[CONTRIBUTION FROM THE NAVAL STORES LABORATORY[1]]

The Chemistry of Pinolic Acid. II. Pyrolysis and Acid-Catalyzed Rearrangement[2]

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cis-dl-Pinolic acid, on rearrangement, during distillation under a water aspirator vacuum, has been reported by a number of workers to yield 2,2,3-trimethyl-3-cyclopenteneacetic acid. It has been found that pyrolysis (distillation at 25 mm.) of pure pinolic acid yields a mixture of cyclobutane acids identified as 2,2-dimethyl-3-vinylcyclobutaneacetic acid and 2,2-dimethyl-3-ethylidenecyclobutaneacetic acid. A similar mixture results from pyrolysis of pinolic acid acetate, 2,2-dimethyl-3-(1-acetoxyethyl)cyclobutaneacetic acid.

Rearrangement to a product having a cyclopentene structure is produced only by acid catalysis. Under these conditions the product formed is 2,2,4-trimethyl-3-cyclopenteneacetic acid and not the 2,2,3-trimethyl isomer.

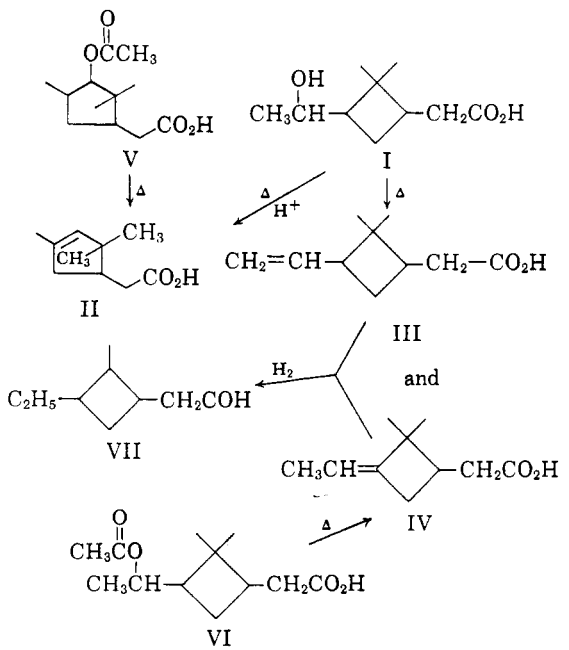
The rearrangement of pinolic acid has been previously reported to occur by both thermal[4,5] and acid-catalyzed[6-8] reactions to yield among other products a cyclopenteneacetic acid derivative. There was, however, some discrepancy in the products formed and in the consistency of their formation.

The purpose of this paper is to report that pyrolysis of pure *cis-dl*-pinolic acid (I) when prepared under certain conditions is not accompanied by rearrangement. Rearrangement to a product having a cyclopentyl structure was produced only by acid catalysis. In this instance, however, the product was not an α-campholenic acid,[9] 2,2,3-trimethyl-3-cyclopenteneacetic acid, as believed by earlier workers but 2,2,4-trimethyl-3-cyclopenteneacetic acid (II) identical with that reported by Park *et al.*[10]

The distillation of *cis-dl*-pinolic acid (pyrolysis), under water aspirator vacuum, yielded a mixture of unsaturated cyclobutaneacetic acids. When the methyl esters of the unsaturated acid mixture were subjected to separation by vapor phase chromatography, two substances were present in a 4:1 ratio, items 5 and 6 (Table I). The infrared spectra of the mixture and the materials isolated from the chromatographic column showed strong absorbances for a trisubstituted olefin.

Reduction of the mixture of acids gave *cis*- and *trans* - pinanic acid, 2,2 - dimethyl - 3 - ethylcyclobutaneacetic acid which was characterized by comparison with authentic samples of the *cis* and *trans* isomers prepared by Schmidt and Fisher.[11]

The formation of pinic acid[12] (2,2-dimethyl-3-carboxycyclobutaneacetic acid) as the major degradative oxidation product of the acid mixture established that the major component in the pyrolysate was 2,2-dimethyl-3-vinylcyclobutaneacetic acid (III). The second and minor constituent in the olefinic acid mixture was believed to be 2,2-dimethyl-3-ethylidenecyclobutaneacetic acid (IV).



