to the combination of such allyl radicals with NF_2. Overall, after correction for the decay of CH_3CHFCH_2 radicals, our experiments are in excellent agreement with the analysis of the N_2F_4–propylene system through consideration of addition and abstraction of F atoms as the primary reactions with propylene.

The measured terminal/central ratio of 1.35 is in sharp contrast with the ratio of about 15 found for thermal hydrogen atom addition to propylene.[5] The former indicates a very moderate preference for reaction away from the CH_3 group of propylene, consistent with the characterization of atomic fluorine as a rather indiscriminate, highly reactive species. Relatively small directional preferences have also been found for ^{18}F atom addition to asymmetric fluoroethylenes.[3] Evaluation of the origin of this CH_3 orientation effect requires additional experiments with other asymmetric olefins, which depend in turn upon satisfactory resolution of the difficulty caused by the reactivity of HI with other substituted olefins under our experimental conditions.

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(9) This research was supported by AEC Contract No. AT-(04-3)-34, Agreement No. 126.

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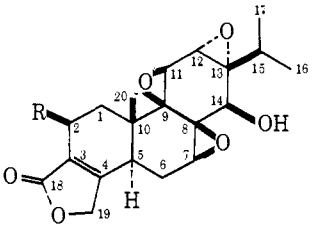
Triptolide and Tripdiolide, Novel Antileukemic Diterpenoid Triepoxides from *Tripterygium wilfordii*[1-3]

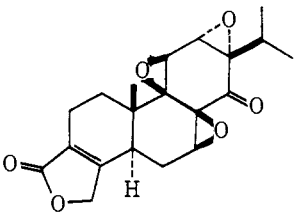
Sir:

The antileukemic activity of *Maytenus ovatus* and its active principle, maytansine,[2] prompted us to investigate other plants of the Celastraceae family. An alcoholic extract of *Tripterygium wilfordii* Hook F.[4] was found to show significant activity *in vivo* against the L-1210 and P-388 leukemias in the mouse and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB).[5] We report herein the isolation and structural elucidation of triptolide (**1**) and tripdiolide (**2**), two novel antileukemic[6] diterpenoid triepoxides. These compounds and the companion cytotoxic ketone triptonide (**3**) appear to be the first reported natural products containing the 18(4→3) *abeo*-abietane skeleton and the first recognized diterpenoid triepoxides.

Fractionation of an ethanol extract, guided by assay against KB, L-1210, and P-388, revealed that the inhibitory activity was concentrated in the ethyl acetate layer of an ethyl acetate–water partition. Chromatography of the ethyl acetate soluble material on silica gel yielded a KB cytotoxic fraction (A) on elution with chloroform and an *in vivo* active fraction with 5% methanol in chloroform. The latter fraction was further chromatographed on SilicAR CC-7 to yield triptolide-enriched fraction (B) on elution with chloroform and tripdiolide-enriched fraction (C) with 1% methanol in chloroform. Further chromatography of fraction B on SilicAR CC-7 gave triptolide (**1**) (0.001%): $C_{20}H_{24}O_6$; mp 226–227°; $[\alpha]^{25}D$ −154° (*c* 0.369, CH_2Cl_2); uv max (EtOH) 218 nm (ε 14,000); ir (KBr) 2.89, 5.64, 5.93, 8.05, 8.52 μ; mass spectrum *m/e* 360.1600 (M^+) (calcd, 360.1573); nmr ($CDCl_3$) τ 9.03 (3 H, d, $J_{15,16}$ = 7 Hz, 16-CH_3), 8.90 (3 H, d, $J_{15,17}$ = 7 Hz, 17-CH_3), 8.78 (3 H, s, 20-CH_3), 7.17 (1 H, d, *J* = 11 Hz, OH), 6.54 (1 H, d, $J_{6\alpha,7}$ = 5 Hz, 7-H), 6.48 (1 H, d of d, *J* = 11 Hz, $J_{12,14}$ = 1 Hz, 14-H), 6.40 (1 H, d of d, $J_{11,12}$ = 3 Hz, $J_{12,14}$ = 1 Hz, 12-H), 6.00 (1 H, d, $J_{11,12}$ = 3 Hz, 11-H), 5.22 (2 H, m, 19-CH_2).



