250.8° dec. No depression in melting point was observed on admixture with authentic IV.

The aqueous extracts were evaporated in a cold air stream to leave an amorphous, light brown solid, which was taken up in nitromethane, treated with Norit and allowed to crystallize. A total of 0.029 g. (7.0%) of VI, which melted at 195.5–197.5° dec. (first crop), and on being mixed with authentic VI[3] (201.8–202.4° dec., cor.) the sample melted at 198.0–199.5° dec.

Kinetic Study of the Reactions of II and III with Sodium Bicarbonate.—All runs were made by dissolving and diluting to 50 ml., 1.000 g. of either II or III in acetone. The resulting solution was divided into 5.0-ml. portions which were placed in a constant temperature bath until temperature equilibrium had been reached. The reaction was started by adding 5 ml. of 0.25 *M* sodium bicarbonate. Quenching was effected by adding 25 ml. of 1.14 *M* nitric acid after the appropriate time interval. The reaction mixture was extracted twice with 10- and 5-ml. portions of chloroform, respectively, and the combined chloroform extracts were washed with two 5-ml. portions of 1.14 *M* nitric acid which were then added to the original aqueous solution. Bromide ion was then determined by titration with silver nitrate using the Volhard method. Blank determinations showed no bromide ion to be present. Data are summarized in Table I.

Effect of Change in *p*H on the Hydrolysis of II.—Runs similar to the preceding were made on II using as the alkaline initiator 5 ml. of a mixture which was 0.125 *M* in sodium bicarbonate and 0.125 *M* in sodium carbonate. In addition the change in apparent *p*H as the reaction proceeded was followed by means of a Beckman model H-2 *p*H meter. For this purpose a sample of 0.500 g. of II (0.00141 mole) in 25 ml. of acetone was used with 25 ml. of the alkaline initiator (see Figs. 1 and 2).

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

$\Delta^{5,7}$-Steroids. XVII.[1] Steroidal Cyclic Ketals. IX.[2] Transformation Products of Reichstein's Substance S

BY ROSE ANTONUCCI, SEYMOUR BERNSTEIN AND ROBERT H. LENHARD

RECEIVED JANUARY 11, 1954

Reichstein's Substance S (I) on reaction with ethylene glycol (benzene, *p*-toluenesulfonic acid) was converted into Δ^5-pregnene-17α,21-diol-3,20-dione 3,20-bisethylene ketal (IIa). The 21-acetate (IIb) of the latter on allylic bromination followed by dehydrobromination gave $\Delta^{5,7}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate 3,20-bisethylene ketal (IIIb). This intermediate, in turn, was transformed into $\Delta^{4,7}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate 20-ethylene ketal (IV), $\Delta^{4,7}$-pregnadiene-17α,21-diol-3,20-dione (Va), Δ^7-allopregnene-17α,21-diol-3,20-dione (VIII), and $\Delta^{5,7,9(11)}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate 3,20-bisethylene ketal (VII). The latter readily formed a maleic anhydride adduct product (IX).

In this paper we wish to report on the application of certain transformations developed in this Laboratory[1,3] on the important Reichstein's Substance S (I) in which the C3 and 20 carbonyl groups are protected as ethylene ketals.

In a previous publication,[3c] it was shown that Reichstein's Substance S acetate on treatment with ethylene glycol (benzene, *p*-toluenesulfonic acid) afforded the C3-mono-ethylene ketal, Δ^5-pregnene-17α,21-diol-3,20-dione 21-acetate 3-ethylene ketal. The condensation of the C20-carbonyl group with ethylene glycol was prevented by the 21-acetate group. A similar finding was observed with desoxycorticosterone acetate[3b] and cortisone acetate.[3c] Moreover, cortisone was converted into its 3,20-bisketal.[3c] Accordingly, Reichstein's Substance S (I) also has now been converted into the 3,20-bisketal (IIa). Acetylation with acetic anhydride–pyridine gave the 21-acetate (IIb). Bromination of IIb with N-bromosuccinimide (NBS) followed by dehydrobromination with *s*-collidine in xylene produced the $\Delta^{5,7}$-diene (IIIb). The 17α,21-diol (IIIa) was obtained on alkaline hydrolysis.