Its reduction to pinanic acid established the structure of this compound was a cyclobutane derivative isomeric to III. The infrared absorbance at 12.20 μ

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(4) F. Tiemann and M. Kershbaum, *Ber.*, **33**, 2665 (1900).

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(8) M. Harispe and D. Mea, *Bull. soc. chim. France*, 1562 (1960).

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(10) J. D. Park, R. L. Settine, B. A. Parkin, Jr., and G. W. Hedrick, *J. Org. Chem., in press.*

(11) G. A. Schmidt and G. S. Fisher, *J. Am. Chem. Soc.*, **76**, 5426 (1954).

(12) J. B. Lewis and G. W. Hedrick, *J. Org. Chem.*, **24**, 1870 (1959).

TABLE I

RESULTS OF VAPOR PHASE CHROMATOGRAPHIC SEPARATIONS[a] AND PHYSICAL DATA OF ESTERS USED

Compound	Retention Time, Min.	B.P., Mm.	$n^{20}D$	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1. Methyl 2,2,4-trimethyl-3-cyclopenteneacetate	2.5	88–89 10 mm.	1.4512	$C_{11}H_{18}O_2$	72.43	9.89	72.09	10.02
2. Methyl 2,2,3-trimethyl-3-cyclopenteneacetate	3	Known compound[7]						
3. Methyl 2,2,4-trimethyl-3-hydroxycyclopentaneacetate	13.5	95–96 0.2 mm.	1.4657	$C_{11}H_{20}O_3$	65.97	10.07	65.66	10.03
4. Methyl 2,2,4-trimethyl-3-acetoxycyclopentaneacetate	10	97–98 0.2 mm.	1.4508	$C_{13}H_{22}O_4$	64.44	9.15	64.40	9.25
5. Methyl 2,2-dimethyl-3-vinylcyclobutaneacetate[b]	2.25	84–85 10 mm.	1.4495	$C_{11}H_{18}O_2$	72.43	9.89	72.28	9.99
6. Methyl 2,2-dimethyl-3-ethylidenecyclobutaneacetate[b]	2							
7. Methyl 2,2-dimethyl-3-(1-acetoxyethyl)cyclobutaneacetate	10	85–86 0.2 mm.	1.4456	$C_{13}H_{22}O_4$	64.44	9.15	64.20	9.34
8. Methyl 2,2-dimethyl-3-(1-hydroxyethyl)cyclobutaneacetate	11	83–84 0.05 mm.	1.4595	$C_{11}H_{20}O_3$	65.97	10.07	65.84	10.11
9. Ethyl 2,2-dimethyl-3-ketocyclobutaneacetate	6.5							
10. Diethyl pinate	9	Known compound						

[a] F & M Model 500 gas chromatograph, Craig polyester column, 225°, helium at 50 ml./min. [b] Physical data on mixture of vinyl and vinylidene compounds.

of its methyl ester indicated a trisubstituted double bond. Oxidation produced a keto acid presumably 2,2-dimethyl-3-ketocyclobutaneacetic acid, which had the characteristic infrared absorbance of a cyclobutanone.[13]

No evidence of a product having a cyclopentyl structure has been found in the pyrolysis product.

In a similar manner, the normal acetate of pinolic acid, 2,2-dimethyl-3-(1-acetoxyethyl)cyclobutaneacetic acid,[14] when pyrolyzed gave a mixture of olefinic acids similar to that obtained from the pyrolysis of pinolic acid. Separation by vapor phase chromatography of the methyl esters indicated the two same components, items 5 and 6 (Table II) were present in a 3:7 ratio rather than

TABLE II

EFFECT OF ACID CATALYSTS ON PINOLIC ACID

Catalyst	Molar Ratio of Catalyst to Pinolic Acid	Yield of 2,2,4-Trimethyl-3-cyclopenteneacetic Acid, %
Potassium acid sulfate[a]	0.015 to 0.11	27
Concd. sulfuric acid	0.02 to 0.54	32
Zinc bromide	0.009 to 0.54	28
Zinc bromide	0.004 to 0.54	45
p-Toluenesulfonic acid	0.23 to 1.0	21
Phosphorus pentachloride[b]	0.1 to 0.08	34

[a] Ref. 8. [b] Ref. 6.

the 4:1 as reported for the pinolic acid pyrolysate. Reduction of the unsaturated acid mixture in this instance gave primarily *trans*-pinanic acid identical to *trans*-pinanic acid reported by Schmidt and Fisher.[11] This supports the structure assigned to the ethylidene derivative, since on reduction there is a possibility for the hydrogen to approach from either side of the molecule to form either *cis*- or *trans*-pinanic acid. Oxidation of the unsaturated acid mixture yielded predominately the keto acid above. The presence of cyclopentene derivatives was again lacking.

