REACTIONS OF PENNOGENIN AND RELATED COMPOUNDS.

IV. FORMATION OF (25R,22'R,25'R)-3β,3'β-DIACETOXY-26,22'-EPOXY-16,16'-BIFUROSTA-5,20(22),5',17'(20')-TETRAEN-26'-OL FROM PENNOGENIN DIACETATE UNDER THE ACTION OF $BF_3 \cdot Et_2O$

L. I. Strigina, Ya. V. Rashkes,
V. A. Denisenko, and Yu. M. Mil'grom

UDC 547.918+547.92+543.422.25

A new direction of the reaction of pennogenin diacetate with $BF_3 \cdot Et_2O$ has been discovered in which a previously unknown dimeric steroid is formed – (25R,22'R,25'R)-3β,3'β-diacetoxy-26,22'-epoxy-16,16'-bifurosta-5,20(22),5',17'(20')-tetraen-26'-ol, the structure of which has been established as the result of an analysis of IR, UV, ^1H and ^{13}C NMR, and mass spectra. A probable mechanism for the formation of the title compound from pennogenin diacetate is suggested.

(25R)-Spirost-5-ene-3β, 17α-diol (pennogenin) has not hitherto found practical use in the synthesis of steroid hormones. However, the presence of a 17α(OH) group in its molecule makes the idea of creating 16,17-substituted steroids from it an attractive one. The main obstacle on the pathway of the development of such a method is the high lability of the 17α(OH), which is capable of being split off in the course of the opening of the spiroketal system. New possibilities appeared after a method of protecting the hindered 17α(OH) group had been found [1]. Continuing investigations of the products of the transformation of pennogenin diacetate (2) in the reaction with $BF_3 \cdot Et_2O$, we have isolated a compound (1a) containing, according to its mass and NMR spectra, twice as many carbon atoms as (2). In the present paper we give a proof of the structure of (1a) and express considerations concerning the possible mechanism of its formation from (2).

The mass number of the molecular ion in the mass spectrum of (1a) was 908 a.m.u. This corresponds to the molecular mass of two molecules of (2) – AcOH × 2, while the maximum peak was that of an ion with m/z 454. As compared with (2), the IR of (1a) lacked the characteristic bands of a spiroketal chain. The strongest bands were those of an OAc group and one with ν 1040 cm^{-1}, which can be assigned to a C–O bond of the ketal type and to CH_2OH deformation vibrations. The presence of a CH_2OH group was confirmed by bands with ν 3640 cm^{-1} (weak) and ν 3528 cm^{-1} (H-bond). The UV spectrum of (1a) showed no selective absorption.

In the ^{13}C NMR spectra of (1a) (C_6D_6, $CDCl_3$) (Table 1), 58 signals of carbon atoms were recorded.

According to the ^{13}C NMR spectrum (C_6D_6) taken by the J-modulation method [2], (1a) contained ten methyl, 20 methylene, 13 methine, and 15 quaternary carbon atoms. The assignment of the signals of the C–1(1')–C-11(11') and CH_3-19(19') atoms was made by comparison of the spectra of (1a) and (2) [3]. The assignment of the signal with δ 37.2 ppm in the ^{13}C NMR spectrum (C_6D_6) of (1a) to C–10(10') was confirmed by an experiment with noise off-resonance decoupling. The values of the ^{13}C NMR CSs of the CH_3-18(18'), CH_3-21(21'), and CH_3-27(27') groups in any combination did not agree with those of (2) and other known products of the transformation of (2) and of pennogenin [3-5]. The assignment of the signals of CH_3-21 (δ_C 11.7 ppm, δ_H 1.65 ppm), CH_3-21' (δ_C 12.5 ppm, δ_H 2.05 ppm), C-17 (δ_C 65.7 ppm, δ_H 2.90 ppm) and also of C-26' (δ_C 67.8 ppm, δ_H 3.31 ppm), C-6' (δ_C 121.7 ppm, δ_H 121.7 ppm, δ_H 5.48 ppm) was made from the results of $^{13}C\{^1H\}$ selective heteronuclear resonance in C_6D_6. The values of the ^{13}C CSs of the C-12, C-13, and C-14 atoms were close to

