Notes

A department for short papers of immediate interest.

An Intermediate in the Grignard Reaction[1]

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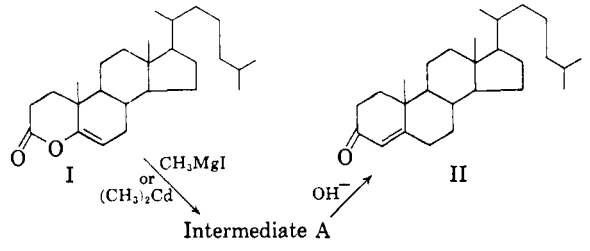
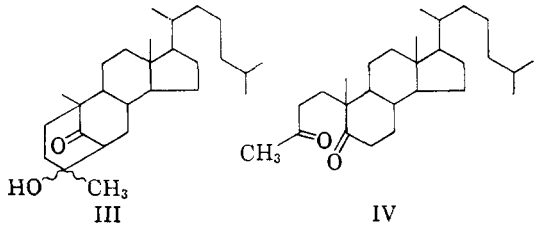
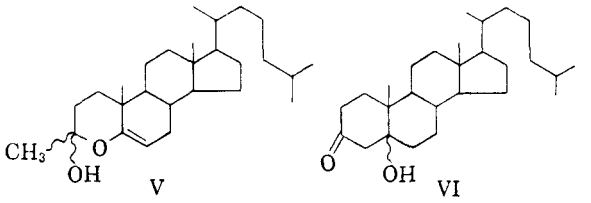
In the Grignard reaction for the introduction of isotopic carbon into the cholestenone nucleus we obtained a crystalline intermediate (A), melting at 174–178°, which gave an analysis corresponding to a methyl adduct to the enol lactone (I).[4] This intermediate was obtained after mild hydrolysis of the Grignard product in almost quantitative yield. Infrared data indicated the presence of a hydroxyl (3600 cm.$^{-1}$) and a ketone (1720 cm.$^{-1}$) group. Treatment with acid or alkali converted it to cholestenone (II).



The identical intermediate (A) was obtained upon treatment of the enol lactone I with excess dimethylcadmium, although in lesser yield. It would appear that the mode of addition of the methyl Grignard reagent and of dimethylcadmium to the enol lactone and rearrangement is similar.

The following are the several formulations for the intermediate (A) which are considered on the basis of our findings and those of several other investigators. The evidence establishes structure III (3-hydroxy-4,5-seco-3,6-cyclocholestan-5-one) for this methyl adduct.[5] Our studies with model systems for this reaction further substantiate this structure.[6]





The diketone IV has been synthesized by Schmid and Kagi[7] by an independent method and also isolated by Heard and Ziegler[8] and shown to have quite different properties (a colorless oil, $[\alpha]_D^{19}$ +60° in chloroform) from intermediate A. These findings and the fact that this structure could not account for the presence of a hydroxyl peak in the infrared would eliminate structure IV as the intermediate A.

The hemiacetal structure V has been proposed by Heard and Ziegler[8] who also prepared this intermediate by the Grignard method (they reported m.p. 164–175°, $[\alpha]_D^{23}$ +10° in chloroform). They based their structure on the evidence of a positive tetranitromethane test indicating presence of unsaturation and on conversion of this intermediate to the diketone IV on vacuum distillation. They ascribed the ketone peak in the infrared spectrum of this intermediate to contamination mainly by the diketone IV.

When we purified our sample of intermediate A further by chromatography and recrystallization, we obtained material melting at 176–178°, $[\alpha]_D^{24}$ +14.5 in chloroform. The ketone and hydroxyl peaks in the infrared remained pronounced. A tetranitromethane test on this sample was negative. This indicated that the compound does have both hydroxyl and carbonyl functions and lacks unsaturation. Further evidence against structure V lies in the absence of an enol ether peak in the region of 1665 cm.$^{-1}$ in the infrared spectrum.[9]

The arguments against structure VI for intermediate A are two-fold. A steroid 3-ketone would

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(4) G. I. Fujimoto, *J. Am. Chem. Soc.*, **73**, 1856 (1951).

