IGALAN, A NEW SESQUITERPENE LACTONE FROM *Inula grandis*

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We have reported the isolation of two new sesquiterpene lactones, called "grandulin" and "grandicin" from the herb Inula grandis Schrenk. [1]. In this paper we give the results of a study of one of the lactones from the roots of this plant.

Two lactones with the compositions $C_{15}H_{20}O_2$, one of which was shown to be identical with alantolactone and the second with isoalantolactone, have been previously isolated from the essential oil of the roots of this species [2, 3]. Since on distillation with steam, and especially under pressure, many lactones undergo degradation, and a considerable number of them are not volatile at all under these conditions, it was of interest to study the lactones isolated under milder conditions by extraction with petroleum ether.

Using a known method [4], we isolated from the roots 4.67% of a lactone fraction consisting of an oily partially crystallizing mass containing, according to TLC, eight substances with R_f 0.9, 0.84, 0.76, 0.68, 0.58, 0.52, 0.25, and 0.00. The first two substances were present in predominating amounts and were revealed with vanillin in sulfuric acid in the form of bright crimson spots; the others were present in traces and gave brick-red and violet colors.

The lactone fraction was separated chromatographically on alumina. On elution with petroleum ether, the first fractions yielded a mixture of substances with R_f 0.9, 0.84, and 0.76 from which, on standing, a component with the composition $C_{15}H_{20}O_2$ crystallized; it had mp 79–79.5°C, $[\alpha]_D^{20}$ +105° (c 1.38, chloroform), R_f 0.84, and was readily soluble in methanol, ether, and acetone and insoluble in water; it distilled in steam without change. The substance had the properties of a lactone, dissolving in aqueous solutions of caustic alkalis on heating and precipitating in the initial state (IR spectrum, mp, R_f) on subsequent acidification.

Its IR spectrum had bands at (cm^{-1}) 1770 (γ-lactone carbonyl), 1660, 1410, and 1110 (exocyclic methylene group conjugated with a lactone carbonyl), 1640 (primary-tertiary double bond), 909 ($RCH{=}CH_2$ group), and 892 ($R{-}\underset{\underset{R}{|}}{C}{=}CH_2$ group) [5, 6]. The presence of an exocyclic methylene group attached to a lactone ring was confirmed by the preparation of a hydrochloride having mp 105°C. In the IR spectrum of this substance the absorption bands at 1660, 1410, and 1110 cm^{-1} had disappeared.

The reduction of the lactone with sodium borohydride gave a diol with mp 83–85°C in whose IR spectrum the carbonyl band at 1770 cm^{-1} had disappeared and the broad absorption band of a hydroxyl group had appeared in the 3200–3400 cm^{-1} region.

From its composition and chemical properties the substance isolated is a sesquiterpene lactone resembling alantolactone in its composition and melting point. However, a comparison of the IR and NMR spectra of the two substances, as well as the depression of the melting point (20°C) given by a mixture of this lactone with an authentic sample of alantolactone showed that they are different. Attempts to obtain the well-crystallizing tetrahydroalantolactone by a known method [7] also failed to give a satisfactory result.

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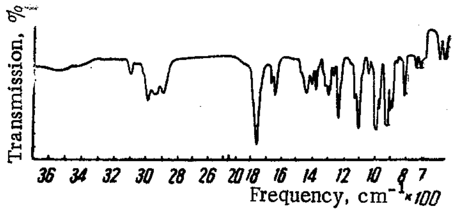


Fig. 1. IR spectrum of igalan (in KBr).

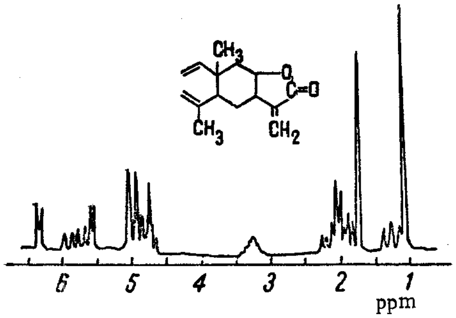


Fig. 2. NMR spectrum of igalan (in CCl_4).

On the basis of its physicochemical properties we may conclude that the substance that we have isolated is a new sesquiterpene lactone, and we have called it "igalan."

