The Cyclization of Geranic Acids. Preparation of a Cyclobutanone[1]

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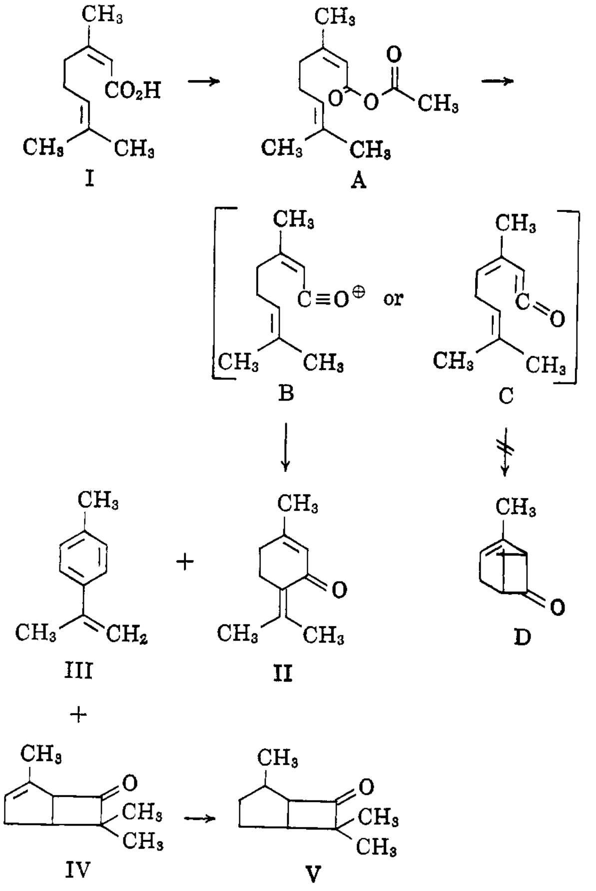
The cyclization of a mixture of *cis-* and *trans*-geranic acids provides piperitenone, *p*-methyl-α-methylstyrene and the cyclobutanone IV. Basic degradation of IV led to α-fencholenic acid (VI). In aqueous sulfuric acid IV was converted to 3-methyl-2-cyclohexenone and the isomeric lactones XII and XIII. In the presence of acid, IV rearranged to the isomeric bicyclic ketone XV. Pyrolysis of IV provided a mixture of piperitenone, isopiperitenone, and the aldehyde XXI.

The monoterpenoid, piperitenone (II), is a minor component[2] of the essential oil *Mentha puleguium var. Villona Benth.* It has been prepared by the dehydrobromination of 1,8-dibromo-*p*-menthan-3-one[3] or in low yield by the condensation of methyl vinyl ketone and mesityl oxide,[4] but the most convenient source of II is the acetic anhydride–sodium acetate cyclization[5] of geranic acids (I). We have repeated the cyclization as reported by Schinz, *et al.*, and the reaction products that were obtained are the subject of this article.

The starting material, a mixture of *cis-* and *trans*-geranic acids (I), is readily available by the silver oxide oxidation[6] of citral. The neutral fraction obtained from the cyclization was obviously a mixture of products, since the infrared spectrum showed carbonyl bands at both 5.62 and 5.97 μ. Separation of the mixture by preparative gas–liquid partition chromatography or by thin layer chromatography showed that at least three products were formed. These products could be more conveniently separated on a large scale by a combined distillation and a semicarbazone-formation sequence (see Experimental Section). One product that was isolated in 26% yield proved to be piperitenone (II). The second component was an aromatic hydrocarbon, $C_{10}H_{12}$. The n.m.r. spectrum of the hydrocarbon showed four aromatic ring protons in A_2B_2 pattern, a methyl group attached to an aromatic ring, a second methyl attached to a double bond, and a vinylidene group. This evidence, along with the characteristic ultraviolet spectrum,[7] established that the hydrocarbon must be *p*-methyl-α-methylstyrene (III). Presumably, this material was formed by the protonation of II followed by dehydration.

The third component of the mixture proved to be of greater interest. Analysis of the material indicated that it was isomeric with piperitenone (II), but the infrared spectrum showed a 5.62-μ ketone carbonyl band and also suggested the presence of a trisubstituted double bond (3.28, 12.49 μ). Since hydrogenation led to only a dihydro derivative that still contained a strained carbonyl group according to its infrared spectrum, the condensation product was most likely a bicyclic compound. If cyclization of geranic acid proceeds *via* ketene intermediate C reacting by a thermal cycloaddition-type mechanism,[8] the most reasonable structure for the product would be chrysanthenone (D).

SCHEME I



This possibility was eliminated by comparison of the infrared spectrum of the ketone with that of chrysanthenone.[9] The high-absorption (ϵ 260) ultraviolet spectrum of the ketone at 310 mμ indicated that the double bond was located β,γ to the carbonyl group with some π-bond overlap.[10] The n.m.r. spectrum of the ketone suggested a dimethyl group adjacent to the carbonyl, a single hydrogen on the carbon atom between the carbonyl and a double bond and confirmed a vinyl methyl group. The mass spectrum of the ketone confirmed the formula $C_{10}H_{14}O$ and also showed very intense peaks at m/e 80 and 70, which were indicative of methylcyclopentadiene and dimethylketene ions. On the basis of these data we propose that *the cyclization of*

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(1) Preliminary communication: J. J. Beereboom, *J. Am. Chem. Soc.*, **85**, 3525 (1963).

