362. *Steroidal Sapogenins. Part XL.* Reaction of 12-Oxo-sapogenins with Selenium Dioxide: Synthesis of 3β-Hydroxypregna-5,9(11),16-trien-20-one from Botogenin.*

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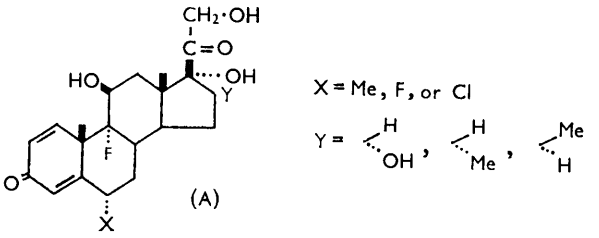
Selenium dioxide dehydrogenates botogenin or its acetate to 9,11-dehydro-derivative, thus proving the stability (previously denied) of the spiroketal system to this reagent. An alternative four-step dehydrogenation of the acetate is also described. The dehydro-derivative has been degraded to 3β-acetoxypregna-5,9(11),16-trien-20-one.

From much recent work it has emerged that compounds of type (A) will, in general, have high biological anti-inflammatory activity without sodium retention; consequently any intermediate that can afford a compound of this type might find wide application. From this standpoint 3β-acetoxypregna-5,9(11),16-trien-20-one (VI) appears useful since the requisite substitution at positions 6, 9(11), and 16 should be possible in view of the unsaturation present and widely differing reactivity of the three double bonds. This paper reports the preparation of compound (VI) from the naturally occurring botogenin (12-oxodiosgenin) [1] (I).



Previous work [2,3] with botogenin (and its 25-epimer) has been directed towards moving the 12-keto-function to position 11, and both 11-oxo- and 11α-hydroxy-diosgenin have

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[1] (*a*) Marker and Lopez, *J. Amer. Chem. Soc.*, 1947, **69**, 2397; (*b*) Walens, Serota, and Wall, *ibid.*, 1955, **77**, 5196; *J. Org. Chem.*, 1957, **22**, 182.

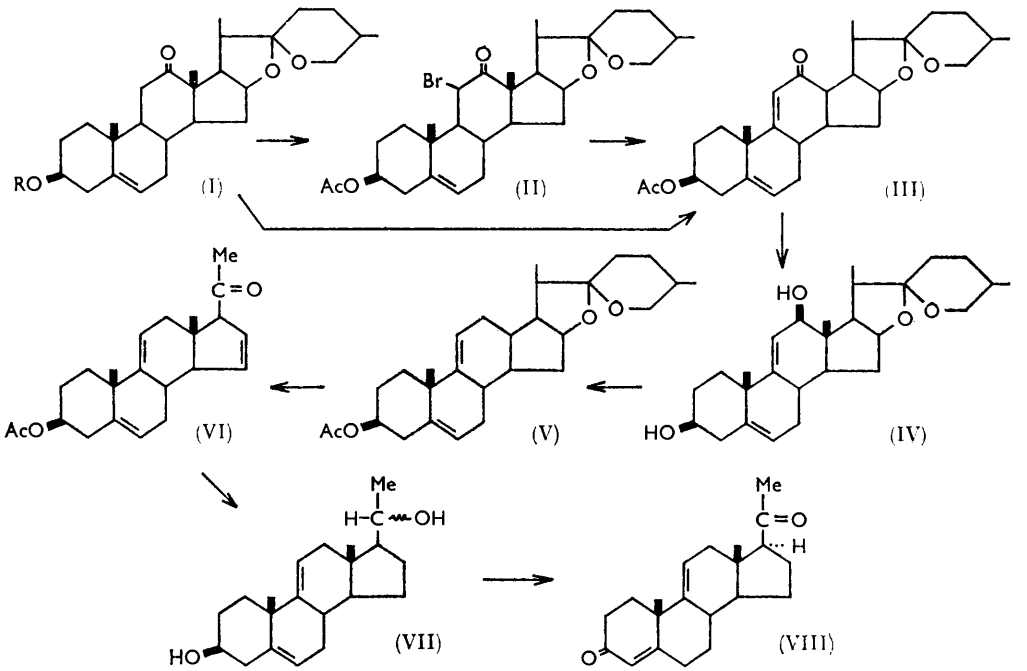
[2] Rothman and Wall, *J. Amer. Chem. Soc.*, 1957, **79**, 3228; *J. Org. Chem.*, 1958, **23**, 1741; Halpern and Djerassi, *J. Amer. Chem. Soc.*, 1959, **81**, 439.

