[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S. A.]

Steroids. LXXVIII.[1] Di-17α-(Δ⁵-androstene-3β,17β-diol)-acetylene, A By-product from the Reaction of Dehydroepiandrosterone with Acetylene

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RECEIVED OCTOBER 28, 1955

The reaction between dehydroepiandrosterone (I) and acetylene in the presence of potassium *t*-amyl oxide, which is known to yield 17α-ethinyl-Δ⁵-androstene-3β,17β-diol (IIa) as the major product, has been shown to produce di-17α-(Δ⁵-androstene-3β,17β-diol)-acetylene (IVa) as a by-product. The dehydration, Oppenauer oxidation and complete hydrogenation of the tetrol IVa are described. The reaction between dehydroepiandrosterone (I) and acetylenedimagnesium bromide does not lead to the tetrole IVa, but produces 17α-ethinyl-Δ⁵-androstene-3β,17β-diol (IIa) in excellent yield.

The reaction between dehydroepiandrosterone (I) and acetylene in the presence of potassium *t*-amyl oxide to yield 17α-ethinyl-Δ⁵-androstene-3β,17β-diol (IIa)[3] is an important step in the production of 17-ethinyltestosterone (III), since the latter is obtained from IIa by Oppenauer oxidation.[4] As is usual in the reaction of saturated ketones with acetylene when potassium *t*-butoxide or *t*-amyl oxide is employed as condensing agent,[5a] the monosubstituted acetylene IIa is obtained smoothly and in high yield.[3] Nevertheless we have now found that a second product is formed in the reaction between dehydroepiandrosterone and acetylene, which we believe to be the disubstituted acetylene IVa. In this paper we describe the evidence for the assignment of this structure and certain reactions which have been carried out with this C-40 compound containing the novel *sym*-di-17α-androstanyl-ethane carbon skeleton.

The condensation of I with acetylene in ether–benzene solution with potassium *t*-amyl oxide as condensing agent was carried out as described by Stavely.[3] The major product IIa with m.p. 240–242° was crystallized and removed. The mother liquors dissolved in a little ether were then allowed to stand for several weeks, whereupon the very insoluble by-product with m.p. 303–305° crystallized. The structure IVa, derived by condensation between two molecules of steroid and one of acetylene, was indicated for this substance by the elemental analysis, molecular weight determination and the absence of the 17-carbonyl band in the infrared.

Further evidence for the correctness of the structure IVa for the by-product was provided through its dehydration to di-17-(Δ⁵,¹⁶-androstadiene-3β-ol)-acetylene (V). Di-Δ¹-cyclohexenylacetylene has been shown to absorb in the ultraviolet with λ_{max} 262.5 mμ (log ε 4.10) and 275.5 mμ (log ε 3.95).[6] A bathochromic shift of *ca.* 3 mμ is shown by Δ¹-cyclopentenyl-Δ¹-cyclohexenylacetylene, which exhibits λ_{max} 265 mμ (log ε 4.18) and 278 mμ (log ε 4.06).[6] The spectrum of di-Δ¹-cyclopentenylacetylene, containing the same chromophoric system as V, does not seem to have been recorded but would be expected to show another bathochromic shift of the same magnitude, *viz.*, to exhibit λ_{max} *ca.* 268 and 281 mμ. When the by-product under investigation was dehydrated with boiling formic acid[7] and subsequently saponified, a substance was obtained which showed an ultraviolet spectrum with λ_{max} 272 mμ (log ε 4.21) and 285 mμ (log ε 4.14) that clearly indicated the presence of the di-Δ¹-cyclopentenylacetylene chromophore, as in V.

The Oppenauer oxidation of the tetrol IVa proceeded normally and produced the diol-dione VI. The ultraviolet spectrum of this substance (λ_{max} 240 mμ, log ε 4.52) was in accord with the presence of two Δ⁴-3-ketone groupings, each of which is known to absorb at λ_{max} 241 mμ, log ε 4.22.[8]

The tetrol IVa on acetylation yielded the 3,3′-diacetate IVb. The catalytic hydrogenation of this ester in acetic acid over a platinum catalyst resulted in the uptake of *ca.* 4 equivalents of hydrogen, as expected, and the completely saturated tetrol diacetate VIIb (further characterized through saponification to the saturated tetrol VIIa) was produced. Rather unexpectedly, the yield of the hydrogenation product VIIb was only about 50% and several other substances were formed which have not yet been further investigated.