(2) Y. R. Naves, *Helv. Chim. Acta*, **25**, 732 (1942).

(3) A. A. Penfold, G. R. Ranage, and J. L. Simonsen, *J. Chem. Soc.*, 1496 (1939).

(4) E. D. Bergmann and P. Bracha, *J. Org. Chem.*, **26**, 4685 (1961), and the references cited therein.

(5) C. Balant, C. A. Vodoz, H. Kappeler, and H. Schinz, *Helv. Chim. Acta*, **34**, 722 (1951).

(6) (a) K. Bernhauer and R. Forster, *J. prakt. Chem.*, **147**, 199 (1936); (b) G. A. Howard and R. Stevens, *J. Chem. Soc.*, 161 (1960).

(7) M. J. Murray and W. F. Galloway, *J. Am. Chem. Soc.*, **70**, 3867 (1948).

(8) J. D. Roberts and C. M. Shartz, *Org. Reactions*, **12**, 1 (1962).

(9) Kindly supplied by Dr. G. Whitman.

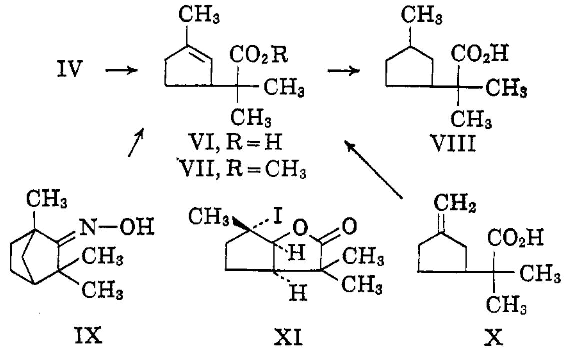
(10) R. C. Cookson and N. F. Wariyar, *J. Chem. Soc.*, 2302 (1956).

geranic acids leads to the cyclobutanone, 2,6,6-trimethylbicyclo[3.2.0]2-hepten-7-one (IV). (See Scheme I.)

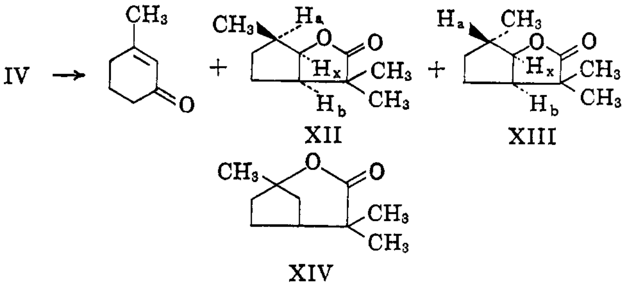
Since both II and IV are stable under the reaction conditions in which they are formed, it would appear likely that they arise from a common intermediate such as B or C. A recent communication[11] reports the cyclization of several unsaturated acids under the same conditions used for the cyclization of geranic acid.

Treatment of IV with refluxing methanolic potassium hydroxide provided α-fencholenic acid (VI) in good yield. The ester VII was prepared from VI by refluxing in methanol containing sulfuric acid or by allowing VI to react with ethereal diazomethane. Dihydrofencholenic acid (VIII) was prepared from VI by catalytic hydrogenation. α-Fencholenic acid has been prepared[12] by the hydrolysis of fenchone oxime (IX) or by rearrangement of γ-fencholenic acid (X).[13]

While Tarbell and Loveless[13b] have established the structure of dihydro-α-fencholenic acid by synthesis, the position of the double bond in α-fencholenic acid (VI) has not been established. This was accomplished by the iodolactonization procedure that has been used by van Tamelen[14] and others[15] to determine the position of the double bond in relation to a carboxylic acid function. Reaction of VI with iodine in aqueous sodium bicarbonate provided the iodolactone XI in good yield. Zinc–acetic acid reduction of XI regenerated α-fencholenic acid. The infrared spectrum of XI showed the presence of a strained lactone absorption band (5.61 μ). The n.m.r. spectrum showed a downfield methyl group singlet (δ 2.20) that was assigned to a CH_3–C–I arrangement. The spectrum also showed a low-field single proton doublet (δ 5.10, J = 5.0 c.p.s.) that can be accounted for by a proton attached to a carbon also holding the lactone oxygen and being coupled with only a single proton on adjacent carbon atoms. This evidence establishes that the iodolactone possesses structure XI and therefore α-fencholenic acid must be VI.