[3] Cf. Romo, *Bol. Inst. Quim. Mex.*, **7**, 1955, 53.

been described. The latter, in particular, would be a useful precursor [4] for 9(11)-dehydrodiosgenin (V), but the multi-stage conversion of botogenin (I) into 11α-hydroxydiosgenin made a more direct route to 9(11)-dehydrodiosgenin desirable.

Rothman and Wall [2] prepared the 11,23-dibromide (II) by a two-stage sequence from botogenin acetate (I; R = Ac), and dehydrobromination of this with collidine followed by reductive removal of the 23-bromine atom with zinc led to the $\Delta^{9(11)}$-12-ketone (III) in 19% overall yield from botogenin acetate.

In the bile acid series it is known that 12-ketones can be oxidized to $\Delta^{9(11)}$-12-ketones by selenium dioxide [5] in the presence of acetic acid but reports [6] about the instability of the spiroketal system to selenium dioxide have discouraged its use with steroidal sapogenins. However, we find that botogenin acetate and selenium dioxide in t-butyl alcohol containing some pyridine give a 70% yield of the $\Delta^{9(11)}$-12-ketone (III; 25a-epimer [7]).*



Similarly, correllogenin [1b] the 25b-epimer of botogenin smoothly afforded the corresponding $\Delta^{9(11)}$-12-ketone (III, 25b-epimer); and the naturally occurring mixture of botogenin and correllogenin gave the corresponding mixture 25-epimers. A similar reaction with hecogenin acetate (I; reduced 5α-H) afforded 89% of the known 9(11)-dehydrohecogenin acetate,[8] illustrating the general applicability of the procedure.

Reducing compound (III) with sodium borohydride gave the $\Delta^{5,9(11)}$-3β,12β-diol (IV),

* After the completion of this work Mazur (*J. Amer. Chem. Soc.*, 1959, **81**, 1454) reported the conversion of hecogenin acetate into its $\Delta^{9(11)}$-analogue in 36% yield by oxidation with selenium dioxide in t-butyl alcohol containing some acetic acid.

[4] For the conversion of 11α-alcohols into 9(11)-unsaturated steroids see Fried and Sabo (*J. Amer. Chem. Soc.*, 1953, **75**, 2273), and Rosenkranz, Mancera, and Sondheimer (*ibid.*, 1954, **76**, 2227).

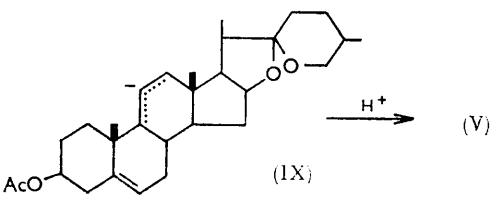
[5] Schwenk and Stahl, *Arch. Biochem.*, 1947, **14**, 125.

[6] Marker and Rohrmann, *J. Amer. Chem. Soc.*, 1939, **61**, 846; contrast Hirschmann, Snoddy, and Wendler (*ibid.*, 1953, **75**, 3252).

[7] For nomenclature of the side chain see Djerassi, Grossnickle, and High (*J. Amer. Chem. Soc.*, 1956, **78**, 3166, footnote 10; see also Lardon, Schindler, and Reichstein (*Helv. Chim. Acta*, 1957, **40**, 678), and Djerassi and Fishman (*J. Amer. Chem. Soc.*, 1955, **77**, 4291).

[8] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 303.

whose diacetate, on treatment with lithium and ethylamine,[9] underwent hydrolysis of the 3β-acetate and reductive acetolysis of the allylic 12β-acetate, affording $^{9(11)}$-dehydrodiosgenin (V). Reductive elimination of allylic ethers or acetates takes place *via* a mesomeric carbanion,[9,10] in this case (IX); protonation of this intermediate is very probably a thermodynamically controlled process: * one may confidently assign the trisubstituted double-bond structure (V) rather than the disubstituted Δ^{11}-isomer * to the product. The sapogenin side chain of 9(11)-dehydrodiosgenin (V) was then degraded



by the standard Marker procedure,[11] to afford the desired 3β-acetoxypregna-5,9(11),16-trien-20-one (VI).

