Tetrahedron Letters No.14, pp. 1729-1734, 1968. Pergamon Press. Printed in Great Britain.

THE STRUCTURE OF DIGACETIGENIN

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(Received in UK 19 December 1967)

The structure of digacetigenin proposed by Shoppee et al.(1) as a revision of their previous structure appears to be incorrect when the fragmentation pattern and the relative abundance of some of the major ions in the mass spectrum are considered.

Recent work in this laboratory* on the mass spectrum of lineolone and iso-lineolone, and the mass spectral studies of other workers(2) on the stereospecificity of the fragmentation of the digitanols shows that the conformation of the C_{17}-acetyl side chain may be determined from the relative abundance of the M-18 and m/e 43 ions.

In those compounds in which the C_{17}-acetyl side chain has the ß-conformation it may form a hydrogen bond with the 14ß-hydroxyl group. This bonding inhibits the elimination of the 14ß -hydroxyl group and of the C_{17}-acetyl group. Conversely, in the isomeric $C_{17}\alpha$-acetyl compounds where hydrogen bonding with the 14ß-hydroxyl group does not occur, there is facile elimination of the 14ß-hydroxyl group and the 17α-acetyl group. The effect of the hydrogen bond on the elimination of the acetyl side chain is not as pronounced as the effect on the 14ß-hydroxyl group, but in those compounds (except the deacylcongurangogenins) which have the $C_{17}\alpha$-acetyl group the m/e 43 is the base peak of the spectrum. These effects are shown in Table 1.

*Details of the mass spectrum of lineolone and iso-lineolone are to be published elsewhere.

TABLE 1

A Comparison of the Relative Abundance of M^+, M^+-18 and m/e 43

Compound	M^+	M^+-18	m/e 43
17α-H			
iso-Lineolone	1.5	10.8	68
Digipurpurogenin(2)	12	12	76
Deacylcongurangogenin(2)	1	6	100
17β-H			
Lineolone	0.2	54.2	100
iso-Digipurpurogenin(2)	3	40	100
iso-Deacylcongurangogenin(2)	5	100	70
Digacetigenin	2.7	59.8	100

A comparison of the relative abundance of the M^+, M^+-18 and m/e 43 ions of digacetigenin with those of known structure (Table 1) shows that this compound should have the structure (I) shown in Fig. 1. As the optical rotatory dispersion curve of α-digiprogenin closely resembles that of digacetigenin(3), and since Satoh(4,5) has shown that α-digiprogenin belongs to the 17β-H series of digitanols, this is further evidence for the proposed structure of digacetigenin.

The fragmentation pathway, illustrated* in Fig. 1, accounts for the majority of major peaks. These ions all arise by simple loss of water, acetic acid or the acetyl side chain, except ions II and III which arise from carbon-carbon bond cleavage in the stepwise elimination of ring D. These latter reactions confirm the positioning of the C_{15} ketone and offer additional evidence for placing the tertiary hydroxyl group at C_{14} rather than C_{17}. They also show that the secondary

*The specific formulae illustrated are intended to be formal representations only and simply relate the fragmentation pattern to the structure of the intact molecule.

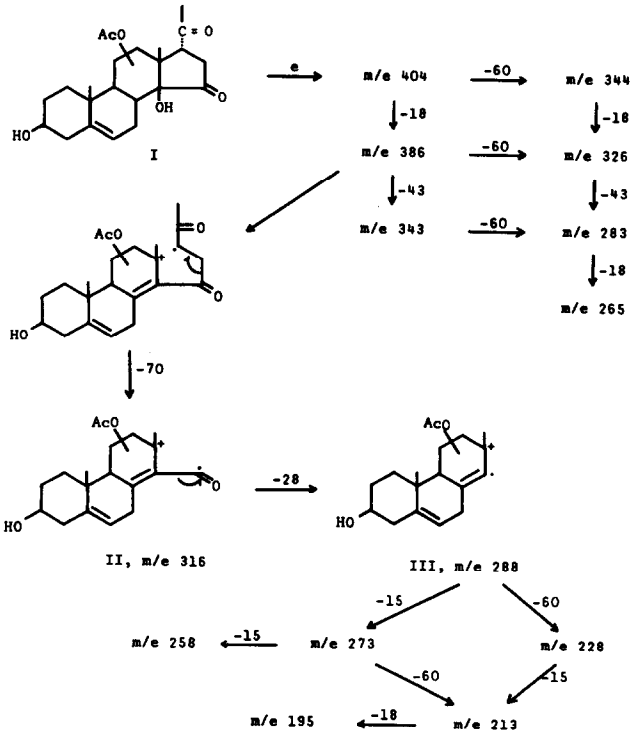


FIG. 1

MAIN FRAGMENTATION PATHWAY OF DIGACETIGENIN

acetoxy group is not in ring D. To further substantiate the C_{15} carbonyl group is the occurrence of the series of peaks at m/e 155, 137, 122 and 79 arising from ring D in a manner analogous to 5α, 14β-androstan-15-one(6). Metastable peaks are recorded in Table 2(a).

