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A NEW DITERPENOID WITH LABDANE SKELETON

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In spite of the close botanical analogy with Marrubium vulgare, Marrubium incanum (collected in Jugoslavia) contains only a very small quantity of marrubiin.

After chromatography of the acetone extract on silica-gel we isolated, together with small quantities of other diterpenoids and several flavanoids, a crystalline substance (I), $C_{20}H_{26}O_5$, m.p. 172-173°, $[\alpha]_D^{20}$ +48° (c=1% in CH_3OH), λ_{max} 212 mμ (ε=10300), 290 mμ (ε<100), as the most abundant terpenoid constituent. The physical properties of I correspond with those described by L. A. Salei, D.P. Popa and G. V. Lazur'evskiy (1) for peregrinine, a compound isolated from Marrubium peregrinum, which possesses the same molecular formula but whose structure has not been elucidated.

The spectral features of compound I were: ν_{max} (KBr) 3597 (strong), 3560 (weak), 1780 (strong, broad), 1710 (weak), 875 cm^{-1}; N.M.R. 0,95 (3H, d, J=6 cps, $>CH-C\underline{H}_3$), 1,04 (3H, s, $\geqslant C-C\underline{H}_3$), 1,28 (3H, s, $\geqslant C-C\underline{H}_3$), 4,70 (1H, poorly resolved triplet, multiplet width 10-12 cps), 6,23, 7,21, 7,32 (1H, m, H_β, H_α, H_α furan); M.S. 346, 328, 302, 95, 94, 81.

The I.R., N.M.R., U.V. and Mass spectra indicated the presence of a β-substituted furan in the molecule, and this was also confirmed by a purple colour in the Ehrlich test.

The hydroxyl group of compound I resists both acetylation with acetic anhydride in pyridine at room temperature and oxidation with chromic anhydride in pyridine. Oxidation of I with Jones reagent (2) at 0° over a period of 2h yielded the maleic anhydride (II), $C_{20}H_{24}O_7$, m.p. 193-196°, ν_{max} ($CHCl_3$) 3600, 1838, 1779, 1761, 1710, 1639 cm^{-1}.

The presence of a γ-lactone group in I, indicated by an absorption band at

1780 in the infrared, was confirmed by alkaline hydrolysis of I to the hydroxy-acid (III), $C_{20}H_{28}O_6$, m.p. 137-140°, $[\alpha]_D^{20}$ +5,5°, ν_{max} (nujol) 1730, 1681 cm^{-1}. The latter on heating with anhydrous solvents reformed the original lactone (I). Treatment of III with diazomethane yielded the corresponding methyl ester (IV), $C_{20}H_{30}O_6$, m.p. 121-122°, $[\alpha]_D^{20}$ -12,8°. Oxidation of IV with chromic anhydride in pyridine gave the oily ketomethylester (V), $C_{21}H_{28}O_6$, ν_{max} ($CHCl_3$) 1733 (sh), 1710, 878 cm^{-1} which lacked resonance in the N.M.R. attributable to a proton of the type $\underline{H}-\overset{|}{\underset{|}{C}}-OH$.

The presence of a ketone in the molecule of I was indicated by its U.V. and I.R. spectra and by the reaction of I with thiosemicarbazide which yielded the corresponding thiosemicarbazone (λ_{max} 268 mμ).

Reduction of I with lithium aluminium hydride in tetrahydrofuran gave a crystalline tetrol (VI), $C_{20}H_{32}O_5$, m.p. 195-197°, $[\alpha]_D^{20}$ +20,9°; N.M.R. (C_5D_5N) 3,72 (1H, m, $>C\underline{H}-O-$), 4,53 and 4,77 (2H, AB quartet, J=12 cps, $-C\underline{H}_2-OH$), 4,69 (1H, m, $>C\underline{H}-O-$).

Acetylation of VI with acetic anhydride and pyridine on a steam bath yielded an oily triacetate (VII), $C_{26}H_{38}O_8$; N.M.R. 4,53 (1H, poorly resolved triplet, $>C\underline{H}-OCOCH_3$), 4,44 and 4,56 (2H, AB quartet, J=12 cps, $-C\underline{H}_2-OCOCH_3$), 5,38 (1H, m, $>C\underline{H}-OCOCH_3$), 2,04, 2,06, 2,10 (3H, s, $C\underline{H}_3-COO-$).