Lithium in liquid ammonia selectively reduced the Δ^{16}-double bond of this αβ-unsaturated ketone (VI). A mild alkali treatment to complete hydrolysis of the 3-acetate group, followed by an Oppenauer oxidation of the crude reduction product (VII), then afforded pregna-4,9(11)-diene-3,20-dione [12] (VIII). This sequence of reactions further established the correctness of the structure (VI).

Experimental

Rotations were determined for chloroform and ultraviolet light absorption spectra for 95% ethanol solutions. We are grateful to Dr. L. J. Throop and his staff for these measurements and for the infrared spectra which were obtained with a Perkin–Elmer model 21 spectrophotometer with a sodium chloride prism. The elemental analyses were carried out by Dr. A. Bernhardt, Mülheim/Ruhr, Germany.

$\Delta^{9(11)}$-Dehydrobotogenin Acetate [*3-Acetoxy-22α,25a-spirosta-5,9(11)-dien-12-one*] [7],† (III).—(a) *From the dibromide* (II). 3β-Acetoxy-11α,23-dibromo-22α,25a-spirost-5-en-12-one (II) (Halpern *et al.*[2]) (5·0 g.) in collidine (60 c.c.) was heated under reflux for 1 hr. The cooled solution was added to ice-water, and the product extracted with ether (4 × 200 c.c.). The combined ether solutions were washed successively with 2N-hydrochloric acid, 5% sodium hydrogen carbonate solution, and water. Removal of the ether *in vacuo* from the dried solution (Na_2SO_4) afforded a non-crystalline product (4·4 g.), $\lambda_{max.}$ 238—240 mμ (ε 6300). After the addition of zinc dust (28 g.) a solution of this crude product in ethanol (200 c.c.) was heated under reflux for 8 hr. Filtration and removal of the ethanol *in vacuo* gave a product which was adsorbed from benzene on alumina (250 g.). Elution with benzene (1200 c.c.) afforded *$\Delta^{9(11)}$-dehydrobotogenin acetate* (III) (1·46 g.), m. p. 180—190°, $\lambda_{max.}$ 238 mμ (ε 10,470), raised by several crystallisations from ethyl acetate–hexane to 196—197°, $[\alpha]_D$ −34°, $\lambda_{max.}$ 238 mμ (ε 11,750), $\nu_{max.}$ (in KBr) 1730, 1668, 1597, 1245, 983, 920, 902, and 865 cm.$^{-1}$ (Found: C, 74·6; H, 8·6; O, 16·8. $C_{29}H_{40}O_5$ requires C, 74·3; H, 8·6; O, 17·1%).

(b) *Oxidation of botogenin acetate* (I) *by selenium dioxide.* Selenium dioxide (45 g.) was added to a solution of botogenin acetate (I) (167 g.) (m. p. 215—220°, $[\alpha]_D$ −57°) in t-butyl

* A kinetically controlled protonation of our intermediate (IX) would probably lead to the same product since steric hindrance to the approach of a proton source is less at position 12(α) than at position 9(α).

† The use of α and β to designate the stereochemistry at position 22 follows from the recommendations of the International Union of Pure and Applied Chemistry (" Nomenclature of Organic Chemistry, 1957," Butterworths Scientific Publications, London, 1958, p. 77.

[9] Hallsworth, Henbest, and Wrigley, *J.*, 1957, 1969.
[10] Birch, *Quart. Rev.*, 1950, **4**, 69.
[11] Marker and Rohrmann, *J. Amer. Chem. Soc.*, 1939, **61**, 3592; 1940, **62**, 518.
[12] Shoppee and Reichstein, *Helv. Chim. Acta*, 1941, **24**, 351.

alcohol (8 l.) containing pyridine (13·5 c.c.) and heated under reflux with stirring in an atmosphere of nitrogen for 24 hr. A further 45 g. of selenium dioxide and 13·5 c.c. of pyridine were then added and heating was continued under the same conditions for a further 72 hr. The cooled mixture was then filtered through Celite to remove the precipitated selenium and the solvent was then removed *in vacuo*. The solid residue was triturated with water (2 × 2·5 l.), filtered, and recrystallised from methanol (10 g. of charcoal), to afford $\Delta^{9(11)}$-dehydrobotogenin acetate (III) (117 g., 70%), m. p. 193—197°, raised by several recrystallisations from methanol to 201—202°, $[\alpha]_D$ −32°, $\lambda_{max.}$ 238 mμ (ε 11,480). The mixed m. p. with the product prepared as described in method (a) showed no depression and the infrared spectra of the two products were identical.