An earlier report from this laboratory has shown that under some conditions acid-catalyzed acylation of pinolic acid yields 2,2,4-trimethyl-3-acetoxycyclopentaneacetic acid (V).[10] Pyrolysis of this acetate has given a 2,2,4-trimethyl-3-cyclopenteneacetic acid (II). This same acid was formed when the distillation of pinolic acid was attempted in the presence of a number of acid catalysts (Table II). At no time was a product isolated which had the α-campholenic acid structure reported by earlier workers. A limited study on the nonacidic materials has established the formation of a significant amount of the Δ-lactone of 2,2,4-trimethyl-3-hydroxycyclopentaneacetic acid in these acid-catalyzed rearrangements in addition to the unsaturated acid.

During the course of this work, pinolic acid acetate, 2,2-dimethyl-3-(1-acetoxyethyl)cyclobutaneacetic acid, was prepared without the use of an acid catalyst. Its physical constants were slightly different from those previously reported.[14]

To establish the effectiveness of separation of the various cyclobutane, cyclopentene, and cyclopentane derivatives by vapor phase chromatography, methyl esters were prepared by use of diazomethane and subjected to separation. The

(13) L. J. Bellamy, *Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1958, p. 129.

(14) B. A. Parkin and G. W. Hedrick, *J. Org. Chem.*, **25**, 1417 (1960).

esters prepared with retention times and physical data are tabulated in Table I. This procedure was highly desirable for determining the composition of acids obtained in both the acid-catalyzed and pyrolysis reactions.

EXPERIMENTAL

cis-dl-Pinolic acid (I). *cis-dl*-Pinolic acid was prepared by the method previously reported.[10,14] The methyl ester (10 g., 76%) was prepared with excess diazomethane in ether solution from 12 g. of pinolic acid. The physical data are tabulated in Table I with data of other esters.

2,2-Dimethyl-3-(1-acetoxyl)cyclobutaneacetic acid (VI). A solution of 186 g. (1.0 mole) of *cis-dl*-pinolic acid (m.p. 104–105°), and 500 ml. of glacial acetic acid (8.75 moles) in 260 ml. of xylene was refluxed for 2 days with removal of the water azeotropically. The resultant solution was stripped of solvent at reduced pressure to a pot temperature of 120°. Distillation of the residue yielded 184 g. (81%) of a crystalline acetate, b.p. 125°10.1 mm., m.p. 70–73°. Recrystallization from methanol–water mixture yielded 104 g. of pure material, m.p. 84–85°. The previously reported m.p. was 71–73°.[14]

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83; neut. equiv., 228.17. Found: C, 63.03; H, 8.86; neut. equiv., 228.20.

Infrared spectral and vapor phase chromatographic analyses of the methyl ester prepared by diazomethane as above showed no contamination by hydroxyl containing material or rearranged acetate.[10] The methyl ester had principal absorption bands at 3.49, 5.83, 7.01, 7.40, 7.69, 9.40, 9.75, 9.95, 10.60, 10.85, 11.01, 11.91 μ.

Pyrolysis of pinolic acid (I). Pinolic acid, 100 g. (0.54 mole) was added to a distilling flask equipped with a 6-in. column packed with protruded metal and heated to 275–285°/25 mm. Water was eliminated, then the product (70 g., 70% distilled), b.p. 150–151°/25 mm. The distillate was dissolved in ether and the acids extracted with dilute aqueous bicarbonate solution. Acidification of the aqueous layer followed by distillation of the oil layer which separated gave a colorless material, b.p. 136–137°/10 mm., $n^{20}D$ 1.4644, 60 g. (71%). Strong absorbonces at 6.04 and 11.00 μ and a weak absorbancy at 12.20 μ in the infrared indicated the presence of vinyl and trisubstituted olefinic groups. The methyl esters (Table I) of the acid mixture were prepared with diazomethane and separated by vapor phase chromatography. Two components separated in a 4:1 ratio. The mixture of esters and the major constituent collected from the chromatographic column had strong vinyl olefin absorbances in the infrared at 3.30, 6.04, and 11.00 μ.

