Determination of rate of acetolysis of I. The kinetic procedure used was essentially the same as that of Winstein and Adams.[2(d)]

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PRINCETON, N. J.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, WEIZMANN INSTITUTE OF SCIENCE]

Synthesis and Reactions of 3β-Acetoxy-20-ethynyl-5-pregnen-20-ol

FRANZ SONDHEIMER, NAFTALI DANIELI, AND YEHUDA MAZUR

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The reaction between 3β-acetoxy-5-pregnen-20-one (Ia) and sodium acetylide in liquid ammonia is shown to yield the 20-ethynyl carbinol II mentioned in the title. Dehydration of the latter with phosphorus oxychloride in pyridine led to the 20-ethynyl-$\Delta^{20(21)}$-ethylene III. Hydration of II gave the keto-diol Va, which could be oxidized by the Oppenauer method to the corresponding Δ^4-3-ketone VI, a homolog of 17α-hydroxyprogesterone. Reaction of the keto-diol Va with sodium hypobromite and subsequent methylation yielded the bisnorcholanic acid derivative VII. 3β-Acetoxy-5,16-pregnadien-20-one (VIII) was found not to react with sodium or lithium acetylide in liquid ammonia, whereas the 16β-hydroxy-20-ketone Ib and the 16α-benzyloxy-20-ketone Ic were converted to the 16-dehydro-20-ketone VIII under these conditions.

Although the reaction of androstan-17-one derivatives with acetylene is well known and is of industrial importance,[1] the corresponding reaction of pregnan-20-ones with acetylene has not been reported previously. We were interested whether the latter type of reaction could be carried out successfully, since its extension to 16-dehydro- or 16-oxygenated-pregnan-20-ones might result in the synthesis of the steroidal sapogenins, while its application to 21-hydroxypregnan-20-one derivatives could lead to substances belonging to the bufo-scilla group of cardiac-active steroids.[2]

In practice, we have now found that the reaction between 3β-acetoxy-5-pregnen-20-one (pregnenolone acetate) (Ia) and sodium acetylide in liquid ammonia proceeds smoothly and after reacetylation gives 3β-acetoxy-20-ethynyl-5-pregnen-20-ol (II), m.p. 193°, in 70% yield. The structural assignment is based on the infrared spectrum (presence of a terminal acetylene, absence of a saturated ketone) and the elemental analysis. Although a new asymmetric center is introduced in the conversion of Ia to II, only one isomer of the latter was isolated. This is presumably the 20β-hydroxy isomer (convention of Fieser and Fieser[3]), since the reaction of pregnan-20-ones with lithium aluminum hydride[4] and with sodium borohydride[5] gives this isomer predominantly.

A number of transformations involving the 20-ethynyl-20-hydroxy grouping of II were carried out. Treatment with phosphorus oxychloride in hot pyridine resulted in dehydration[6] and yielded a conjugated vinyl-acetylene, m.p. 105°, the spectral properties of which indicated it to be the $\Delta^{20(21)}$-ethylene III rather than the $\Delta^{17(20)}$-ethylene IV. Thus in the ultraviolet, the substance showed a maximum at 223 mμ (ε 10,500); this is compatible with the monosubstituted vinyl-acetylene structure III (*cf. trans*-pent-2-en-4-yne, λ_{max} 223 mμ[7]; pent-2-en-4-yn-1-ol, λ_{max} 223 mμ[8]), but is at too low a wave length for the α,β,β-trisubstituted vinyl-acetylene IV (*cf.* the β,β-disubstituted vinyl-acetylene 2-methylpent-2-en-4-yn-1-ol, λ_{max} 226 mμ[9]). In the infrared, the product showed a band at 11.14 μ, the position to be expected of a disubstituted terminal acetylene.[10]

The acetylene grouping of the acetylenic carbinol II could readily be hydrated by means of a methanolic boron trifluoride–mercuric oxide–trichloroacetic acid catalyst,[6,11] a reaction which also caused saponification of the acetate grouping at C-3. The resulting 20-acetyl-5-pregnene-3β,20-diol (Va), m.p. 239°, thus obtained in over 70% yield, on acetyla-

(1) *Inter al.*, L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937); H. E. Stavely, *J. Am. Chem. Soc.*, **61**, 79 (1939).

(2) *Cf.* F. Sondheimer, N. Stjernström, and D. Rosenthal, *J. Org. Chem.*, **24**, 1280 (1959).

(3) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948).

(4) *Inter al.*, W. Klyne and E. Miller, *J. Chem. Soc.*, 1972 (1950); R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 2283 (1951).

(5) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).

(6) *Cf.* J. C. Hamlet, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 2652 (1951).

