mole) and 312.0 g. (2.4 moles) of aminoethylmorpholine[15] was heated at a bath temperature of 175–180° for thirty-eight and one-half hours. The cooled reaction mixture was suspended in about 2–2.5 liters of ether. The hygroscopic precipitate was separated by filtration and washed well with ether. The filtrate, after removal of the ether and excess aminoethylmorpholine, was distilled *in vacuo*. The product, a viscous yellow liquid, b. p. 127–144° at 0.01 mm.[16] was obtained in 89% yield (144.7 g.).

Method B. 2-Benzylaminolepidine (III).—A mixture of 31.6 g. (0.2 mole) of 2-aminolepidine and 4.6 g. of lithium amide[17] in 100 ml. of dry toluene[18] was refluxed for two hours in an oil-bath at 120–130°. After cooling somewhat, 25.3 g. (0.2 mole) of benzyl chloride in 50 ml. of dry toluene was added and the mixture refluxed twenty-one and one-half hours longer. The mixture was filtered and the precipitate washed well with ether. After removal of the ether and toluene from the filtrate, the residue was distilled *in vacuo*, yielding 36.9 g. (74.2%) of a viscous orange oil, b. p. 156–167° at 0.03 mm.[16] The product solidified on rubbing with petroleum ether, m. p. 72.4–73.0°.

Method C. 2-(4-Methoxybenzyl)-aminolepidine (X).—A solution of 31.6 g. (0.2 mole) of 2-aminolepidine and 27.2 g. (0.2 mole) of anisaldehyde in 50 ml. of formic acid (practical grade, 85–90%) was refluxed for sixteen days.[19] Water and ice were added to the cooled solution which was then made alkaline and extracted with chloroform. After drying over anhydrous potassium carbonate and removing the solvent, the residue was distilled under reduced pressure. The viscous yellow oil weighed 35.0 g. (62.7%) and distilled at 181–187° at 0.05 mm.[16]

Method D.—Since compounds XIV–XXIV were all prepared in exactly the same way, only the general method is described, and the results summarized in Table I. A mixture of 0.04 mole of the secondary amine, III–XIII, 2.5 g. of lithium amide and 100 ml. of dry toluene was refluxed for two hours. After cooling somewhat, 7.5 g. (0.052 mole) of β-dimethylaminoethyl chloride hydrochloride followed by 50 ml. of toluene were added and the reaction mixture refluxed an additional nineteen to twenty hours. After removing the lithium chloride and solvent (as in method B), the residue was distilled *in vacuo*.

Method E.—This method is the same as the previous except for the amounts of reactants, which were changed to include 0.05 mole of the diamine (I or II), 1.6 g. of lithium amide and 8.2 g. (0.065 mole) of benzyl chloride. The results are summarized in Table I.

(15) The author is indebted to the Sharples Chemical Co. for samples of several of their products.

(16) Since the product was distilled in a Claisen flask with a wide side-arm, the actual distillation pressure was much higher.

(17) Purchased from Metalloys Corp., Minneapolis, Minn.

(18) The toluene was dried over calcium hydride, a sample of which had been generously contributed by the Metal Hydrides Co., Inc.

(19) This is probably not the optimum length of time for this particular reaction. In a model experiment, using benzaldehyde, a 21.1% yield of crude product, isolated as the hydrochloride, was obtained after a nineteen hours' reflux period. The yield rose to 37.2% when the refluxing was extended over a sixteen-day period. In the case of some of the substituted benzaldehydes, better yields might be expected with less tarry by-products if the reflux period were shortened.

Summary

2-Benzyl-, substituted benzyl-, thenyl- and substituted thenyl-aminolepidines were prepared by treating 2-aminolepidine with the appropriate alkyl halide in the presence of lithium amide, or with an aldehyde in the presence of formic acid. 2-Lepidylaminoalkylamines were prepared by refluxing 2-chlorolepidine in excess of the alkylene diamine. The former products were then condensed with β-dimethylaminoethyl chloride hydrochloride in the presence of lithium amide and the latter similarly treated with benzyl chloride. These N,N-disubstituted-2-lepidylamines were prepared as possible antihistaminic agents.