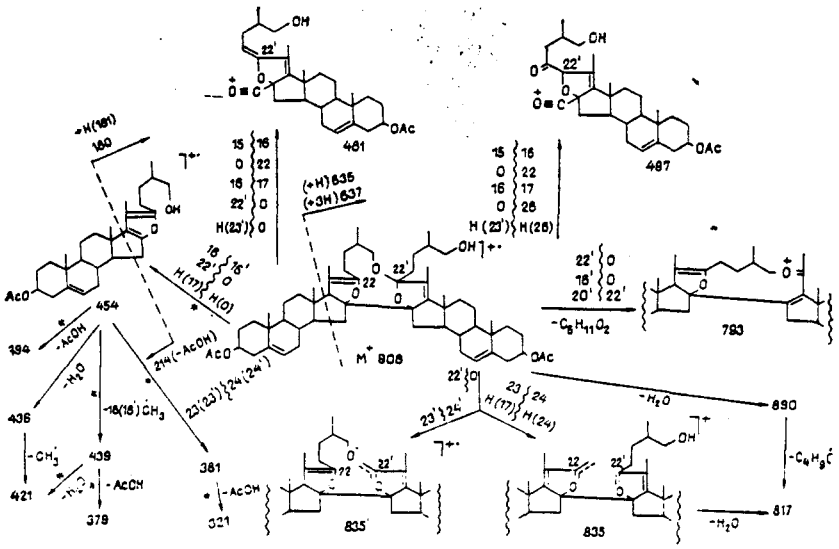
Pacific Ocean Institute of Bioorganic Chemistry, Far Eastern Branch, USSR Academy of Sciences, Vladivostok. Institute of Chemistry of Plant Substances, Uzbek SSR Academy of Sciences, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 202-208, March-April, 1990. Original article submitted May 11, 1989.

0009-3130/90/2602-0161$12.50

TABLE 1. Chemical Shifts of the Carbon Atoms of (1a) (0 – TMS)

C atom	Type of atom	δC, ppm	
		$CDCl_3$	C_5D_5N
1 and 1′	CH_2	37,0	37,2
2 and 2′	CH_2	27,9	28,2
3 and 3′	CH	73,8	73,7
4 and 4′	CH_2	38,1	38,4
			38,6
5 and 5′	C	139,6	139,9
		140,4	140,6
6 and 6′	CH	122,2	122,3
		121,6	121,7
7 and 7′	CH_2	30,4	31,7
		31,2	30,9
8 and 8′	CH	31,9	32,2
		31,6	32,0
9 and 9′	CH	50,0	50,3
		50,7	50,9
10 and 10′	C	37,0	37,2
11 and 11′	CH_2	21,4	21,4
		20,3	20,6
12 and 12′	CH_2	39,3[a]	39,8[a]
		36,0[b]	36,4[b]
13	C	42,5	42,7
13′		44,3	44,6
14	CH	56,0	56,4
14′		54,5	54,9
15 and 15′	CH_2	36,4[b]	37,0[b]
		39,0[a]	39,6[a]
16 and 16′	C	97,1	97,4
		98,1	98,4
17	CH	65,1	65,7
17′	C	144,4	145,6
18	CH_3	14,3[c]	14,6[c]
18′		23,2	23,1
19 and 19′	CH_3	19,3	19,3
		19,4	19,4
20	C	106,2	105,8
20′		134,5	133,7
21	CH_3	11,5	11,7
21′		12,1	12,3
22	C	150,9	151,
22′		118,7	118,8
23	CH_2	33,9	33,8
23′		23,4	23,7
24	CH_2	29,1	29,2
24′		32,9	33,4
25 and 25′	CH	35,2	35,3
		35,6	35,7
26	CH_2O	72,7	72,1
26′		68,1	67,8
27 and 27′	CH_3	14,8[c]	15,0[c]
		16,6	16,7
28 and 28′	$CH_3\underline{C}O$	170,2	169,2
29 and 29′	$\underline{C}H_3CO$	21,4	20,9

