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REVISED STRUCTURE OF ARISTOLACTONE

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On the acceptance that aristolactone, $C_{15}H_{20}O_2$ - a crystalline sesquiterpenoid isolable from Aristolochia reticulata and A. serpentaria[1,2] - was not an α,β-unsaturated lactone[2] and that the derived methyl dihydrooxoaristate suffered isomerisation under the influence of base to yield an α,β-unsaturated ketone[2], the results of an n.m.r. spectral study of aristolactone and certain of its derivatives taken in conjunction with a chemical degradation affording a mixture of stereoisomeric germacranes were recently interpreted[3] in terms of structure I for aristolactone. This formulation, however, had several unsatisfactory facets. Thus it was necessary to invoke a base-catalysed transannular hydride shift in order to rationalise the formation of the γ-keto ester, methyl oxoaristate, through the action of methoxide ion on aristolactone; to postulate an hydrogenolysis and relactonisation lacking precise analogy in order to account for the products

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[1] J. B. Stenlake and W. D. Williams, J. Pharm. Pharmacol., 6, 1005 (1954).

[2] J. W. Steele, J. B. Stenlake and W. D. Williams, J. Chem. Soc., 3289 (1959).

[3] M. Martin-Smith, S. J. Smith, J. B. Stenlake and W. D. Williams, Tetrahedron Letters, No. 24, 1639 (1963).

obtained by the action of lithium aluminium hydride on aristolactone and its acid rearrangement product, isoaristolactone; to assign barely resolved absorption at ca. 3.2 τ (intensity one proton) in the n.m.r. spectra of aristolactone and isoaristolactone to the proton on C-8; and to invoke non-bonded interactions in order to explain the observed absence of conjugation between the 7,8 and isopropylene double bonds.

Further work designed to explain these inconsistencies has now demonstrated that aristolactone is in fact an α,β-unsaturated lactone in accordance with the 3.27 τ absorption in the n.m.r. spectrum - despite the apparent anomalies in the ultraviolet[2] and infrared[3] (measured in carbon tetrachloride solution) spectra of the parent compound and its derivatives, and despite the failure of aristolactone to react in the Legal test or to form an ammonia adduct[4]. Thus complete ozonolysis of both aristolactone and isoaristolactone in methylene dichloride at 0°C, catalytic hydrogenation of the products and treatment with alkaline peroxide, in each case afforded a quantity of carbon dioxide consistent with the generation of 2 moles of α-keto acids per mole of lactone. Further, study of the course of hydrogenation of dihydroisoaristolactone (the known first intermediate in the catalytic reduction of aristolactone[2,5]) by means of ultraviolet spectroscopy showed the appearance of absorption at λ max 218 mμ (ε = 6,550) after the uptake of ca. 1 mole of hydrogen. Although the product was not obtained in crystalline form, this experiment makes it apparent that aristolactone presents a situation strictly analogous to that observed with gafrinin[6] in which strong end absorption arising from a

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[4] Cf. K. F. W. Hansen, Ber., 64, 67 (1931); L. Ruzicka and P. Pieth, Helv. Chim. Acta, 14, 1090 (1931).

[5] J. B. Stenlake and W. D. Williams, J. Chem. Soc., 2114 (1955).

[6] J. P. de Villiers, J. Chem. Soc., 2049 (1961).

trisubstituted double bond superimposed upon the absorption from an α,β-unsaturated γ-lactone gives an apparent absorption maximum at 205 mμ.

Re-examination of the action of aqueous base on methyl oxoaristate and its dihydro derivative, methyl dihydrooxoaristate, has revealed that the latter compound does not suffer isomerisation into an α,β-unsaturated ketone as previously reported[2]. Moreover the n.m.r. spectrum of isooxoaristic acid, the α,β-unsaturated ketone formed by treatment of methyl oxoaristate with aqueous base and which is isolable in high yield only by carefully controlled acidification of the reaction mixture (NaH_2PO_4 proving satisfactory), shows but a single vinylic proton absorbing at 4.92 τ (apparent triplet, J = 7 c.p.s.) and absorptions at 8.13 τ, 8.18 τ and 8.43 τ each of intensity 3 protons attributable to three vinyl methyl groups. The generation of the two new vinyl methyl groups absorbing at low field in passing from methyl oxoaristate to isooxoaristic acid together with the disappearance of infrared absorption in the 3080 cm^{-1} and 900 cm^{-1} regions clearly indicates the conversion of the isopropylene group of methyl oxoaristate into an isopropylidene function lying in conjugation with the keto group in isooxoaristic acid. This evidence, therefore, when taken in conjunction with the earlier studies[2,3,5], permits partial formulation of aristolactone as II, methyl oxoaristate (the formation of which from an α,β-unsaturated lactone is unexceptional[7]) as III and isooxoaristic acid as IV, with the position of the remaining trisubstituted double bond[3] confined to the 3,4 or 4,5 positions. That it occupies the 3,4 position in accordance with biogenetic expectations follows from the discovery of a series of very mild acid-catalysed transannular ring closures to decalin derivatives suffered by methyl oxoaristate and its immediate derivatives,

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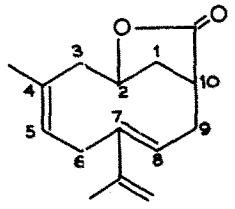
[7] W. D. Paist, E. R. Blout, F. C. Uhle and R. C. Elderfield, J. Org. Chem., 6, 273 (1941); L. C. McKean and F. S. Spring, J. Chem. Soc., 1989 (1954).