In an attempt to obtain the acetylenic by-product IVa by a preparative route, dehydroepiandrosterone (I) was allowed to react with acetylenedimagnesium bromide in ether–tetrahydrofuran. Although the reaction of this organometallic reagent with ketones in general yields predominantly the acetylenic glycols derived by condensation between two molecules of ketone with one of acetylene,[5b] we found to our surprise that in this case 17α-ethinyl-Δ⁵-androstene-3β,17β-diol (IIa) was produced in excellent yield and no trace of the tetrol IVa could be detected. Although the monosubstituted acetylenic alcohols of type IIa have been isolated previously from the condensation between ketones and acetylenedimagnesium bromide,[9] this appears to be the first case where a high yield of the monosubstituted acetylene and none of the disubstituted acetylene has been obtained. This phenom-

(1) Paper LXXVII, B. Löken, S. Kaufmann, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 1738 (1956).

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(3) H. E. Stavely, THIS JOURNAL, **61**, 79 (1939).

(4) H. H. Inhoffen and W. Hohlweg, *Naturwissenschaften*, **26**, 96 (1938); L. Ruzicka, K. Hofmann and H. F. Meldahl, *Helv. Chim. Acta*, **21**, 371 (1938).

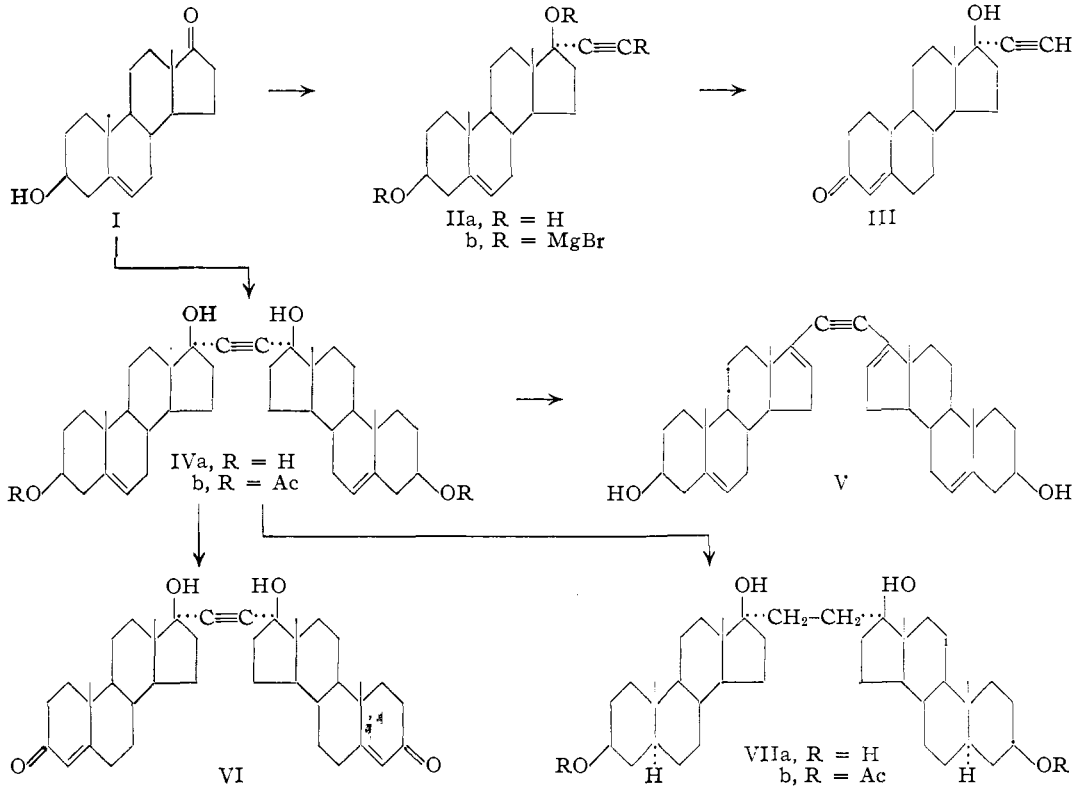
(5) For references see A. W. Johnson, "The Chemistry of the Acetylenic Compounds," Edward Arnold and Co., London, 1946, Vol. I, (a) p. 15; (b) p. 138.