$\Delta^{9(11)}$-*Dehydrocorrellogenin Acetate* (III) (25*b*-*Epimer*).—Selenium dioxide (500 mg.) was added to a solution of correllogenin acetate * (I; 25*b*-epimer) (1·0 g.) in t-butyl alcohol (45 c.c.) containing pyridine (0·15 c.c.) and heated under reflux for 96 hr. The cooled mixture was filtered through Celite and the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with water, dried, and recovered *in vacuo*. Crystallisation of the product from methylene dichloride–hexane afforded $\Delta^{9(11)}$-*dehydrocorrellogenin acetate* (III; 25b-epimer) (620 mg.), which after several crystallisations from methylene dichloride–hexane had m. p. 219—220°, $[\alpha]_D$ −42°, $\lambda_{max.}$ 238 mμ (ε 12,590), $\lambda_{max.}$ (in KBr) 1735, 1675, 1600, 1250, 985, 918, 896, and 850 cm.$^{-1}$ (Found: C, 73·9; H, 8·4. $C_{29}H_{40}O_5$ requires C, 74·3; H, 8·6%).

Oxidation of the acetate of the naturally occurring mixture of 25-epimers gave similarly a mixture of 25-epimers (65% yield), m. p. 190—196°, $[\alpha]_D$ −37°, $\lambda_{max.}$ 238 mμ (ε 11,960).

$\Delta^{9(11)}$-*Dehydrohecogenin Acetate* (III; 5α-H).—Selenium dioxide (27 g.) was heated with hecogenin acetate (I; 5α-H) (54 g.) in t-butyl alcohol (2·4 l.) containing pyridine (8·0 c.c.) as above. The cooled mixture was filtered on Celite and the solvent removed *in vacuo*. The residual solid was suspended in water (2 l.) with stirring for 15 min. Filtration afforded $\Delta^{9(11)}$-dehydrohecogenin acetate (III; 5α-H) (48·2 g., 89%) that after one crystallisation from methanol had m. p. 215—217°, $[\alpha]_D$ −9°, $\lambda_{max.}$ 238 mμ (ε 11,700) (lit.,[13] m. p. 218—220°, $[\alpha]_D$ −8·7°).

$\Delta^{5,9(11)}$-22α,25a-*Spirostadiene*-3β,12β-*diol* (IV).—Sodium borohydride (6·0 g.) in water (8·0 c.c.) was heated with $\Delta^{9(11)}$-botogenin acetate (III) (10·0 g.) in tetrahydrofuran (250 c.c.) for 3 hr. Addition of ice-water (1·5 l.) containing acetic acid (10 c.c.) and filtration afforded 22α,25a-spirosta-5,9(11)-diene-3β,12β-diol (IVa) (9·35 g.), m. p. 185—192°, raised by several crystallisations from benzene–hexane to 218—220°, $[\alpha]_D$ −107°. This diol had no selective ultraviolet absorption (Found: C, 76·0; H, 9·4; O, 14·7. $C_{27}H_{40}O_4$ requires C, 75·7; H, 9·4; O, 14·9%). With acetic anhydride in pyridine under reflux for 3 hr. it afforded 3β,12β-diacetoxy-22α,25a-spirosta-5,9(11)-diene, m. p. 191—193° (from methanol–chloroform), $[\alpha]_D$ −120° (Found: C, 72·4; H, 8·8; O, 18·8. $C_{31}H_{44}O_6$ requires C, 72·6; H, 8·7; O, 18·7%).