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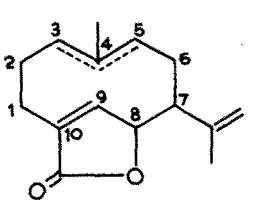

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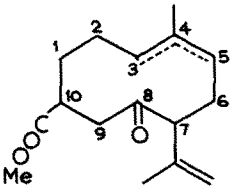

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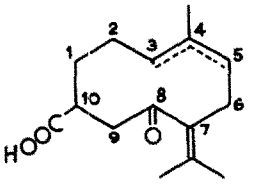

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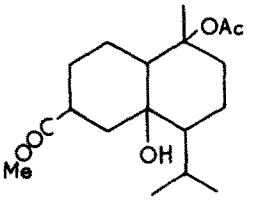

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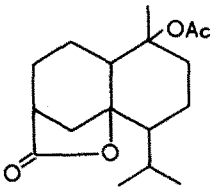

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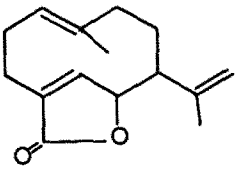

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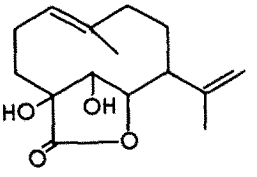

VIII

including isooxoaristic acid.

Thus, treatment of methyl oxoaristate with cold glacial acetic acid for 48 hours afforded net addition of the elements of acetic acid[8] to give a compound $C_{18}H_{28}O_5$ m.p. 85°, $[\alpha]_D$ -49° (EtOH) showing two ester carbonyl peaks and a hydroxyl peak in the infrared. The n.m.r. spectrum showed the

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[8] Compare the cyclisation of pyrethrosin under the influence of chromic oxide in acetic acid - D. H. R. Barton and P. de Mayo, J. Chem. Soc., 150 (1957).

presence of two vinylic protons (absorptions at 5.08 τ and 5.2 τ each showing fine splitting and each of intensity 1 proton), the absence of protons on carbon atoms bearing oxygen functions and the absence of methyl groups attached to carbon atoms bearing hydrogen. Catalytic reduction of this compound (hydrogen uptake 1 mole) afforded the same derivative, $C_{18}H_{30}O_5$, m.p. 91°C, $[\alpha]_D$ -74° (EtOH) as was formed by the action of cold glacial acetic acid on methyl dihydrooxoaristate. The n.m.r. spectrum of this saturated compound showed, as to be expected, the complete absence of vinylic protons and the presence of two doublets at 9.02 τ and 9.10 τ each of intensity 3 protons and J = 7 c.p.s. arising from the isopropyl methyl groups. Formulation of the compound m.p. 91°C as V was confirmed by its conversion into the lactone VI, m.p. 166-167°C, through the action of acetic anhydride and by its conversion into cadalene (identical with a specimen formed from oil of cade by the method of Henderson and Robertson[9]) through the action of lithium aluminium hydride followed by selenium dehydrogenation. Lactone VI also results from the direct action of acetic anhydride on methyl dihydrooxoaristate.

That the acid catalysed isomerisation of aristolactone into isoaristolactone must involve the 3,4 double bond follows from the non-identity of the so called "dihydroneoaristolactone" and "dihydroisoneoaristolactone"[3] obtained from these two compounds by the action of lithium aluminium hydride (a reaction clearly involving a 1,4 addition to the α,β-unsaturated lactone system, the enolate anion so formed preventing reduction beyond the saturated lactone stage) since positional isomerism of the 9,10 double bond would necessitate a common intermediate in the reductions, and from the formation of the same two isomeric saturated lactones on catalytic hydrogenation of both "dihydroneoaristolactone" and "dihydroisoneoaristolactone"

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[9] G. G. Henderson and J. M. Robertson, J. Chem. Soc., 2811 (1926).

(hydrogen uptake 2 moles in each case) which proves that the stereochemistry at C-7 and C-8 must be the same in both aristolactone and isoaristolactone.

Biogenetic considerations suggest that aristolactone is correctly portrayed as VII and the n.m.r. absorptions of the protons of the methyl group attached to C-4 at 8.52 τ in aristolactone and at 8.41 τ in isoaristolactone would not be inconsistent with a change in configuration of the 3,4 double bond from trans to cis in going from aristolactone to isoaristolactone since the protons of a methyl group on a trans double bond generally absorb at slightly higher field than the protons of methyl groups attached to cis double bonds[10]. Final determination of this point, like the establishment of the stereochemistry at C-7 and C-8, however, will be established by X-ray analysis when systematic nomenclature for the aristolactone series will become possible. The non-identity of the stereoisomers obtained from the catalytic reductions of "dihydroneoaristolactone" and "dihydroisoneoaristolactone" with the isomeric hexahydroisoaristolactones[3] shows that reduction of the 9,10 double bond by lithium aluminium hydride and by catalytic hydrogenation generate opposite stereochemistry at C-10.

Attempts to confirm structure VII for aristolactone by application of the Cope rearrangement[11] led only to insoluble resins.

That the diol formed by the action of potassium permanganate on aristolactone[2] results from attack on the double bond conjugated with the lactone carbonyl group and so is correctly portrayed as VIII follows from its n.m.r. spectrum which shows the absence of absorption in the 3.2 τ region.

Acknowledgements: The authors wish to express their gratitude to Dr. P. Bladon who kindly determined n.m.r. spectra. S.J.S. acknowledges tenure of a Todd Research Trust Fund Grant.

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[10] R. B. Bates and D. M. Gale, J. Amer. Chem. Soc., 82, 5749 (1960).

[11] A. C. Cope and E. M. Hardy, J. Amer. Chem. Soc., 62, 441 (1940); S. J. Rhoads, Chapter 11 in "Molecular Rearrangements", P. de Mayo, editor, John Wiley and Sons, Inc., New York, 1963.