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THE STEREOCHEMISTRY OF ATISINE. A CHEMICAL CORRELATION OF ATISINE AND THE RESIN ACIDS.

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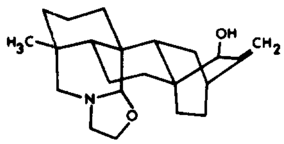
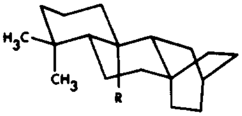
ApSimon, Edwards and Howe have reported(1) the degradation of atisine (I) to the aldehyde II. We now wish to report the transformation of the aldehyde II into the corresponding hydrocarbon, III, and the preparation of IV, the enantiomer of III, from abieta-6,8-diene (V).

This sequence represents the first correlation of the *tetracarbocyclic* ring system in atisine with the resin acids and further confirms the mirror-image relationship(2) at C-11, C-12 and C-13 (phenanthrene numbering, see VII) in these two series. ApSimon and Edwards have previously reported(3) the transformation of atisine and podocarpic acid to a common tricyclic enantiomeric intermediate in which the asymmetry at C-13 has been destroyed. Vorbrueggen and Djerassi have established(4) the absolute configuration of the *Garrya* group of alkaloids, which had previously been correlated with the atisine group via a common tricyclic intermediate(5).

The starting material for the synthesis of IV was the Diels-Alder adduct formed from abieta-6,8-diene (V) and maleic anhydride. It is known (6) that both levopimaric acid

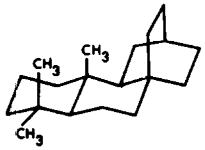


I

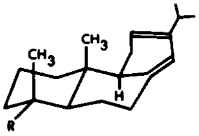


II R = CHO

III R = CH_3

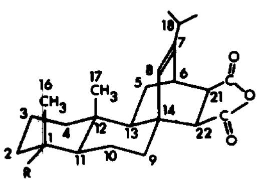


IV



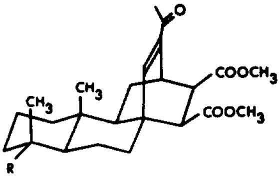
V R = CH_3

VI R = COOH



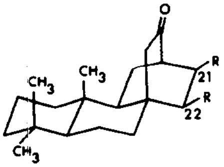
VII R = COOH

VIII R = CH_3



IX R = $COOCH_3$

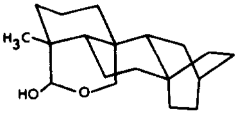
X R = CH_3



XI R = $COOCH_3$

XII R = H, $\Delta^{21(22)}$

XIII R = H



XIV

(VI) and abietic acid react with maleic anhydride to yield maleopimaric acid (VII), the stereochemistry of which is known to be that depicted by VII (7,8,9). The formation of maleopimaric acid from abietic acid presumably involves a prior thermal isomerization to levopimaric acid(10). Similarly, reaction of crude abieta-7,14(9)-diene (prepared by Wolff-Kishner decomposition of the semicarbazone of abieta-7,14(9)-dien-15-al(11) in diethylene glycol-KOH at 200°) with maleic anhydride in p-cymene at 160° for eight hours gave, after chromatography over silica gel, the adduct VIII, m.p. 110-111°, (C,77.79,77.65; H,8.94,9.14%), $\gamma_{max.}^{CCl_4}$ 1850 and 1770 cm^{-1} (anhydride). The structure VIII was assigned on the basis of: (a) analogy with maleopimaric acid (VII); (b) analysis of the nuclear magnetic resonance spectrum, which we have already discussed(7); (c) the further transformations reported below.

The anhydride VIII was transformed to the corresponding cis-dimethyl ester, m.p. 124-125°, $\gamma_{max.}^{CCl_4}$ 1730 cm^{-1}, by the action of methanolic diazomethane or by treatment of the disodium salt with dimethyl sulfate. Ruzicka and St. Kaufman have described(12) the transformation of the trimethyl ester corresponding to VII to the unsaturated ketone IX by the action of ozone in acetic acid. Similarly, the diester of VIII was treated with ozone in acetic acid at room temperature until the absorbance at 240 mμ had reached a maximum. The ketone X, m.p. 167-168° (C,72.18; H,8.61%). $[\alpha]_D$ + 39° (c 0.21 in MeOH), $\lambda_{max.}^{EtOH}$ 240 mμ (logϵ =3.98), $\nu_{max.}^{CCl_4}$ 1745,1730,1667,1610 cm^{-1}, was isolated in 35% yield via the Girard derivative. The nuclear magnetic resonance spectrum, which is in agreement with the assigned structure, has been reported(7).

