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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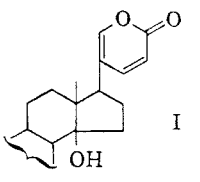
An attempt is described to synthesize the steroidal lactone VII which contains the same 5′-α-pyrone grouping at the 17β-position as do the natural cardiac-active steroids of the bufo-scilla type (I). 3β,21-Dihydroxy-5-pregnen-20-one (IIb) was converted to the di-(2′-tetrahydropyranyl) ether IIc which 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.

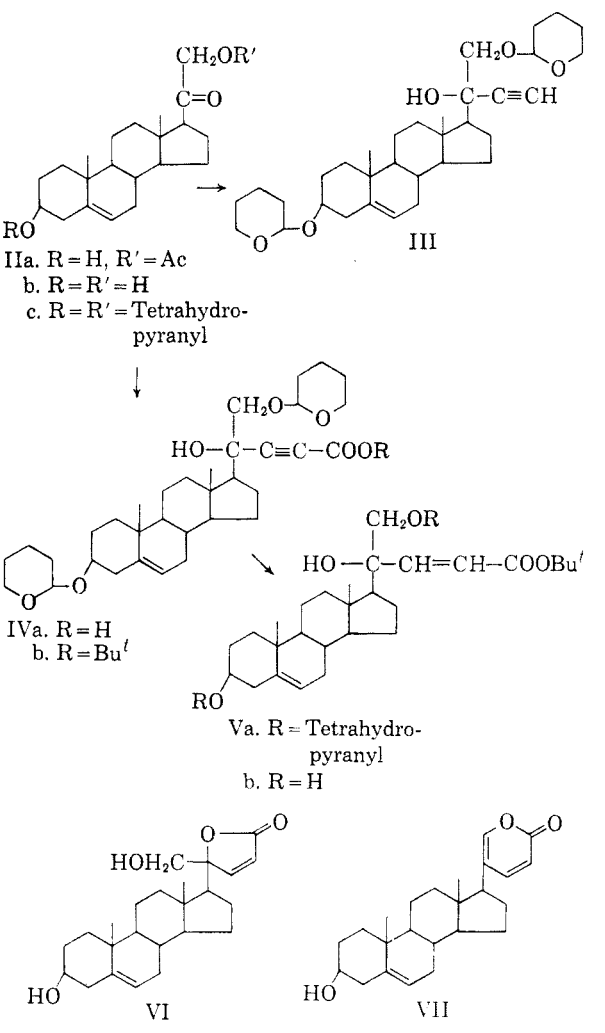
(2) For reviews see R. B. Turner, *Chem. Revs.*, **43**, 1 (1948); L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 3rd Edition, 1959, Chapter 20.

struction of the 5-substituted α-pyrone grouping at the 17β-position of the steroid. This problem has been investigated previously by Fried and Elderfield,[3] who developed a synthesis of 5-alkyl-α-pyrones which however failed when the alkyl group is branched at the α-position.

In connection with a general program aimed at the synthesis of the steroidal cardiac aglycones, we were interested in developing a synthetic route to steroids carrying a 5′-α-pyrone at C-17 and which might ultimately be applied to 14β-hydroxy-steroids to yield the natural compounds of type I. In this paper we report an attempt to reach this objective in the case where the steroid part is the 3β-hydroxy-5-androstene grouping. Although this work has not yet led to the desired α-pyrone VII, certain results of interest were obtained which are recorded.

The starting material for our work was 3β,21-dihydroxy-5-pregnen-20-one 21-monoacetate (IIa), which on hydrolysis with alcoholic potassium hydroxide yielded the corresponding diol IIb. In order for further reactions to be carried out at C-20, it was necessary to protect the 3- and 21-hydroxyl groups. The diol IIb was therefore allowed to react with 2,3-dihydropyran in the presence of phosphorus oxychloride, whereby the 3,21-di-(2′-tetrahydropyranyl) ether IIc, m.p. 131–135°, was produced in *ca.* 40% yield.[4] The melting point of this substance, as well as of the subsequent ones containing the tetrahydropyranyl ether grouping, was not sharp and could be gradually raised by repeated crystallization. This phenomenon undoubtedly is due to the fact that two new asymmetric centers are introduced non-stereospecifically during the formation of the di-ether and consequently IIc is a mixture of stereoisomers.[5] For this reason no attempt was made usually to obtain samples of the various tetrahydropyranyl ethers with constant melting point.

