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ADDITION OF GRIGNARD REAGENTS TO STEROID EPOXIDES I.

A NEW ROUTE TO A-NORSTEROIDS*

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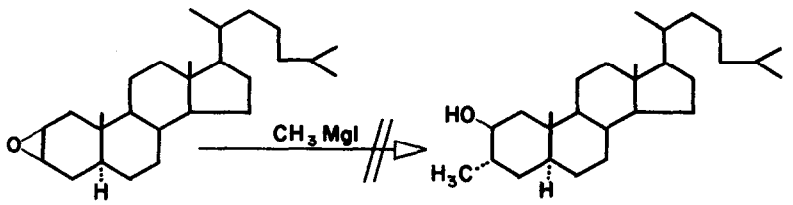
In connection with our study of the action of lead tetraacetate on 2β-hydroxysteroids (1) we were interested in the synthesis of 2β-hydroxy-3α-methyl-5α-cholestane (II).



I II

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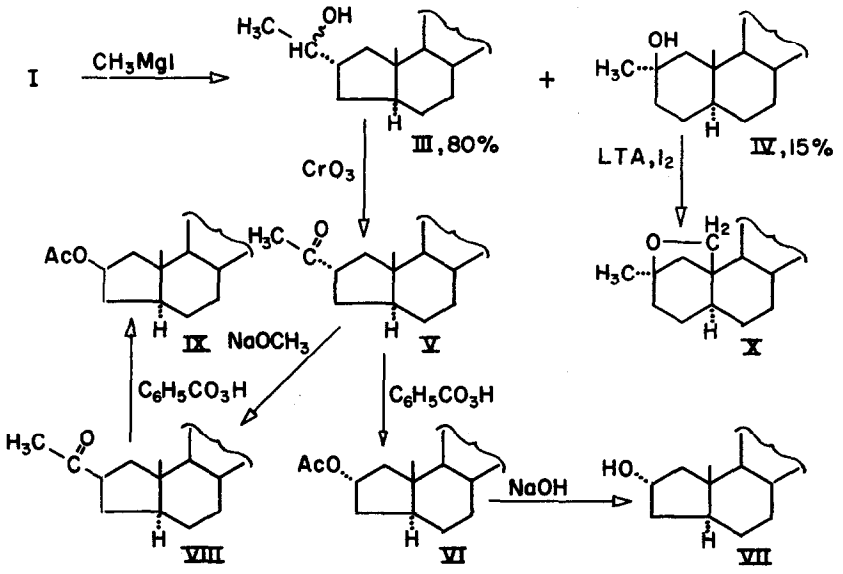
In view of the known diaxial opening of 5α,6α-epoxides with methyl Grignard reagents (2), we anticipated that the addition of methylmagnesium iodide to 2β,3β-epoxy-5α-cholestane (I) would give the desired compound II.



However, when I was treated with methylmagnesium iodide under the usual conditions, the reaction took an unexpected course yielding an A-norsteroid in 80% yield, besides other minor products. In no case were we able to obtain the desired II, from the above reaction.

The main product 2α-(1'-hydroxyethyl)-A-nor-5α-cholestane (III)* consisted of a mixture of two epimeric secondary alcohols. One had m.p. 77-79°, $[\alpha]_D^{25}$ + 31° ($CHCl_3$), ν_{max}^{KBr} 3440 cm^{-1}, and the other had m.p. 114.5-115.5°, $[\alpha]_D^{25}$ + 100° ($CHCl_3$), ν_{max}^{KBr} 3410 cm^{-1}. Both the epimers upon oxidation with Jones reagent (3) gave the same ketone, 2α-acetyl-A-nor-5α-cholestane (V), m.p. 80-80.5°, $[\alpha]_D^{28}$ + 4° ($CHCl_3$), ν_{max}^{KBr} 1707 cm^{-1}. The structure of V follows from its elemental analysis, infrared and NMR spectral data and a study of other chemical reactions. The infrared spectrum of V showed an absorption at 1707 cm^{-1} characteristic of a saturated ketone and the NMR spectrum** exhibited a peak at 2.15 ppm indicating the presence of an acetyl group. Baeyer-Villiger oxidation of V gave (90% yield) 2α-acetoxy-A-nor-5α-cholestane (VI), m.p. 95-96°, $[\alpha]_D^{26}$ + 19° ($CHCl_3$), ν_{max}^{KBr} 1733 and 1240 cm^{-1}. Hydrolysis of VI with 1N sodium hydroxide in 85% alcohol yielded the 2α-hydroxy-A-nor-5α-cholestane (VII), m.p. 155.5-156°, $[\alpha]_D^{26}$ + 24° ($CHCl_3$), ν_{max}^{KBr} 3300 and 1050 cm^{-1}. The physical constants of our