(6) H. Bastron, R. E. Davis and L. W. Butz, THIS JOURNAL, **65**, 973 (1943).

(7) *Cf.* H. H. Inhoffen, W. Logemann, W. Hohlweg and A. Serini, *Ber.*, **71**, 1024 (1938).

(8) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953), Table 7.

(9) *Inter al.*, R. Lespieau, *Bull. soc. chim.*, **39**, 991 (1926); Zal'kind and Gverdtsiteli, *Zhur. Obschchei. Khim.*, **9**, 971 (1939); W. E. Bachmann and J. Controulis, THIS JOURNAL, **73**, 2636 (1951); C. A. Grob and P. Payot, *Helv. Chim. Acta*, **36**, 839 (1953).



enon doubtless is due to the extreme insolubility of the intermediate complex IIb in the solvent system employed. In accord with this, when the complex IIb was prepared from 17α-ethinyl-Δ^5-androstene-3β,17β-diol (IIa) and three equivalents of ethylmagnesium bromide in ether–tetrahydrofuran and treated with dehydroepiandrosterone (I) (a reaction which generally produces the disubstituted acetylenes[10]), the monosubstituted acetylene IIa was recovered completely.

The presently described production of 17α-ethinyl-Δ^5-androstene-3β,17β-diol (IIa) from dehydroepiandrosterone (I) and acetylene dimagnesium bromide is of considerable commercial importance, since the yield is as satisfactory as that obtained by the potassium *t*-amyl oxide method[2] and the danger inherent in the handling of metallic potassium is avoided.

Experimental[11]

Di-17α-(Δ^5-androstene-3β,17β-diol)-acetylene (IVa).—The reaction between acetylene and dehydroepiandrosterone (I) in the presence of potassium *t*-amyl oxide was carried out essentially as described by Stavely.[3] The 17α-ethinyl-Δ^5-androstene-3β,17β-diol (IIa) with m.p. 240–242°, $[\alpha]_D$ −124°, was obtained in *ca.* 80% yield. The mother liquors dissolved in a little ether were allowed to stand for several weeks, when a precipitate had appeared. It was collected and crystallized from ethanol–dioxane. In this way a 2–3% yield of the tetrol IVa was obtained with m.p. 303–305°, $[\alpha]_D$ −122° (dioxane), ν_{max}^{mull} free hydroxyl band only, no high intensity absorption in the ultraviolet.

Anal. Calcd. for $C_{40}H_{58}O_4$: C, 79.69; H, 9.69; mol. wt., 602.9. Found: C, 79.16; H, 9.77; mol. wt., 610.1.

The 3,3'-diacetate IVb was obtained by heating 1 g. of the tetrol IVa with 5 cc. of pyridine and 5 cc. of acetic anhydride for 1 hour on the steam-bath, when complete solution had occurred. Isolation in the usual way, followed by crystallization from chloroform–hexane, furnished 1.06 g. of the tetrol diacetate IVb with m.p. 294–297°, $[\alpha]_D$ −156°, ν_{max}^{mull} 1736 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{44}H_{62}O_6$: C, 76.92; H, 9.10. Found: C, 76.98; H, 9.12.

Dehydration of the Tetrol IVa to Di-17-($\Delta^{5,16}$-androstadien-3β-ol)-acetylene (V).—The tetrol IVa (1 g.) was boiled under reflux with 30 cc. of 90% formic acid for 6 hours. The solution first turned blue and then dark brown. The cooled solution was poured into water and the product was extracted with chloroform. The organic extract was washed with sodium carbonate solution, dried, evaporated and the residue was saponified through boiling for 1 hour with 1 g. of potassium hydroxide in 100 cc. of methanol. Addition of water yielded 0.81 g. of material with m.p. 168–173°, which contained the tetraenyne V. The latter was separated by chromatography on 40 g. of neutral alumina; it was eluted with benzene–chloroform and after crystallization from chloroform–hexane showed m.p. 216–218°, λ_{max} 272 and 285 mμ, log ϵ 4.21 and 4.14, respectively.

