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THE STRUCTURE OF METAGENIN

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PREVIOUSLY, 25D,5β-spirostane-2β,3β,x-triol was proposed by us[1] as the structure of metagenin, a sapogenin isolated from Metanarthecium luteo-viride Maxim., and it was also reported that the position of the unknown hydroxyl group in metagenin was limited to C-6, C-7 or C-11. We have now completely established the structure of this sapogenin to be 25D,5β-spirostane-2β,3β,11α-triol (I) from the following experimental results.

Samogenin from Metagenin

Metagenin acetonide (Ia), obtained in the usual manner as described earlier,[1] was converted to metagenone (II), m.p. 248°,* $[\alpha]_D^{25}$ - 4.0°, I.R. λ_{max}^{Nujol} 2.95μ (hydroxyl) and 5.88μ (ketone), by CrO_3-pyridine oxidation followed by dilute acetic acid hydrolysis. Metagenone gave a diacetate (IIa), m.p. 240-242°, and this diacetate again gave the unchanged parent ketone (II) by the action of alkali.

Although metagenone diacetate underwent the Huang-Minlon reduction[2] and

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[1] K. Takeda, T. Okanishi, K. Hamamoto, A. Shimaoka and N. Maezono, Yakugaku Zassi 77, 175 (1957).

* M.p. not corrected.

[2] Huang-Minlon, J. Amer. Chem. Soc. 68, 2487 (1946).

afforded samogenin diacetate (III),[3,4] m.p. 197-198°, in ca.25% yield when the reaction mixture was acetylated by acetic anhydride, metagenone gave neither a semicarbazone nor a hydrazone under the usual conditions.

From these results, it was confirmed that the two vicinal hydroxyl groups are located at C-2 and C-3, that both are β-oriented, and that the A/B ring juncture is cis. Furthermore, the position of the keto group in metagenone at C-6 is excluded by the stability of the substance to alkali.

Reduction of Metagenone

$NaBH_4$ reduction of metagenone afforded a new triol (IV), m.p. 134-136°, $[\alpha]_D^{25}$ - 47,3°, I.R. λ_{max}^{Nujol} 2.93 and 3.01μ (hydroxyl), epi-metagenin, while with Na and isopropyl alcohol it afforded metagenin. In the case of $LiAlH_4$ reduction of diacetyl metagenone, it gave epi-metagenin as a main product together with a small amount of metagenin. epi-Metagenin gave only a diacetate (IVa), m.p. 175°, I.R. λ_{max}^{Nujol} 2.85μ (hydroxyl), 7.88, 7.93 and 8.18μ (acetate), by the action of acetic anhydride-pyridine at room temperature and epi-metagenin acetonide (IVb), m.p. 218-221°, was not affected by cathylation.[5] On the other hand, metagenin acetonide (Ia) readily gave a cathylate (Ic), m.p. 159°, and it also gave an acetonide acetate (Ib), m.p. 202-204°, under very mild conditions. These findings indicate that the third hydroxyl group in metagenin and its epimeric one in epi-metagenin has an equatorial and an axial conformation, respectively.

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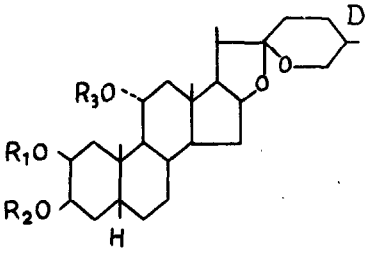
[3] C. Djerassi and J. Fishman, J. Amer. Chem. Soc. 77, 4291 (1955).

[4] The authors are indebted to Dr. C. Djerassi for his kind donation of the valuable sample of samogenin diacetate.

[5] L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romers and T. J. Utne, J. Amer. Chem. Soc. 74, 3309 (1952).



I $R_1=R_2=R_3=H$ Metagenin

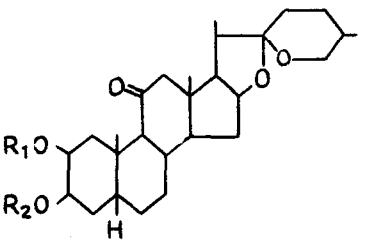
Ia $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!=\!<\begin{matrix}CH_3\\CH_3\end{matrix}$ $R_3=H$

Ib $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!=\!<\begin{matrix}CH_3\\CH_3\end{matrix}$ $R_3=Ac$

Ic $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!=\!<\begin{matrix}CH_3\\CH_3\end{matrix}$ $R_3=C_2H_5OCO$

Id $R_1=R_2=H$ $R_3=Ac$

Ie $R_1=R_2=Ms$ $R_3=Ac$

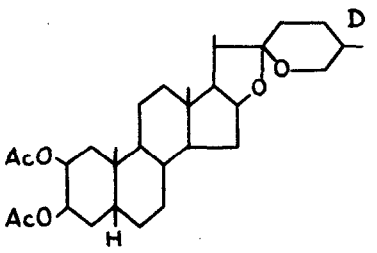


II $R_1=R_2=H$ Metagenone

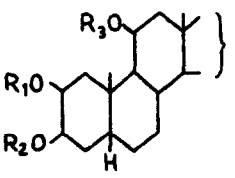
IIa $R_1=R_2=Ac$

IIb $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!=\!<\begin{matrix}CH_3\\CH_3\end{matrix}$