Acidic degradation of the ketone IV in methanolic hydrogen chloride led to methyl α-fencholenate (VII). With aqueous sulfuric acid IV provided a mixture of 3-methyl-2-cyclohexenone and two isomeric lactones, XII and XIII. The structure of the ketone was established by comparison of the infrared and ultraviolet spectra with that of an authentic sample.[16] The mixture of lactones, which behaved as a single component on several columns used for g.l.p.c., was finally separated into two isomeric lactones, $C_{10}H_{16}O_2$, which showed very similar infrared spectra, including a strained lactone band at 5.63 μ. The n.m.r. spectra of the lactones were also very similar and each showed a high-field methyl group split into a doublet by coupling with one adjacent hydrogen (J = 6 c.p.s.). One lactone, XII, also had a low-field single-proton triplet (J = 6 c.p.s.) assignable to the proton attached to the carbon bonding the lactone oxygen. The other lactone, XIII, showed a corresponding low-field absorption that was split into a double doublet (J = 6 c.p.s., 2.5 c.p.s.). Since the fusion of two five-membered rings under the conditions employed requires that the rings be *cis* to each other, the system H_x–C–C–H_b forms a very slight dihedral angle and would be expected to have a reasonably large coupling constant (6 c.p.s.). Similarly, the system H_a–C–C–H_x of XII also forms a dihedral angle close to 0° and should have a large coupling constant. This results in the triplet for H_x noted in the spectrum of XII. In contrast, the dihedral angle formed by H_a–C–C–H_x in XIII is about 120° and leads to the prediction of a small coupling constant for these two protons. This results in H_x of XIII showing up as a pair of doublets with the observed coupling constants.



The mixture of lactones XII and XIII could also be obtained by refluxing α-fencholenic acid (VI) in aqueous acid and steam distilling the product or by refluxing methyl α-fencholenate (VII) in toluene containing p-toluenesulfonic acid monohydrate. In contrast, refluxing VI in toluene with p-toluenesulfonic acid monohydrate provided the δ-lactone XIV.

Refluxing IV in toluene with p-toluenesulfonic acid monohydrate caused a series of rearrangements to the isomeric ketone XV. The infrared spectrum of XV showed that the cyclobutanone ring had been destroyed and replaced by a less strained ketone absorbing at 5.72 μ. The high absorbancy in the ultraviolet spectrum [301 mμ (ϵ 323)] indicated a double bond located β,γ to the carbonyl group. Upon catalytic reduction, XV was converted to only a dihydro derivative XVI; so XV must be bicyclic. The n.m.r. spectrum of XV suggested a *gem*-dimethyl group adjacent to the carbonyl group (δ 1.03, 1.13), a single proton located on a carbon between the carbonyl group and the double bond (δ 3.13), and a vinylidene group (δ 4.92, 5.16). The presence of a vinylidene group was also indicated in the infrared spectrum by absorption at 11.26 μ. The structure of XV was established by sodium periodate–potassium permanganate oxidation[17] to the nonenolizable β-diketone XVII, which showed two carbonyl absorption bands in the infrared spectrum at 5.66 and 5.74 μ. The

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[11] G. P. Chiusoli and G. Agnes, *Proc. Chem. Soc.*, 310 (1963).

[12] G. B. Cockburn, *J. Chem. Soc.*, **75**, 501 (1899); O. Wallach, *Ann.*, **379**, 182 (1911).

[13] (a) F. W. Semmler and K. Bartelt, *Chem. Ber.*, **40**, 432 (1907); (b) D. S. Tarbell and F. C. Loveless, *J. Am. Chem. Soc.*, **80**, 1963 (1958).

[14] E. E. van Tamelen and M. Shamma, *ibid.*, **76**, 2315 (1954).

[15] H. O. House, R. G. Carlson, and H. Babad, *J. Org. Chem.*, **28**, 3359 (1963), and the references cited therein.

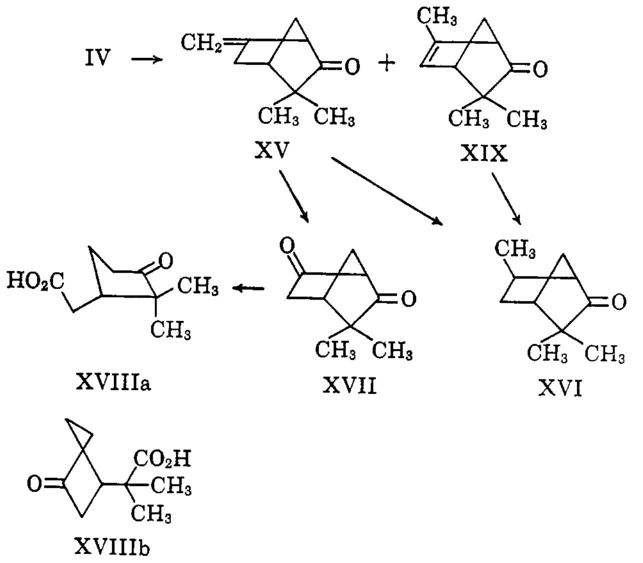
[16] L. I. Smith and J. F. Rouault, *J. Am. Chem. Soc.*, **65**, 631 (1943).