Di-17α-(Δ^4-androsten-17β-ol-3-one)-acetylene (VI).—A solution of 0.3 g. of aluminum isopropoxide in 5 cc. of dry toluene was added to a solution of 1 g. of the tetrol IVa in 50 cc. of dry toluene and 6 cc. of cyclohexanone and the mixture was boiled under reflux for 1 hour. The volatile components were then removed by steam distillation, the resulting solid was collected and the organic material was extracted with ethyl acetate. Crystallization from ethyl acetate–hexane produced 0.66 g. (66%) of the diol-dione VI with m.p. 294–296°, $[\alpha]_D$ −51° (dioxane), ν_{max}^{mull} 1660 cm.$^{-1}$ and free hydroxyl band, λ_{max} 240 mμ, log ϵ 4.52.

Anal. Calcd. for $C_{40}H_{54}O_4$: C, 80.23; H, 9.08. Found: C, 79.96; H, 9.27.

***sym*-Di-17α-(androstane-3β,17β-diol)-ethane 3,3'-Diacetate (VIIb).**—A solution of 3 g. of the acetylenic tetrol di-

(10) J. Cymerman, I. M. Heilbron, A. W. Johnson and E. R. H. Jones, *J. Chem. Soc.*, 141 (1944), and references cited there.

(11) Melting points are uncorrected. Unless noted otherwise, rotations were determined at 20° in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Mrs. P. López and Miss M. T. Cárdenas for these measurements as well as for the infrared spectra, which were determined with a Perkin-Elmer model 12C single beam spectrophotometer with sodium chloride prism. Thanks are also due to Mrs. A. González for the microanalyses and to Miss R. Pérez Negron for her skillful technical assistance.

acetate IVb in 150 cc. of glacial acetic acid was shaken in hydrogen over 0.25 g. of a prereduced platinum catalyst at 22° and 592 mm. In 4 hours 4.1 equivalents of hydrogen had been absorbed and uptake ceased. The catalyst was removed and the filtrate was poured into water. The precipitate was collected, washed well with water and dried, when it weighed 2.95 g. and showed m.p. *ca.* 165–175°. Crystallization from chloroform–methanol furnished 1.49 g. (49%) of the saturated tetrol diacetate VIIIb with m.p. 286–292° (introduced at 280°), $[\alpha]_D$ −34°, ν_{max}^{mull} 1736 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{43}H_{70}O_6$: C, 76.03; H, 10.15. Found: C, 75.71; H, 10.08.

Chromatography of the mother liquors on 100 g. of neutral alumina afforded three different substances. The first (0.12 g.) showed m.p. 228–232°, the second (0.32 g.) showed m.p. 258–263° and the third (0.03 g.) showed m.p. 276–279° (depressed on admixture with VIIb). These substances have not yet been further investigated.

***sym*-Di-17α-(androstane-3β,17β-diol)-ethane (VIIa).**—A solution of 0.2 g. of the diacetate VIIb in 10 cc. of dioxane and 30 cc. of methanol was treated with 0.2 g. of potassium hydroxide in 3 cc. of water and boiled under reflux for 1 hour. Concentration to a small volume followed by addition of water gave a precipitate which was collected, washed with water and dried. Crystallization from dioxane produced 0.14 g. of the saturated tetrol VIIa with m.p. 329–335°, ν_{max}^{mull} free hydroxyl band only. The rotation could not be determined due to the compound's extreme insolubility.

Anal. Calcd. for $C_{40}H_{66}O_4$: C, 78.64; H, 10.89. Found: C, 78.70; H, 11.04.

17α-Ethinyl-Δ⁵-androstene-3β,17β-diol (IIa) from Dehydroepiandrosterone (I) and Acetylenedimagnesium Bromide.—A slow stream of purified acetylene was passed for 3 hours under anhydrous conditions through 25 cc. of a 3 *N* ethereal solution of methylmagnesium bromide (Arapahoe Chemical Co.), diluted with 100 cc. of anhydrous tetrahydrofuran. A solution of 5 g. of dehydroepiandrosterone in 50 cc. of tetrahydrofuran was then added and the mixture was boiled under reflux for 15 minutes, whereby a bulky precipitate was formed. Cooling and pouring into 1 l. of water containing 20 cc. of concentrated sulfuric acid produced the crude 17α-ethinyl-Δ⁵-androstene-3β,17β-diol (IIa) as a precipitate, which on collection, washing with water and drying weighed 5.2 g. and showed m.p. 228–232°. One crystallization from chloroform–hexane yielded 4.5 g. (83%) with m.p. 238–240°, $[\alpha]_D$ −123°, ν_{max}^{mull} free hydroxyl band only. Identity with an authentic sample was demonstrated through non-depression in m.p. on admixture and infrared comparison; reported[3] m.p. 240–242°, $[\alpha]^{25}D$ −119°.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.93; H, 9.47.