IIc $R_1=R_2=Ms$



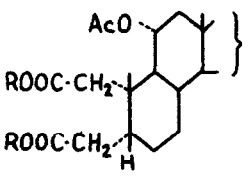
III Samogenin Diacetate



IV $R_1=R_2=R_3=H$ epi-Metagenin

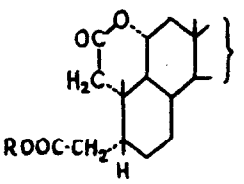
IVa $R_1=R_2=Ac$ $R_3=H$

IVb $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!=\!<\begin{matrix}CH_3\\CH_3\end{matrix}$ $R_3=H$



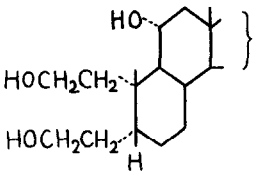
V R=H

Va $R=CH_3$

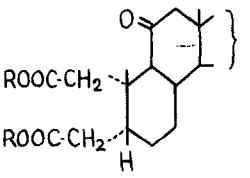


VI R=H δ-Lactone

VIa $R=CH_3$

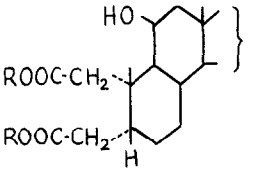


VII



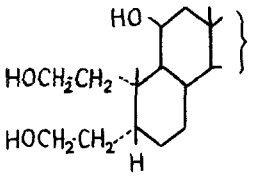
VIII R=H Metagenic Acid

VIIIa R=CH_3

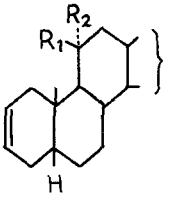


IX R=H

IXa R=CH_3

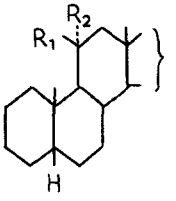


X



XIa R_1=H R_2=OAc

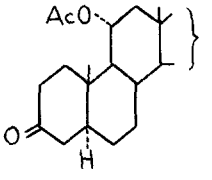
XIb R_1, R_2 >=< O



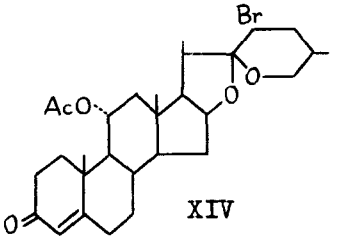
XII R_1=H R_2=OH

XIIa R_1=H R_2=OAc

XIIb R_1, R_2 >=< O



XIII



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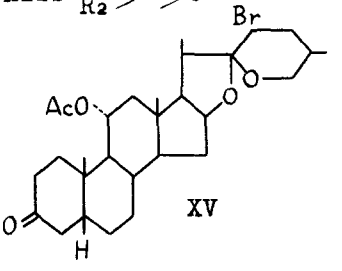

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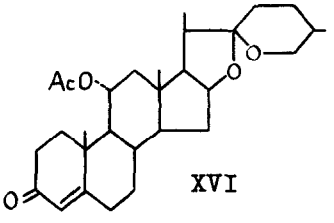

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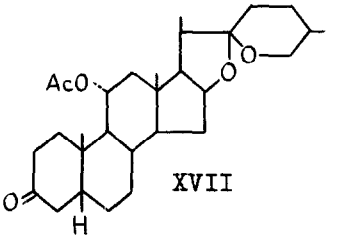

XVII

Formation of δ-Lactone

CrO_3 oxidation of the x-monoacetyl derivative (Id), m.p. 219°, which was obtained from metagenin acetonide acetate (Ib) by the action of dilute acetic acid, gave an acetoxy A-seco acid (V), m.p. 282° (decomp.), $[\alpha]_D^{20}$ - 67,6°, (dimethyl ester (Va), m.p. 98-100°), and this seco acid readily afforded a δ-lactone (VI), m.p. 248°, $[\alpha]_D^{20}$ - 53,4°, I.R. λ_{max}^{Nujol} 5.75 (δ-lactone) and 5.81 μ (carboxylic acid), (methyl ester (VIa), m.p. 172°), by saponification with acid or alkali. The same δ-lactone was also obtained from dimethyl metagenate (VIIIa)[1] when treated with Na and isopropyl alcohol or directly from metagenin itself with CrO_3 in acetic acid at 15° as a by-product of metagenic acid (VIII). This lactone afforded a triol (VII), m.p. 208°, with $LiAlH_4$. On the other hand, another hydroxy A-seco acid (IX), m.p. 222° (decomp.), I.R. λ_{max}^{Nujol} 2.78 (hydroxyl), 5.88 and 5.93 μ (carboxylic acid), (dimethyl ester (IXa), m.p. 163°), was obtained by $NaBH_4$ reduction of dimethyl metagenate (VIIIa). This hydroxy A-seco acid resisted lactone formation and its dimethyl ester was oxidized back to the parent dimethyl metagenate. The hydroxyl group of this seco acid was not affected by mild acetylation. This acid gave a triol (X), m.p. 216-217°, different from the above-mentioned triol (VII).

