STRUCTURE OF THE CARDIAC AGLYCONE SYRIOGENIN

Ya. V. Rashkes and N. K. Abubakirov

UDC 547.926.543.51

In 1961, Masler, Bauer, et al. [1], in studying the cardiac glycosides of Asclepias syriaca L., isolated from the epigeal part of this plant five compounds of cardenolide nature, including a new cardiac alkaloid – syriogenin – and two of its glycosides. On the basis of the difference in molecular rotations between diacetylsyriogenin and acetyluzarigenin, the Czechoslovakian authors proposed the structure of 12β-hydroxyuzarigenin for the new aglycone. Brüschweiler et al. [2] found this aglycone in small amount in the milky juice of Calatropis procera R. Br., but they expressed doubt [3] as to the correctness of the structure prepared by Masler et al. [1].

On the basis of the presence in the mass spectrum [2] of the syriogenin of an ion with m/e 201, assumed to be absent from the spectrum [3] of digoxigenin (12β-hydroxydigitoxigenin), the Swiss investigators suggested that the third hydroxy group in the molecule of syriogenin must be present in one of the following positions: C_1, C_6, C_7, or C_{11}. In a later paper, Braun et al. [4] gave a second spectrum of digoxigenin containing the peak mentioned above with m/e 201, and at a considerable intensity. Brüschweiler et al. [3] had apparently assumed erroneously that with a hydroxy group present at C_{12} decomposition of the syriogenin ion of type *a* [5, 6] should lead to the appearance of an ion with m/e 203, and not 201. In actual fact, as follows from work on the fragmentation of the cardenolides [4-7], the C_{12} atom is retained in ions of type *a*. In the spectra of syriogenin and digoxigenin the oxygen-containing variety of these ions includes 219 mu (203+16), and after the elimination of a molecule of water ions with m/e 201 arise.

In later publications, the same authors [3] did not return to the question of the structure of syriogenin. Having available a sample of this compound given to us in 1962 by the Czechoslovakian workers who discovered it [1], we have attempted to solve this question by a more detailed investigation of the mass spectrum of syriogenin.

The spectrum of the sample taken on a MKh-1303 instrument at a temperature of the inlet system of 160°C and with an ionizing voltage of 40 V (Fig. 1a) agrees with the spectrum of syriogenin given by Brüschweiler et al. [2].

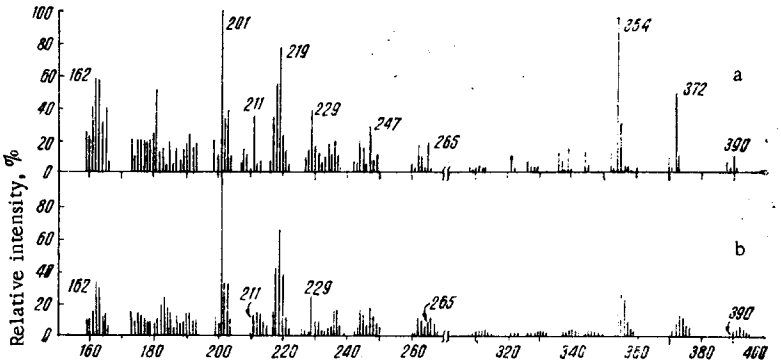


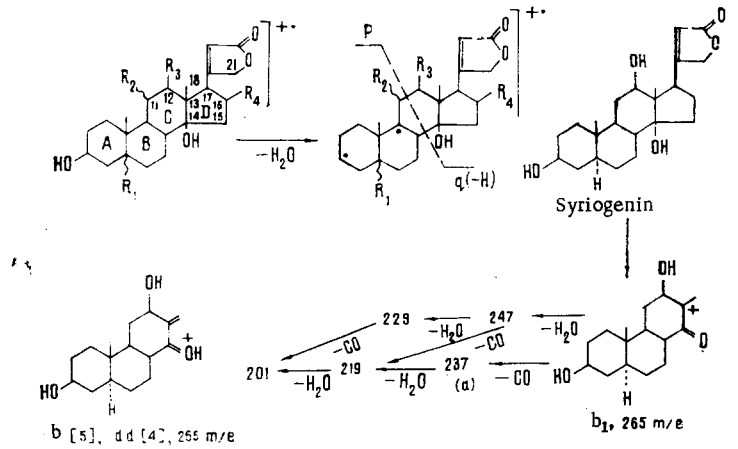
Fig. 1. Mass spectrum of syriogenin (a) and of [D]syriogenin (b).

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 615-617, September-October, 1974. Original article submitted June 19, 1973.

TABLE 1. Mass Numbers of the Ions p and q

Aglycones	m/e		
	mother ions	p	q
Syriogenin R_1 = α-H; R_2, R_4 = H; R_3 = β-OH	372 (M−H_2O)	162	211
Digoxigenin [4] R_1 = β-H; R_2, R_4 = H; R_3 = β-OH	372 (M−H_2O)	162	211
Digitoxigenin R_1 = β-H; R_2, R_3, R_4 = H	356 (M−H_2O)	162	195
Periplogenin R_1 = β-OH; R_2, R_3, R_4 = H	354 (M−$2H_2O$)	160	195
Gitoxigenin R_1 = β-H; R_2, R_3 = H; R_4 = β-OH	354 (M−$2H_2O$)	162	193
Sarmentogenin [3] R_1 = β-H; R_2 = α-OH; R_3, R_4 = H	354 (M−$2H_2O$)	160	195
Mallogenin [4] R_1 = α-H; R_2 = β-OH; R_3, R_4 = H	354 (M−$2H_2O$)	160	195

To establish the position of this secondary hydroxyl in the syriogenin molecule it proved to be useful to study the fragments formed in the decomposition of the steroid nucleus. The presence in the spectrum of ions with m/e 111 and 244 excludes positions C_{16} and C_{15} for the secondary OH group.