The condensation between the di-ether IIc and sodium acetylide in liquid ammonia proceeded normally[6] and furnished the acetylenic carbinol III, m.p. 176–180°. As expected the infrared spectrum of this substance showed the presence of a terminal acetylene group and the absence of a carbonyl group. It has been shown by E. R. H. Jones and coworkers that α-hydroxy-acetylenes can be carboxylated by reaction of the corresponding di-Grignard derivatives in benzene solution



with carbon dioxide, preferably in an autoclave.[7] However all attempts to carboxylate the acetylenic carbinol III by this method failed and in no case was any of the required acid IVa obtained.

Bachmann and Raunio[8] described a method for preparing γ-hydroxy-α,β-acetylenic acids which involves the addition of a mixture of a ketone and methyl propiolate to sodamide in liquid ammonia, whereby a mixture of the acetylenic hydroxy-ester and hydroxy-acid is produced. When this method was applied to the keto-di-tetrahydropyranyl ether IIc under conditions which in our hands worked reasonably well with cyclohexanone, the product contained nitrogen and neither the hydroxy-acid IVa nor the corresponding methyl ester could be isolated. This failure appeared to be due to the ready reaction between the methyl ester grouping and liquid ammonia. For this reason we prepared the less reactive hitherto unknown *t*-butyl propiolate from propiolic acid and isobutylene and allowed the sodium derivative of this ester to

(3) J. Fried and R. C. Elderfield, *J. Org. Chem.*, **6**, 566 (1941).

(4) *Cf.* A. C. Ott, M. F. Murray, and R. L. Pederson, *J. Am. Chem. Soc.*, **74**, 1239 (1952) for the preparation of a 21-tetrahydropyranyl ether of a 21-hydroxy-20-ketosteroid (37% yield).

(5) *Cf.* C. W. Greenhalgh, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

(6) *Cf.* F. Sondheimer, N. Danieli, and Y. Mazur, *J. Org. Chem.*, **24**, 1278 (1959).

(7) L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 503 (1946); E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1423 (1949).

(8) W. E. Bachmann and E. K. Raunio, *J. Am. Chem. Soc.*, **72**, 2530 (1950).

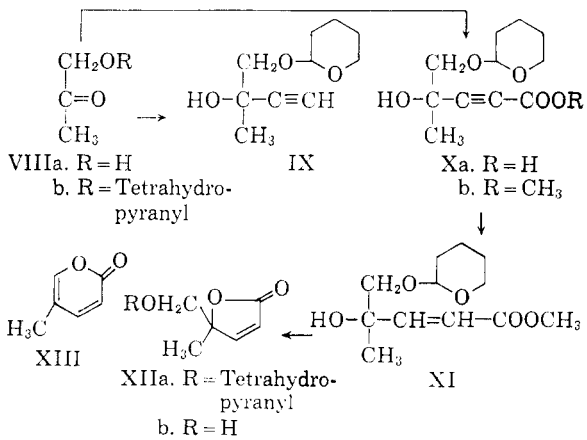
react with the ketone IIc. This reaction gave in 24% yield the required *t*-butyl acetylenic ester IVb, m.p. 174–177°, the structure of which follows from the empirical formula and the infrared spectrum (presence of acetylene bond and unsaturated ester).

Partial hydrogenation of the ester IVb in benzene and pentane over a "Lindlar" palladium catalyst[9] resulted in the smooth uptake of one molar equivalent of hydrogen and led to the *cis*-ethylenic ester Va, m.p. 169–172°, the infrared spectrum of which showed that it no longer contained an acetylenic bond. Treatment of this substance with dilute acid in dioxane resulted in the loss of the two tetrahydropyranyl ether groupings and gave the highly crystalline insoluble *cis*-ethylenic triol ester Vb, m.p. 242–244°, with infrared and ultraviolet (λ_{max} 208 mμ, ε 9800) properties in accord with the assigned structure.