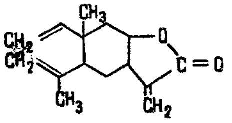
The NMR spectrum of igalan contains the signals of methyl groups [one on the double bond giving a singlet at 1.65 ppm (3H) and one attached to a quaternary carbon atom giving a singlet at 0.98 ppm (3H)], an exocyclic methylene group conjugated with a lactone carbonyl giving doublets at 6.14 and 5.48 ppm (J = 4.5 Hz), and two methylene groups giving singlets at 4.92, 4.82, 4.75, and 4.65 ppm (1H each). In addition, there are the signals of an olefinic proton (in the 5.5–5.85 ppm region, J = 10 Hz) and of a lactone proton (superposed on the signals at 4.62–4.75 ppm), and also that of a vicinal proton in a lactone ring (multiplet at 3.2–3.4 ppm, 1H).

Catalytic hydrogenation in the presence of Raney nickel gave a dihydro derivative in whose NMR spectrum the signals of the conjugated exocyclic methylene group disappeared while a doublet appeared at 0.83 ppm, J = 5 Hz (3H) corresponding to a methyl group on a lactone ring. The other signals had not changed their positions.

Catalytic hydrogenation over platinum (according to Adams) in acetic acid in the presence of perchloric acid gave a mixture which, according to mass spectrometry, consisted of a hexahydro derivative with a small amount of tetrahydro derivative which was impossible to separate. In the NMR spectrum of the product the signals of the exocyclic and the two terminal methylene groups disappeared and a strong doublet appeared in the 0.65–0.85 ppm region. The lactone proton appeared in the form of a complex signal of five bands in the 4.35–4.65 ppm region, J = 5.5 Hz, which shows the linear linkage of the rings and the cis configuration of the lactone ring [6].

To confirm the linear linkage we studied the UV spectra of igalan and some other lactones in concentrated sulfuric acid. It is known that many substances that do not absorb in the UV region are converted into products with characteristic absorption maxima on dissolution in concentrated sulfuric acid because of dehydration and dehydrogenation [8–11]. The UV spectra of the resulting compounds are extremely specific and give valuable information on the structure of the initial substances. Such studies have not been performed for this group of sesquiterpene lactones, and we therefore studied the UV spectra in sulfuric acid of santonin, tauremisin (angular linkage), and alantolactone (linear linkage) 3 and 24 h after dissolution (Table 1). We see from the table that only 3 h after the lactones had been dissolved in sulfuric acid two absorption maxima appeared: I in the 224–269 nm region (log ε 3.65–3.85) and II at 245–340 nm (log ε 3.58–5.04). After 24 h changes had occurred in the positions of the maxima: in the lactones of the angular type maximum I had undergone a hypsochromic shift and II a bathochromic shift. In alantolactone, with the linear linkage, the position of maximum I had not changed while II had shifted slightly in the short-wave direction. In igalan the changes that took place were similar to those for alantolactone, which indirectly shows the linear linkage of the lactone ring.

The chemical properties and spectral characteristics given permit the conclusion that igalan is a lactone of the elemane type and that it probably has the following structure:



Lactones of a similar type have been isolated from several representatives of the family Compositae [6]. On the basis of biogenetic data Rangavan et al. suggested the precursor of alantolactone and of iso- and dihydroalantolactones is the germacranolide inunolide which is present in the Inula racemosa root [12] together with the lactones mentioned. By analogy with dihydrocostunolide [5], formed by the pyrolysis of

TABLE 1. UV Spectra of Some Lactones in Concentrated Sulfuric Acid

Lactones	After 3 h		After 24 h	
	λ_{max}	1 ε	λ_{max}	log ε
Tauremisin	240; 345	3,65; 5,04	237; 344	3,71; 4,04
Santonin	269; 320	3,87; 3,[illegible]9	247; 328	3,89; 3,8[illegible]
Alantolactone	237; 327	3,68; 3,58	237; 325	3,80; 3,75
Igalan	224; 310	3,89; 4,01	224; 305	3,87; 4,38

saussurea lactone, inunolide gave a low yield of a product to which the authors ascribed a structure of the elemane type analogous to that of igalan. The isolation of igalan from *Inula grandis* Schrenk. under mild conditions shows that elemanolides may be not only products of the transformation of germacranolides but also true natural substances. The lactones contained in plants of the genus *Inula* are extremely diverse. These plants have been found to contain derivatives of eudesmane [7], germacrane [12], guaiane [13], spirolactones [14], and a lactone of the elemane type now isolated by us for the first time.