[17] R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

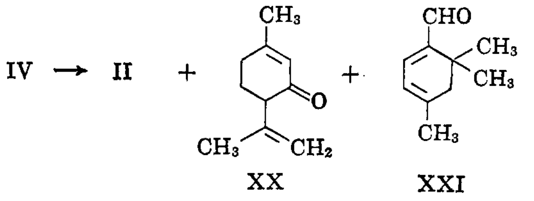
n.m.r. spectrum of XVII still showed the *gem*-dimethyl group and a low-field single-proton absorption due to the proton on the carbon attached to the two carbonyl groups. The remaining protons of XVII showed up in a series of complicated multiple peaks at δ 2.1–3.0. In contrast, XV had a one-proton absorption at δ 1.75 which can be assigned to the bridge proton that does not lie over the carbonyl π-electron cloud. Mild base treatment of XVII generated the expected keto acids XVIIIa or XVIIIb with infrared absorption bands at 5.74 and 5.86 μ.

A minor by-product that was formed in the acidic rearrangement of IV proved to be another isomeric ketone XIX. The n.m.r. spectrum of XIX showed a methyl group attached to a double bond that held one proton. Since hydrogenation gave a dihydro ketone whose infrared spectrum was identical with that of XVI, the structure XIX was assigned to it. (See Scheme II.)

SCHEME II



Pyrolysis of the ketone IV at 340° provided a mixture of isopiperitenone[18] (XX) and piperitenone (II) as the major products. A minor pyrolysis product was the aldehyde XXI. The n.m.r. spectrum of XXI showed three methyl singlets (δ 1.21, 1.21, 1.92), a methylene peak (δ 2.12), two olefin bond protons (δ 6.00, 6.63), and an aldehydic proton (δ 9.44). The structure of XXI was established by comparison to an authentic sample prepared[19] from 3-methylcrotonaldehyde. When the pyrolysis of IV was tried at temperatures above 400°, the products isolated were piperitenone (II) and *m*-xylene. Presumably, the latter was formed by demethylation and decarbonylation of XXI under the strenuous reaction conditions.



Experimental Section

Cyclization of Geranic Acid.—A solution of geranic acid (319 g., 1.9 moles, approximately 70% *trans* and 30% *cis* by g.l.p.c.) and 120 g. of anhydrous sodium acetate in 350 ml. of acetic anhydride was stirred and refluxed for 16 hr. The dark red solution was poured into 2 l. of ice and water and stirred 2 hr. The suspension was extracted several times with ether, and the combined ether layers were repeatedly washed with 5% sodium hydroxide solution and once with water. The combined aqueous washes were acidified and extracted with chloroform. Evaporation of chloroform provided 42 g. of oil that was mostly unreacted geranic acids.

The ether layer above was evaporated and the residue was distilled through a 36-in. spinning-band column at 2 mm. to give two fractions: (A) b.p. 40–43°, and (B) b.p. 118–120°. Fraction B (64 g., 26%) was essentially pure piperitenone (II): 2,4-dinitrophenylhydrazone, m.p. 184–185° (lit.[2] m.p. 184–184.5°). The g.l.p.c. of fraction A (78 g.) showed essentially two peaks with an area ratio of about 10 to 1. A sample of the component present in smaller quantity was collected by preparative g.l.p.c.: $\lambda_{\max}^{\mathrm{CH_3OH}}$ 247, 283, and 294 mμ (ϵ 12,500, 5100, and 2000); $\delta_{\mathrm{CDCl_3}}$ = 2.13 (3H, multiplet), 2.33 (3H, singlet), 5.04 (1H, multiplet), 5.35 (1H, multiplet), 7.15, and 7.33 (4H in an A_2B_2 pattern) p.p.m., which identifies the compound as 4-methyl-α-methyl-styrene (III). From the g.l.p.c. it was estimated that about a 5% yield of III was formed in the reaction. The principal component of fraction A was the bicyclic ketone IV obtained in 28% yield. It was most easily purified by the procedure given below.

Semicarbazone Purification of $C_{10}H_{14}O$ Ketone IV.—To a solution of 45 g. of crude IV in 50 ml. of ethanol was added a solution of 33.5 g. of semicarbazide hydrochloride and 25 g. of sodium acetate in 100 ml. of water and 75 ml. of ethanol. The solution was boiled for 20 min. and then left at room temperature for 16 h. Filtration gave 51 g. of white crystals, m.p. 194–197°. Two recrystallizations from methanol yielded pure material (38 g.), m.p. 199.6–201°.

Anal. Calcd. for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.65; H, 8.28; N, 20.08.

A mixture of 36 g. of the semicarbazone and 57 g. of phthalic anhydride in 100 ml. of water was steam distilled until 300 ml. of distillate had been collected. The distillate was extracted several times with pentane which was dried and evaporated to yield 23.6 g. of pure IV: b.p. 86–88° (20 mm.); $\lambda_{\max}^{\mathrm{CCl_4}}$ 3.28, 5.62, 12.49 μ; $\lambda_{\max}^{\mathrm{CH_3OH}}$ 310 mμ (ϵ 260); $\lambda_{\max}^{\mathrm{isooctane}}$ 312 mμ (ϵ 204), 323 mμ (ϵ 168); $\delta_{\mathrm{CDCl_3}}$ = 1.12 (3H, singlet), 1.19 (3H, singlet), 1.75 (3H, narrow multiplet), 2.55 (3H, complex multiplet), 4.03 (1H, broad multiplet), 5.46 (1H, multiplet) p.p.m. The mass spectrum of IV showed the following peaks in order of decreasing intensities: 80, 79, 106, 70, 41, 42, and 91. In addition, there was a weak molecular ion peak at 150.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.04; H, 9.20.

