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THE STRUCTURE OF ARISTOLACTONE

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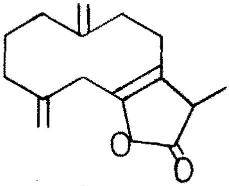
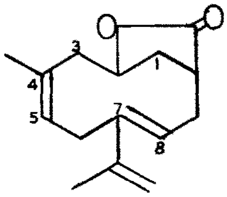
In an earlier publication[1] structure I was tentatively assigned to aristolactone, $C_{15}H_{20}O_2$, a crystalline sesquiterpenoid occurring in Aristolochia reticulata and A. serpentaria. Nuclear magnetic resonance studies have now shown this structure to be untenable but, when taken in conjunction with new chemical evidence, support structure II for aristolactone.



I



II

Reaction of the mixture of diols resulting from the lithium aluminium hydride reduction of hexahydroisoaristolactone* with excess of methane-

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

* The present work has shown that the material previously designated isohexahydroisoaristolactone is in fact a mixture of 2 diastereoisomers, correctly to be regarded as diastereoisomeric hexahydroisoaristolactones. Derivatives obtained from this material without any fractionation will also be diastereoisomeric mixtures.

sulphonyl chloride, followed by treatment with lithium aluminium hydride, afforded a mixture of hydrocarbons resolvable into 3 components by gas liquid chromatography employing a 50 metre capillary column with polypropylene glycol as stationary phase. On catalytic hydrogenation the mixed hydrocarbons (consisting of 2 olefins and one saturated hydrocarbon - *vide infra*) gave rise to a mixture of 3 diastereoisomeric germacranes, each of which corresponded in g.l.c. retention time to one of the 3 diastereoisomers present in a sample of synthetic germacrane (confirmed after admixture of the two specimens). Thus aristolactone, unlike the calarane derivative aristolone[2], which occurs in *Aristolochia debilis*[3], is derived from the germacrane skeleton.

Comparison of the n.m.r. spectra of isoaristolactone[1] and methyl oxoaristate[1] with those of their dihydro derivatives shows the conversion of an isopropenyl group into an isopropyl group. Thus absorptions representing overlapping doublets which appear as barely resolved triplets with intensity 3 protons at 8.14 τ and 8.33 τ respectively in the former compounds are replaced by a pair of superposed doublets of total intensity 6 protons and $J = 6$ c.p.s. at 8.94 τ and 9.11 τ respectively in the dihydro compounds, whilst the complex absorption in the 5 τ region is reduced in intensity by 2 protons in passing from the parent compounds to the hydrogenated derivatives. The methyl group of the isopropenyl function in aristolactone itself is seen as a barely resolved apparent triplet, intensity 3 protons at 8.17 τ. The presence of an isopropenyl function necessitates that the lactonic carbonyl group of aristolactone and its derivatives arise from one of the ring methyl groups of germacrane, and the infrared absorption frequencies

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[2] G. Buchi, F. Greuter and T. Tokoroyama, *Tetrahedron Letters*, No. 18, 827 (1962).

[3] F. Furukawa and N. Soma, *J. Pharm. Soc., Japan*, **81**, 559 (1961).

(measured in carbon tetrachloride solution) of this function at 1769 cm^{-1} in hexahydroisoaristolactone, at 1764 cm^{-1} in dihydroisoaristolactone and at 1765 cm^{-1} in both aristolactone and isoaristolactone show it to belong to a saturated γ-lactone in all four compounds. That the lactone is derived from a secondary alcohol follows from the conversion of aristolactone into the keto-ester, methyl oxoaristate[1,4], and from the n.m.r. absorption at 5.2 τ in the fully saturated hexahydroisoaristolactone having intensity one proton. This absorption which appears as a triplet ($J = 8$ c.p.s.) is also discernible in the n.m.r. spectra of aristolactone, isoaristolactone and dihydroisoaristolactone but merges with vinylic proton absorption.

The n.m.r. spectra of aristolactone, isoaristolactone and methyl oxoaristate show the absence of any methyl group attached to carbon bearing hydrogen and so the second ring methyl group of germacrane must form part of a trisubstituted double bond system in all three compounds. Absorption from this methyl group appears as barely resolved peaks of intensity 3 protons at 8.52 τ in aristolactone, 8.48 τ in methyl oxoaristate, 8.52 τ in methyl dihydrooxoaristate, 8.41 τ in isoaristolactone and 8.40 τ in dihydroisoaristolactone.