(7) J. L. H. Allan and M. C. Whiting, *J. Chem. Soc.*, 3314 (1953).

(8) L. J. Haynes, I. M. Heilbron, E. R. H. Jones, and F. Sondheimer, *J. Chem. Soc.*, 1583 (1947).

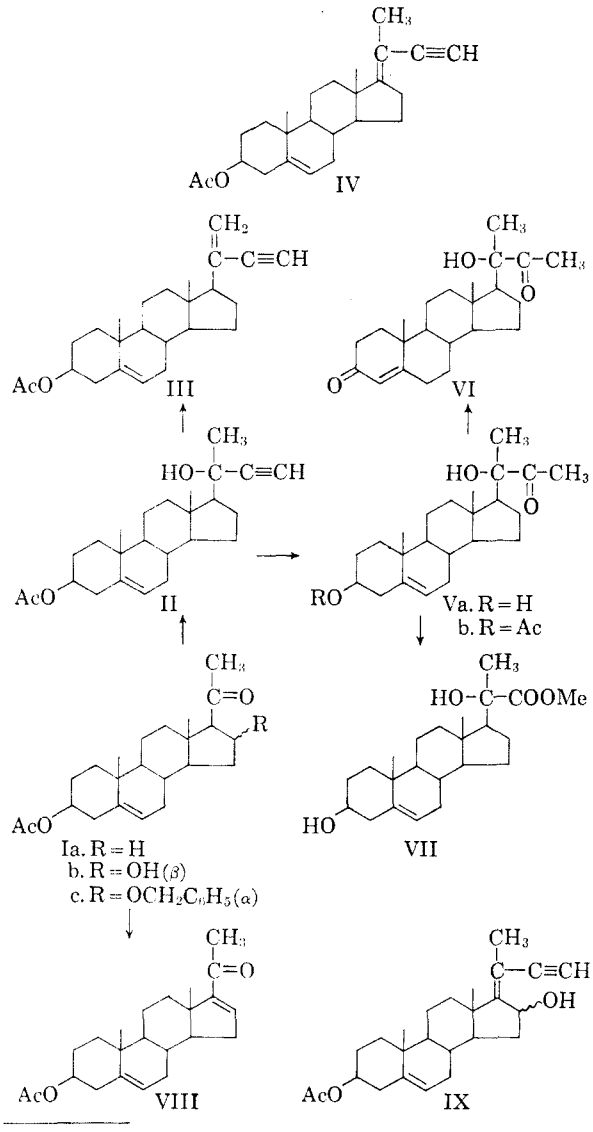
(9) R. Ahmad and B. C. L. Weedon, *J. Chem. Soc.*, 3286 (1953).

(10) *Cf.* N. Sheppard and D. M. Simpson, *Quart. Revs. (London)*, **6**, 1 (1952), Table 7. The starting material II showed a weaker band in the same region, so this evidence can be accepted only with some reserve.

(11) *Inter al.*, A. O. Zoss and G. F. Hennion, *J. Am. Chem. Soc.*, **63**, 1151 (1941); A. M. Islam and R. A. Raphael, *J. Chem. Soc.*, 4086 (1952).

tion gave the 3-monoacetate Vb, m.p. 237°. On Oppenauer oxidation, the keto-diol Va gave 20-acetyl-20-hydroxy-4-pregnen-3-one VI, m.p. 193°, which may be regarded as a homolog of 17α-hydroxyprogesterone.[12] Reaction of the keto-diol Va with sodium hypobromite converted the methyl ketone grouping to a carboxylic acid and after treatment with diazomethane yielded methyl 3β,20-dihydroxybisnor-5-cholenate VII, m.p. 202°.

It may be of interest to mention that we could not achieve the synthesis of 20-ethynylpregnane derivatives hydroxylated at C-16, which might have been convertible to the steroidal sapogenins by application of some of the above described reactions. Thus, treatment of 3β-acetoxy-5,16-pregnadien-20-one (VIII) with sodium or lithium acetylide[13] in liquid ammonia or with acetylenemonomagnesium bromide in tetrahydrofuran[14] after re-acetylation yielded only recovered starting material; in no case was the 16-dehydro analog of II obtained, which on treatment with acid was expected to rearrange to 3β-acetoxy-20-ethynyl-5,17(20)-pregnadien-16-ol (IX). The action of sodium or lithium acetylide on 3β-acetoxy-16β-hydroxy-5-pregnen-20-one (Ib)[15] as well as on 3β-acetoxy-16α-benzyloxy-5-pregnen-20-one (Ic)[16] caused β-elimination of the grouping at C-16 and after re-acetylation gave the Δ[16]-20-one VIII in high yield, while the action of acetylenemonomagnesium bromide[14] on the 16α-benzyloxy compound Ic resulted in the complete recovery of starting material. This line of investigation was abandoned when another route to the required 16-hydroxylated-20-substituted pregnane derivatives was found.[17]