The atoms of the left half of the structure of (1a) have been designated as C-1–C-29 and those of the right half C-1′–C-29′; a, b, c – the assignments within a column may be interchanged.



Scheme 1. Main directions of the fragmentation of (1a) under electron impact.

those of $\Delta^{20(22)}$-furostenes [6, 7]. The considerably greater descreening of C-12 in the spectrum of (1a) as compared with (2) ($\Delta\delta$ +6.3 ppm) reflects the existence in the former of $\gamma_{H,H}$ interaction of α-H-12 and α-H-17. The presence in the (1a) molecule of the $\Delta^{20(22)}$ bond was also confirmed by the values of the ^{13}C CSs of the C-17, C-20, C-21, and C-22

TABLE 2. Chemical Shifts of the H-Atoms of (1a)

H-atom	δ_H, ppm	
	$CDCl_3$	C_6D_6
H-18	0,64 s	0,84 s
H-18′	1,12 s	1,22 s
H-27	0,80 d J = 7,4 Hz	0,78 d J = 7,4 Hz
H-27′	0,94 d J = 6,8 Hz	0,89 d J = 6,8 Hz
H-21	1,55 s	1,65 s
H-21′	1,79 s	2,05 s
H-19	1,02 s	0,89 s
H-19′	1,06 s	0,94 s
$\underline{CH_3}-CO \times 2$	2,03 s 2,04 s	1,73 s 1,74 s
H_e-26	3,46 m J = 8,5 Hz	3,74 dd J_{gem} = 12,9 Hz J_{vic} = 1,35 Hz
H_a-26		3,61 dd J_{gem} = 12 Hz J_{vic} = 7 Hz
H_e-26′		3,25 dd J_{gem} = 10,2 Hz
H_a-26′		J_{vic} = 6 Hz
H-3 and H-3′	4,64 m $W_{1/2}$ = 10,4 Hz	4,83 m $W_{1/2}$ = 12,2 Hz
H-6	5,3 br.d J = 4 Hz	5,32 br.d J = 5 Hz
H-6′	5,42 br.d J = 4,3 Hz	5,48 br.d J = 5 Hz

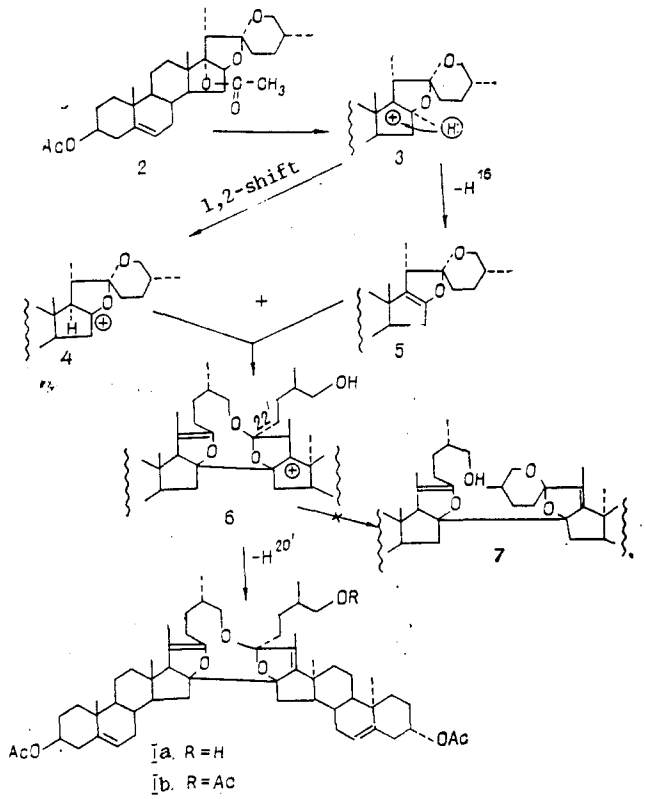
signals. The assignment of the C-12′, C-13′, and C-14′ signals was compatible with the presence of a $\Delta^{17'(20')}$ bond [4]. The descreening of C-16(16′), due to the effect of alkylation, showed the presence of a C-16—C-16′ bond.

