Tetrahedron Letters, No. 11, pp. 376-381, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE STRUCTURE OF GRINDELIC ACID, A NEW DITERPENE ACID

L. Panizzi, L. Mangoni and M. Belardini

Istituto di Chimica Organica dell'Universita, Roma

(Received 2 June 1961)

AN INVESTIGATION on the chemical constitution of the resin[1] from Grindelia robusta is at present in progress in this Institute. In this preliminary communication we wish to report the first results obtained from the examination of the fraction containing water-insoluble, light petroleum soluble acids.[2]

Methylation of these with diazomethane gave a mixture of esters that we have been able to separate into several components by means of chromatography on alumina. The principal component, eluted with light petroleum-ether 9:1, was a colourless, crystalline solid, m.p. 70-70.5° (from methanol), $[\alpha]_D = -134.1^\circ$ (in methanol), with a molecular formula $C_{21}H_{34}O_3$(I).[3] By mild hydrolysis with N potassium hydroxide it afforded an acid $C_{20}H_{32}O_3$(II) m.p. 100-101° (from acetic acid), $[\alpha]_D = -102.2^\circ$, to which we have given the name "grindelic acid". With diazomethane, it again produced ester (I).

---

[1] The present knowledge on the chemical constitution of the resin from Grindelia robusta is based upon an old work of F.B. Power and F. Tutin, which reports that this resin consists mainly in unidentified liquid unsaturated acids [Chem.Zentr. I, 1401 (1908)].

[2] Our starting material was a commercial dry hydro-alcoholic extract of the plant.

[3] Satisfactory analyses were obtained for all compounds reported. Melting points were determinated on a Kofler block and have not been corrected. Ultra-violet measurements were made on ethanol solutions. Specific rotations were determined on chloroform solutions (unless otherwise indicated) at room temperature.

The majority of degradation experiments were made upon methyl ester (I), which was more easily obtained and purified. It was unsaturated, giving a positive reaction with tetranitromethane and with potassium permanganate. Catalytic hydrogenation of (I) in the presence of platinum oxide at atmospheric pressure yielded liquid saturated dihydrogrindelic acid methyl ester $C_{21}H_{36}O_3$ (III).

Grindelic acid methylester (I) failed to give the reactions of alcohols and carbonyl compounds. It had no marked light absorption above 210 mμ; the ethylenic bond and ester group were not in conjugation. The infrared spectrum of (I) (in Nujol) showed no hydroxyl band, only one carbonyl band at 1740 cm^{-1} (unconjugated ester), a band at 1095 cm^{-1}, which could probably be assigned to a five- or six-membered ring ether, and a low intensity band, missing in dihydroester (III), at 835 cm^{-1}, which made the presence of a trisubstituted double bond in (I) very probable.

All these data permitted the hypothesis that grindelic acid might be a bicyclic diterpene unsaturated acid, with an ether bridge and with the carboxyl group in a sterically unhindered position.

At the first confirmation of this hypothesis, selenium dehydrogenation of the ester (I) gave 1,2,5-trimethylnaphthalene, characterized as its 1,3,5-trinitrobenzene adduct.

On high pressure and high temperature hydrogenation with a palladium-charcoal catalyst, methyl grindelate (I) afforded, beyond the dihydroester (III), a small but significant quantity of a saturated hydrogenolized ester. Its infra-red spectrum showed a hydroxyl band, but the ether band at 1095 cm^{-1} had disappeared. This latter was missing also in the product obtained by refluxing ester (I) with acetic anhydride. On the contrary, dihydroester (III) was stable in the same conditions. A probable allylic nature of ether bridge in (I) was deduced.