A number of transformations were then carried out with the intermediate, $\Delta^{5,7}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate 3,20-bisethylene ketal (IIIb): *i.e.*, hydrolysis, hydrogenation and dehydrogenation.

Treatment of IIIb with aqueous acetic acid selectively hydrolyzed the C3-ketal group, and $\Delta^{4,7}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate 20-ethylene ketal (IV) was obtained. However, hydrolysis with sulfuric acid–methanol removed both of the ketal groups to afford $\Delta^{4,7}$-pregnadiene-17α,-21-diol-3,20-dione (Va). The 21-acetate (Vb) was obtained by acetylation with acetic anhydride–pyridine.

Hydrogenation of IIIb in alcohol–ethyl acetate or ether–alcohol with W2 Raney nickel catalyst gave Δ^7-allopregnene-17α,21-diol-3,20-dione 21-acetate 3,20-bisethylene ketal (VIb). Alkaline hydrolysis removed the C21-acetate group, and VIa was obtained. Hydrolysis of the latter with sulfuric acid–methanol gave Δ^7-allopregnene-17α,21-diol-3,20-dione (VIII).

Mercuric acetate dehydrogenation converted IIIb into the $\Delta^{5,7,9(11)}$-acetate bisketal (VII). The latter readily formed a maleic anhydride adduct product.

The structures of the various new compounds described above were supported by the following considerations, other than elemental and infrared spectral analyses, and methods of synthesis.

$\Delta^{5,7}$-Pregnadiene-17α,21-diol-3,20-dione 3,20-bisethylene ketal (IIIa), and its acetate (IIIb) showed the characteristic ultraviolet absorption maxima of a $\Delta^{5,7}$-steroid, namely at 271, 281.5 and 293 mμ.[4] In