The values of the ^1H CSs and the quantitative characteristics of the signals of the H atoms in the ^1H NMR spectra (C_6D_6, $CDCl_3$) of (1a) (Table 2) gave an additional confirmation of the structure of (1a). The presence of singlet signals with δ 1.55 ppm (CH_3-21) and δ 1.79 ppm (CH_3-21′) is compatible with the presence of $\Delta^{20(22)}$ and $\Delta^{17'(20')}$ bonds. Each of the H-6 and H-6′ signals corresponds in its integral intensity to half the sum of the H-3(3′) signals. For confirmation of the assignment of the CH_2-26(26′) signals we used aromatic solvent shifts. Thus, in the replacement of $CDCl_3 \rightarrow C_6D_6$ the multiplets corresponding to these protons separated.

The form of the signal of the ABX system of CH_2-26 in the ^1H NMR spectrum (C_6D_6) of (1a) showed a considerable limitation of the mobility of the corresponding fragment. The form of the signal of the AB part of the CH_2-26′ group having a small difference in the values of the ^1H CSs of the H_e-26′ and H_a-26′ protons showed the possibility of free rotation around the C-25′—C-26′ bond. This was also confirmed by the equality of the SSCCs ($J_{25,26a} = J_{25,26e}$). When CD_3OD was added to a solution of (1a) in C_6D_6, the signal corresponding to CH_3-27′ shifted downfield, while the signal of CH_3-27 remained unchanged.

An analysis of the mass spectrum of (1a) gave weighty arguments in favor of the structure shown (Scheme 2) and permitted the rejection of the alternative structure (7), which should have NMR characteristics close to those of (1a).

The major fragments in the mass spectrum of (1a) (Scheme 1) can be separated into three main groups, formed by: 1) the initial cleavage of the C-16—C-16′ bond, taking place readily; 2) the cleavage of the C-22′—O bond, and 3) the cleavage of the bonds of the steroid skeleton. The cleavage of the first such bond is initiated by isomerization of the C-17′—C-20′ π-bond and the rupture of the C-22′—O bridge with the simultaneous migration of H-17 to the oxygen atom at C-26. As a result, ions with m/z 454 and of identical structure are formed



Scheme 2. Scheme of the transformation of pennogenin diacetate into (1a).

from both parts of the initial M^+ ion. The most important ways in which each of these identical ions breaks down are the splitting out of the angular C-18(18') methyl group (ion m/z 439) and the cleavage of the C-23(23')—C-24(24') bond (ion with m/z 381). All these processes are accompanied by the elimination of AcOH from C-3(3'), while ions including a hydroxymethyl group also lose H_2O.

The main consequence of the initial cleavage of the C-22'—O bond consists in different methods of formation of the $(M - 73)^+$ ions with m/z 835. One of them is realized with the aid of simple C-23'—C-24' cleavage and the other by a rearrangement in the other part of the molecule. The latter, losing H_2O, is converted into an ion with m/z 817. In the field of high mass numbers, the spectrum of (1a) has a weak peak of an ion with m/z 793 the appearance of which can also be regarded as a consequence of the cleavage of the C-22'—O bond followed by the elimination of the elements of ring E'.