Both aristolactone and isoaristolactone show absorption attributable to four vinylic protons (three in the 5 τ region and one at ca 3.2 τ) out of a total absorption of 20 protons thus showing the third double bond to be trisubstituted. Since the planar nature of the γ-lactone ring necessitates true conjugation between the carbonyl group and any double bond α,β to it, the absence of ultraviolet absorption attributable to conjugation[1,4] places this last double bond in association with the isopropenyl group where true conjugation is not achieved due to the operation of non-bonded interactions. That it is the double bond associated with the isopropenyl group which is

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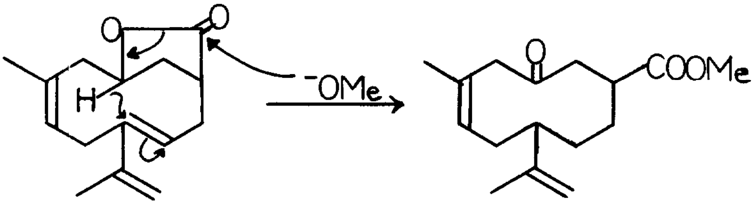
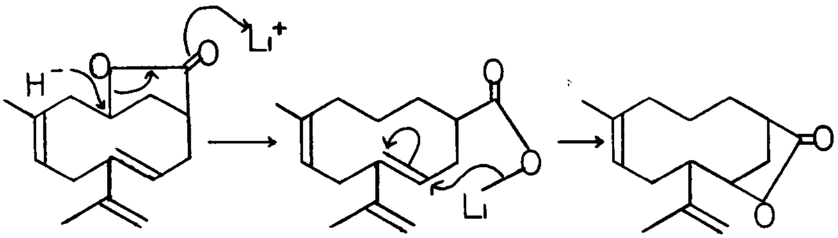
[4] J. B. Stenlake and W. D. Williams, J. Chem. Soc., 2114 (1955).

involved in the conversion of aristolactone into methyl oxoaristate is shown by the retention of the absorption attributable to the methyl group on the other trisubstituted double bond in both methyl oxoaristate and methyl dihydrooxoaristate. The base catalysed isomerisations of these last two compounds into α,β unsaturated ketones[1] place this double bond initially β,γ to the ketonic group and hence β,γ to the lactone acyloxy oxygen in aristolactone. The formation of methyl oxoaristate then finds a ready rationalisation on the basis of a transannular hydride shift as in III.



III

The placing of the double bond bearing the isopropenyl group as shown in II and not in the alternative position follows from a reinvestigation of the so-called "oxoaristaldehyde" and "isooxoaristaldehyde"[1]. Nuclear magnetic resonance studies clearly showed that these compounds are not aldehydes as previously suggested[1] whilst the absence of hydroxyl absorption in the infrared together with carbonyl absorption frequencies at 1765 cm^{-1} (measured in carbon tetrachloride solution) show them to be γ-lactones which are now termed dihydroneoaristolactone and dihydroisoneoaristolactone, in agreement with their lower oxidation state as evidenced by the presence of 3 vinylic protons in their n.m.r. spectra. Their formation (like that of methyl oxoaristate) is accompanied by loss of the proton absorption at <u>ca</u> 3.2 τ which is now assignable to the proton on C-8, the shift to low field being ascribable to interaction with the carbonyl group of the lactone as evidenced from inspection of models. The n.m.r. spectra of both dihydroneoaristolactone and dihydroisoneoaristolactone show a doublet (intensity 1 proton, J = 8 c.p.s.) at *ca* 6τ replacing the triplet at 5.2τ in the aristolactone series, thus indicating a change in the lactone ring system. The formation of dihydroneoaristolactone is rationalised in IV. The isoaristolactone series differ from the aristolactone series by shift of the 4:5 double bond into the 3:4 position. The formation of dihydroisoaristolactone on catalytic hydrogenation of aristolactone has several analogies[5]. The inability of isoaristolactone to undergo a transformation analogous to the formation of methyl oxoaristate from aristolactone apparently lies in the changes induced in the geometry of the 10-membered ring which serve to prevent the transannular hydride shift.



IV

The formation of the mixture of the two germacrenes and one germacrane isomer from the mixed methanesulphonates derived from the diols obtained from hexahydroisoaristolactone can be rationalised on the basis of a

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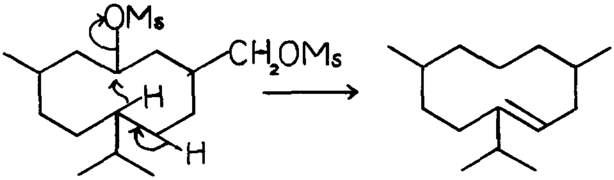
[5] D. S. Irvine, W. Laurie, A. S. McNab and F. S. Spring, *J. Chem. Soc.*, 2029 (1956); R. Howe and F. J. McQuillin, *ibid.*, 2670 (1956); J. B. Bream, D. C. Eaton and H. B. Henbest, *ibid.*, 1974 (1957).

transannular hydride shift occurring as an alternative reaction to hydrogenolysis (V), a phenomenon having analogy in the alternative



V

elimination reactions observed on complex metal hydride reductions of certain steroidal sulphonate esters[6]. Satisfactory account of the observed number of hydrocarbons is given if one of the diastereoisomeric dimethanesulphonates gives rise solely to one diastereoisomeric germacrene whilst the other affords the second germacrene and the germacrane. The two diastereoisomeric germacrenes like the two diastereoisomeric hexahydroisoaristolactones arise from stereoisomerism at C-4, the hydrogenation of the 7:8 double bond in aristolactone being stereospecific owing to the influence of the lactone ring, as can be seen on inspection of models. In the germacranes stereoisomerism is possible at both C-4 and C-7 thus accounting for the 3 diastereoisomers.

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[6] G. Bancroft, Y. M. Y. Haddad and G. H. R. Summers, J. Chem. Soc., 3295 (1961).