(5) Evidence for this structure was first presented at the XIVth International Congress of Pure and Applied Chemistry, Zurich, Switzerland, July 1955.

(6) K. D. Zwahlen, W. J. Horton, and G. I. Fujimoto, *J. Am. Chem. Soc.*, **79**, 3131 (1957).

(7) H. Schmid and K. Kagi, *Helv. Chim. Acta*, **33**, 1582 (1950).

(8) R. D. H. Heard and P. Ziegler, *J. Am. Chem. Soc.*, **73**, 4036 (1951).

(9) H. Rosenkrantz and M. Gut, *Helv. Chim. Acta*, **36**, 1000 (1953).

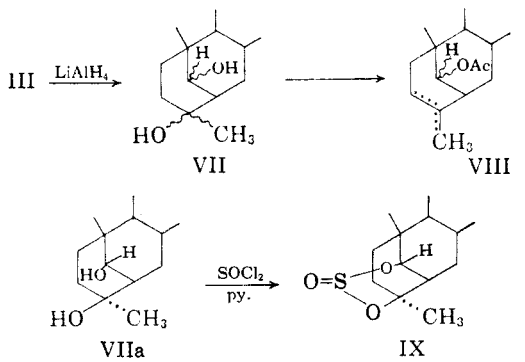
be expected to form derivatives fairly readily.[10] This has not been our experience with intermediate A. It failed to form either a semicarbazone or an oxime under the usual mild conditions[11] and only the starting substance (A) was recovered

When the ketone function in intermediate A was reduced with lithium aluminum hydride, a dihydroxy product was obtained which could not be acetylated when treated with acetic anhydride and pyridine (*vide infra*). If a steroid 3α- or 3β-hydroxyl group had been formed, it would have been expected to acetylate readily under these conditions.[10]

Structure III does satisfy the experimental observations for the intermediate A. Molecular model of structure III shows that the ketone is in a somewhat hindered, bridged position and would not be expected to form derivatives easily. This would account for the failure to form a semicarbazone or an oxime.

The hindered nature of the hydroxyl groups in the product (mixture of isomers VII) of the lithium aluminum hydride reduction of intermediate A is consistent with formulation III. As mentioned above, the diols VII failed to acetylate on standing overnight in acetic anhydride and pyridine. However, when the diols were treated with *p*-toluenesulfonic acid in benzene and acetic anhydride, an oil was obtained from which was isolated in over 50% yield an unsaturated acetate (VIII, m.p. 74.5–75.5°). This substance gave a positive tetranitromethane test.

A cyclic sulfite ester (IX) of the type obtained in our previous work[6] resulted from treatment of the diol mixture VII with thionyl chloride in benzene and pyridine. Efforts to obtain optimal yields of IX were not attempted, but indications are that the isomer VIIa is probably a major product of the hydride reduction. It appears that both III and VII consist of a mixture of 3α- and 3β-hydroxyl isomers and that the 3β-hydroxyl is the preponderant one.



(10) See for example Fieser & Fieser, *Natural Products Related to Phenanthrene*, Reinhold Publishing Corp., New York, N. Y., 1949, p. 125.

(11) *Cf.* Shriner and Fuson, *Identification of Organic Compounds*, 3rd Edit., J. Wiley & Sons, Inc., New York, 1948, pp. 170 and 202.

Further support for the structure III comes from the interpretation of the nuclear magnetic resonance spectrum of this intermediate.[12] This spectrum indicates that:

1. The resonance peak for a proton on a double bond (as would be required for structure V) is absent.

2. The C-19 methyl peak is shifted appreciably from the position for the corresponding peak in cholesterol, although the C-18 methyl peak is in the identical position for both. This would favor structure III over VI since the C-19 methyl in VI would be expected to have a peak like cholesterol.