Treatment of I with sodium borohydride in methanol afforded the dihydroxylactone (VIII), $C_{20}H_{28}O_5$, m.p. 130-132°, $[\alpha]_D^{20}$ +11°, ν_{max} (KBr) 3595, 1748, 877 cm^{-1}; N.M.R. 3,69 (1H, m, $>C\underline{H}-OH$), 4,92 (1H, m, $>C\underline{H}-O-$).

This dihydroxylactone (VIII) with chromic anhydride in pyridine reformed I.

VIII was converted to a monoacetate (IX) by acetylation at room temperature, $C_{22}H_{30}O_6$, m.p. 132-133°, $[\alpha]_D^{20}$ -2°, ν_{max} (KBr) 3480, 1770, 1738, 873 cm^{-1}, N.M.R. 2,15 (3H, s, $C\underline{H}_3-COO-$), 4,85 (1H, m, $>C\underline{H}-O-$), 5,07 (1H, poorly resolved triplet, $>C\underline{H}-O-$).

On treatment of the dihydroxylactone (VIII) with toluene-p-sulphonylchloride and pyridine at room temperature we isolated the corresponding sulphonate derivative (XI), $C_{26}H_{34}O_7S$, m.p. 145-147°, $[\alpha]_D^{20}$ +2°. The latter, when heated in refluxing pyridine, eliminated toluene-p-sulphonic acid to give the unsaturated compound (X), $C_{20}H_{26}O_4$, m.p. 126-128°, $[\alpha]_D^{20}$ +16°, ν_{max} (nujol) 3570, 1748, 878 cm^{-1}, U.V. λ_{max} 210 mμ (ε=9700); N.M.R. 0,96 (3H, d, J=6 cps, $>CH-C\underline{H}_3$), 1,07 (3H, s, $\geq C-C\underline{H}_3$), 1,32 (3H, s, $\geq C-C\underline{H}_3$), 4,74 (1H, m, $>C\underline{H}-O-$), 5,77 (2H, d, J=2,5 cps, $-C\underline{H}=C\underline{H}-$), 6,28, 7,25, 7,37 (1H, m, H_β, H_α, H_α furan).

The catalytic reduction of X with Pd/C in dioxane yielded, among other products, a dihydroderivative (XIII), identical with marrubiin (XIII), the stereochemistry of which has recently been stated (3).

The results given above allow the formulation of I as a keto-marrubiin. The presence of the ketone group at position 3 was established on the basis of the following results.

Ozonolysis of I afforded a ketodilactone (XIV), $C_{17}H_{22}O_5$, m.p. 218-220°, $[\alpha]_D^{20}$ +24,8°, λ_{max} 290 mμ (ε<90), ν_{max} ($CHCl_3$) 1776, 1764, 1712 cm^{-1}.

Bromination of XIV in acetic acid yielded the corresponding α-bromoketone (XV), $C_{17}H_{21}O_5Br$, m.p. 206-208°, $[\alpha]_D^{20}$ -76°, λ_{max} 318 mμ (ε<50), ν_{max} ($CHCl_3$) 1790, 1777, 1718 cm^{-1}; N.M.R. 0,94 (3H, s, $\geq C\text{-}C\underline{H}_3$), 1,00 (3H, d, J=6 cps, $>CH\text{-}C\underline{H}_3$), 1,82 (3H, s, $\geq C\text{-}C\underline{H}_3$), 4,73 (1H, poorly resolved triplet, $>C\underline{H}\text{-}O\text{-}$), 4,47 (1H, four lines, $J_{AX}+J_{BX}$=15 cps, $Br\text{-}\overset{|}{C}\underline{H}\text{-}CH_2\text{-}$). The axial configuration of the bromine atom in XV arises from the comparison of the U.V. and I.R. spectra of XV with those of the unsubstituted ketone (XIV) (bathochromic shift 28 mμ, unchanged I.R. carbonyl absorption).

