THE ISOLATION AND STRUCTURE OF NAHAGENIN

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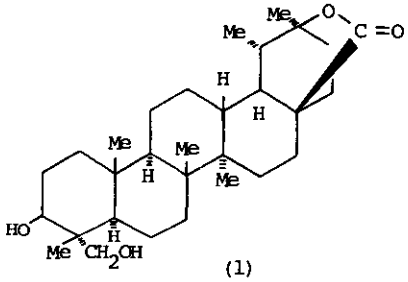
ABSTRACT: — The isolation and structure of a new sapogenin, nahagenin (1), from the medicinal plant *Fagonia indica* Linn is presented.

Fagonia indica Linn[1] (zygophyllaceae) is a small spiny undershrub which is widely distributed in Pakistan. An aqueous decoction of the leaves and young twigs is a popular remedy for the treatment of various skin lesions. The plant is claimed to be a remedy for cancer in its early stages and preliminary pharmacological tests of aqueous extracts on mice have shown some anti-cancer activity.[2] An Ames mutagenicity test has also indicated marginal activity.[3] Prior investigations have revealed triterpenoids,[4-6] carbohydrates, saponins,[7] alkaloids,[8] sapogenins,[9-13] fatty acids[14] and amino acids.[15] We now wish to report the isolation of a new sapogenin, nahagenin (1).



(1)

The crude saponins, obtained from the ethanolic extract of the aerial parts of the fresh plants, were hydrolysed with 20% ethanolic HCl to afford the corresponding sapogenins. Silica gel chromatography with elution by pet. ether, pet. ether-$CHCl_3$, $CHCl_3$, and finally $CHCl_3$-MeOH afforded two crystalline compounds which were further purifed by crystallization. The first of these nahagenin (1), m.p. 290°C, analyzed for $C_{30}H_{48}O_4$ and this was confirmed by high resolution mass spectrometry (m/z = 472.3540 meas, 472.3552 for $C_{30}H_{48}O_4$). Major peaks in the MS occurred at m/z of 454, 436, 424, 409, 395 and 261. The IR spectrum ($CHCl_3$) showed peaks at 1740 cm^{-1} and 3460 cm^{-1} suggesting a δ-lactone and hydroxy groups. The substance readily afforded a diacetate (m/z = 556) but was found to be remarkably inert to attempted hydrolysis of the lactone.

The ^1H NMR showed no olefinic protons. The ^{13}C NMR (100 MHz) confirmed the presence of thirty carbons and chemical shifts and multiplicities are given