The final step involved the hydrolysis of the ester grouping of Vb. This reaction might be expected to lead either to the desired α-pyrone VII (by spontaneous dehydration of the corresponding 20-hydroxy compound, a substance which might also be isolated as such) or the unsaturated 5-membered lactone VI. Which of these products would be formed depends on whether lactonization occurs more readily with the primary 21-hydroxyl group to form a δ-lactone or with the tertiary 20-hydroxyl group to form a γ-lactone. In fact preliminary experiments to hydrolyze Vb both under acidic and basic conditions led to mixtures from which no definite conclusions could be drawn.

In view of this result and since the materials in the steroid series were scarce, it was decided to investigate the mode of lactonization of a compound of type Vb in a simpler series where materials were more easily available.

The series chosen was the one where the methyl group replaces the Δ^5-androsten-3β-ol nucleus, the starting material being the very readily available acetol (1-hydroxy-2-propanone) (VIIIa).[10] This ketol was smoothly converted in *ca.* 70% yield to the liquid 2′-tetrahydropyranyl ether VIIIb, which proved to be rather unstable and was best used directly for subsequent reactions. Condensation with sodium acetylide in liquid ammonia furnished the acetylenic carbinol IX, the structure of which follows from its infrared spectrum (presence of acetylenic hydrogen, absence of ketone) as well as from the fact that on being warmed with aqueous periodic acid it gave the typical very pungent odor of methyl ethynyl ketone.[11]



Attempted carboxylation of the acetylenic carbinol IX by treatment of the di-Grignard complex with carbon dioxide[7] again was unsuccessful and none of the acid Xa could be isolated. It is of interest that in this case as well as in the above-described attempted carboxylation of III, some allenic material (infrared band at 5.02μ) was formed and this may be the reason why α,β-dihydroxy-acetylenic β-tetrahydropyranyl ethers of type III and IX cannot be carboxylated by the Jones procedure.[7] In order to circumvent this difficulty, the ketol tetrahydropyranyl ether VIIIb was again condensed directly with an ester of propiolic acid by means of sodamide in liquid ammonia.[8] In this series the reaction with methyl propiolate succeeded and gave 25% of the required acetylenic ester Xb, which showed the expected infrared and ultraviolet (λ_{max} 210 mμ, ε 4500) spectral characteristics.

Catalytic semihydrogenation of the acetylenic ester Xb over a "Lindlar" palladium catalyst[9] proceeded normally and yielded the *cis*-ethylenic ester XI. When an attempt was made to purify this substance by chromatography on alumina, not only was a purified sample of XI obtained, but also a less polar substance. This latter proved to be the γ-lactone ether XIIa as evidenced by the infrared spectrum (carbonyl band at 5.69 μ), ultraviolet spectrum (λ_{max} 214 mμ, ε 8700) and elemental composition. This lactone was not present prior to chromatography and the loss of methanol from the ester XI must have been caused by the alumina.

Finally the ethylenic ester XI was treated with hydrochloric acid in aqueous methanol, whereby the tetrahydropyranyl ether grouping was cleaved and lactonization occurred. The water-soluble product was clearly the hydroxy-γ-lactone XIIb since in the infrared it showed only one sharp band in the carbonyl region at 5.70 μ.

The present synthesis therefore proceeds in the same way as when no extra hydroxyl group is present β- to the *cis*-ethylene[12] and is not directly applicable to the synthesis of 5-substituted α-pyrones of type I. The desired objective might however be reached by a suitable modification of the route described, *e.g.* by dehydration at C-20 of

(9) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(10) P. A. Levene and A. Walti, *Org. Syntheses*, **Coll. Vol. II**, 5 (1943).

(11) *Inter al.*, K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(12) L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 954 (1946).

the acetylenic hydroxy-esters IVb and Xb prior to partial hydrogenation, and work along these lines is being continued.

Very recently and after completion of the work described in this paper, we were informed by Professor C. A. Grob (University of Basel, Switzerland) that he, Professor Kuno Meyer, and coworkers had independently carried out a similar scheme to ours and had reached the same conclusions.