The most important factor permitting the rejection of the alternative structure (7) is the presence in the mass spectrum of (1a) of unidentified peaks of fragments with m/z 497 and 496 ($C_{30}H_{41}O_6$ and $C_{30}H_{40}O_6$), each containing six oxygen atoms. Ions with this composition can be formed only from structure (1a) and not from (7). One of the most probable pathways for the origin of the ion with m/z 497 is given in Scheme 1. In addition to these acts of bond cleavage and H migration, isomerization of the 22', 23'-epoxy into a 23'-keto group takes place.

In the spectrum of (1a), processes are observed that are characteristic for pennogenin derivatives: cleavage of the C-13—C-17 and C-8—C-14 bonds [8]. Ions with m/z 180 and 181 are formed from the m/z 454 ions at the expense of rings E(E') with the substituents attached to them. When the charge is localized on the ABC (A'B'C') ring system, the elimination of AcOH from C-3(3') leads to the formation of ions with m/z 214. A process related to this also takes place in the molecular ion, from which ions with m/z 635 (454 + 181) and 637 arise.

Of other ions with mass numbers greater than 454 a.m.u., the mass spectrum of (1a) contains the peak of an ion with m/z 481 formed by a mechanism resembling the formation of the ion with m/z 497. The compositions of all the ions discussed with m/z values less than 637 were confirmed by accurate measurements of their masses. The transitions confirmed by metastable peaks are indicated in Scheme 1 by asterisks.

The facts given permit the statement that, in the course of its reaction with $BF_3 \cdot Et_2O$, pennogenin diacetate (2) is converted into a previously unknown compound having the structure (25R,22'R,25'R)-3β,3'β-diacetoxy-26,22'-epoxy-16,16'-bifurosta-5,20(22),5',17'(20')-tetraen-26'-ol (1a). The configuration at C-22' was determined from a consideration of a Dreiding model of (1a), which showed that of the two 22S-epoxy and 22R-epoxy groups the latter is the only possible one from the point of view of steric interactions.

A suggested mechanism of the transformation of (2) into (1a) (see Scheme 2) includes electrophilic attack on the C-17—OAc bond followed by the anionoid splitting out of OAc^- and the formation of a C-17 carbocation (3). Stabilization of (3) can take place in two directions: 1) a 1,2-hydride shift of H-16, leading to the carbocation (4), stabilized through the free electron pair of the neighboring oxygen atom; and 2) the ejection of H-16 with the formation of Δ^{16}-diosgenin (5). Simultaneously, the opening of rings F and F' leads to the formation of a C-26—O—C-22' bond. The ejection of H-22', stabilizing (6), leads to (1a).

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker WM-250 spectrometer at working frequencies of 250 and 62.9 MHz, respectively. The accuracy of the measurements of the CS values was better than 0.01 ppm in the ^1H spectrum and better than 0.1 ppm in the ^{13}C NMR spectrum. All the mass-spectrometric measurements were performed on a MKh 1310 instrument with a SVP5 system for the direct introduction of the sample at a temperature of the ionization chamber of 180°C and of the evaporator bulb of 150-180°C, an ionizing voltage of 60 V, and a collector current of 40 μA. In the recording of the overall spectrum R = 1200, and in the measurement of accurate masses R = 10,000. The IR and UV spectra were recorded on Specord 75IR and Specord M-40 instruments, respectively. Melting points were determined on a Boëtius stage and specific rotations on a Perkin-Elmer 141 polarimeter.

