

ISOROSENOLIC ACID, A NEW DITERPENOID CONSTITUENT
OF TRICHOHECIUM ROSEUM LINK*

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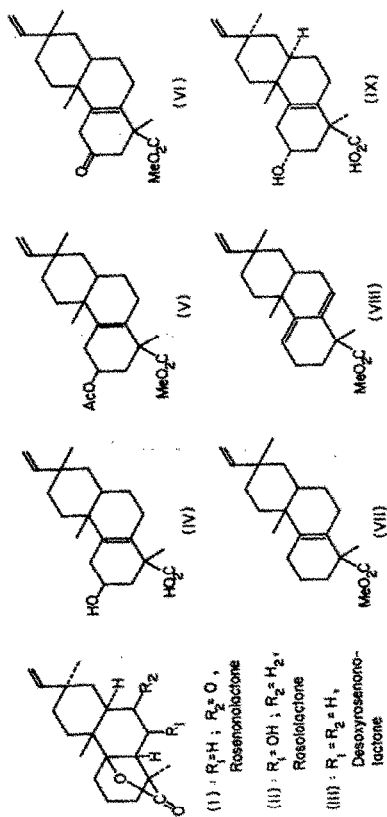
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The structures and absolute stereochemistry of the diterpenoid lactones (I-III) of Trichothecium roseum have recently been confirmed¹. During these studies a minor** acidic constituent of the fermentation was isolated. The structure and stereochemistry of this new metabolite, isorosenolic acid, m.p. 193°, $[\alpha]_D^{20}$, have now been examined and the expression (IV) derived for the new acid.

* Diterpenoids V

** The best yield was 4 mg/litre of culture medium; in later runs this fell to <0.5 mg/litre



Analytical and mass spectral data established the formula $C_{20}H_{30}O_3$ (Found: † C, 75.40; H, 9.30; M, 318; $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50; M, 318). The functional features were revealed in the infrared spectrum as hydroxyl ($3400, 1020\text{ cm}^{-1}$) carboxylic acid (1695 cm^{-1}) and vinyl ($3070, 907\text{ cm}^{-1}$) groupings. The ultraviolet spectrum exhibited olefinic absorption at $203\text{ m}\mu$ ($\epsilon 6000$).

Catalytic hydrogenation ($H_2/Pd/C$; 10%) in ethanolic solution confirmed the tricyclic framework when first a dihydro acid m.p. 184° ($\epsilon 210; 1400$; absence of vinyl grouping at 907 cm^{-1}) and on further reduction a tetrahydro acid m.p. 230° (transparent above $200\text{ m}\mu$) could be isolated.

Isorosenolic acid formed a liquid ester acetate $C_{23}H_{36}O_4$ (V) $[\alpha]_D^{20}$ whose n.m.r. spectrum (60 mc; Table 1) revealed a close correspondence in the chemical shifts of appropriate protons when compared with the spectrum of rosololactone (II) (Table 1). The secondary nature of the hydroxyl group

Table 1: n.m.r. data (60 m.c.) of methyl isorosenolate acetate (V) and rosololactone (II) (δ from T.M.S. = 0) in $CDCl_3$

	$\begin{array}{c} H \\ \diagdown \\ C = CH_2 \end{array}$	$J^* \text{ cis}$	$J \text{ trans}$	$\begin{array}{c} H & H \\ \diagdown & / \\ C = & C \\ / & \diagdown \\ H & H \end{array}$	$J \text{ trans}$
V	5.84	10	17.5	4.90	17.5
II	5.82	10	17.5	4.90	17.5

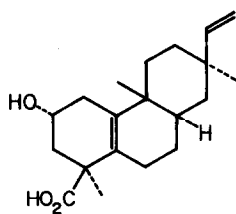
	$\begin{array}{c} H \\ \diagdown \\ C = C \\ / \\ H \end{array}$	$J \text{ cis}$	$\begin{array}{c} \diagdown \\ CH_3 \\ \diagup \\ CO \end{array}$
V	4.87	10	1.28
II	4.88	10	1.28

† Satisfactory analytical data were obtained for all new compounds--only the first set of these is included.

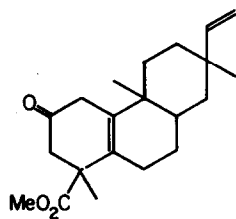
infrared from the n.m.r. spectrum was confirmed by Chromium (VI) oxidation of the acid followed by esterification and isolation of a keto ester (VI) m.p. 136°; ν 1705 cm^{-1} and 1730 cm^{-1} . Reduction of the latter via mercaptal formation and treatment with Raney nickel, now gave an ester, VII, identical with the rosadiene ester previously obtained² from desoxyrosenonolactone (III).