Treatment of 3β,12β-*Diacetoxy*-22α,25a-*spirosta*-5,9(11)-*diene with Lithium and Ethylamine*.—A solution of the diacetate (500 mg.) in ethylamine (20 c.c.) was added with stirring to a solution of lithium (125 mg.) in ethylamine (25 c.c.) at 5° and kept at this temperature for 20 min. Addition of solid ammonium chloride (5·0 g.), evaporation of the ethylamine, and addition of water afforded a solid precipitate which was removed and dried at 60°. Acetic anhydride (1·0 c.c.) was then added to a solution of this product in pyridine (7·0 c.c.). After 16 hr. at room temperature addition of water, filtration, and crystallisation of the solid product from acetone–hexane afforded 3β-acetoxy-22α,25a-spirosta-5,9(11)-diene (V) (310 mg.), m. p. 185—190° raised by further crystallisations to 196—197°, $[\alpha]_D$ −78° (Found: C, 76·6; H, 9·4; O, 14·0. $C_{29}H_{42}O_4$ requires C, 76·6; H, 9·3; O, 14·0%).

3-*Acetoxypregna*-5,9(11),16-*trien*-20-*one* (VI).—$\Delta^{9(11)}$-Dehydrodiosgenin acetate (V) (3·0 g.) in acetic anhydride (15 c.c.) was heated at 195° (vapour of nitrobenzene under reflux in Mexico, D.F.) in a sealed glass tube for 3 hr. The cooled solution was poured into ice-water, and the product isolated by extraction with ethyl acetate. The combined extracts were washed with 5% sodium carbonate solution and water and then dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded a product which was dissolved in a mixture of acetic acid (47 c.c.), water (17·7 c.c.), and methylene dichloride (38 c.c.) and cooled to 0°. A solution of chromium

* Triangular fractional crystallisation of the acetates of the naturally occurring mixture of botogenin and correllogenin from ethyl acetate–hexane afforded pure correllogenin acetate, m. p. 213—215°, $[\alpha]_D$ −67°, characterized by infrared bands at 1728, 1698, 1240, 984, 916, 896, and 851 cm.$^{-1}$.

[13] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 303.

trioxide (1·41 g.) in water (2·34 c.c.) and acetic acid (23·4 c.c.) was then added during 45 min. at 0° and the whole was stirred at room temperature for a further 2 hr. Addition of water and isolation with methylene dichloride afforded a product which was heated under reflux for 1 hr. in acetone (20 c.c.) and water (9 c.c.) containing potassium hydroxide (1·5 g.). Addition of ice-water and isolation with ether gave a product which was heated at 90° for 1 hr. in pyridine (20 c.c.) containing acetic anhydride (5·0 c.c.). The product from the acetylation was isolated by the addition of ice-water to the reaction mixture, followed by extraction with ether. The ether solution was washed free from pyridine with 2N-hydrochloric acid and water. Removal of the ether from the dried solution (Na_2SO_4) and crystallisation of the residue from hexane afforded 3-acetoxypregna-5,9(11),16-trien-20-one (VI) (1·35 g.), m. p. 160—163°, raised by several crystallisations from hexane to 170—172°, $[\alpha]_D$ +53°, $\lambda_{max.}$ 238—240 mμ (ε 8915) (Found: C, 77·8; H, 8·7. $C_{23}H_{30}O_3$ requires C, 77·9; H, 8·5%).

Conversion of the Ketone (VI) *into Pregna-4,9(11)-diene-3,20-dione* (VIII).—A solution of the product (VI) (500 mg.) in dry dioxan (40 c.c.) was added during 5 min. to one of lithium (500 mg.) in liquid ammonia (500 c.c.). The blue colour was discharged by solid ammonium chloride. After evaporation, addition of water and extraction with ethyl acetate afforded a product which was heated under reflux for 30 min. in methanol (50 c.c.) containing potassium hydroxide (1·0 g.). Neutralisation with acetic acid, removal of the bulk of the solvent on the steam-bath, and addition of water afforded a precipitate (400 mg.) which was collected and dried at 90°. A solution of this product in dry toluene (10 c.c.) containing cyclohexanone (2 c.c.) and aluminium isopropoxide (800 mg.) was heated under reflux for 25 min. Water (50 c.c.) was then added and the solution was distilled until the distillate was essentially free from toluene and cyclohexanone. Extraction of the residue with benzene afforded a product which was adsorbed from 1 : 1 benzene–hexane (50 c.c.) on alumina (15 g.). Elution with benzene (150 c.c.) and one crystallisation from benzene–methylene dichloride afforded the diketone (VIII) (130 mg.), m. p. 110—113°, raised by one further crystallisation to 119—120°, $[\alpha]_D$ +149° (lit., m. p. 122°, $[\alpha]_D$ +145°). The m. p. was undepressed on admixture with an authentic sample.

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