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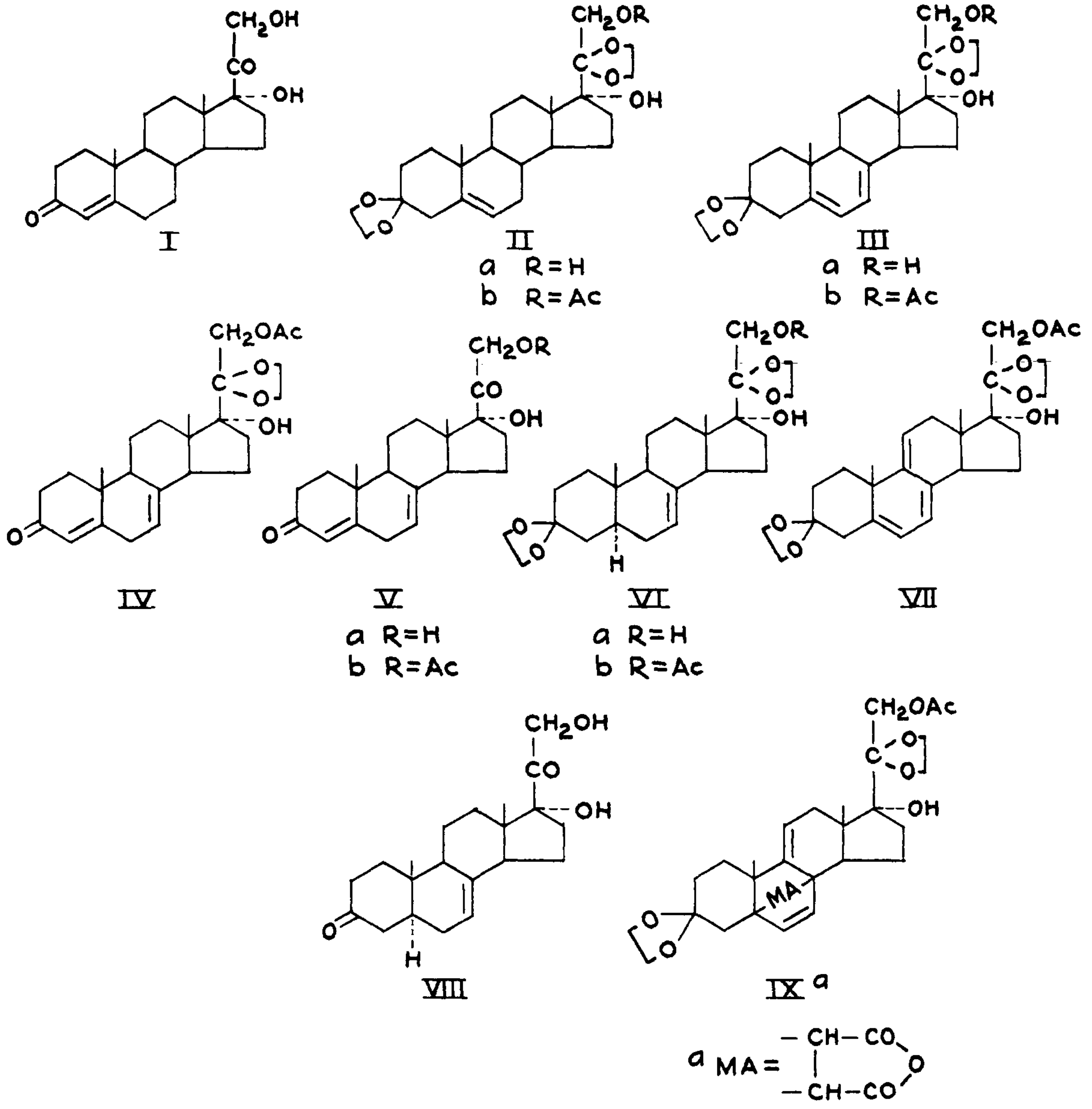
[1] Paper XVI, S. Bernstein, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 1418 (1953).

[2] Paper VIII, S. Bernstein, R. Littell and J. H. Williams, THIS JOURNAL, **75**, 4830 (1953).

[3] (a) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952); (b) R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax and J. H. Williams, *ibid.*, **17**, 1369 (1952); (c) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *ibid.*, **18**, 70 (1953).

[4] W. Huber, G. W. Ewing and J. Kriger, THIS JOURNAL, **67**, 609 (1945); see also, S. Bernstein, L. Binovi, L. Dorfman, K. J. Sax and Y. SubbaRow, *J. Org. Chem.*, **14**, 433 (1949); and R. Antonucci, S. Bernstein, D. Giancola and K. J. Sax, *ibid.*, **16**, 1126 (1951).

FLOW SHEET



the case of the acetate (IIIb), the molecular extinction coefficients of the maxima were lower than those usually observed for the $\Delta^{5,7}$-chromophore. This may be ascribed to the influence of the C17-side chain, but not of the 3-ketal. The latter point is borne out by recent work with $\Delta^{5,7}$-3-ethylene ketals, where the extinction coefficients are "normal."[3a]

We have recently proposed that *generally* a Δ^5-ethylene ketal has a more *negative* optical rotation than the corresponding $\Delta^{5,7}$-3-ethylene ketal,[1] in contrast to the well-known opposite correlation for Δ^5- and $\Delta^{5,7}$-3-hydroxysteroids.[5] Here, also, Δ^5-pregnene-17α,21-diol-3,20-dione 3,20-bisethylene ketal (IIa) and its acetate (IIb) have a more negative optical rotation than their respective $\Delta^{5,7}$-analogs (IIIa and b).