EXPERIMENTAL[13]

3β,21-Dihydroxy-5-pregnen-20-one 3,21-di-(2'-tetrahydropyranyl) ether (IIc). A solution of 3.4 g. of potassium hydroxide in 20 cc. of water was added to a solution of 11.8 g. of 3β,21-dihydroxy-5-pregnen-20-one 21-monoacetate (IIa) (m.p. 179–183°) in 450 cc. of methanol. The solution was then allowed to stand at room temperature under nitrogen for 2 hr. Glacial acetic acid (5 cc.) was added, the solution was evaporated to small volume and poured into 600 cc. of water. The crystalline precipitate was collected, washed well with water, and dried. The resulting diol IIb (9.0 g.; 86%) showed m.p. 155–159° and was used in the next step. On crystallization from methanol-ether, a specimen with m.p. 171–173° was obtained, which showed a sharp band at 5.82 μ (20-ketone) in the infrared.

Freshly distilled phosphorus oxychloride (16 drops) was added dropwise with shaking to a solution containing 1 g. of the crude diol IIb and 5 cc. of 2,3-dihydropyran (freshly distilled from sodium hydroxide) in 25 cc. of dry chloroform, at room temperature. The reaction mixture, which spontaneously warmed up to *ca.* 40°, was then allowed to stand with the exclusion of moisture for 1.5 hr. It was poured into a saturated sodium bicarbonate solution and ether was added. The ether layer was washed with salt solution and was then dried and evaporated. The residue on crystallization from ether–pentane yielded 0.59 g. (39%) of the di-ether IIc, probably as a mixture of stereoisomers, m.p. 131–135°; infrared band at 5.82 μ (20-ketone), no hydroxyl band.

Anal. Calcd. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.44; H, 9.51.

In another experiment the total product was chromatographed on 100 g. of alumina. Petroleum ether–benzene (1:1) eluted the di-ether IIc (0.53 g.; 35%), which after one crystallization from ether–petroleum ether showed m.p. 132–136° and had the identical infrared spectrum as that of the previously obtained material.

20-Ethynyl-5-pregnene-3β,20,21-triol 3,21-di(2'-tetrahydropyranyl) ether (III). A solution of 220 mg. of the di-ether IIc in 15 cc. of dry ether was added to a solution of sodium acetylide in liquid ammonia (previously prepared from 500 mg. of sodium in *ca.* 60 cc. of liquid ammonia by conversion to sodamide by the addition of a little ferric nitrate, and then by the passage of purified acetylene for 20 min.). The mixture was stirred and cooled in a Dry Ice–acetone bath for 4 hr. while a slow stream of acetylene was passed through. Ammonium chloride (5 g.) was then added, the ammonia was allowed to evaporate, and water and ether were added to the residue. The ether extract was washed with salt solution and was then dried and evaporated. The crystalline residue (180 mg.; m.p. *ca.* 120–140°) was chromatographed on 8 g. of alumina. Benzene-ether then eluted 115 mg. (50%) of the acetylenic carbinol III which after one crystallization from ether showed m.p. 176–180°, $[\alpha]_D$ −16°; infrared band at 3.01 μ (acetylenic hydrogen), no band at *ca.* 5.8 μ.

Anal. Calcd. for $C_{33}H_{50}O_5$: C, 75.24; H, 9.57. Found: C, 75.14; H, 9.46.

t-Butyl propiolate. Concentrated sulfuric acid (2 cc.) was added carefully to a mixture of 21 g. of propiolic acid (prepared from propargyl alcohol by the method of Wolf[14]) and 150 cc. of dry isobutylene in a pressure bottle cooled to −10°. The solution was well stoppered and allowed to stand for 20 hr. at room temperature. The solution was again cooled to −10°, the bottle was opened and the excess isobutylene was allowed to evaporate. The residue was poured into excess of aqueous sodium carbonate solution which was then well extracted with ether. The organic extract was dried over potassium carbonate. Distillation yielded 24.3 g. (64%) of *t*-butyl propiolate, b.p. 52–53° at 27 mm., n_D^{20} 1.4174.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.98; H, 8.21.