Compound I with N sodium hydroxide in refluxing $CH_3OH\text{-}H_2O$ afforded the norketone (XVI), $C_{19}H_{28}O_4$, m.p. 146-148°, $[\alpha]_D^{20}$ -13°, ν_{max} ($CHCl_3$) 1705 cm^{-1}; N.M.R. 0,99 (3H, d, J=6cps, $>CH\text{-}C\underline{H}_3$), 1,08 (3H, d, J=6 cps, $>CH\text{-}C\underline{H}_3$), 1,37 (3H, s, $\geq C\text{-}C\underline{H}_3$), 4,00 (1H, m, $>C\underline{H}\text{-}OH$), 6,29, 7,21, 7,33 (1H, m, H_β, H_α, H_α furan). Oxidation of XVI with chromic anhydride in pyridine yielded the corresponding diketone (XVII), $C_{19}H_{26}O_4$, m.p. 120-122°, $[\alpha]_D^{20}$ -11°, ν_{max} ($CHCl_3$) 1713 cm^{-1}. The monodehydration of XVI with $POCl_3$ in pyridine at room temperature followed by acid isomerization of the double bond gave the oily α,β-unsaturated ketone, (XVIII), $C_{19}H_{26}O_3$, λ_{max} 252 mμ (ε=13800), ν_{max} ($CHCl_3$) 1660, 1606 cm^{-1}; N.M.R. 1,03 (3H, d, J=6 cps, $>CH\text{-}C\underline{H}_3$), 1,30 (3H, s, $\geq C\text{-}C\underline{H}_3$), 1,81 (3H, s, $>C=\overset{|}{C}\text{-}C\underline{H}_3$), 6,31, 7,23, 7,37 (1H, m, H_β, H_α, H_α furan).

The minor constituents of Marrubium incanum are at present under investigation.

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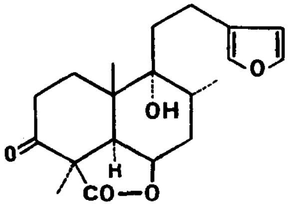

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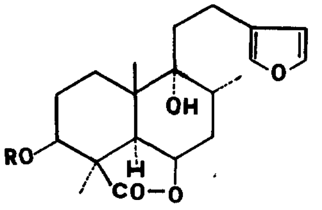
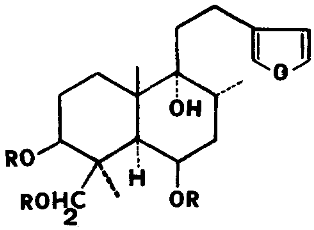


VIII R=H

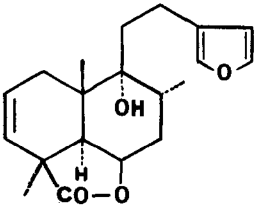
IX $R=COCH_3$

XI $R=O_2S-C_6H_4-CH_3$



VI R=H

VII $R=COCH_3$



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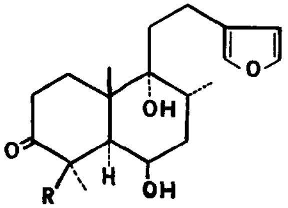
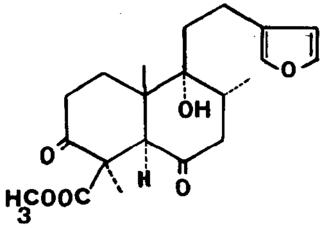


III R=COOH

IV $R=COOCH_3$

XVI R=H



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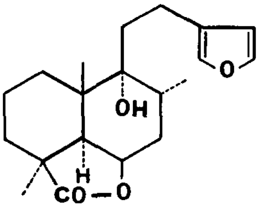

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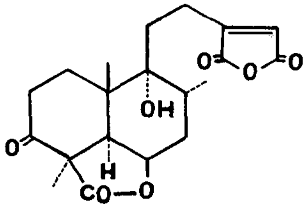

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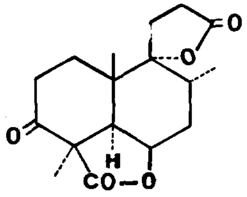

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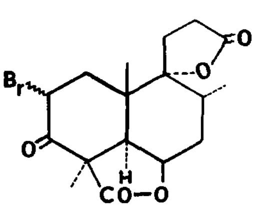

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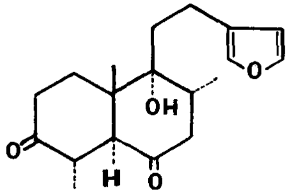
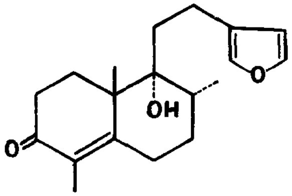


XVII



XVIII