A 2,4-dinitrophenylhydrazone of IV was formed in the usual manner and recrystallized from ethanol, m.p. 120–122°.

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 57.85; H, 5.75; N, 16.71.

Stability of IV in Acetic Anhydride.—A solution of 1.5 g. of IV, 2 ml. of acetic anhydride, 0.3 ml. of acetic acid, and 600 mg. of sodium acetate was refluxed for 16 hr. The solution was poured into 20 ml. of ice-water, and after stirring several hours, the product was removed by ether extraction. The combined ether layers were washed several times with water and 5% sodium hydroxide, dried, and evaporated to give 896 mg. of IV as shown by infrared spectra and g.l.p.c. comparison.

Hydrogenation of IV.—A suspension of 500 mg. of platinum oxide in 5 g. (33 mmoles) of IV and 100 ml. of hexane was hydrogenated at 50 p.s.i. for 12 hr. to give a hydrogen uptake equivalent to 39 mmoles. After removal of the catalyst and hexane, the remaining oil was distilled yielding V: 4.3 g.; b.p. 124–126° (150 mm.); $\lambda_{\max}^{\mathrm{CCl_4}}$ 5.63 μ; $\lambda_{\max}^{\mathrm{CH_3OH}}$ 309 mμ (ϵ 53); $\delta_{\mathrm{CDCl_3}}$ = 0.96 (3H, singlet), 1.03 (3H, doublet, J = 6 c.p.s.), 1.22 (3H, singlet), 1.5–2.7 (6H, complex multiplet), 3.54 (1H, triplet, J = 7 c.p.s.) p.p.m.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.79; H, 10.70.

Treatment of V with 2,4-dinitrophenylhydrazine in ethanol–water containing some sulfuric acid gave yellow needles which after two recrystallizations from methanol melted at 103–104°.

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[18] Y. R. Naves, *Bull. soc. chim. France*, 1881 (1961).

[19] F. G. Fischer and K. Löwenburg, *Ann.*, **494**, 263 (1932); E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3334 (1955).

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.87; H, 6.02; N, 16.93.

Basic Degradation of IV.—A solution of 20 g. of IV and 200 ml. of 20% potassium hydroxide in 95% ethanol was refluxed for 16 hr. The solution was concentrated *in vacuo* to about 50 ml. and diluted with 200 ml. of water. Ether extraction provided 4.5 g. of red oil that was largely starting material by g.l.p.c. and infrared spectra comparison. The water layer was acidified with sulfuric acid and extracted with ether. After drying the ether over anhydrous sodium sulfate and evaporation, there was obtained 13 g. of oil which was taken up in 50 ml. of hexane, purified with activated charcoal, and allowed to crystallize to yield 10.3 g. of α-fencholenic acid (VI): m.p. 45–46°; $\lambda_{max}^{CCl_4}$ 5.88 μ; δ_{CDCl_3} = 1.0 (3H, singlet), 1.14 (3H, singlet), 1.75 (3H, narrow multiplet), 1.85–2.00 (4H, complex multiplet), 3.07 (1H, broad multiplet), 5.25 (1H, triplet, J = 1 c.p.s.), 11.26 (1H, singlet) p.p.m.

Refluxing VI in methanol containing a small amount of sulfuric acid, or treatment of VI with ethereal diazomethane provided the methyl ester VII: b.p. 84–85° (2 mm.); $\lambda_{max}^{CCl_4}$ 5.77 mμ; δ_{CDCl_3} = 1.08 (3H, singlet), 1.13 (3H, singlet), 1.72 (3H, narrow multiplet), 1.85–2.40 (4H, complex multiplet), 3.04 (1H, broad multiplet), 3.67 (3H, singlet), 5.20 (1H, narrow multiplet) p.p.m.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.32; H, 10.01.

Dihydro-α-fencholenic Acid (VIII).—One gram of VI in 50 ml. of hexane was hydrogenated at 50 p.s.i. at room temperature using 200 mg. of platinum oxide as the catalyst, to provide 800 mg. of dihydro-α-fencholenic acid (VIII): $\lambda_{max}^{CS_2}$ 5.92 μ; δ_{CDCl_3} = 0.99 (3H, doublet, J = 5.5 c.p.s.), 1.17 (6H, singlet), 1.30–2.50 (8H, complex multiplet), 11.94 (H, singlet) p.p.m.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.73; H, 10.63.

Iodolactone XI.—A suspension of 1 g. of VI in 40 ml. of water was neutralized with 5% sodium hydroxide and treated with 300 mg. of sodium bicarbonate and 2 g. of iodine. After stirring the suspension for 16 hr., it was extracted with three 30-ml. portions of ether. The ether portion was washed with sodium thiosulfate solution until colorless, dried over anhydrous sodium sulfate, and evaporated. The solid residue (1.09 g.) was crystallized from methanol–water to give 976 mg. of XI: m.p. 74–75°; $\lambda_{max}^{CCl_4}$ 5.61 μ; δ_{CDCl_3} = 1.25 (3H, singlet), 1.31 (3H, singlet), 1.40–2.00 (4H, complex multiplet), 2.20 (3H, singlet), 2.92 (1H, broad multiplet), 5.10 (1H, doublet, J = 5 c.p.s.) p.p.m. XI readily decomposed on standing at room temperature but could be stored at 0° for extended periods.