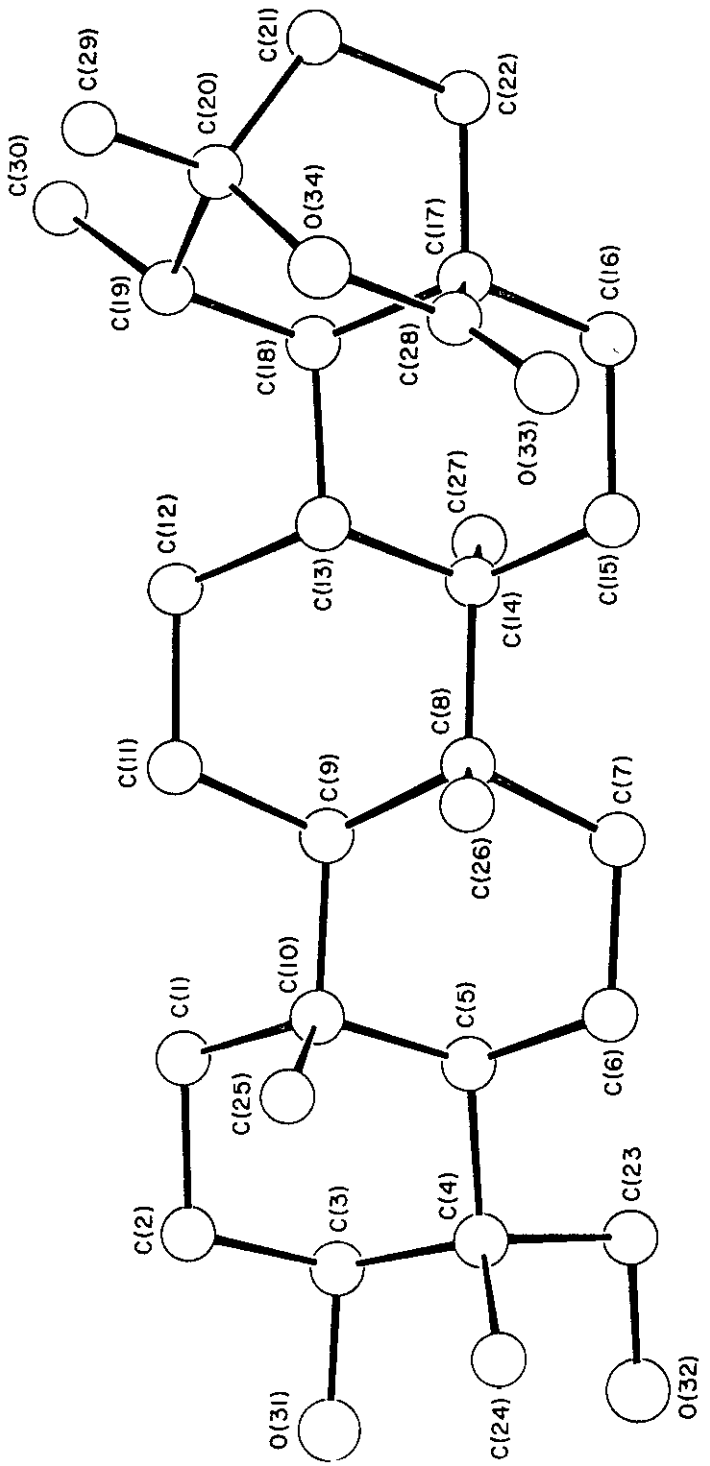


Figure 1. A computer generated perspective drawing of nahagenin. Hydrogens are omitted for clarity.

in Table 1. The carbon atoms in the A and B rings were readily recognized by comparison with corresponding signals of known pentacyclic triterpenoids.[16] Six quaternary centers and six methyl groups were also identified. The ^{13}C NMR displayed a resonance at δ 177.29 for the carbonyl carbon and three resonances at δ 84.27(s), 76.54(d) and 71.92(dd) for the oxygen bearing carbons C(20), C(3) and C(23) respectively.

An unambiguous structure determination was carried out by a single crystal x-ray diffraction analysis. Crystals of nahagenin formed in the monoclinic system with a = 12.370(2), b = 6.7688(8), c = 15.832(2)Å and β = 100.28(1)°. All unique diffraction maxima with $2\theta \leq 114°$ were collected on an automated four-circle diffractometer with variable speed, 1° ω-scans. Of the 1972 reflections surveyed, 1509 (77%) were judged observed ($|F_o| \leq 3\sigma(F_o^2)$) after correction for Lorentz, polarization and background effects. The structure was solved by a multisolution weighted tangent formula approach with five special and one general reflection forming the variable starting set.[17] Fullmatrix least-squares refinements with anisotropic nonhydrogens and fixed isotropic hydrogens have converged to a standard crystallographic residual of 0.0585.[18] Figure 1 is a computer generated perspective drawing of the final x-ray model.

As expected nahagenin is a pentacyclic triterpene with a δ-lactone added to the E ring. All of the carbocyclic rings are joined in a trans-anti fashion. In general bond distances and angles agree well with general accepted values.[18] Preliminary studies on the saponins present indicate that nahagenin is a genuine aglycone of the parent saponin, the structure of which is currently under investigation.

TABLE-I

Carbon	Chemical Shift(s)	Multiplicity	Carbon	Chemical Shift(s)	Multiplicity
C(1)	38.51	d.d	C(16)	25.15	t
C(2)	27.28	t	C(17)	42.06	s
C(3)	76.54	d	C(18)	50.51	d
C(4)	41.86	s	C(19)	48.37	d
C(5)	49.99	d	C(20)	84.27	s
C(6)	18.35	t	C(21)	41.98	t(?)
C(7)	32.22	t	C(22)	33.68	t
C(8)	40.51	s	C(23)	71.92	d.d
C(9)	42.83	d	C(24)	11.30	q
C(10)	37.05	s	C(25)	15.69	q
C(11)	20.96	t	C(26)	16.63	q
C(12)	27.05	t	C(27)	23.98	q
C(13)	27.59	d	C(28)	177.29	s
C(14)	41.08	s	C(29)	14.26	q
C(15)	26.87	t	C(30)	23.98	q

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