EXPERIMENTAL

The NMR spectra were taken on a JNM-4H-100/100 MHz instrument, the IR spectra on a UR-20 spectrometer, and the UV spectra on a Hitachi spectrophotometer. The fractions were analyzed chromatographically in a thin fixed layer of alumina in a benzene–methanol–ethyl acetate (94 : 3 : 3) system. The spots were revealed by spraying the chromatogram successively with a 1% solution of vanillin in conc H_2SO_4 and with methanol.

Isolation of Igalan. A 6.4-kg sample of the dried and comminuted roots collected in April-May 1969, in the Chimgan District (Tashkent Region) was treated with petroleum ether (4 × 20 liters). The extracts were evaporated in vacuo to a volume of 500 ml (460 g). The concentrate (200 g) was dissolved in 1.2 liter of petroleum ether and extracted with 1.5 liter of 60% acetone and then with 1.5 liter of 90% ethanol. The ethanolic extract was concentrated to small volume and treated with chloroform (5 × 200 ml). Distillation of the chloroform extract gave 130.2 g of lactone fraction (4.67%), which was transferred to a chromatographic column (8 cm in diameter and 20 cm high) filled with neutral alumina (activity grade III). The column was eluted with petroleum ether, petroleum ether containing 2-20% benzene, benzene, a benzene–methanol mixture (99 : 1 to 95 : 5), and methanol, 300-ml fractions being collected. The concentrations of fractions 1-6 yielded 84.64 g of an oily, partially crystallizing liquid. The precipitate (about 20 g) was filtered off with suction and recrystallized repeatedly from 50% methanol. This gave a colorless crystalline substance with mp 79-79.5°C, $[\alpha]_D^{20}$ + 105° (c 1.38, chloroform), R_f 0.84. UV spectrum: λ_{max} 202 nm (log ε 3.99). Found %: C 77.20, 77.10; H 9.32, 9.13. Mol. wt. 232 (by mass spectrometry). $C_{15}H_{20}O_2$. Calculated %: C 77.58; H 8.66. Mol. wt. 232.

Preparation of Igalan Hydrochloride. A solution of 0.3 g of the substance in 20 ml of ethanol was placed in ice and saturated with gaseous HCl, after which it was evaporated in vacuo to one-half of the original volume. On cooling the liquid deposited acicular crystals with mp 103-119°C which, after repeated crystallization from 90% ethanol and drying in vacuo over P_2O_5, had mp 105°C.

Reduction of Igalan with Sodium Borohydride. A solution of 0.3 g of the substance in 20 ml of 90% ethanol was treated with 0.9 g of sodium borohydride. The solution was left at room temperature for 18 h and was then diluted with water. The reaction product was extracted with hexane. This gave 0.15 g of acicular crystals with mp 83-85°C, R_f 0.18.

Hydrogenation of Igalan over Raney Nickel. A 0.1 g sample of the substance in 15 ml of ethanol was hydrogenated over 0.05 g of freshly prepared catalyst at room temperature. Reduction ceased after the absorption of 1 mole of hydrogen (about 10 ml of H_2). The solution was filtered, evaporated, diluted with water, and extracted with ether. This gave an oily substance with R_f 0.40, M^+ 234.

Hydrogenation of Igalan over Platinum. A 1-ml quantity of 57% $HClO_4$ and 0.2 g of PtO_2 (according to Adams) was added to 0.3 g of the substance in 10 ml of glacial acetic acid, and hydrogenation was carried out at room temperature, 107 ml of hydrogen being absorbed. The solution was filtered, diluted with water, and extracted with ether. Elimination of the solvent yielded an oily liquid with M^+ 236 and 238^+. IR spectrum, cm^{-1}: 1770 and 1690. There was no absorption band at 1660, 1640, 910, 896, or 820 cm^{-1}.

CONCLUSIONS

A new sesquiterpene lactone $C_{15}H_{20}O_2$ with mp 79-79.5°C, $[\alpha]_D^{20}$ + 105° (chloroform) has been isolated from the roots of Inula grandis Schrenk., and we have called it "igalan." On the basis of chemical and spectral characteristics, it has been established that its most probable structure is eleman-8,11-olide.

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