In the attempt to find support for this hypothesis the next reactions on ester (I) were made. Reduction with lithium aluminium hydride gave liquid primary alcohol $C_{20}H_{34}O_2$ (IV) (I.R. bands at 3390, 1105, 835 cm^{-1}). Reduction of the latter with lithium in anhydrous ethylamine proceeded very smoothly, giving diol $C_{20}H_{36}O_2$ (V) m.p. 104-105°, $[\alpha]_D = +86.6^\circ$. Its I.R. spectrum showed a hydroxyl band, but did not show the bands at 1105 and 835 cm^{-1}. The double bond was accordingly shifted into a tetrasubstituted position.[4]

When catalytically reduced (platinum oxide in acetic acid), the diol (V) gave a saturated diol $C_{20}H_{38}O_2$ (VI), m.p. 121-122°, $[\alpha]_D = +28.5^\circ$. It was not an α-glycol, because it did not react with lead tetraacetate. Oxidation of (VI) with chromic acid in acetone[5] and then methylation with diazomethane gave an oily hydroxy-ester $C_{21}H_{38}O_3$ (VII) (I.R. bands at 3510 and 1735 cm^{-1}). One of the hydroxyl groups of (VI) was accordingly tertiary.

Dehydration of the hydroxy-ester (VII) with phosphoryl chloride in ice-cold pyridine afforded a mixture of unsaturated esters, among which a conjugated isomer predominates. This, isolated by chromatography on aluminium oxide, was a liquid with the composition $C_{21}H_{36}O_2$ (VIII). Its infra-red spectrum showed bands at 1720 cm^{-1} (conj. ester) and at 1645 cm^{-1} (conj. double bond). In ultra-violet, it had an absorption maximum at 221 mμ (log $\varepsilon = 4.17$). The ester (VII) must consequently be a tertiary β-hydroxyester.

This was confirmed by ozonolysis of (VIII) (in ethyl acetate at -60°), which produced a liquid ketone that was identified as the known 15,16-bisnorlabdan-13-one (IX) by its infra-red spectrum and by formation of 2,4-dinitrophenylhydrazone $C_{24}H_{36}O_4N_4$, m.p. 144-145° and of semicarbazone $C_{19}H_{35}ON_3$, m.p. 187-188° $[\alpha]_D = +32.6^\circ$.[6] As a further confirmation, hypoiodite

---

[4] A.S. Hallsworth et al., J.Chem.Soc. 1969 (1957).

[5] A. Bowers, T.G. Halsall and E.R. Jones, J.Chem.Soc. 2555 (1953).

[6] J.D. Cocker and T.G. Halsall, J.Chem.Soc. 4262 (1956).

oxidation of (IX) gave iodoform and an acid $C_{17}H_{30}O_2$ m.p. 140-141.5°, $[\alpha]_D$ = +42.3°, identified as 14,15,16-trisnorlabdanoic acid (X).[6]

The compounds (V), (VI), (VII), (VIII), (IX) and (X) must consequently have the structure reported in Chart 1.

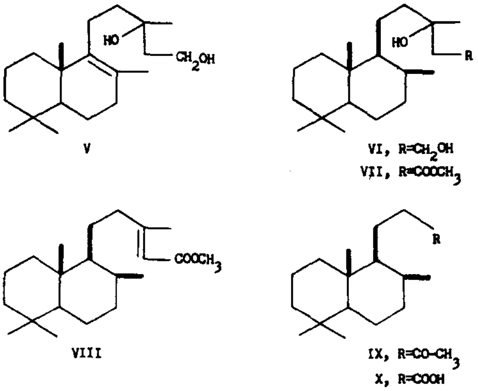


Chart 1.