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Steroidal Sapogenins. XXXIII. Transformations in the 12-Ketosteroid Series[2]

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RECEIVED SEPTEMBER 26, 1955

The behavior of steroids with C-12,20-diketonic substitution cannot be predicted from observations taken on C-11,20-diketosteroids or on C-ring unsubstituted compounds. The C-12,20-dicarbonyl interaction affects the reactivity of side chain groups markedly and affects the ease of introduction of new groups into the side chain. New series of Δ⁴-12-ketopregnenes (seven compounds) and 12-ketopregnanes (three compounds) are prepared and their properties noted. Attempts to prepare 4-pregnene-17α,21-diol-3,12,20-trione by the hecogenin route have not yet been successful.

In continuing our program of preparation of C-ring lactone hormone analogs[3] we desired to prepare the 12-keto derivative XIII of Reichstein's compound S as a starting material. The conversion of hecogenin to XIII has not been effected to date.[4] The following experiments record the preparation of the 21-desoxy derivative VI and the 16α,17α-epoxide derivative of 12-keto S from hecogenin.

A group in England[5] and we, independently, were able to convert hecogenin to the 4,5-dihydro*allo* compound XIV. Attempts to apply the bromination procedure of the Syntex workers for the introduction of the Δ⁴-olefinic bond[6] into this compound failed completely in spite of many experimental variations. We thought it might be possible to avoid this impassé by establishing the α–β unsaturation prior to the complete elaboration of the dihydroxyacetone side chain.

Hecogenin was converted to 16α,17α-epoxy*allo*-pregnan-3β-ol-12,20-dione acetate essentially as described previously,[7] and saponification followed by mild oxidation with chromium trioxide–pyridine complex gave the 3-ketone I. Bromination with three equivalents of bromine, followed by treatment with sodium iodide and sodium bisulfite gave the new compound 16α,17α-epoxy-4-pregnene-3,-12,20-trione (II). The proof of structure is based on the elementary analysis, the strong ultraviolet absorption in accord with Δ⁴-3-one structure[8] and the infrared spectrum showing ketone and α,β-unsaturated ketone bands at 1714 and 1670 cm.$^{-1}$. Hydroxyl bands were absent, indicating that the epoxide linkage was unaltered by the over-all bromination and subsequent treatments. The yield of unsaturated triketone II, 68%, was exceptionally good for this reaction. Treatment of II with hydrobromic acid diluted with acetic acid[9] gave the new bromohydrin III in 76% yield showing a strong infrared hydroxyl band at 3470 cm.$^{-1}$

(1) A Laboratory of the Eastern Utilization Research Branch, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) Paper XXXII, R. F. Mininger, M. E. Wall, R. G. Dworschack and R. W. Jackson, submitted to *Arch. Biochem. Biophys.*

(3) (a) E. S. Rothman, M. E. Wall and C. R. Eddy, THIS JOURNAL, **76**, 527 (1954); (b) E. S. Rothman and M. E. Wall, *ibid.*, **77**, 2228 (1955); (c) **77**, 2229 (1955).

(4) This compound has, however, been prepared from bile acids; W. J. Adams, D. K. Patel and V. Petrow, *J. Chem. Soc.*, 4688 (1954).

(5) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *ibid.*, 2209 (1954).

(6) G. Rosenkranz, St. Kaufmann, J. Pataki and C. Djerassi, THIS JOURNAL, **72**, 1046 (1950).

(7) G. P. Mueller, R. E. Stobaugh and R. S. Winniford, *ibid.*, **75**, 4888 (1953). See also reference 3c.

(8) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953); *cf.* p. 63.

(9) P. L. Julian, E. Meyer, W. J. Karpel and I. R. Waller, THIS JOURNAL, **72**, 5145 (1950); see also refs. 3c and 7.