3. An additional methyl peak to the number found in cholesterol is present in the spectrum. When the sample is dissolved in pyridine this chloroform-*d* methyl peak shifts towards lower field about 8 c.p.s., while dissolving cholesterol in pyridine has only a slight effect on the positions of the methyl peaks.

4. This extra methyl group is attached to a carbon bearing no protons.

The above findings are consistent only with structure III.

EXPERIMENTAL[13]

3-Hydroxy-4,5-seco-3,6-cyclocholestan-5-one (III). Dimethylcadmium in benzene was prepared according to Cason[14] from methylmagnesium bromide (0.24 g. of magnesium) and 1.00 g. of cadmium chloride. A solution of 1.00 g. of 5-hydroxy-3,5-seco-A-norcholest-5-en-3-oic acid lactone (I) in 25 ml. of benzene was added, and the mixture was refluxed for 3 hr. with stirring. It was then allowed to stand overnight at room temperature. To it was added 50 ml. of ice water and 3 ml. of dilute hydrochloric acid, the layers were separated and the aqueous solution extracted with ether. The organic solutions were combined and washed several times with water, dried over sodium sulfate, and the solvents distilled. The pale yellow oil (0.92 g.) obtained was dissolved in hexane and chromatographed on 40 g. of silica. The fraction in the 10% butanone in hexane eluate weighed 0.30 g. (29%) m.p. 140–174°. A single crystallization from acetone gave a melting point of 174–176° and material for analysis melted at 176–178°, undepressed when mixed with III from the Grignard reaction.[4]

4,5-Seco-3,6-cyclocholestan-3,5-diol (VII). A suspension of 3.00 g. of III in 50 ml. of ether was added to a slurry of 0.50 g. of lithium aluminum hydride in 50 ml. of ether. After 1 hr. a slight excess of water was added dropwise, the ether was decanted, and the salts were washed several times with ether. Distillation of the ether *in vacuo* and crystallization of the residue from acetone–methylene chloride gave 1.59 g. of VII (53%) m.p. 188–193°. After several crystallizations from ether-acetone a sample melted at 189–194°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.95. Found: C, 80.24; H, 12.02.

Dehydration and acetylation of VII *to yield* VIII. A solution of 0.50 g. (1.25 mmol.) of VII and 0.24 g. of *p*-toluenesulfonic acid monohydrate in 10 ml. of benzene and 10 ml. of

(12) The assistance of Dr. J. N. Shoolery of Varian Associates in obtaining and interpreting the NMR spectrum is gratefully acknowledged. The sample was run in chloroform-*d* and also in pyridine at 60 Mc.

(13) Melting points have been taken on a Kofler hot stage and are corrected.

(14) J. Cason, *J. Am. Chem. Soc.*, **68**, 2079 (1946).

acetic anhydride was allowed to stand at room temperature overnight. After addition of 0.21 g. (2.5 mmol.) of sodium acetate the solvents were removed *in vacuo*. The residue was collected in ether and the ether was filtered and evaporated. The residual oil crystallized from acetone at −80°; m.p. 50–56° (0.30 g., 57%). After crystallization from methanol VIII melted at 71–74°. Further crystallization from the same solvent gave a sample melting at 74.5–75.5°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 80.98; H, 11.31.

The test for unsaturation with tetranitromethane was positive. When the diols VII was allowed to stand in pyridine–acetic anhydride overnight, only unchanged VII was recovered.

Cyclic sulfite ester IX *of* VIIa. A solution of 1.20 g. of diol VII in 45 ml. of benzene with 1 ml. of thionyl chloride and 3 drops of pyridine was allowed to stand 2 hr. at room temperature. Removal of the solvents *in vacuo* gave a dark brown tar. From an ethanol extract of the tar a pale yellow oil was obtained which was chromatographed on 50 g. of silica. The benzene eluate weighed 0.130 g. and melted at 136–139°. Several crystallizations from methanol-acetone and finally from acetone gave a sample of IX melting at 139–141.5°.