Anal. Calcd. for $C_{10}H_{15}IO_2$: C, 40.83; H, 5.14; I, 43.15. Found: C, 41.05; H, 5.18; I, 43.23.

The same compound could be prepared from α-fencholenic acid (VI) derived from fenchone oxime.

A solution of 100 mg. of the iodolactone XI in 30 ml. of cooled acetic acid was stirred for 5 min. with 400 mg. of zinc dust. Filtration and evaporation provided an oil that was taken up in chloroform and extracted several times with 5% sodium hydroxide. Acidification and ether extraction of the aqueous layer gave after evaporation 48 mg. of an oil whose infrared spectrum was identical with that of VI.

Acidic Degradation of IV. A. Methanolic Hydrochloric Acid.—A solution of 13 g. of IV in 50 ml. of methanol was treated for 5 min. with gaseous hydrogen chloride with ice-bath cooling. After standing at room temperature for 48 hr., the solution was evaporated *in vacuo* and the product was distilled. After removal of a forerun (b.p. 60–80° at 2 mm., 3.6 g.) there was obtained 8.05 g. of the methyl α-fencholenate (VII), b.p. 84–87° (2 mm.), that was identical in all respects with VII described above.

B. Water–Sulfuric Acid.—A suspension of 3.6 g. of IV in 20 ml. of water and 9 ml. of concentrated sulfuric acid was stirred and refluxed for 18 hr. The dark oily suspension was steam distilled. Four 25-ml. ether extractions of the distillate provided after evaporation, 1.5 g. of oil. G.l.p.c. analysis of the oil on several columns showed essentially two components that were easily separated on a preparative scale. The lower retention time (R_t) fraction proved to be 3-methyl-2-cyclohexenone by comparison of the infrared spectra with that of an authentic sample. The higher R_t fraction gave the correct analysis for $C_{10}H_{16}O_2$.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; mol. wt., 168. Found: C, 71.52; H, 9.75; mol. wt., 173.

This material was finally separated on a 0.25 in. × 10 ft. column packed with 25% diethylene glycol adipate on acid-washed Celite using a column temperature of 190°. Two fractions were obtained: XII [R_t 15.0 min.; $\lambda_{max}^{CCl_4}$ 5.63 mμ; δ_{CDCl_3} = 1.15 (3H, doublet, J = 6 c.p.s.), 1.20 (3H, singlet), 1.30 (3H, singlet), 1.50–2.70 (6H, complex multiplets), 4.80 (1H, triplet, J = 6.0 c.p.s.) p.p.m.] and XIII [R_t 16.3 min.; $\lambda_{max}^{CCl_4}$ 5.63 mμ; δ_{CDCl_3} = 1.05 (3H, doublet, J = 6 c.p.s.), 1.19 (3H, singlet), 1.28 (3H, singlet), 1.50–2.60 (6H, complex multiplets), 4.48 (1H, pair of doublets, J = 6 and 2.5 c.p.s.) p.p.m.].

Treatment of 2 g. of the acid VI under the conditions of the preceeding reaction gave after steam distillation and extraction 830 mg. of an equal mixture of the lactones XII and XIII.

***p*-Toluenesulfonic Acid Catalyzed Rearrangement of IV.**—A solution of 5 g. of IV and 500 mg. of *p*-toluenesulfonic acid in 25 ml. of toluene was refluxed for 24 hr. The cooled solution was washed with water, 5% sodium hydroxide, and water. After evaporation of the toluene *in vacuo*, there remained 4.47 g. of an oil that was purified by preparative g.l.p.c. using a 10 ft. × 0.25 in. copper column packed with 25% tris(tridecyl) tricarballylate on silicone-treated Chromosorb W with the column temperature programmed between 125 and 220°. Three components were eluted: (a) R_t 18.4 min., (b) R_t 19.8 min., and (c) R_t 23.6 min.

Component a was shown to be starting material IV by comparison of infrared spectra.

Component c was shown to be XV: $\lambda_{max}^{CCl_4}$ 3.26, 5.72, 6.02, 11.26 μ; $\lambda_{max}^{CH_3OH}$ 301 mμ (ϵ 323); δ_{CDCl_3} = 1.03 (3H, singlet), 1.13 (3H, singlet), 1.75 (1H, doublet, J = 11 c.p.s.), 2.04 (1H, doublet, J = 11 c.p.s.), 2.40 (3H, multiplet), 3.13 (1H, multiplet), 4.92 (1H, multiplet), 5.16 (1H, multiplet) p.p.m. The mass spectrum of XV showed the following peaks in order of decreasing intensity: 79, 80, 41, 27, 39, 77, 117, 78, 107, 53, 150, 43, and 51.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.81; H, 9.43.