1, R = H
2, R = OH



3

The structure and stereochemistry of triptolide (**1**) were determined by direct X-ray crystallographic analysis. Crystals of triptolide are monoclinic with space group $P2_1$ and a = 13.420 (1), b = 6.256 (1), and c = 11.593 (1) Å, and β = 118.09 (1)°. There are two molecules in the unit cell. The intensities of 1071 reflections, measured by counter diffractometry with monochromatic Cu Kα radiation, were used in the structure analysis. The phase problem was solved by the use of symbolic addition[7] and tangent formula refinement procedures,[8] and the atomic parameters were refined by block-diagonal least-squares methods to give R = 0.078. Isotropic thermal parameters were assumed for all atoms. Of the 24 hydrogen atoms 14 were identified from a final difference electron-density function and included with fixed parameters in the refinement process.

A consistent indication of the correct absolute configuration is provided both by the results of Hamilton's R-factor ratio test[9] and by the measurement of intensity differences in selected Friedel pairs of reflections.[10] For parameters corresponding to each of the two possible enantiomeric structures the values of R are 0.0785 and 0.0783, when the anomalous dispersion terms[11] for oxygen are taken into account, suggesting a significant distinction between the two configurations at the 90% confidence level. For the 13 structure amplitudes where the magnitude of the difference between $F(hkl)$ and $F(\bar{h}\bar{k}\bar{l})$ is calculated to be greatest, the observed

(1) Tumor Inhibitors. LXXIV. Part LXXIII is ref 2.

(2) S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger, and R. F. Bryan, *J. Amer. Chem. Soc.*, **94**, 1354 (1972).

(3) Supported by grants from the National Cancer Institute (CA-11718 and CA-11760) and American Cancer Society (T-275 and T-541), and a contract with Chemotherapy, National Cancer Institute (NIH 71-2099).

(4) Roots were collected in Taiwan in Aug 1971. We thank Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture, Beltsville, Md., for supplying the plant material. We gratefully acknowledge also the supply of a cytotoxic alkaloid fraction by Dr. M. Beroza, U. S. Department of Agriculture, Beltsville, Md.

(5) Cytotoxicity and *in vitro* activity were assayed as in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(6) Triptolide and tripdiolide showed significant antileukemic activity against the L-1210 and P-388 leukemias at the 0.1 mg/kg level, and cytotoxicity (ED_{50}) against KB cell culture at 10^{-3}–10^{-4} μg/ml.

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differences all have the same sign as expected although the actual numerical agreement is indifferent. A view of the molecular structure as found in the crystal is shown in Figure 1.

Chromatography of fraction A on SilicAR CC-7 followed by preparative tlc on silica gel and SilicAR CC-7 gave triptonide (**3**) (0.001%): $C_{20}H_{22}O_6$; mp 251–252°; $[\alpha]^{25}D$ −175° (*c* 0.148, CH_2Cl_2); uv max (EtOH) 218 nm (ε 12,000); ir (KBr) 5.63, 5.81, 5.92 μ; mass spectrum (CI) *m/e* 359.1474 $(M + 1)^+$ (calcd, 359.1495); nmr ($CDCl_3$) τ 9.01 (3 H, d, $J_{15,16}$ = 7 Hz, 16-CH_3), 8.92 (3 H, d, $J_{15,17}$ = 7 Hz, 17-CH_3), 8.82 (3 H, s, 20-CH_3), 6.50 (1 H, d, $J_{6\alpha,7}$ = 5 Hz, 7-H), 6.08, 5.86 (d, $J_{11,12}$ = 3 Hz, 11,12-H), 5.19 (2 H, m, 19-CH_2). The characteristics of triptonide, including the molecular weight and carbonyl ir absorption at 5.81 μ, supported the 14-dehydrotriptolide structure **3**. The structural assignment was confirmed by oxidation of triptolide (**1**) with CrO_3–pyridine complex in dichloromethane, whereupon triptonide was obtained in excellent yield.