Anal. Calcd. for $C_{27}H_{46}O_3S$: C, 71.95; H, 10.29. Found: C, 72.42; H, 10.17.

Treatment of IX with alcoholic potassium hydroxide regenerated the diol VIIa.

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Structure of a Supposed Tetraphenylcyclobutane

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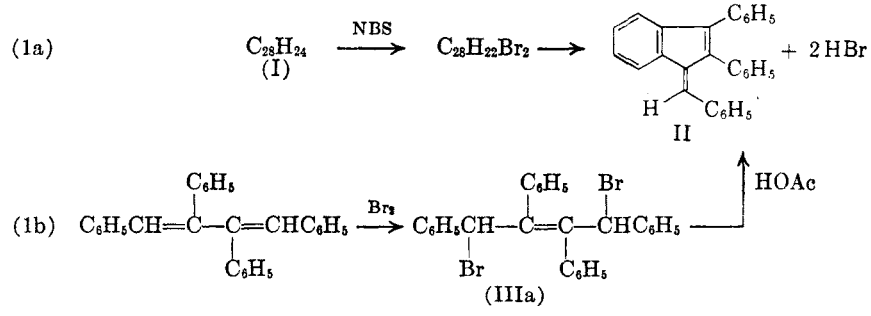
Recently Morton, Flood, and Bright[1] reported the isolation of a hydrocarbon $C_{28}H_{24}$ (I) which they believed to be a previously unreported isomer of 1,2,3,4-tetraphenylcyclobutane. We were interested in investigating the reaction of such cyclobutanes with *N*-bromosuccinimide, and by chance, we happened to choose their compound for study rather than the other previously reported isomers.[2,3]

Compound I readily underwent reaction with two moles of *N*-bromosuccinimide in refluxing carbon tetrachloride to yield a very labile dibromide which decomposed on further refluxing of the solution to afford hydrogen bromide and a brilliant yellow hydrocarbon, $C_{28}H_{20}$ (II). II was obtained in about 40% yield and was shown to be 1-benzylidene-2,3-diphenylindene by comparison with an authentic sample of this benzofulvene prepared from tetraphenylbutadiene by the usual route[4] (Eq. 1b). Although this result (Eq. 1a) is not mechanistically incompatible with the formulation of I as a tetraphenylcyclobutane, as witness Eq. 2, some question arose concerning the structure of I when we learned from Dr. Emil White[5] that the other isomers[2,3] of 1,2,3,4-tetraphenylcyclobutane do not behave in this fashion.

The reported[6] m.p. of one of the geometric isomers of 1,2,3,4-tetraphenyl-1-butene is the same as that of I, and since treatment of this tetraphenylbutene with two moles of N-bromosuccinimide might be expected to give the dibromide (III) which yields II on decomposition, we synthesized[6] a sample of this olefin for comparison with I. The synthetic sample of 1,2,3,4-tetraphenyl-1-butene was identical in every respect with I. It is thus clear that I is one of the geometric isomers of 1,2,3,4-tetraphenyl-1-butene rather than a tetraphenylcyclobutane.

Morton, Flood, and Bright[1] isolated I (15%) as a by-product of the formation of stilbene (80%) from the reaction of benzyl chloride with excess potassium amide in liquid ammonia. It seems possible that I may arise from some such side reaction as 3:



(1) J. M. Morton, E. A. Flood, and N. F. H. Bright, *Can. J. Chem.*, **35**, 1097 (1957).

(2) M. Pailer and U. Müller, *Monatsh.*, **79**, 615 (1948).

(3) J. D. Fulton and J. D. Dunitz, *Nature*, **160**, 161 (1947).

(4) A. Orechoff, *Ber.*, **47**, 89 (1914).

(5) E. H. White, private communication.

(6) E. Bergmann, D. Winter, and W. Schreiber, *Ann.*, **500**, 122 (1933).