A 2,4-dinitrophenylhydrazone of XV was prepared in the usual way and recrystallized from methanol, m.p. 126–128°.

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.16; H, 5.27; N, 16.94.

A semicarbazone was prepared and recrystallized from methanol, m.p. 225–227° dec.

Anal. Calcd. for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.51; H, 8.04; N, 20.18.

Hydrogenation of XV.—A solution of 1 g. of XV in 100 ml. of hexane was hydrogenated at 50 p.s.i. using 100 mg. of platinum oxide as catalyst. Removal of the catalyst and evaporation of the solvent provided 900 mg. of XVI: b.p. 100° (10 mm.); $\lambda_{max}^{CDCl_4}$ 5.73 μ; δ_{CDCl_3} = 0.96 (3H, doublet, J = 6 c.p.s.), 1.02 (3H, singlet), 1.08 (3H, singlet) p.p.m.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 59.05; H, 10.74.

A 2,4-dinitrophenylhydrazone of XVI was prepared in the usual way and recrystallized from methanol, m.p. 154–155°.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.64; H, 6.14; N, 17.02.

Oxidation of XV.—To a solution of 6 g. of sodium periodate in 25 ml. of water and 25 ml. of acetone was added 775 mg. of XV in 10 ml. of acetone. The solution was cooled to 0°, and 220 mg. of potassium permanganate in 5 ml. of water was added dropwise over 10 min. The suspension was stirred at room temperature for 3 hr. and then filtered and thoroughly washed with acetone. The acetone was removed by evaporation *in vacuo* and the remaining solution was extracted with ether. The ether was dried over anhydrous sodium sulfate and evaporated to give 660 mg. of oil. A sample of the product was collected by preparative g.l.p.c. (XVII): $\lambda_{max}^{CCl_4}$ 5.66, 5.74 μ; δ_{CDCl_3} = 1.03 (3H, singlet), 1.26 (3H, singlet), 2.15–2.80 (5H, complex multiplets), 3.22 (1H, singlet) p.p.m.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.86; H, 7.73.

A solution of 16 mg. of XVII in 1 ml. of methanol was heated to boiling with 0.5 ml. of 5% sodium hydroxide. Water (1 ml.) was added and the solution was washed several times with ether. The aqueous layer was acidified and extracted with ether. Evaporation of the ether extract gave 6 mg. of XVIIIa or XVIIIb: $\lambda_{max}^{CCl_4}$ 5.75, 5.86 μ.

Component b was shown to be XIX: $\lambda_{max}^{CCl_4}$ 5.73 μ; $\lambda_{max}^{CH_3OH}$ 305 mμ (ϵ 282); δ_{CDCl_3} = 1.04 (3H singlet), 1.13 (3H, singlet), 1.80 (3H, doublet, J = 1.9 c.p.s.), 2.20 (2H, multiplet), 2.67 (1H, multiplet), 2.83 (1H, multiplet), 6.16 (1H, multiplet) p.p.m.

Hydrogenation of XIX.—Hydrogenation of 50 mg. of XIX in 10 ml. of hexane with 12 mg. of platinum oxide as a catalyst at atmospheric pressure provided 42 mg. of XVI, identified by infrared spectra comparison with that of the previously described sample of XVI.

Pyrolysis of IV.—A 3 × 35 cm. Pyrex tube filled with $^3/_{16}$-in. glass helices and equipped with a micro addition funnel and a nitrogen inlet tube at the top and a round-bottom flask immersed in a Dry Ice–acetone bath at the bottom was used for the pyrolysis. One gram of IV in 10 ml. of hexane was passed through the column heated at 340° over 2.5 hr. with a nitrogen flow rate of 20 cc./min. The condensate was allowed to warm to room temperature with no appreciable amounts of volatile materials distilling. The hexane was removed by vacuum evaporation at 25° to leave 790 mg. of oil. Analysis by g.l.p.c. on a 0.25 in. × 10 ft. column packed with 20% DC-550 silicone oil on Diatoport S at 200° showed a number of very weak, low retention time peaks and three major peaks at 7.9, 12.3, and 16 min. Samples of the major peaks were isolated by preparative g.l.p.c. using the same column.

The 7.9-min. R_t component was shown to be 1-formyl-3,6,6-trimethyl-1,3-cyclohexadiene (XXI): $\lambda_{max}^{CCl_4}$ 3.69, 5.95, 6.09 μ; $\lambda_{max}^{CH_3OH}$ 310 mμ (ϵ 9800) [lit.[19] $\lambda_{max}^{C_6H_{14}}$ 309 mμ (ϵ 9000)]; δ_{CDCl_3} = 1.21 (6H, singlet), 1.92 (3H, narrow multiplet), 2.12 (2H, narrow multiplet), 6.00 (1H, broad multiplet), 6.63 (1H, doublet, J = 5.5 c.p.s.), 9.44 (1H, singlet) p.p.m.; semicarbazone m.p. 211–213° (lit.[19] m.p. 213°). The infrared spectra of an authentic sample of the aldehyde prepared from 3-methylcrotonaldehyde was identical with the infrared spectra of the above sample.[20]