Chromatography of fraction C on SilicAR CC-7 followed by preparative tlc on alumina gave tripdiolide (**2**) (0.001%): $C_{20}H_{24}O_7$; mp 210–211°; $[\alpha]^{25}D$ −138° (*c* 0.139, CH_2Cl_2); uv max 217 nm (ε 11,000); ir (KBr) 2.78, 2.88, 5.63, 5.93 μ; mass spectrum (CI) *m/e* 377.1621 $(M + 1)^+$ (calcd, 377.1600); nmr ($CDCl_3$) τ 8.59 (3 H, s, 20-CH_3), 8.24 (1 H, bs, 2-OH), 5.29 (1 H, m, 2-H), 5.14 (1 H, t, *J* = 1.5 Hz, 19-CH_2). Characterization of tripdiolide as a 2-hydroxytriptolide was based on its empirical formula and nmr spectrum. Furthermore, the marked downfield shift of the C-20 methyl group signal of **2**, relative to **1** and **3**, indicated a 1,3-diaxial interaction of the hydroxyl group and the angular methyl group,[12,13] and supported the 2β-hydroxytriptolide structure **2**.

The postulated structure **2** was confirmed by direct X-ray analysis. Crystals of tripdiolide are isostructural with those of triptolide. The space group is $P2_1$ with *a* = 13.680 (2), *b* = 6.253 (1), and *c* = 11.864 (1) Å, and β = 119.05 (1)°. Monochromatic Mo Kα radiation was used to measure the intensities of 1472 reflections significantly above background. The structure was solved by the direct attribution of the phases for the reflections in triptolide to the corresponding reflections in tripdiolide, and the additional oxygen atom was clearly revealed from a difference electron-density function calculated in this way. The structure was refined in the same way as for triptolide to *R* = 0.082, with the contributions from 15 identifiable hydrogen atoms included.

The diepoxide functionality has been shown to confer tumor-inhibitory activity upon certain classes of acyclic synthetic compounds[14,15] as well as the naturally occurring cyclohexane diepoxide, crotepoxide.[16] The α,β-unsaturated lactone function has been shown to be important for the tumor-inhibitory activity of several classes of terpenoids.[17] Investigations are in progress

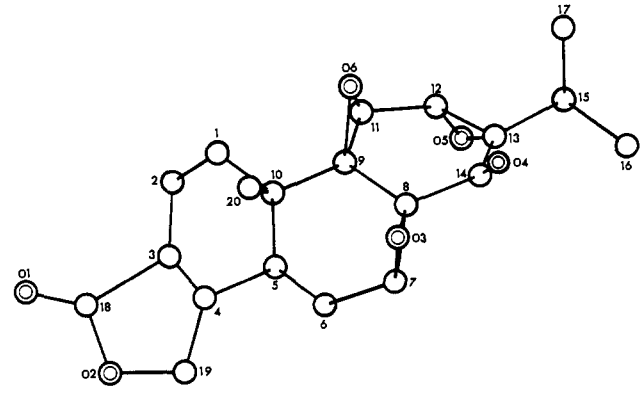

Figure 1. View of the molecule of triptolide as seen in projection down the *b* axis of the unit cell and showing the numbering scheme adopted. Atoms are carbon unless otherwise indicated. The molecule is shown in the presumed absolute configuration with respect to a right-handed axial system.

to determine the potential significance of the epoxide and unsaturated lactone functions, and of intramolecular catalysis by the hydroxyl groups of the selective alkylation of biological macromolecules by these functions, in relation to the tumor-inhibitory activity of the triptolides.

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Cholesteric Solids

Sir:

We report iridescent substances that combine the optical properties of cholesteric liquid crystals with the mechanical properties of solids at room temperature. These compositions are glasses that provide the full visible spectrum of cholesteric colors and remain unchanged for years.[1]

Cholesteryl hydrogen phthalate is the key ingredient for these compositions. This compound melts at 165° to an isotropic liquid that supercools easily and becomes birefringent (cholesteric focal conic) at 100°. There is no indication of devitrification in 1 year at ambient laboratory temperatures. Crystal growth is slow between 80 and 100° and negligible at higher and lower temperatures. A maximum in the nucleation rate of a supercooled cholesteric has been described,[5] but since the maximum in this instance coincides with a phase change we ascribe slow crystal growth above 100° to the absence of ordered material. Slow rates at low temperature are due to high viscosity. The temperature dependence of the limiting high-shear

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