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* Correct analyses were obtained for all new compounds.

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compounds VI and VII are in agreement with those described by Shoppee and Sly (4). The configurations assigned by Shoppee and Sly for these compounds have been revised by Fuchs and Loewenthal (5), and this revision was subsequently confirmed by Dauben, et al (6). Baeyer-Villiger oxidation of an acetyl group to the corresponding acetate is known to proceed without inversion of configuration (7). Accordingly, the acetyl group in V must have the α configuration. Furthermore, isomerization of ketone V with sodium methoxide in methanol led to 2β-acetyl-A-nor-5α-cholestane (VIII), m.p. 67-68°, $[\alpha]_D^{26}$ + 18° ($CHCl_3$), ν_{max}^{KBr} 1715 cm^{-1}, agreeing with the one described by Mousseron, et al (8). Oxidation of VIII with perbenzoic acid gave 2β-acetoxy-A-nor-5α-cholestane (IX), m.p. 74-78°, $[\alpha]_D^{26}$ + 17° ($CHCl_3$), ν_{max}^{KBr} 1735 and 1242 cm^{-1}. The infrared spectrum of IX was identical with that of an authentic sample kindly provided by Prof. Shoppee. Thus the assigned structure and configuration of V were confirmed.

In addition to the A-norsteroid, we have also separated a tertiary hydroxy compound, 2α-methyl-2β-hydroxy-5α-cholestane (IV) m.p. 148-149°, $[\alpha]_D^{26}$ + 48° ($CHCl_3$), ν_{max}^{KBr} 3380 and 1020 cm^{-1} in 15% yield. Its structure was established by direct comparison with an authentic sample, prepared by the reaction of methylmagnesium iodide with 2-keto-5α-cholestane. The axial configuration of the hydroxyl group in IV was established by

converting it to 2α-methyl-2β,19-oxido-5α-cholestane (X), m.p. 97-99°, $[\alpha]_D^{28}$ + 16° ($CHCl_3$), ν_{max}^{KBr} 1023 cm^{-1} (ether linkage), by the action of lead tetraacetate and iodine in boiling benzene (9). In the NMR spectrum of X, the C-19 methyl peak at 1 ppm was absent. Instead, a single peak at 3.76 ppm appeared, indicating a pair of equivalent protons due to the C-19 methylene function (1).

Rearrangement of the epoxides under the influence of magnesium halides is well known (10). Treatment of cyclohexene oxide with methylmagnesium iodide results in ring contraction and yields cyclopentylmethylcarbinol (11). Henry (12) noted that in some instances, epoxides are first isomerized in the presence of magnesium halides to the corresponding aldehydes or ketones which then react with Grignard reagents.

In steroids, the addition of Grignard reagents has been investigated primarily with the 5,6-epoxides (2). The possibility of ring contraction in 5α,6α-epoxysteroids under the influence of magnesium halides was investigated by Turner (13), who found that no ring contraction occurred. Similarly in the case of 4,5-epoxides no ring contraction was observed and normal addition of Grignard reagent took place (14). However, in another instance it was reported (15) that when a 11β,12β-epoxysteroid was treated with methylmagnesium iodide, ring C was contracted

to a five-membered ring. A consideration of these results suggests that, if the epoxide ring is attached to a carbon atom which is part of a ring junction (as in 5,6-epoxysteroids) normal epoxide opening occurs under the action of Grignard reagents; whereas, with epoxides at other positions rearrangements are possible. For further evaluation of these transformations, we are currently investigating the action of Grignard reagents on epoxide functions located at various positions of the steroid nucleus.

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