Correlation of isorosenolic acid with rosane series was also made by pyrolysis of the ester acetate (V) to the heteroannular diene (VIII) identical with the compound obtained³ from rosolololactone (II). The failure of isorosenolic acid to lactonise suggested that the carboxylic acid and the secondary hydroxyl group were on opposite faces of the molecule, given that heteroannular diene formation located the alcoholic function at C₁ or C₂.

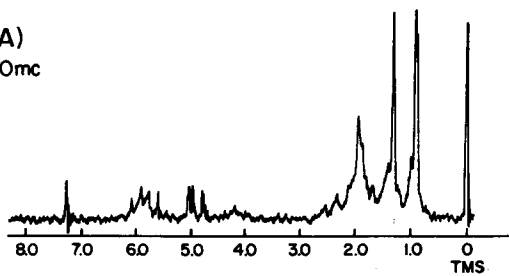
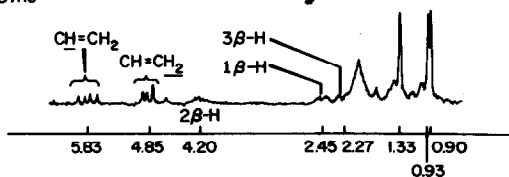
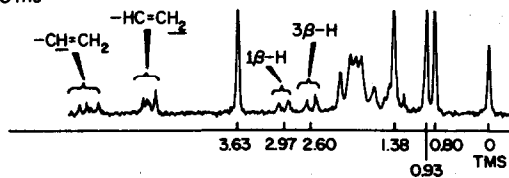
Confirmation of structure and stereochemistry (IV) now followed from measurement of n.m.r. spectra using double and triple irradiation. The 60 m.c. spectrum of IV (Fig. 1A) shows a broad resonance at $\delta = 6.06$ (CO₂H and OH) while the AEX pattern of the vinyl group appears at $\delta = 5.83$ and 4.85 (see Table 1). The width (25 c.p.s.) of the resonance at $\delta = 4.2$ (CHOH) suggested that this proton was coupled to at least two axial neighbours. The 100 m.c. spectrum with double resonance⁴ (Fig. 1B) shows that in fact that hydroxyl group can only be located at C-2 since the proton at C₂ is axially oriented and coupled to two axial as well as one or two equatorial protons. Thus observation of the resonance of the C-2 protons while irradiating at the frequency of the proton at $\delta = 2.45$ reveals a broad triplet (2 axial, 1 equatorial coupling). The same pattern is observed when the proton at $\delta = 2.27$ is irradiating with the second r.f. field. However, the C-2 proton signal reduces to a broad singlet (axial-equatorial coupling \rightarrow broadening) when it is irradiated with a frequency midway between the two



(A) and (B)



(C)

(A)
60mcIrr. between
1 α -H and 3 α -HIrr. 2 β -H
and 1 α -HIrr. 2 β -H
and 3 α -HIrr. 3 β -H(B)
100mc
Irr. 1 β -H(C)
100mc

C₁ and C₃ axial proton resonances. When the axial C₁, C₂ and C₃ protons resonance frequencies were used to irradiate the C₁ and C₃ β (equatorial) protons, these could be observed (right hand side Fig. 1B) as singlets at $\delta = 2.45$ and $\delta = 2.27$. The unequal chemical shift of the 1β and 3β protons indicates the 5:10 location of the tetra-substituted double bond.

In the 100 m.c. spectrum of the keto-ester (Fig. 1C) we find that the broad resonance at $\delta = 4.2$ is absent ($> \underline{\text{CHOH}} \rightarrow \text{C} = \text{O}$) and the C₁ and C₃ equatorial protons have moved downfield (C₁-H 2.45 → 2.97 and C₃-H 2.27 → 2.60).

Structure (IV) embodies the unique rationale of this evidence and taken in conjunction with the correlation with rosololactone¹ allows the absolute stereochemistry (IX) to be written for isorosenolic acid.

Acknowledgements

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References

1. A. I. Scott, S. A. Sutherland, D. W. Young, L. Guglielmetti, D. Arigoni, G. Ferguson and G. A. Sim, Proc. Chem. Soc., 000 (1964).
2. D. W. Young, Ph. D. Thesis, Glasgow, 1963.
3. A. Harris, A. Robertson and W. B. Whalley, J. Chem. Soc., 1799 (1958).
4. N. S. Hacca, M. E. Wolff and R. Kwok; J. Am. Chem. Soc., **84**, 4976 (1962).