EXPERIMENTAL[18]

3β-Acetoxy-20-ethynyl-5-pregnen-20-ol (II). A catalytic amount of ferric nitrate was added to a solution of 3.5 g. of sodium in *ca.* 250 cc. of liquid ammonia, with stirring and Dry Ice–acetone cooling. When the conversion to sodamide was complete, a stream of acetylene was passed in for 0.5 hr. A solution of 5 g. of 3β-acetoxy-5-pregnen-20-one (Ia) in 250 cc. of ether was added gradually during 0.5 hr., and the mixture was stirred with continued cooling for a further 5 hr. Ammonium chloride (15 g.) was added and the ammonia was allowed to evaporate overnight. Water was added to the residue and the organic material was extracted with a mixture of ether and ethyl acetate. The resulting material was re-acetylated by means of acetic anhydride and pyridine (16 hr. at room temperature). The product was chromatographed on 250 g. of alumina. Elution with benzene-ether (9:1) to (4:1) yielded 3.75 g. (70%) of the acetylenic carbinol II, m.p. 186–190°. Crystallization from acetone-hexane gave the analytical sample, m.p. 192–193°, $[\alpha]_D$ −43°, infrared band at 3.01 μ (terminal acetylene) and 5.78 μ (acetate), as well as a free hydroxyl band.

Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44. Found: C, 77.87; H, 9.67.

20-Ethynyl-5,20(21)-pregnadien-3β-ol Acetate (III). Phosphorus oxychloride (5 cc.) was added dropwise during 5 min. to a solution of 150 mg. of the acetylenic carbinol acetate II in 10 cc. of pyridine. The mixture was then heated on a boiling steam-bath under reflux for 1 hr., moisture being excluded. It was then cooled and poured onto ice. The organic

(12) In the Clauberg assay for progestational activity by injection in the rabbit (carried out by the Endocrine Laboratories, Madison 1, Wis.), the diketo-alcohol VI was found to be inactive. Similarly, A. Wettstein [*Helv. Chim. Acta*, **24**, 311 (1941)] had found the corresponding progesterone and desoxycorticosterone acetate analogs to be biologically inactive.

(13) *Cf.* W. Oroshnik and A. D. Mebane, *J. Am. Chem. Soc.*, **71**, 2062 (1949).

(14) E. R. H. Jones, L. Skatteböl, and M. C. Whiting, *J. Chem. Soc.*, 4765 (1956).

(15) B. Löken, S. Kaufmann, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 1738 (1956).

(16) H. Hirschmann, F. B. Hirschmann, and M. A. Daus, *J. Am. Chem. Soc.*, **74**, 539 (1952).

(17) N. Danieli, Y. Mazur, and F. Sondheimer, *Chem. & Ind. (London)*, 1724, 1725 (1958).

(18) Melting points are uncorrected. All chromatograms were carried out with Merck "acid-washed" alumina. Rotations were determined at room temperature in chloroform solution. Ultraviolet spectra were measured in 95% ethanol solution of a Unicam Model S.P. 500 spectrophotometer and infrared spectra in chloroform solution on a Baird double-beam recording spectrophotometer. Analyses were carried out in our microanalytical department under the direction of Erich Meier.

material was extracted with ether and the ether extract was washed with dilute sulfuric acid, sodium bicarbonate solution, and water. Drying, evaporation, and chromatography on 7 g. of alumina gave fractions eluted with pentane and pentane-benzene (9:1) which on crystallization from methanol yielded 82 mg. (57%) of the vinyl-acetylene III, m.p. 90–95°. Two further crystallizations from methanol furnished a pure sample, m.p. 103–105°, λ_{max} 223 mμ (ε, 10,500), infrared band at 3.02 μ (terminal acetylene), 5.78 μ (acetate), and 11.14 μ (terminal methylene), no hydroxyl band.

Anal. Calcd. for $C_{25}H_{34}O_2$: C, 81.92; H, 9.35. Found: C, 81.56; H, 8.99.