Both $\Delta^{4,7}$-3-ketosteroids, $\Delta^{4,7}$-pregnadiene-17α,21-diol-3,20-dione (Va) [and its acetate (Vb)] exhibited an ultraviolet absorption maximum at 239 and 238–239 mμ, respectively. This observation conforms with the generalization that $\Delta^{4,7}$-3-ketosteroids exhibited a maximum at about 237–238 mμ.[1,6]

$\Delta^{5,7,9(11)}$-Pregnatriene-17α,21-diol-3,20-dione 21-acetate 3,20-bisethylene ketal (VII) exhibited ultraviolet absorption maxima at 312, 325 and 340–341 mμ with an inflection at 296–297 mμ. This selective absorption is a well-known characteristic of a $\Delta^{5,7,9(11)}$-steroid.[7] It is to be noted that here also the side-chain has a hypochromic effect on the extinction coefficients. In addition, the structure

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(5) S. Bernstein, W. J. Kauzmann and E. S. Wallis, *J. Org. Chem.*, **6**, 319 (1941); D. H. R. Barton and W. Klyne, *Chemistry and Industry*, 755 (1948).

(6) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(7) (a) R. A. Morton, I. M. Heilbron and F. S. Spring, *Biochem. J.*, **24**, 136 (1930); (b) A. Windaus, M. Deppe and C. Roosen-Runge, *Ann.*, **537**, 1 (1938); (c) R. A. Morton and A. J. A. de Gouveia, *J. Chem. Soc.*, 916 (1934); (d) R. Antonucci, S. Bernstein, D. Giancola and K. J. Sax, *J. Org. Chem.*, **16**, 1159 (1951).

of the triene VII was supported by its highly positive optical rotation,[7b,d,8] and, as noted, by its ready formation of a maleic anhydride adduct product.[9]

Experimental

Melting Points.—All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

Optical Rotations.—The sample was dissolved in chloroform to make a 2-ml. solution, and the rotation was determined in a 1-dm. semimicro tube at wave length 5893 Å. (D).

Absorption Spectra.—The ultraviolet spectra were determined in absolute alcohol with a Beckman spectrophotometer (Model DU). The infrared spectra (Nujol mulls) were determined with a Perkin–Elmer spectrophotometer (Model 21).

Petroleum Ether.—The fraction used was either b.p. 64–66° or 66–68°, and was purified with concentrated sulfuric acid and potassium permanganate.

Δ^{5}-Pregnene-17α,21-diol-3,20-dione 3,20-Bisethylene Ketal (IIa). A.—A mixture of Reichstein's Substance S (I, 5 g.), ethylene glycol (40 ml.), benzene (250 ml.) and *p*-toluenesulfonic acid monohydrate (150 mg.) was treated in the same manner as described in a previous publication[3a] (reflux 7 hours). It was cooled, made alkaline with sodium bicarbonate solution, and allowed to stand at room temperature overnight. The solid material (impure IIa) at the interface was collected by filtration, and was washed with benzene, water and ether; 2.49 g., mixture of solid and viscous oil. Two crystallizations from acetone (petroleum ether wash) gave 1.4 g. (22% yield)[10] of IIa; m.p. 211.5–217.5°, with previous softening; λ_{max} none in ultraviolet.

The filtered reaction mixture[11] was extracted with benzene. The extract was evaporated at reduced pressure, and the residue was recrystallized from acetone–petroleum ether, and acetone (petroleum ether wash); 0.8 g., m.p. below 190°. This fraction was not investigated further.

B.—In another run, the product obtained by essentially the above procedure was purified for characterization; m.p. 215–217.5° (from acetone–ether); infrared, λ_{max} 3425, 1095 cm.$^{-1}$; $[\alpha]^{30}_{D}$ −32° (13.65 mg., α_D −0.22°), $[M]_D$ −139.

Anal. Calcd. for $C_{25}H_{38}O_6$ (434.55): C, 69.09; H, 8.81. Found: C, 69.00; H, 8.79.

