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CYCLIZATION OF METHYL TRANS, TRANS-FARNESATE EMPLOYING CATION EXCHANGE RESINS

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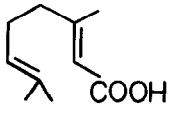
The biogenetically patterned cyclization of polyenes[1] and polyene epoxides[2] with acid catalysts has recently attracted great interest in view of the biosynthesis of sterols and triterpenoids[3] from squalene 2, 3-oxide.

We wish to report that ion exchange resins can also affect stereospecific cyclizations of C_{15}-polyenes to give mono- and bicyclic products in yields exceeding those obtained by the common Lewis acid catalysts.

A trial cyclization of geranic acid (1) by treatment with Amberlite IR-120 in dioxane at 70° for 12 hours gave α-cyclogeranic acid (2),[4,5] m. p. 103-105° in 70% yield; cyclization in 3:1 v/v water:dioxane afforded in 63% yield the acyclic 7-hydroxygeranic acid (3),[4] b. p., 112° (0.2 mm Hg); NMR ($CDCl_3$) 1.20 (6H, s, C_7-methyls), 2.14 (3H, d, J 1.4 cps, C_3-Me), 5.70 ppm (1H, m, C_2-H). The trans compound 3 was contaminated with a small amount of the cis isomer 3a as evidenced from the NMR peak at 1.90 ppm (d, J 1.8 cps, C_3-Me).



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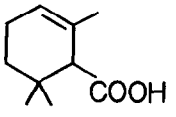

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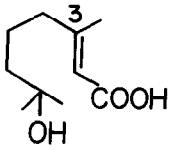

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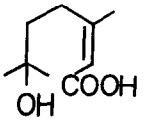

3a

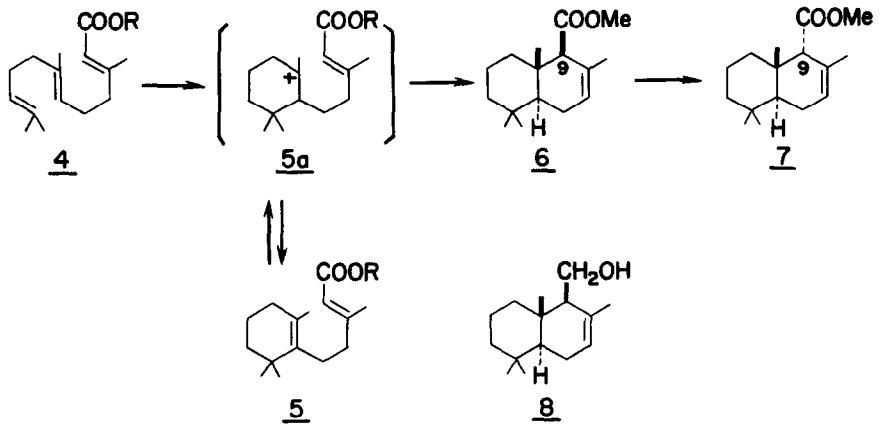

TABLE I. Cyclization of methyl farnesate 4 (R=Me)

200 mg of 5/1 g of XE-100 2 ml of solvent

Solvent	°C	hr	recovery of 4 (%)	product yields (%) 5	6	7
AcOH	40	24	17	59	11	3
	60	24	3	13	42	15
	80	12	5	19	31	15
	80	24	2	3	34	29
dioxane	80	24	26	49	11	3
blank*	80	24	94	0	0	0

*: in AcOH with no resin.

Cyclization of trans, trans-farnesic acid (4, R=H),[6] purified through its S-benzylthiuronium salt,[7] with IR-120 or Amberlite XE-100 in dioxane at 70° for 12 hours gave the monocyclo product[4] 5 (R=H),[5] m. p. 117-118°, in 30% yield.

On the other hand, cyclization of the methyl ester 4 (R=Me) under the conditions shown in Table I afforded products[4] 5 (R=Me),[5] 6[1] and 7,[1] which were separated by gas chromatography employing SE-30 (20%) or SE-30 (5%) columns, column temperature 180°, injection temperature 270°, carrier gas He, flow rate 71 ml/min.

The structure[4] of methyl monocyclofarnesate (5, R=Me) was established by its identity with the methylation product of monocyclofarnesic acid (5, R=H), while that of bicyclofarnesate 6, m. p. 49-50° was established by its reduction with lithium aluminum hydride to natural drimenol 8,[8] m. p. 93-94°. The NMR spectrum of compound 7, oil, was almost identical with that of bicyclofarnesate 6, the only clear difference being the appearance of 9-H as a broad signal at 2.35 ppm in 7 and 2.81 ppm in 6 (in CCl_4); the IR and MS spectra of 6 and 7 were also very similar. The 9-epibicyclofarnesate structure 7 also received full support from equilibration studies, i.e., a 2:1 equilibrium was attained between 6 and 7 when 40 mg of either compound was warmed at 50°C for 24 hours in 1 ml of DMSO containing 100 mg (10 equiv.) of sodium methoxide.

Treatment of methyl monocyclofarnesate 5 (R=Me) with XE-100 in acetic acid at 60°C for 24 hours gave 5, 6 and 7 in respective yields of 10%, 55% and 20% and no methyl farnesate 4. Furthermore, treatment of methyl bicyclofarnesate 6 with XE-100 or p-Toluene sulfonic acid in acetic acid at 80°C for 12 hours and 24 hours first afforded a mixture of 6 and 7 which was eventually converted into 7; on the other hand, similar treatment of 7 effected no change. This evidence indicates that the resin-catalysed cyclization of methyl farnesate to products 5, 6 and 7 proceeds through the carbonium ion intermediate 5a (R=Me) in a step-wise manner; however, possibility of the co-occurrence of a concerted cyclization to 6 and 7 still cannot be excluded.

The cyclization of squalene and its 2,3-oxide[9] and 2,3-, 22,23-diepoxide[10] with XE-100 was carried out in various solvents (acetic acid, formic acid, acetic anhydride, dioxane, benzene, DMSO, and their mixtures) under different conditions. Although the NMR

and IR spectra indicated the absence of olefinic methyls and trisubstituted double bonds in some of the products, it has not been possible to isolate any cyclization product in amounts sufficient for characterization, excepting the acyclic 3-keto and 3, 22-diketo compounds.

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