From these results it is clear that the unknown hydroxyl group in metagenin is located on the same side as the acetic acid residue of samogenic acid, in other words, this hydroxyl group must be α-oriented. Furthermore, as this hydroxyl group has an equatorial conformation, C-11 is the most probable position for this group. Comparison of the molecular rotation values of the corresponding metagenin and epi-metagenin derivatives also support this assignment (cf. Table 1).[6] However

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[6] L.F. Fieser and M. Fieser, Steroids p. 179 Reinhold, New York (1959).

there remain some doubtful points in this assumption from the following facts: (i) metagenone acetate was affected by the Huang-Minlon reduction and afforded samogenin as described above; (ii) the rotatory dispersion curve of metagenone (peak at $[\alpha]_{330}$+ 112°, trough at $[\alpha]_{262.5}$ - 720°) is almost identical with that of 7-keto cholanic acid derivatives,[7,8] although this could also be compatible with an 11-keto sapogenin[9] because of the strong negative background rotation[9] of the spiroketal side chain.

Table 1. Molecular Rotation Values of Metagenin and Epi-metagenin Derivatives

	Sapogenin		Diacetate		Acetonide	
	$[\alpha]_D$	M_D	$[\alpha]_D$	M_D	$[\alpha]_D$	M_D
Metagenin (A)	-82°	-368°	-67°	-359°	-86°	-419°
epi-Metagenin (B)	-47°	-212°	-50°	-264°	-56°	-272°
M_D (B) - M_D (A)	+156°		+95°		+147°	

Elimination Reaction of the Vicinal Hydroxyl Groups in Metagenin and the Synthesis of 11α-Hydroxy-25D,5β-spirostane

For further confirmation we next examined the elimination reaction of the vicinal two hydroxyl groups in metagenin by the method of C. Djerassi and J. Fishman.[3] 2,3-Dimesyloxy-x-acetyl-metagenin (Ie), m.p. 225° (decomp.),

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[7] C. Djerassi and W. Closson, J. Amer. Chem. Soc. 78, 3761 (1956).

[8] The rotatory dispersion curve of metagenone was kindly measured by Dr. C. Djerassi of Stanford University.

[9] C. Djerassi and R. Ehrlich, J. Amer. Chem. Soc. 78, 440 (1956).

obtained from the x-monoacetate (Id) by the usual manner, was converted into the Δ^2-derivative (XIa), m.p. 165°, with NaI in acetone and this was reduced catalytically to the saturated monoacetoxy derivative (XIIa), m.p. 187-188° (free alcohol (XII), m.p. 182,5-183°, $[\alpha]_D^{25}$ - 77°). A similar reaction was carried out on metagenone and the ketone (XIIb), m.p. 172-173°, $[\alpha]_D^{25}$ - 48°, was obtained through IIc, m.p. 208° (decomp.), and XIb, m.p. 178°. This ketone also gave the above-mentioned monohydroxy sapogenin (XII) with Na and isopropyl alcohol but was resistant to Huang-Minlon reduction.

Finally, 11α-hydroxy-25D,5β-spirostane or its acetate was synthesized from 11α-acetoxy-tigogenone (XIII).[10,11] The introduction of the double bond at C-4 was carried out by the method reported by J. Romo,[11] but the bromine atom at C-23 was eliminated after saturation of the double bond,[12] since XIV[13] (free alcohol, m.p. 197°, decomp.) was rather resistant to debromination and the yield of XVI was very low. The Huang-Minlon reduction of the saturated acetoxy ketone (XVII), m.p. 205-207°, afforded the anticipated 11α-hydroxy derivative, and the latter was also obtained directly from XV by the same reaction with simultaneous debromination. The resulting 11α-hydroxy-25D,5β-spirostane or its acetate was identical in all respects with the corresponding degradation product of metagenin.

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[10] J. H. Chapman, J. Elks, G. H. Phillips and L. J. Wyman, J. Chem. Soc. 1956, 4344.

[11] J. Romo, C.A. 50, 12088 (1956); Bol. inst. quim. U.N.A.M. 7, 53 (1955).

[12] O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, J. Amer. Chem. Soc. 75, 1286 (1953).

[13] Attempts to crystallize the acetate (XIV) were unsuccessful.

This is the first example of an 11-oxygenated steroidal sapogenin isolated from a plant source. A more detailed report of this work will be published in due course in the Chem. Pharm. Bull.