Δ^{5}-Pregnene-17α,21-diol-3,20-dione 21-Acetate 3,20-Bisethylene Ketal (IIb).—The bisketal (IIa, 1.4 g.) in pyridine (4 ml.) was treated with acetic anhydride (2 ml.) (room temperature, 23 hours). Addition of water and filtration gave 1.48 g. (96% yield), of impure IIb, m.p. 200–217° with previous softening. Crystallization from methanol gave pure IIb; 1.26 g., m.p. 213–217°; infrared, λ_{max} 3545, 1740, 1258, 1105 cm.$^{-1}$; $[\alpha]^{28}_{D}$ −35° (13.2 mg., α_D −0.23°), $[M]_D$ −167.

Anal. Calcd. for $C_{27}H_{40}O_7$ (476.59): C, 68.04; H, 8.46. Found: C, 67.84; H, 8.58.

$\Delta^{5,7}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate 3,20-Bisethylene Ketal (IIIb).—The Δ^{5}-acetate-bis-ketal (IIb, 0.5 g., 0.00105 mole) in carbon tetrachloride (15 ml.) and petroleum ether (5 ml.) was brominated with NBS (0.23 g.) in the usual manner of this Laboratory.[4] Addition of *s*-collidine (0.2 ml.) to the refluxing mixture, evaporation and dehydrobromination carried out in xylene (15 ml.) containing additional *s*-collidine (0.1 ml.) gave 0.19 g. of crude material (from acetone); m.p. 192–205°; λ_{max} 241–242 mμ (ϵ 3400), 271 mμ (ϵ 8100), 281.5 mμ (ϵ 8600) and 293 mμ (ϵ 5100). Crystallization from methanol, and dilute acetone gave 74 mg. (15% yield) of pure IIIb; m.p. 212–215°; λ_{max} 271 mμ (ϵ 9500), 281.5 mμ (ϵ 10100) and 293 mμ (ϵ 5900); infrared, λ_{max} 3590, 1750, 1230, 1100 cm.$^{-1}$; $[\alpha]^{33}_{D}$ −17° (18.9 mg., α_D −0.16°), $[M]_D$ −81.

Anal. Calcd. for $C_{27}H_{38}O_7$(474.57): C, 68.33; H, 8.07. Found: C, 68.14; H, 8.20.

In another run, there was obtained m.p. 214.5–215.5° (from acetone); λ_{max} 271 mμ (ϵ 9900), 282 mμ (ϵ 10400) and 294 mμ (ϵ 6100); $[\alpha]^{26}_{D}$ −17° (15.8 mg., α_D −0.13°).

$\Delta^{5,7}$-Pregnadiene-17α,21-diol-3,20-dione 3,20-Bisethylene Ketal (IIIa).—The $\Delta^{5,7}$-acetate-bis-ketal (IIIb, 1.27 g.) in 2.5% aqueous alcoholic (1:2) potassium hydroxide (30 ml.) was refluxed for 0.5 hour. Addition of water and chilling gave crystals which were collected; 1.16 g. (quantitative "crude" yield), m.p. 204–210° with previous softening. Crystallization from acetone (petroleum ether wash) gave 0.59 g. of IIIa; m.p. 212–215.5° with previous softening; λ_{max} 271 mμ (ϵ 10600), 281.5 mμ (ϵ 11200) and 293 mμ (ϵ 6500); infrared, λ_{max} 3450, 1103 cm.$^{-1}$; $[\alpha]^{24}_{D}$ −13° (9.35 mg., α_D −0.06°), $[M]_D$ −56.

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.44; H, 8.49.

$\Delta^{4,7}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate 20-Ethylene Ketal (IV).—The $\Delta^{5,7}$-acetate-bis-ketal (IIIb, 0.42 g.) in 90% (v./v.) aqueous acetic acid (35 ml.) was heated on the steam-bath for 0.5 hour. It was cooled, treated with water (about 200 ml.) and was allowed to stand at 5° overnight. The crystals so obtained were collected; 0.26 g., m.p. 145–148.5° with previous softening. Successive crystallizations from acetone–petroleum ether, aqueous acetone, methanol and aqueous methanol gave 29 mg. of V; m.p. 159.5–161.5°; λ_{max} 239 mμ (ϵ 14300); infrared, λ_{max} 3485, 1733, 1680, 1626, 1234, 1092 cm.$^{-1}$; $[\alpha]^{27}_{D}$ +14° (10.25 mg., α_D +0.07°), $[M]_D$ +60.