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3α,12α-Dihydroxy-etiocholan-16-one[1a]

BY CHARLES W. MARSHALL[1b] AND T. F. GALLAGHER

In a previous communication[2] it was reported that ozonization of the enol acetate 3α,12α,20-triacetoxy-Δ^{17}-pregnene (I) yielded, in addition to the anticipated 17-ketosteroid, a second crystalline product melting at 219–220.5°; $[\alpha]^{25}D$ + 40° (chloroform). The product showed an absorption spectrum in the ultraviolet with a maximum at 2490 Å. and the elementary analysis was consistent with the formula $C_{21}H_{38}O_7$. These facts are best explained on the assumption that oxidation by ozone had converted the reactive methylene group at C-16 to a ketone without rupture of the unsaturated bond from C-17 to C-20. A molecular model of (I) demonstrates that the two acetoxy groups at C-20 and C-12 together with the angular methyl group at C-13 can very effectively screen the olefinic linkage between C-17 and C-20, so that these two carbon atoms are almost completely shielded by the substituent groups. It is not surprising under these circumstances that ozone attacks C-16 with the formation of the α,β-unsaturated ketone (II). It is well known that the rate of ozonide formation is relatively slow[3,4] with heavily substituted olefins; the persistence of II in the presence of excess ozone is somewhat unexpected but is probably to be explained by the steric factors which prevented the ozonolysis of the olefinic bond initially.

The absorption spectrum of II is especially

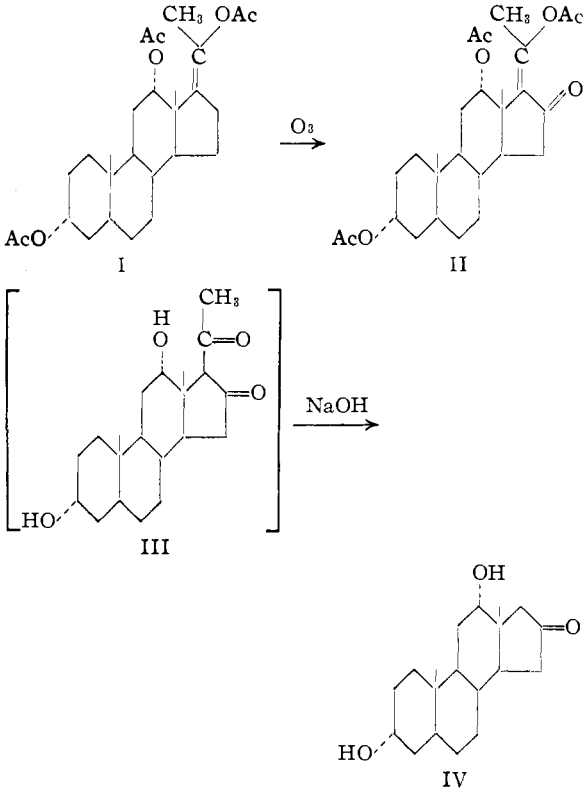
(1) (a) The work described in this paper was supported in part by a grant from the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council. (b) Present address: Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts.

(2) Marshall, Kritchevsky, Lieberman and Gallagher, THIS JOURNAL, **70**, 1837 (1948).

(3) Noller, Carson, Martin and Hawkins, *ibid.*, **58**, 24 (1938).

(4) Harries, *Ber.*, **36**, 1933 (1903).

important since according to the generalizations of Woodward,[5] a maximum at 2490 Å. should be associated with a trisubstituted α,β-unsaturated ketone. Confirmation of the structure was afforded by alkaline hydrolysis. After boiling for one hour with 1 *N* sodium hydroxide in 75% ethanol, four equivalents of acid were produced which clearly indicated the persistence of the enol acetate structure. The neutral product resulting from alkaline hydrolysis agreed well with the empirical formula $C_{19}H_{30}O_3$ and exhibited no specific absorption in the ultraviolet region of the spectrum. The very marked levorotation of the 16-ketone in comparison with the 17-keto analog is noteworthy. Cleavage of the enol acetate II by alkali would yield the 1,3-diketone (III) which would then undergo further cleavage[6,7,8] with the formation of acetic acid and the 16-ketosteroid.