In one of our preceding papers [6] we have shown that because of the splitting out of water with the involvement of the 3β-OH group from the molecular ions of the aglycones of the digitoxigenin series the fragmentation of ring C may take place. This led to the formation of two ions, subsequently denoted by p and q (Scheme). Table 1 gives the mass numbers of the mother ions of this series and of the fragments p and q for some aglycones. Some of the figures have been taken from mass spectra illustrated in the literature.

It follows from Table 1 that the spectra of aglycones having no secondary OH group at C_{12} or in ring D contain a peak with m/e 195. In gitoxigenin, the ions p and q arise after the elimination of the 16β-OH group, in view of which the latter contains 193 amu. Conversely, in the spectra of syriogenin and digoxigenin, the ion q with m/e 195 is displaced by 16 mu through the presence of an additional oxygen atom and C_{12} (m/e 211). However, according to Braun, ions with m/e 211 (type dg [4]) are characteristic for all aglycones containing two OH groups in any positions in rings A, B, and C. They correspond to ions of type c according to Fayez [5] and are formed by the successive ejection of three molecules of water from ions with m/e 256 (type dd [4]) (see Scheme).

The results of our experiments show that the appearance of an ion with m/e 211 in this way has no fundamental significance. We deuterated a sample of syriogenin with CD_3OD. As in the case of other cardenolides, this led to an additional shift of the M^+ peak by 2 mu. This phenomenon is caused by the exchange of the hydrogen atoms at C_{21} under mass spectrometric conditions [6, 8]. With the presence of a hydroxyl attached to the C_{12} atom in the syriogenin molecule and the fragmentation of the ion M−H_2O by the cleavage of the C_{11}−C_{12} bond, ion p with m/e 162 does not undergo an isotopic shift, and ion q with m/e 211 is shifted by four mu (C_{12}−OD, C_{14}−OD, C_{21}−D_2). The mass spectrum of the deutero analog (Fig. 1b) confirms our hypothesis. Similar results were obtained for digitoxigenin, gitoxigenin, and periplogenin deuterated under the same conditions, in the spectra of which ions p are not displaced and ions q prove to be shifted by 3 mu.

Furthermore, the spectrum of D-syriogenin shows that the ion with m/e 211 is not formed by the elimination of water from the ion with m/e 229 (type df [4]), since this ion contains practically no isotopic label. This fact also throws doubt on the structure of the ions of type c [5] (see Scheme). Previous authors

[4, 5, 7] have assumed that these ions arise through $C_{13}-C_{17}$ and $C_{14}-C_{15}$ cleavages and the migration of hydrogen from C_{18} into the neutral fragment. For the spectrum of D-syriogenin, this mechanism would lead to displacements of the peaks with m/e 265, 247, and 229 by 3, 2, and 1 mu, respectively. In actual fact, the shifts amount to 2, 1, and 0 mu. Consequently, in our opinion, the structure b_1 is preferable for ions of the type under consideration (see Scheme).

The form b_1 may serve as one of the sources of the series of ions of type *a* [4-7] formed by the elimination of the keto group from ring C.

The 5α-H configuration of syriogenin is confirmed by the fact that its molecular ion is more stable than that of digoxigenin. We have reported a similar correlation previously in a consideration of the mass spectra of the acetates of uzarigenin and digitoxigenin [6]. We are inclined to consider that the Czechoslovakian authors gave the structure of syriogenin correctly, and it is in fact 12-hydroxyuzarigenin.

SUMMARY

The results of a study of the mass spectra of syriogenin and its D-analog confirm that this cardiac aglycone has the structure of 3β,12β,14-trihydroxy-5α,14β-card-20(22)-enolide.

LITERATURE CITED

1. L. Masler, S. Bauer, O. Bauerova, and D. Šikl, Coll. Czech. Chem. Commun., 27, 872, 895 (1962).
2. F. Brüschweiler, W. Stöcklin, A. Stöckel, and T. Reichstein, Helv. Chim. Acta, 52, 2086 (1969).
3. F. Brüschweiler, K. Stockel, and T. Reichstein, Helv. Chim. Acta, 52, 2276 (1969).
4. P. Brown, F. Brüschweiler, and G. R. Pettit, Helv. Chim. Acta, 55, 531 (1972).
5. M. B. E. Fayez and S. A. R. Negm, Chem. Ind., 40, 1361 (1968); J. Pharm. Sci., 61, 765 (1972).
6. Ya. V. Rashkes, M. B. Gorovits, G. K. Makarichev, and N. K. Abubakirov, Khim. Prirodn. Soedin., 747 (1971).
7. G. Spiteller, Z. Analyt. Chem., 197, 1 (1963).
8. M. R. Yagudaev and Ya. V. Rashkes, Khim. Prirodn. Soedin., 750 (1972).