Anal. Calcd. for $C_{25}H_{34}O_6$ (430.52): C, 69.74; H, 7.96. Found: C, 69.37; H, 8.12.

$\Delta^{4,7}$-Pregnadiene-17α,21-diol-3,20-dione (Va).—The $\Delta^{5,7}$-bis-ketal (IIIa, 0.56 g.) in methanol (20 ml.) and 8% (v./v.) sulfuric acid (2 ml.) was refluxed (nitrogen atmosphere) for 40 minutes. Water was added; the mixture was cooled, and the crystals were collected; 370 mg. (83% "crude" yield), m.p. 205–213° with previous softening and browning. Four crystallizations from acetone–petroleum ether gave pure Va; 70 mg.; m.p. 219–222° with previous softening and browning; λ_{max} 238–239 mμ (ϵ 14800); infrared, λ_{max} 3470, 1710, 1667, 1630, 1100, 1095 cm.$^{-1}$; $[\alpha]^{24}_{D}$ +34° (19.4 mg., α_D +0.33°), $[M]_D$ +117.

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 72.98; H, 8.38.

$\Delta^{4,7}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate (Vb).—The 17α,21-diol (Va, 140 mg.) in pyridine (1 ml.) was acetylated with acetic anhydride (1 ml.) (room temperature overnight). The mixture was cooled, water was added, and the crude acetate was collected; 157 mg. (quantitative "crude" yield), m.p. 184–198° with previous softening. Five crystallizations from acetone–petroleum ether gave pure Vb; 32 mg., m.p. 206–211° with previous softening; λ_{max} 238–239 mμ (ϵ 14000); infrared, λ_{max} 3412, 1755, 1730, 1660, 1623 cm.$^{-1}$; $[\alpha]^{24}_{D}$ +76° (11 mg., α_D +0.42°), $[M]_D$ +293.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.27; H, 7.88.

Δ^{7}-Allopregnene-17α,21-diol-3,20-dione 21-Acetate 3,20-Bisethylene Ketal (VIb).—To a solution of IIIb (0.7 g.) in alcohol (130 ml.) and ethyl acetate (50 ml.) was added Raney nickel catalyst (W2, about 3 g.), and the mixture was shaken overnight in a hydrogen atmosphere at room temperature and atmospheric pressure. Filtration and concentration gave crystals; 0.45 g., m.p. 170–172°; λ_{max} none. Two crystallizations from methanol gave 0.25 g., m.p. 180–182°.

A 50-mg. portion was crystallized an additional two times from methanol; 37 mg., m.p. 181–182.5°; infrared, λ_{max} 3448, 1750, 1240, 1225, 1093 cm.$^{-1}$; $[\alpha]^{22}_{D}$ −7° (13.65 mg., α_D −0.05°), $[M]_D$ −33.

Anal. Calcd. for $C_{27}H_{40}O_7$ (476.59): C, 68.04; H, 8.46. Found: C, 67.69; H, 8.41.

In another run, the hydrogenation was carried out in ether–alcohol; m.p. 180–181°; $[\alpha]^{26}_{D}$ −7° (10.7 mg., α_D −0.04°).

Δ^{7}-Allopregnene-17α,21-diol-3,20-dione 3,20-Bisethylene Ketal (VIa).—The Δ^{7}-acetate-bis-ketal (VIb, 0.5 g.) in 2.5% alcoholic potassium hydroxide (10 ml.) was refluxed for 0.5 hour, treated with water and cooled. The resulting crystals were collected; wt. not recorded (moist), m.p. 189.5–196°, cloudy melt. Crystallization from methanol gave 253 mg.