t-Butyl 3β,20,21-trihydroxychol-5-en-22-ynate 3,21-di-(2'-tetrahydropyranyl) ether (IVb). A suspension of sodamide in liquid ammonia was prepared by adding a trace of ferric nitrate to a solution of 0.4 g. of sodium in *ca.* 200 cc. of liquid ammonia and stirring the mixture which was cooled in a Dry Ice–acetone bath until the conversion to sodamide was complete. A solution of 2.23 g. of *t*-butyl propiolate in 10 cc. of ether was then added and the cooled mixture was stirred for 20 min. The di-ether IIc (1.2 g.) dissolved in 40 cc. of ether was added and stirring and cooling were continued for a further 5 hr. Ammonium chloride (5 g.) was then added and the ammonia was allowed to evaporate. Water and ether were added to the residue and the organic layer was washed with salt solution, dried, and evaporated. The residue was chromatographed on 100 g. of alumina. Elution with benzene-ether (1:1) yielded 0.36 g. (24%) of the ester IVb, m.p. 174–177°. Three crystallizations of a sample from benzene–petroleum ether gave long needles, m.p. 194–196°, $[\alpha]_D$ −45°; infrared bands at 4.46 μ (acetylene) and 5.86 μ (unsaturated ester).

Anal. Calcd. for $C_{38}H_{58}O_7$: C, 72.81; H, 9.33. Found: C, 72.48; H, 9.16.

t-Butyl 3β,20,21-trihydroxy-5,20-(cis)-choladienate (Vb). A solution of 100 mg. of the acetylenic ester IVb in 20 cc. of benzene and 20 cc. of pentane was shaken in hydrogen over 100 mg. of a "Lindlar" palladium catalyst[9] at room temperature and atmospheric pressure. After 50 min., 1.03 molar equivalents of gas had been absorbed and uptake had become very slow. The catalyst was removed and the solvent was evaporated. The residual crystalline *cis*-ethylenic ester Va showed m.p. 169–172°, infrared band at 5.85 μ (unsaturated ester), no band at *ca.* 4.5 μ.

The total hydrogenated material was dissolved in 16 cc. of dioxan and 2 cc. of 5% aqueous sulfuric acid was added. The solution was allowed to stand at room temperature for 16 hr., by which time a highly crystalline precipitate had separated. This material was collected and the filtrate was diluted with water, whereby a further quantity of crystals was obtained. The very insoluble material on crystallization from chloroform-ethanol yielded 45 mg. (61%) of the triol ester Vb, m.p. 242–244°, λ_{max} 208 mμ (ε 9800); infrared band in KBr at 5.86 μ (unsaturated ester) and free hydroxyl band, no band at *ca.* 4.5 μ (no acetylene).

Anal. Calcd. for $C_{28}H_{44}O_5$: C, 73.00; H, 9.63. Found: C, 73.43; H, 9.38.

Acetol 2'-tetrahydropyranyl ether (VIIIb). Freshly distilled phosphorus oxychloride (30 drops) was added with shaking to a solution containing 15 g. of freshly distilled acetol

(13) Melting points and boiling points are uncorrected. Rotations were determined at 20–25° in chloroform solution. Ultraviolet spectra were measured in isopropanol solution on a Unicam Model S.P. 500 spectrophotometer and infrared spectra in chloroform solution (unless specified otherwise) on a Baird double-beam recording spectrophotometer. The alumina used for all chromatograms was prepared from Alcoa activated alumina, grade F-20 (Aluminum Co. of America, Pittsburgh, Pa.) through neutralization with ethyl acetate and reactivation for 4 hr. at 200° (35 mm.). Analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.

(14) V. Wolf, *Ber.*, **86**, 735 (1953).

(VIIIa)[10] and 35 cc. of 2,3-dihydropyran (distilled from sodium hydroxide) in 250 cc. of dry chloroform. The reaction mixture, which spontaneously warmed to *ca.* 50°, was then allowed to stand for 1.5 hr., moisture being excluded. The solution was poured into a saturated sodium bicarbonate solution, with stirring, and the chloroform layer was separated and dried over potassium carbonate. Distillation of the solvent and then of the residue yielded 22.2 g. (69%) of the tetrahydropyranyl ether VIIIb, b.p. 100–105° at 23 mm., n_D^{20} 1.4465; infrared band at 5.82 μ (saturated ketone), no hydroxyl band. The substance was stored at −10° or used directly for the next step, since it decomposed on being allowed to stand at room temperature.