Experimental[9]

Ozonolysis of 3α,12α,20-Triacetoxy-Δ17-pregnene.—A preliminary run, using 296 mg. of the enol acetate (I) in 400 ml. of a 1:1 mixture of anhydrous methanol and ethyl acetate at −30° employing 5 mole equivalents of ozone in a rapidly flowing 6% stream, resulted in the recovery of 103 mg. of unchanged product. No other crystalline material was isolated. Two reactions were then carried out as follows. In the one case, 1.0 g. of the enol acetate (I) was dissolved in 400 ml. of methanol–ethyl acetate, chilled to −70° and three mole equivalents of ozone in a 6% stream were passed through the solution during 14 minutes. In the other instances, 1.26 g. of the enol acetate in 400 ml. of the same solvent mixture were chilled to −40° and three mole equivalents of ozone in a 5% stream dispersed through a fritted glass plate were passed through the solution during 61 minutes. At the end of each experiment a 5% palladium–calcium carbonate catalyst (2.5 g.) was added and the mixture shaken in an atmosphere of hydrogen until there was no further uptake (less than 15 minutes). After removal of the catalyst and solvent, the resinous solids were subjected to fractionation on aluminum oxide. Earlier fractions, eluted with petroleum ether and 5 to 25% benzene in petroleum ether yielded a crystalline substance later identified as (II); the later fractions with 50% benzene yielded 3α,12α-diacetoxy-etiocholan-17-one. Rechromatography provided very little additional crystalline material and high vacuum sublimation at 100° of a crude crystalline mixture (melting range 145–195°) yielded a crystalline sublimate of the diacetoxy 17-ketone. The total yield of crude crystalline 3α,12α,20-triacetoxy-Δ17-pregnen-16-one (II) from both reactions was 359 mg. (15.5%) of which 221 mg. derived from the rapid ozonolysis at −70° and 138 mg. from the slower ozonolysis at −40°.

3α,12α,20-Triacetoxy-Δ17-pregnen-16-one (II).—The ill-formed prisms melting 200–213° from the early chromatographic fractions were combined and after recrystallization from petroleum ether, ethyl ether and ethyl acetate–petroleum ether, 170 mg. of pure substance was obtained as large rectangular prisms, m. p. 219–220.5°; $[\alpha]^{28}D$ +40° (chloroform), and ϵ_{2490} = 11,200 (ethanol). The saponification equivalent on boiling one hour with 1 *N* sodium hydroxide in 75% ethanol was 117; calculated for mol. wt. 474.6 = 118.5.

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.32; H, 8.07. Found: C, 68.06; H, 8.12.

3α,12α-Dihydroxy-etiocholan-16-one (IV).—70.5 mg. of II was heated in an atmosphere of nitrogen under reflux with 1 *N* sodium hydroxide in 75% ethanol for one hour. The solution was cooled, diluted and neutralized with sulfuric acid. Sodium chloride was added to the suspension which was then extracted with ether and washed with 5% sodium chloride. After removal of the solvent the residue was crystalline. Recrystallization from petroleum ether–ethyl acetate and ethyl ether yielded 27.7 mg. of pure product as long slender prisms, m. p. 219–220°; $[\alpha]^{26}D$ −108° (chloroform). From 2250 to 3500 Å. there was no selective absorption.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.28; H, 9.66.

The product gave no color with *m*-dinitrobenzene and alkali under the usual conditions for the Zimmermann reaction for 17-ketosteroids; in contrast 3α,12α-dihydroxy-etiocholan-17-one gave 70% of the color obtained with an equimolar amount of 3β-hydroxyandrostan-17-one.

We wish to express our appreciation to Dr. H. Wilson of the Sloan-Kettering Institute for the colorimetric estimations.

Summary

3α,12,20-Triacetoxy-Δ17-pregnene upon ozonolysis yielded 3α,12α,20-triacetoxy-Δ17-pregnen-16-one which upon alkaline hydrolysis was converted to 3α,12α-dihydroxyetiocholan-16-one.

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(5) Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942).
(6) Hauser, Swamer and Ringler, *ibid.*, **70**, 4023 (1948).
(7) Bradley and Robinson, *J. Chem. Soc.*, **129**, 2356 (1926).
(8) Adkins, in Gilman's "Organic Chemistry," Vol. I, 2nd Ed., John Wiley & Sons, New York, N. Y., 1943, p. 1070.
(9) Melting points are corrected. Microanalyses by Dr. Joseph Alicino, Metuchen, N. J.