The 12.3-min. R_t component was identified as isopiperitenone (XX): $\lambda_{max}^{CH_3OH}$ 236 mμ (ϵ 10,800); $\lambda_{max}^{CCl_4}$ 3.26, 5.97, 6.10, 11.23 μ; δ_{CDCl_3} = 1.77 (3H, narrow multiplet), 1.97 (3H, narrow multiplet), 2.00–2.50 (4H, broad multiplet), 2.96 (1H, triplet, J = 8 c.p.s.), 4.78 (1H, narrow multiplet), 4.96 (1H, narrow multiplet), 5.92 (1H, narrow multiplet) p.p.m.; 2,4-dinitrophenylhydrazone m.p. 155–156° (lit.[18] m.p. 155–156°). One drop of 0.1 N sodium hydroxide added to a methanolic solution of XX quantitatively isomerized it to piperitenone (II) as shown by the change in the ultraviolet spectra of the solution.

The 16.0-min. R_t component was identified as piperitenone (II): 2,4-dinitrophenylhydrazone m.p. 184–185°.

When the pyrolysis was conducted at lower temperatures (250°), considerable starting material was recovered along with XXI and XX but no II. At higher temperatures (400°) II and *m*-xylene were the only products isolated. Both piperitenone (II) and V were recovered unchanged when they were pyrolyzed at 340°.

Lactonization of the Methyl Ester VII.—A solution of 1 g. of VII and 1 g. of *p*-toluenesulfonic acid in 45 ml. of toluene was refluxed for 16 hr. The solution was washed with water, 5% sodium hydroxide, and water. Evaporation of the toluene provided 940 mg. of oil that was a mixture of the starting methyl ester (30%) and the two isomeric γ-lactones XII and XIII (70%); the identity of the γ-lactones was established by infrared spectra comparison of preparative g.l.p.c. isolated samples.

Lactonization of α-Fencholenic Acid (VI).—Under the conditions described above, 1 g. of VI provided 360 mg. of starting material and 610 mg. of crude δ-lactone XIV, which was crystallized from pentane to give 440 mg. of crystalline product, m.p. 77–78°. A sample of XIV, m.p. 77–78°, prepared from VI and concentrated sulfuric acid,[13a] was identical by infrared spectra and admixture melting point determinations.

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[20] Considerable care had to be exercised in isolating this component to avoid contamination with an impurity that appeared as a weak peak at 8.7 min. Insufficient amounts of this component were available for positive identification, but from the infrared and n.m.r. spectra of the mixture of the two components we believe it to be the nonconjugated aldehyde 1-formyl-4,6,6-trimethyl-2,4-cyclohexadiene.

The Structure of Senegenic Acid, a Nortriterpene Artifact from *Polygala senega*[1]

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Hydrolysis of senegin, the partially purified saponin from *Polygala senega* root, with ethanolic hydrochloric acid gave a complex mixture from which senegenin and a new triterpene acid, senegenic acid, and its monoethyl ester were isolated. Chemical and spectroscopic evidence led to assignment of structures **22** and **24** to senegenic acid and its monoethyl ester, respectively. Senegenin and senegenic acid are artifacts produced during hydrolysis of the senega saponins.

Although the extracts of *Polygala senega* L. (*Polygalaceae*) have been used as an expectorant for centuries, little work has appeared in the literature regarding the chemistry of the saponins of this plant. Quevenne[2] first isolated a saponin from *Polygala senega* which he named "senegin." At a later period Kobert[3] designated a neutral saponin as "senegen" and an acidic saponin as "polygalic acid."

The first chemically significant results on this problem were reported by Wedekind and Krecke[4] who, from the acid hydrolysate of commercial senegin, isolated a sapogenin, which they called senegenin and to which they assigned the formula, $C_{26}H_{46}O_6$. This compound was dibasic, contained two hydroxyl groups as indicated by formation of a diacetate, and gave a dimethyl ester. A more extensive chemical investigation of the sapogenins from *P. senega* was later reported by Jacobs and Isler.[5] The partially purified saponin was hydrolyzed with ethanolic hydrochloric acid to give a sapogenin mixture from which two crystalline sapogenins were isolated on the basis of solubility differences in ethanol. The less soluble compound appeared to be the same as the senegenin of Wedekind and Krecke,[4] although the physical constants differed somewhat. Analytical figures agreed with the molecular formula $C_{30}H_{46}O_8$ or $C_{30}H_{44}O_8$. An inert double bond was suggested by a positive tetranitromethane test and resistance to hydrogenation. Titration indicated the presence of two carboxyl groups and the presence of a lactone was inferred by consumption of a third equivalent of alkali on heating.

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[1] Early phases of this work were carried out in the laboratories of the Rockefeller Institute, New York, N. Y.

[2] P. Quevenne, *J. prakt. Chem.*, **12**, 427 (1837); *Ann. Chem.*, **20**, 34 (1836); **28**, 248 (1838).

[3] R. Kobert, *Pharm. Zentralhalle*, 1631 (1885).

[4] E. Wedekind and R. Krecke, *Ber.*, **57**, 118 (1924).

[5] W. A. Jacobs and O. Isler, *J. Biol. Chem.*, **119**, 155 (1937).