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AN APPROACH TO THE TOTAL SYNTHESIS OF THE DITERPENOID ALKALOIDS.

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In view of the increasing current interest in synthetic approaches to the diterpenoid alkaloids[1] and to the tetracyclic diterpenes[2], we should like to present some of our own preliminary results in this field. Our overall aim is the development of a general approach to the mirror image forms of alkaloids of the atisine (I) and veatchine (II) groups, using podocarpic acid as a source material. The present communication describes some model experiments in the 2,4a-ethanodecahydronaphthalene series, designed to test the applicability of our synthetic scheme to the B/C/D ring system of the atisine group.

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d). R.A.Bell and R.E.Ireland, <u>Tet. Letters</u>, 269 (1963);
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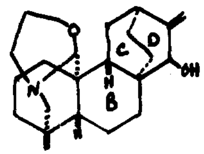
2a). R.B.Turner and K.H.Ganshirt, <u>Tet. Letters</u>, 231 (1961);
b). R.A.Bell, R.E.Ireland and R.A.Partyka, <u>J. Org. Chem.</u>, **27**, 3741 (1962).



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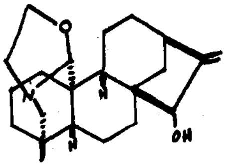

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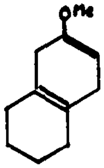

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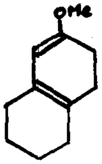

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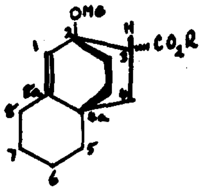

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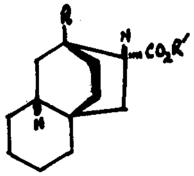

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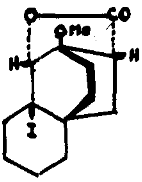

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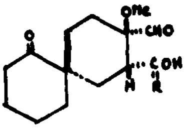

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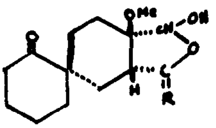

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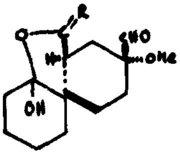

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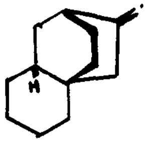

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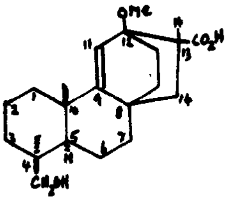

XII

Note:- In all these compounds the 2,4a-ethano bridge has been arbitrarily assigned the β-configuration to simplify nomenclature.

Reduction with lithium in liquid ammonia of 6-methoxytetralin gave the hexalin (III) in good yield[3]. Isomerisation with potassamide in liquid ammonia, under carefully controlled conditions gave a mixture, which was shown by gas-liquid chromatography (polyethylene glycol-adipate stationary phase) to contain 67% of the conjugated hexalin (IV), $\lambda_{max.}$ 270 mμ ($\epsilon_{max.}$ 4900), 12% of unchanged III, and 21% of 6-methoxytetralin (cf. Birch et al.[4]). Reaction of this mixture with ethyl acrylate under nitrogen at 170°, and for fifteen hours gave, after hydrolysis and chromatography on silica gel, a good yield of the tricyclic acid, $\Delta^{1(8a)}$-2-methoxy-2,4a-ethanooctahydronaphthalene-3(α)-carboxylic acid (V, R= H), m.p. 104-105°. Reduction of this product over Adams catalyst proceeded rapidly to give the saturated acid (VI, R= OMe, R'= H), m.p. 115°. The methyl esters of both acids were homogeneous to thin-layer and to gas-liquid chromatography. The formation of a single product on hydrogenation is good evidence for the endo-configuration of the carboxyl group in V (R= H), and for the β-configuration of the 8a-hydrogen in VI, since models show that only in the endo-acid is there any significant hindrance to approach of the catalyst to either face, and that in that configuration the catalyst must approach from the β-face.

Further evidence for the structure of the adduct (V, R= H) is as follows. Treatment with iodine-potassium iodide in aqueous sodium bicarbonate solution, under mild conditions gave, in good yield, the iodo-γ-lactone (VII), m.p. 89-90°, confirming the endo-configuration of the carboxyl group. This together with the nuclear magnetic resonance spectrum of the adduct*, which clearly showed a single vinyl proton at 4.4 ppm, unambiguously places the double bond in the 1(8a)-position as shown. Oxidation of the acid

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[3] A.L.Wilds and N.A.Nelson, J.Amer. Chem. Soc., 75, 5360 (1953).