20-Acetyl-5-pregnene-3β,20-diol (Va). A catalyst was prepared by warming together 0.5 g. of red mercuric oxide, 0.2 cc. of boron trifluoride etherate, 10 mg. of trichloroacetic acid and 1 cc. of methanol. A solution of 2.3 g. of the acetylenic carbinol acetate II in 50 cc. of methanol was then added and the mixture was shaken vigorously at room temperature for 3 hr. It was then poured into dilute sulfuric acid and the product was isolated by means of ethyl acetate. Direct crystallization from acetone-hexane yielded 1.58 g. (73%) of the keto-diol Va, m.p. 231–235°, which after further crystallization showed m.p. 237–239°, $[\alpha]_D$ −118°, infrared band at 5.82 μ (saturated ketone) and free hydroxyl band.

Acetylation (acetic anhydride–pyridine, 16 hr. at room temperature) yielded the 3-monoacetate Vb, which after crystallization from methanol showed m.p. 234–237°, $[\alpha]_D$ −118°, infrared band at 5.78 μ (acetate), 5.82 μ (saturated ketone), and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.46; H, 9.51.

20-Acetyl-20-hydroxy-4-pregnen-3-one (VI). A solution of 3 g. of aluminum isopropoxide in 20 cc. of dry toluene was added to a boiling solution of 1.5 g. of the keto-diol Va in 80 cc. of dry toluene and 30 cc. of cyclohexanone. The mixture was boiled under reflux for another 45 min., moisture being excluded, and it was then cooled and poured into ice. The mixture was distilled in steam until no more organic material passed over. Ethyl acetate was then added to the residue and the organic layer was washed with water, dried, and evaporated. Chromatography on 45 g. of alumina and elution with benzene-ether (9:1) to (4:1) yielded 0.95 g. (64%) of the diketo-alcohol VI, which after crystallization from methanol showed m.p. 191–193°, λ_{max} 241 mμ (ε, 16,100), infrared band at 5.82 μ (saturated ketone), 6.01 μ (unsaturated ketone), and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.68; H, 9.47.

Methyl 3β,20-dihydroxybisnor-5-cholenate (VII). The keto-diol Va (150 mg.) was added to a sodium hypobromite solution (prepared by adding 2 g. of bromine to a cold solution of 15 g. of sodium hydroxide in 150 cc. of water) and the mixture was shaken at room temperature for 16 hr. It was then extracted with ethyl acetate and the aqueous layer after acidification with cold dilute sulfuric acid was again extracted with ethyl acetate. The latter organic extract was washed with sodium bisulfite solution and water and was then dried and evaporated. The residue was dissolved in 10 cc. of chloroform and excess ethereal diazomethane was added. After being allowed to stand overnight, the solution was evaporated to dryness. Crystallization from methanol then yielded 55 mg. (35%) of the dihydroxy-ester VII, m.p. 199–202°, $[\alpha]_D$ −77°, infrared band at 5.79 μ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.13; H, 9.41.

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REHOVOTH, ISRAEL

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

Syntheses in the Cardiac Aglycone Field. I. The Condensation of α-Ketol Tetrahydropyranyl Ethers with Acetylene and with Propiolic Esters

FRANZ SONDHEIMER, NILS STJERNSTRÖM, AND DAVID ROSENTHAL[1]

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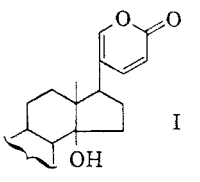
An attempt is described to synthesize the steroidal lactone VII which contains the same 5′-α-pyrone grouping at the 17β-position as do the natural cardiac-active steroids of the bufo-scilla type (I). 3β,21-Dihydroxy-5-pregnen-20-one (IIb) was converted to the di-(2′-tetrahydropyranyl) ether IIc which was allowed to react with sodium acetylide. The resulting acetylenic carbinol III could not be carboxylated, but direct condensation between the keto-di-ether IIc and *t*-butyl propiolate yielded the acetylenic hydroxy-ester IVb. Partial hydrogenation of this substance and subsequent acid treatment yielded the ethylenic triol ester Vb. Similarly acetol 2′-tetrahydropyranyl ether VIIIb on condensation with methyl propiolate and subsequent partial hydrogenation gave the ethylenic ester XI. The latter on acid treatment gave the hydroxy-γ-lactone XIIb rather than the α-pyrone XIII. The present method must therefore be modified if it is to lead to α-pyrones of types VII and XIII.

The important heart-active principles of the bufo-scilla type, such as scillaren A (from the white squill), hellebrin (from the Christmas rose) and bufotalin (from the common European toad), all contain a C/D-*cis* fused steroid nucleus substituted as shown in formula I.[2] One of the difficulties in synthesizing compounds of this type is the con-



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(1) U.S. Public Health Service Postdoctorate Research Fellow, 1956–1957.

(2) For reviews see R. B. Turner, *Chem. Revs.*, **43**, 1 (1948); L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 3rd Edition, 1959, Chapter 20.