3-Methylbut-1-yne-3,4-diol 4-(2'-tetrahydropyranyl) ether (IX). A catalytic amount of ferric nitrate was added to a solution of 4 g. of sodium in *ca.* 300 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 2.1 g. of acetol tetrahydropyranyl ether (VIIIb) in 30 cc. of dry ether was then added and the mixture was stirred with continued cooling for a further 4 hr. Ammonium chloride (25 g.) was added and the ammonia was allowed to evaporate overnight. Water and ether were added to the residue and the organic extract was washed with salt solution, dried, and evaporated. Distillation of the residue yielded 1.28 g. (52%) of the acetylenic carbinol IX as a water-white liquid, b.p. 126–132° at 20 mm., n_D^{20} 1.4667; infrared band at 3.02 μ (acetylenic hydrogen), no band at *ca.* 5.8 μ.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.79; H, 8.79.

Methyl 3-methylbut-1-yne-3,4-diol-1-carboxylate 4-(2'-tetrahydropyranyl) ether (Xb). A suspension of sodamide in liquid ammonia was prepared in the usual way from 0.8 g. of sodium in *ca.* 75 cc. of ammonia, with stirring and Dry Ice–acetone cooling. A solution containing 3 g. of methyl propiolate and 5 g. of acetol tetrahydropyranyl ether (VIIIb) in 20 cc. of dry ether was then added during 10 min. and the mixture was stirred with cooling for a further 10 min. Ammonium chloride (3 g.) was then added and the ammonia was allowed to evaporate. Water and ether were added to the residue and the organic layer was washed with salt solution, dried, and evaporated. The residual brown oil was chromatographed on 90 g. of alumina. Benzene-ether (1:1) eluted 1.9 g. (25%) of the acetylenic ester Xb as a colorless oil. Distillation of a small sample at 100° (bath temp.) at 0.1 mm. yielded the analytical specimen, n_D^{20} 1.4780, λ_{max} 210 mμ (ϵ, 4500); infrared bands at 4.45 μ (acetylene) and 5.84 μ (unsaturated ester).

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.46; H, 7.53.

Attempts to saponify this ester under mild conditions (*e.g.* with dilute aqueous alcoholic potassium hydroxide at room temperature) did not lead to the corresponding acid but resulted in material the infrared spectrum of which showed that it no longer contained an acetylenic bond.

Methyl 3-methylbut-1-(cis)-ene-3,4-diol-1-carboxylate 4-(2'-tetrahydropyranyl) ether (*XI*) *and lactone of 3-methylbut-1-ene-3,4-diol-1-carboxylic acid 4-(2'-tetrahydropyranyl) ether* (XIIa). A solution containing 450 mg. of the acetylenic ester Xb in 10 cc. of benzene and 10 cc. of pentane was shaken in hydrogen together with 400 mg. of a "Lindlar" palladium catalyst[9] at room temperature and atmospheric pressure. After 45 min., 0.95 molar equivalents of gas had been absorbed and uptake had become very slow. The catalyst was removed and the solvent was evaporated. The residue (445 mg.) in the infrared showed a band at 5.85 μ (unsaturated ester) but not at *ca.* 4.5 μ.

A 200-mg. portion of this material was chromatographed on 10 g. of alumina. Elution with benzene-ether (3:1) gave 52 mg. of the γ-lactone ether XIIa as a colorless oil. Distillation of a sample at 120° (bath temp.) at 0.5 mm. gave a purified specimen with spectral data recorded in the theoretical part of this paper.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.43; H, 7.81.

Elution with benzene-ether (1:1) yielded 86 mg. of the ethylenic ester XI as a colorless oil, which after distillation at 100° (bath temp.) at 0.1 mm. showed an infrared band at 5.85 μ (unsaturated ester).

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.09; H, 8.46.

γ-Lactone of 3-methylbut-1-ene-3,4-diol-1-carboxylic acid (XIIb). The unpurified partially hydrogenated ester XI (287 mg.) was dissolved in 5 cc. of methanol and a solution containing 0.5 cc. of concentrated hydrochloric acid and 0.5 cc. of water was added, with shaking. The solution was allowed to stand at room temperature for 24 hr. and was then poured into 50 cc. of saturated salt solution and continuously extracted with ether for 24 hr. The ether extract was dried and evaporated. The residual lactone XIIb (141 mg.), which could be distilled at 100° (bath temp.) at 1 mm., in the infrared showed a hydroxyl band and a well defined band at 5.70 μ (unsaturated γ-lactone). The substance was very soluble in water and gave low carbon values on analysis.

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