(25R,22'R,25'R)-3β,3'β-Diacetoxy-26,22'-epoxy-16,16'-bifurosta-5,20(22),5',17'(20')-tetraen-26'-ol (1a) from (2). Compound (2) (0.5 g) was dissolved in 10 ml of absolute Et_2O, and 10 ml of $BF_3 \cdot Et_2O$ was added. After 30 min, the reaction mixture was poured into 0.5 liter of 5% $NaHCO_3$ and the resulting mixture was stirred for 10 min. The products were extracted with Et_2O, and the extracts were washed with H_2O, dried over anhydrous Na_2SO_4, evaporated, and chromatographed on SiO_2 in the hexane—acetone system (50:0 → 50:2, gradient in 0.2 steps; 50:2 → 50:10, gradient in 1.0 steps; each step with a volume of 0.05 liter).

The fractions (20 ml) were analyzed by TLC (Silufol) in the hexane—acetone (4:1) system. Rechromatography gave (1a) with mp 162-165.5°C (from acetone) $[\alpha]_{578}^{20}$ −77.2° (c 1.62; acetone), IR, cm^{-1} (CCl_4): 3640, 2944, 2856, 1736, 1450, 1440, 1376, 1248, 1160, 1144, 1041, 1000, 960, 928, 896, 880, 840; mass spectrum (m/z, I, %): 908 (M^+, 5), 890 (4), 835 (5), 817 (7), 793 (3), 637 (3), 635 (1), 497 (1), 496 (2), 481 (4), 454 (100), 439 (60), 437 (8), 436 (8), 421 (6), 408 (7), 395 (7), 394 (10), 381 (46), 379 (8), 328 (4), 321 (5), 214 (6), 231 (10), 181 (52), 180 (23). The amorphous acetate (1b) of (1a) was obtained under the usual conditions after chromatography on SiO_2 in the hexane—acetone (50:0 → 50:10) system.

On Silufol in the hexane—Et_2O (1:1) system, the acetate (1b) had R_f 0.5, (1a) had R_f 0.18); ^1H NMR (C_6D_6) (1b) (δ, ppm): 0.83 s (CH_3-18), 1.23 s (CH_3-18'), 0.78 d, J = 7.1 Hz. (CH_3-27), 0.88 d, J = 5 Hz (CH_3-27'), 1.62 s (CH_3-21), 2.05 s (CH_3-21'), 0.88 s (CH_3-19), 0.93 s (CH_3-19'), 1.72 s, 1.73 s, 1.74 s (AcO × 3), 3.74 dd (J_{gem} = 12.9 Hz, J_{vic} = 1.35 Hz, H_e − 26), 3.61 dd (J_{gem} = 12 Hz, J_{vic} = 7 Hz, H_a − 26), 3.93 ddd (J = 10.7 Hz), J_{vic} = 6.4 and 5.5 Hz, H_e − 26, H_a = 26'), 4.85 m (H − 3, H − 3'), 5.33 br.d (H − 6), 5.5 br.d (H − 6').

LITERATURE CITED

1. G. B. Elyakov, T. V. Ilyukhona, A. V. Kamernitskii, T. M. Remennikova, and L. I. Strigina, Izv. Akad. Nauk SSSR, Ser. Khim., 1150 (1977).
2. C. L. Cocq and J. Y. Lallemand, J. Chem. Soc. Chem. Commun., 150 (1981).
3. L. I. Strigina, V. A. Denisenko, Ya. V. Rashkes, and A. V. Kamernitskii, Izv. Nauk SSSR, Ser. Khim., 431 (1987).
4. L. I. Strigina, Ya. V. Rashkes, and V. A. Denisenko, Khim. Prir. Soedin., 367 (1987).
5. K. Nakano, Y. Kashiwada, T. Nohara, T. Tomimatsu, H. Tsukatani, and Kawasaki, Yakugaku Zasshi, 103, 1031 (1982).
6. L. Brown and M. Koreeda, J. Org. Chem., 99, 3875 (1984).
7. Z. C. Liang, R. Aquino, F. De Simone, A. Dini, O. Schettino, and C. Pizza, Planta Med., 344 (1988).
8. H. Budzikiewicz, K. Takeda, and K. Schreiber, Monatsh. Chem., 101, 1003 (1970).