temperature the ether solution of the acid chloride (II) was decanted into a tared flask together with a 50 ml. washing of the pyridine salt residue with benzene. This solution, according to the procedure of Cole and Julian (15) for the application of steroid acid chloride to the dialkyl cadmium coupling technique of Gilman and Nelson (16), would be suitable for the preparation of ketones.

In a two-necked liter flask equipped with a mechanical stirrer were placed 100 ml. of anhydrous ether, 3.2 g. or 0.13 atom of magnesium turnings and a crystal of iodine. Through a dropping

funnel-condenser combination was added slowly at barely reflux temperature 18.5 g. or 0.17 mole of ethyl bromide in 50 ml. of ether. After one hour the magnesium had dissolved. The Grignard reagent was cooled in an ice bath then treated with 13.2 g., 0.07 mole, of anhydrous cadmium chloride washed in with 150 ml. more of the ether. The mixture became opalescent after being stirred one hour more at 25°. It was diluted with 100 ml. of benzene and again cooled in the ice bath.

An aliquot of acid chloride (II) stock solution above, 0.66 mole, from 12.4 g. of the acid (I) was then added from the dropping funnel in 20 minutes while stirring. The mixture became milky and contained some gummy lumps. The ice bath was removed and the mixture stirred at room temperature for one half hour then for 6 hours while refluxing. After standing overnight dilute hydrochloric acid and ice were added to a pH of 4. The ether phase was separated, washed with excess dilute sodium carbonate, dried with sodium sulfate and the solvent distilled to 7 g. of an oily residue. After two fractionations at 2 mm. pressure a fraction of 5.2 g. distilling at 120 to 125° was collected.

Analysis. Calcd. for $C_{11}H_{18}O_3$: C, 66.63; H, 9.15.
Found C, 65.60; H, 8.90.

The new ketone (III) did not give the usual condensations with the carbonyl reagents. However when subjected to the hydantoin reaction of Bucherer and Libe (17) as applied by Henze and Speer (18) by boiling its solution in 50 per cent alcohol with potassium cyanide and ammonium carbonate a product (V) separated which recrystallized from methanol and melted at 318-9°.

Analysis. Calcd. for $C_{12}H_{17}O_3N_3$: N, 16.72.
Found N, 16.70. Molecular weight in acetic acid, 256.

On prolonged heating in alkaline aqueous solution the ketal (III) could be expected to decompose to produce 4-propionylcyclohexanone (IV). A hydantoin would then be formed on the ring carbonyl group and a cyanohydrin on the hindered carbonyl group of the side chain. The derivative would be tentatively identified as a hydantoin cyanohydrin (V) of the diketone (IV) and would confirm the formation of 8-propionyl 1,4-dioxaspiro [4.5] decane (III).

SUMMARY

A stilbestrol-type total synthesis of compounds containing the group, $-\text{CO}-\text{CH}=\text{CH}-$, characteristic of male sex hormones was

proposed to produce cheaper and more potent androgens with higher anabolic activity.

For this purpose 4-cyclohexanone carboxylic acid was prepared by a modification of the Kay and Perkin synthesis. The ethylene glycol ketal, 1,4-dioxaspiro[4.5]decane-8-carboxylic acid, was readily prepared to protect the carbonyl group in later reactions. The carboxylic acid chloride was then produced with thionyl chloride and without purification converted through the Grignard reagent, ethyl magnesium bromide and diethyl cadmium to the ketal ketone, 8-propionyl 1,4-dioxaspiro[4.5]decane and 4-propionyl cyclohexanone which were identified as the hydantoin cyanohydrin.

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