The occurrence of peaks at m/e 138 and 266, followed by decomposition fragments at m/e 120, 105, 77 and m/e 248, 223, 206, 205, 188, 163 and 145 respectively, are explained by a retro-Diels-Alder reaction initiated by the double bond at carbon 5. These series of ions have been shown*(7) to arise from such a process. These reactions, which are similar to those in Fig. 1, are shown diagramatically in Fig. 2 and metastable peaks are recorded in Table 2(b).

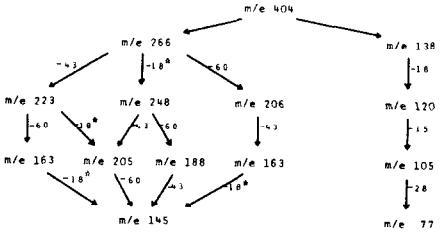
Although it is now firmly established that the acetoxy group is on either C_{11} or C_{12}, there is insufficient evidence available to allow unequivocable assignment. The NMR spectrum (1,8) indicates that the acetoxy group is in an equatorial position as does its ease of hydrolysis. It has been proposed(1) that the acetoxy group is at C_{12} because the

triketone (3β, 14β-dihydroxy-17α-pregn-5-ene 12,15,20-trione) obtained by oxidation of deacetyl-digacetigenin-3-acetate was not equivalent to α-digiprogenin. However, this triketone would not be expected to be equivalent as the conformation at C_{17} is different.

In favour of the 11-position for the acetoxy group is the appearance of the fragments 189 and 154 and their respective decomposition fragments (171, 143 and 111; 96, 83 and 55). These ions appear to originate by a retro-Diels-Alder reaction of the M-60 ion as illustrated in Fig. 3. Metastable peaks are recorded in Table 2(c). The base peak in $\Delta^{9(11)}$-14β-hydroxy-estrone methyl ether originates from this process(9).

Calculation(10) of the shifts for the C_{18} and C_{19} methyl groups also favours the 11α-position (cf. ref.4).

Although digacetigenin is an 11α-or 12β-acetoxy derivative of 3β,14β-dihydroxy-17α-pregn-5-en-15,20-dione, direct evidence will be necessary to establish the exact position of the acetoxy group.



*by 1,4-elimination, cf. ref.1.

FIG. 2

RING B CLEAVAGE AND SUBSEQUENT FRAGMENTATIONS

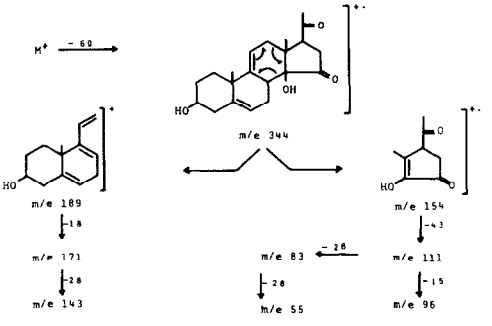


FIG. 3

RING C CLEAVAGE AND SUBSEQUENT FRAGMENTATIONS

*See footnote p1729

TABLE 2

Observed Metastable Peaks for Schemes Discussed

	Fragmentation	Metastable Peak Calculated	Found
(a)	404 → 344	292.9	292.9
	404 → 386	368.8	368.9
	386 → 326	275.3	275.4
	344 → 326	308.9	309
	386 → 343	304.8	305
	343 → 283	233.5	233.8
	326 → 283	245.7	246
	283 → 265	248.1	248.1
	386 → 316	258.7	258.9
	316 → 288	262.5	262.7
	288 → 228	180.5	180.7
	288 → 273	258.8	258.9
	228 → 213	198.9	199
	273 → 258	243.8	244
	213 → 195	178.5	178.8
	155 → 137	121.1	121.2
	122 → 79	51.2	51.3
(b)	404 → 138	47.1	47.2
	138 → 120	104.3	104.5
	120 → 105	91.9	92
	105 → 77	56.5	56.8
	266 → 248	231.2	231.2
	248 → 205	169.4	169.3
	205 → 145	102.5	102.5
	188 → 145	111.8	112
	163 → 145	128.9	129
	206 → 163	128.9	129
	223 → 205	188.5	188.7
(c)	404 → 344	292.9	293
	344 → 154	68.9	69.1
	111 → 96	83.0	83.2
	83 → 55	36.5	36.5
	344 → 189	103.8	104
	189 → 171	154.7	155

EXPERIMENTAL

The mass spectrum of digacetigenin was obtained from an AEI M.S.9 mass spectrometer, with source temperature 110° and 70 e.v. ionisation potential using the direct insertion technique.

ACKNOWLEDGEMENT

The authors would like to thank Professor T. Reichstein (Basel) for the generous donation of digacetigenin.

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