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[8] A. Windaus and O. Linsert, *Ann.*, **465**, 148 (1928).

[9] A. Windaus and A. Lüttringhaus, *Ber.*, **64**, 850 (1931); H. Honigmann, *Ann.*, **508**, 89 (1934).

[10] Generally, no attempt was made to obtain maximal yields for the preparations described herein.

[11] Many times, the bisketal did not separate, and the entire reaction mixture was extracted with benzene. The crude product was fractionally recrystallized from acetone–petroleum ether, and acetone.

of VIa; m.p. 192.5–194° with previous softening. From the mother liquor by concentration and addition of water there was obtained an additional 161 mg., m.p. 189–192°, bubbles in melt, clear at 199°; 91% yield (two fractions). Crystallization of the first fraction from methanol gave 199 mg., m.p. 193.5–194.5°; infrared, λ_{max} 3460, 1092 cm.$^{-1}$; $[\alpha]^{24}$D −7° (18.8 mg., αD −0.07°), [M]D −30.

Anal. Calcd. for $C_{25}H_{38}O_6$ (434.55): C, 69.09; H, 8.81. Found: C, 68.99; H, 8.55.

$\Delta^{5,7,9(11)}$-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate 3,20-Bisethylene Ketal (VII).—A solution of IIIb (0.3 g.) in chloroform (1 ml., dried over anhydrous potassium carbonate) was treated with a solution of mercuric acetate (0.4 g.) in glacial acetic acid (8 ml.) and acetic anhydride (0.1 ml.). The mixture was shaken at 5° overnight, and was then filtered for removal of mercurous acetate. Evaporation at reduced pressure of the filtrate gave an orange solid. Six crystallizations from methanol gave 52 mg. (17% yield) of VII; m.p. 205–207.5°; λ_{max} 312 mμ (ϵ 8100), 325 mμ (ϵ 9200) and 340–341 mμ (ϵ 5800), inflection at 296–297 mμ; infrared, λ_{max} 3530, 1750, 1630, 1230, 1215, 1090 cm.$^{-1}$; $[\alpha]^{27}$D +190° (10.2 mg., αD +0.97°), [M]D +897.

Anal. Calcd. for $C_{27}H_{36}O_7$ (472.56): C, 68.62; H, 7.68. Found: C, 68.53; H, 8.11.

Δ^7-Allopregnene-17α,21-diol-3,20-dione (VIII).—Compound VIa (215 mg.) in methanol (10 ml.) and 8% (v./v.) sulfuric acid (1 ml.) was refluxed for 40 minutes. Water was added; the mixture was cooled, and the crystals were collected; 157 mg. (91% "crude" yield). Two crystallizations from acetone (petroleum ether wash) gave pure VIII; 111 mg., m.p. 245–247.5° with previous softening; infrared, λ_{max} 3380, 3290, 1730, 1705, 1104 cm.$^{-1}$; $[\alpha]^{24}$D −10° (17.45 mg., αD −0.09°), [M]D −35.

Anal. Calcd. for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73. Found: C, 72.58; H, 8.91.

Maleic Anhydride Adduct (IX) of $\Delta^{5,7,9(11)}$-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate 3,20-Bisethylene Ketal.—A mixture of VII (28 mg.), maleic anhydride (11 mg.) and benzene (3 ml.) was refluxed for 17 hours, and evaporated at reduced pressure. The residue was triturated with ether, and the solid was collected; 20 mg., m.p. 233–240° with previous softening (brown melt). Four crystallizations from acetone–petroleum ether gave 13 mg. of IX; m.p. 247–249.5° (brown melt); λ_{max} none; infrared, λ_{max} 3470 1866, 1850, 1785, 1750, 1242, 1228, 1094 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{38}O_{10}$ (570.61): C, 65.25; H, 6.71. Found: C, 65.01; H, 6.92.