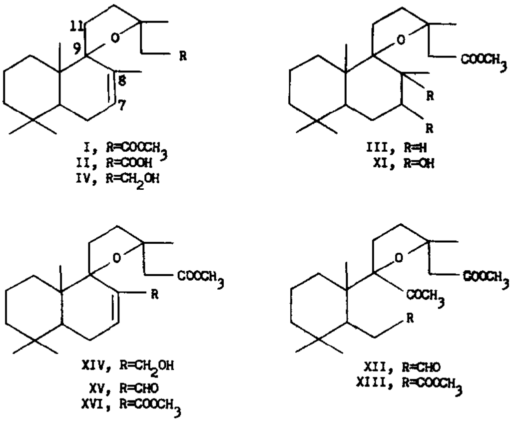
The carbon skeleton and a good part of the structure of grindelic acid were clarified in this way. In the attempt to establish the position of the double bond, and consequently the attack point of the ether bridge in allylic position, ester (I) was submitted to oxidation with osmium tetroxide in ether-pyridine, from which a dihydroxy-ester $C_{21}H_{36}O_5$ (XI), m.p. 122-123°, $[\alpha]_D$ = +19° was obtained. On cleavage with lead tetraacetate in benzene, dihydroxy-ester (XI) gave oily keto-aldehyde (XII) (I.R. bands at 2705, 1740, 1720, 1700 cm^{-1}), which by chromic acid oxidation and then by esterification with diazomethane was transformed into keto-diester $C_{22}H_{36}O_6$ (XIII), m.p. 102-103° (I.R. bands at 1740 and 1700 cm^{-1}). This proved that the double bond of methyl grindelate was actually in a trisubstituted position.

If we assume the ether ring to be five- or six-membered, the only possible position of the double bond are 9.11 or 7.8. The failing of Lieben reaction on keto-ester (XIII) made the former more probable, but this was not found to be the case.[7]

In fact, the attempt to hydroxylate the double bond of (I) by Woodward procedure[8] produced the unsaturated monohydroxy-ester $C_{21}H_{34}O_4$ (XIV), m.p. 115-116°, $[\alpha]_D = -105.3°$. Its infra-red spectrum showed bands at 3425 cm^{-1} (hydroxyl), 1740 cm^{-1} (ester carbonyl) and 1645 cm^{-1} (double bond).[9]

The fact that an allylic primary alcohol group was present in (XIV) was proved by manganese dioxide oxidation[10] of the hydroxy-ester.

When this reaction was made in the absence of oxygen a liquid αβ-unsaturated aldehydo-ester (XV) was obtained, characterized as 2,4-dinitrophenylhydrazone $C_{27}H_{36}O_7N_4$, m.p. 166-168° (λ_{max} 372 mμ; log ε = 4.53). The infra-red spectrum of (XV) showed bands at 2705, 1740, 1695, 1640 cm^{-1}. The ultra-violet spectrum had an absorption maximum at 227 mμ (log ε = 4.03).



I, R=COOCH$_3$
II, R=COOH
IV, R=CH$_2$OH

III, R=H
XI, R=OH

XIV, R=CH$_2$OH
XV, R=CHO
XVI, R=COOCH$_3$

XII, R=CHO
XIII, R=COOCH$_3$

Chart 2.

---

[7] It is known that sterically indered methyl-ketones may fail to give Lieben reaction.

[8] Advances in Organic Chemistry Vol. I, p. 137. Interscience, New York (1960).

[9] An analogous case of allylic oxidation is reported by L.H. Briggs, B.F. Cain and B.R. Davis [Tetrahedron Letters No. 17, 9 (1960)].

[10] R.M. Evans, Quart.Rev. 13, 61 (1959).

When the reaction was allowed to take place in the presence of oxygen, an acid was obtained that by action of diazomethane gave αβ-unsaturated ester $C_{22}H_{34}O_5$ (XVI) m.p. 58-59°, $[\alpha]_D = -96.6°$ ($\lambda_{max} = 211$ mμ; log $\varepsilon = 3.75$. I.R. bands at 1740, 1725, 1640 cm^{-1}). The double bond of (I) must consequently be located in the 7.8 position and the ether bridge must be five-membered. Therefore grindelic acid had structure (II) (chart 2).

In terms of stereochemistry, the obtaining of (IX) and (X) from ester (II) showed that the rings in grindelic acid were trans-fused and that $C_{(10)}$methyl was β-oriented. Research to establish the configuration at $C_{(9)}$ and $C_{(13)}$ is in progress.