Oxidation of the ketone X with H_2O_2-BF_3(13) gave, after aqueous work-up, a 50% yield of the keto diester XI, m.p. 179-180° (C,70.55; H,8.70%, $\lambda_{max.}^{EtOH}$ 284 mμ (log ε =1.45), $\gamma_{max.}^{CCl_4}$ 1750,1728,1410 ($-\overset{\overset{O}{\|}}{C}-C\underline{H}_2-$) cm^{-1}, RD in methanol (c 0.19): $[\alpha]_{589}$ - 51°, $[\alpha]_{298}$ - 940° (trough), $[\alpha]_{265}$ + 281° (peak). The NMR spectrum ($CDCl_3$) showed the C-methyl protons at 9.17τ (6H) and 9.12τ (3H) and the ester methyl protons at 6.35 and 6.38τ (6H). The keto diester XI was saponified with potassium hydroxide in aqueous methanol and the resulting crude diacid (m.p. 290-305°, $\gamma_{max.}^{nujol}$ 1710 cm^{-1}) was subjected to oxidative bisdecarboxylation with lead tetraacetate in pyridine (14) at 45° to give the keto olefin XII, m.p. 123-124° (molecular weight 272, mass spectrum). In agreement with structure XII the infrared spectrum showed a single carbonyl band (1719 cm^{-1}) and a band at 1407 cm^{-1} indicative of a methylene group adjacent to the carbonyl group. The nuclear magnetic resonance spectrum showed the presence of two olefinic protons (3.81τ and 3.95τ) as the AB part of an ABX system ($J_{AB}\sim$8cps, $J_{AX}\sim$2cps, $J_{BX}\sim$6cps). The allylic proton (X) appeared as a poorly resolved octet at 6.98τ, and the C-methyl protons absorbed at 9.11τ(6H) and 9.17τ(3H). The mass spectrum of XII showed an intense peak at m/e 230, corresponding to the loss of ketene ("retro-Diels-Alder reaction"(15)) from the molecular ion.

Hydrogenation of XII over palladium-charcoal yielded the saturated ketone XIII, m.p. 126-127° (molecular weight

274, mass spec.), $\gamma^{CCl_4}_{max.}$ 1717,1404 cm^{-1} ($-CO-CH_2-$), RD in methanol (c 0.12): $[\alpha]_{589}$ + 41°, $[\alpha]_{312}$ + 360 (peak), $[\alpha]_{283}$ + 29° (trough), $[\alpha]_{250}$ + 310°. Wolff-Kishner reduction (Barton modification(16)) of the ketone XIII gave the hydrocarbon IV as glistening white needles (from ethanol) which melted at 86-86.5° (C,87.40,87.71; H,12.32,12.25; molecular weight 260, mass spec.). The nuclear magnetic resonance spectrum ($CDCl_3$) showed broad methine and methylene absorption from 8.05-9.0 τ and three C-methyl peaks at 9.05, 9.15 and 9.18 τ. The hydrocarbon IV showed a plain positive rotatory dispersion curve (in methanol, c 0.073), $[\alpha]_{589}$ + 36°, $[\alpha]_{500}$ + 49°, $[\alpha]_{400}$ + 77°, $[\alpha]_{350}$+120°.[1]

The aldehyde II was prepared from the hemiacetal XIV, obtained by degradation of atisine(1)[2], by the method previously reported(1). Wolff-Kishner reduction of the aldehyde II (sodium, diethylene glycol, hydrazine, 220-235° for 3 days) gave the hydrocarbon III, identical in melting point, infrared spectrum and mass spectrum with the hydrocarbon IV. The hydrocarbon III showed a plain negative rotatory dispersion curve, enantiomorphic with that obtained from the hydrocarbon IV, thus confirming(2,3,4) the mirror-image relationship of these two series.

Acknowledgements: We wish to thank the National Research Council of Canada for financial support, and Dr.

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[1] Very recently(17) Dr. L.H. Zalkow has informed us that they have completed the synthesis of the hydrocarbon IV by a different route.

[2] We wish to extend our most sincere thanks to Dr. O.E. Edwards who generously supplied a sample of the hemiacetal XIV which enabled us to complete this phase of the project.

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