PEARL RIVER, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Poison Ivy "Urushiol"

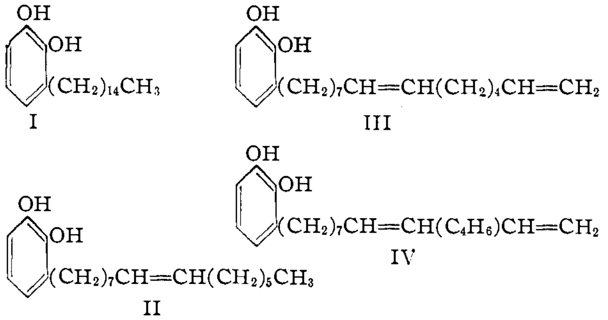
BY WILLIAM F. SYMES[1] AND CHARLES R. DAWSON

RECEIVED DECEMBER 14, 1953

The toxic principle of poison ivy has an olefinic unsaturation of about two double bonds and possesses the carbon skeleton of 3-pentadecylcatechol. It has been found that the dimethyl ether can be separated by chromatography on alumina into four pure components which vary only in their degree of unsaturation in the side chain. One of the components has a completely reduced side chain. The other three contain one, two and three olefinic bonds, respectively. The structures proposed for the olefinic components on the basis of ozonolysis and oxidative degradation experiments are as follows: a mono-olefin, 1,2-dihydroxy-3-(pentadecenyl-8')-benzene; a diolefin, 1,2-dihydroxy-3-(pentadecadienyl-8',11')-benzene and a tri-olefin, 1,2-dihydroxy-3-(pentadecatrienyl-8',11',14')-benzene.

The poison ivy plant (*Rhus toxicodendron radicans*) and the related species poison oak (*R. toxicodendron diversilobum*) and poison sumac (*R. toxicodendron vernix*) probably cause more human suffering annually than any other North American plants. For this reason there has long been interest in establishing the chemical structure of the vesicant principle of *Rhus toxicodendron*.[2] Although McNair concluded in 1921 that the active principle of the poison oak is a catechol compound, he could not further identify it structurally.[3] Thirteen years later the carbon skeleton of the poison ivy principle was first revealed as the result of the work of Hill and his students.[4] They found that hydrogenation of the poison ivy principle gave a compound identical to that obtained on hydrogenation of urushiol, the vesicant oil occurring in the sap of the Japanese lac tree (*Rhus verniciflora*). Majima had established earlier that the structure of hydrourushiol is that of 3-pentadecylcatechol.[5]

Majima's investigation of Japanese lac urushiol extended over a period of 15 years and he finally concluded that it was a mixture of olefinic catechols which could not be separated by distillation. The vesicant oil had an unsaturation equivalent to about two olefinic bonds and on hydrogenation gave the single substance hydrourushiol. Ozonolysis and other oxidative degradations, carried out on dimethylurushiol, led to a variety of products including small amounts of dimethylhydrourushiol. Although his attempts to separate pure ozonides were unsuccessful, the ozonolysis products seemed best accounted for in terms of four components differing only in the number of double bonds in the alkenyl side chain of urushiol. Majima postulated the following structures for the components of urushiol and indicated some uncertainty about the existence of the diolefinic component.[6]



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[1] This paper is based on a portion of the thesis submitted by William F. Symes in 1951 to Columbia University in partial fulfillment of the requirements for the Ph.D. degree in chemistry.

[2] R. Khittel, *Am. J. Pharm.*, **6** [3], 542 (1858); L. Maisch, *ibid.*, **14** [3], 4 (1866); H. Pfaff, *J. Exp. Med.*, **2**, 181 (1897); S. F. Acree and W. A. Syme, *J. Biol. Chem.*, **2**, 547 (1906).

[3] J. B. McNair, THIS JOURNAL, **43**, 159 (1921).

[4] G. A. Hill, V. Mattacotti and W. D. Graham, *ibid.*, **56**, 2736 (1934).

[5] R. Majima, *Ber.*, **48**, 1593 (1915).

[6] R. Majima, *ibid.*, **55B**, 172 (1922).