[4] A.J.Birch, E.M.A.Shoukry and F.Stansfield, J. Chem. Soc., 5376 (1961).

* We are indebted for the measurement of this spectrum to Mr. E.G.Cummins of Perkin Elmer Ltd.

with osmium tetroxide, followed by treatment with lead tetraacetate gave the spiro/$\overline{\ }$5,5$\underline{\ }$7undecanone-γ-lactol (IX, R= O), m.p. 160-162°, which in methylene dichloride solution exhibited bands in the infrared at 1700 cm^{-1} (ketone) and 1730 cm^{-1} (aldehyde), suggestive of an equilibrium between the lactol and the aldehydo-acid (VIII, R= O). Reduction of the methyl ester of the acid (V, R= Me) to the corresponding primary alcohol, followed by a similar oxidative degradative procedure gave a product which was not purified, but which in carbon tetrachloride solution exhibited bands at 1710 cm^{-1} (ketone) and 1735 cm^{-1} (aldehyde). The ketone band was much stronger than the aldehyde band in this spectrum, presumably indicating an equilibrium between the hemiacetal (IX, R= H_2) and the hydroxy-aldehyde (VIII, R= H_2). These data provided strong evidence for the structure V, but the alternative structure X (R= O and H_2) and the corresponding open chain forms remained to be considered as possibilities for the oxidation products, and hence the 4(α)-position for the carboxyl group in the Diels-Alder adduct.

The hydroxy-ester (VI, R= OH, R'= Me) showed evidence of intramolecular hydrogen-bonding in the infrared, in dilute carbon tetrachloride solution/$\overline{\ }$ $\nu_{max.}$ 3593 cm^{-1} (w., OH unbonded) and 3532 cm^{-1} (s., OH bonded)$\underline{\ }$7, a phenomenon which requires a vicinal arrangement of the hydroxyl and methoxycarbonyl groups*. Further, the pK values† for the hydroxy-acid (VI, R= OH, R'= H), 5.45, and for the methoxy acid (VI, R= OMe, R'= H), 5.90, were suggestive of hydrogen-bonding in the anion of the hydroxy-acid. These data enable the structure V (R= H) to be assigned with confidence to the Diels-Alder adduct.

Treatment of the methoxy-acid (VI, R= OMe, R' = H) with boron trichloride in methylene dichloride[5], followed by solution in

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[5] W.Gerrard and M.F.Lappert, J. Chem. Soc., 1486 (1952).

* We are indebted to Mr. F.E.Dunstan of B.I.P.Chemicals Ltd., for recording this spectrum on a Unicam SP 100.

† We thank Dr. W.I.Stephen of this Department for these measurements.

methanol resulted in a good yield of the hydroxy-ester (VI, R= OH, R'= Me), which on hydrolysis furnished the corresponding acid (VI, R= OH, R'= H), m.p.85-87°. Prolonged treatment of the ester with phosphorus pentachloride in dry ether[1h.], followed by hydrolysis gave the chloro-acid (VI, R= Cl, R'= H), m.p. 155-156°, which on reduction with lithium in *tert*-butanol and tetrahydrofuran[6] gave, in good yield, 8a(β)-2,4a-ethanodecahydronaphthalene-3(α)-carboxylic acid (VI, R=R'= H), m.p. 107-108°.

Reduction of the acid to the corresponding primary alcohol with lithium aluminium hydride, followed by formation of the trifluoroacetate, and pyrolysis at 400° [7] yielded 3-methylene-8a(β)-2,4a-ethanodecahydronaphthalene (XI), b.p.170°/0.3 mm. (bath temperature), $\nu_{max.}$ 885 cm^{-1}(s.), 1670 cm^{-1} (m.) and 1750 cm-1 (w.) (exocyclic methylene). This product was homogeneous to gas-liquid chromatography, with the exception of a minute trace of impurity of shorter retention time. The introduction of the hydroxyl group required for the atisine structure (I) has recently been accomplished by standard procedures in a system closely related to ours[1d.].

The procedures outlined in this communication have been applied to suitable podocarpane derivatives to give the tetracyclic acid (XII), m.p. 205-206°, in impractically poor yield[8]. Further work on this, and on the closely related 8,12(β)-ethenopodocarpane derivatives, which are key intermediates in our synthetic scheme, is in hand.

One of us (A.A.O.), thanks the Government of Iraq for the award of a Scholarship.

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[6] R.DeVries and S.Winstein, *J. Amer. Chem. Soc.*, **82**, 5383 (1960).

[7] C.H.DePuy and R.W.King, *J. Amer. Chem. Soc.*, **83**, 2151 (1961).

[8] K.Crowshaw and N.A.J.Rogers, Unpublished work.