Pinanic acid (VII). The above acid mixture (13 g.) was hydrogenated with Adams catalyst in methanol; one equivalent of hydrogen was absorbed. Removal of the catalyst by filtration followed by solvent removal and distillation *in vacuo* yielded 11.5 g. of *cis-* and *trans*-pinanic acids, b.p. 137–138°/9 mm., $n^{20}D$ 1.4472.

A portion of the reduced material was converted to its methyl ester and separated by vapor phase chromatography. The ester consisted of two materials in 7:3 ratio. A comparison of the refractive index and infrared spectrum of the acid mixture with authentic samples of pure *cis-* and *trans*-pinanic acids prepared by Schmidt and Fisher[11] proved the material was predominahtly *cis*-pinanic acid with a lesser amount of the *trans* isomer.

Degradative oxidation of the pyrolysate from I. The pyrolysate was oxidized by the method of Lemiux and Rudloff.[15] The pyrolysate (6.8 g., 0.045 mole) was added dropwise to a stirred mixture of sodium bicarbonate (11.2 g., 0.13 mole), sodium periodate, (50 g., 0.023 mole), and potassium permanganate, (1 g.) in 500 ml. of water. After standing overnight, the mixture was made acid with dilute sulfuric acid, filtered to remove insoluble salts, and the oxidate extracted with ether. A viscous material, neut. equiv. 126, was obtained after removal of the solvent. The crude acid was taken up in toluene (60 ml.) and esterified with ethanol using *p*-toluenesulfonic acid (1 g.) as a catalyst. A crude ester (11.0 g.) was obtained by washing to remove catalyst and stripping *in vacuo*. Two materials were obtained by vapor phase chromatographic separation (Table I) in a 4:1 ratio. The major component was diethyl pinate, item 10, identified by infrared spectral analyses and refractive index.[12] The minor constituent, item 9, a keto ester, had a carbonyl absorption in the infrared at 5.65 μ characteristic of a cyclobutanone derivative.[13]

Acid-catalyzed rearrangement of pinolic acid. (I). Pinolic acid (100 g., 0.54 mole) was heated to a pot temperature of 180°/25 mm., with 1 g. of anhydrous zinc bromide. A vigorous reaction set in and water distilled from the reaction mixture. After the water was removed a colorless liquid distilled, b.p. 150°/25 mm. Extraction of the distillate with aqueous sodium bicarbonate and acidification with mineral acid resulted in, after redistillation, 40 g. (45% of acid), $n^{20}D$ 1.4687, b.p. 138–139°/10 mm., which was identical to 2,2,4-trimethyl-3-cyclopenteneacetic acid (II) obtained by pyrolysis of 2,2,4-trimethyl-3-acetoxy-3-cyclopenteneacetic acid (V) described by Park *et al.*[10] Characterization was accomplished by refractive index, vapor phase chromatography, and infrared spectral analysis.

The effect of a number of acid catalysts (Table II) on pinolic acid, was investigated. Some of these had been used by earlier workers. The acid produced with each catalyst was 2,2,4-trimethyl-3-cyclopenteneacetic acid (II).

In the experiment in which sulfuric acid was used as a catalyst the ether soluble nonacidic material was investigated. Isolation by removal of the ether and subjecting the residue to analysis by vapor phase chromatography gave four substances. The major component, about 50% of the nonacidic portion, was identified as the Δ-lactone of 2,2,4-trimethyl-3-hydroxycyclopentaneacetic acid reported by Park *et al.*[10] This same lactone was observed when zinc bromide or *p*-toluenesulfonic acid was used as catalyst.

Pyrolysis of 2,2-dimethyl-3-(1-acetoxyethyl)cyclobutaneacetic acid (VI). Pyrolysis of 65 g. (0.35 mole) of 2,2-dimethyl-3-(1-acetoxyethyl)cyclobutaneacetic acid at a pot temperature of 276° at atmospheric pressure in a nitrogen atmosphere yielded, after the liberation of acetic acid, 57 g. of organic material, b.p. 235°. The separation into an acidic and nonacidic fraction by means of aqueous sodium bicarbonate gave 42 g. (72% of acid), b.p. 138–139°/10 mm.

Vapor phase chromatographic analysis of the methyl ester of the pyrolysate resulted in separation of the acid mixture into two products, the vinyl and vinylidene cyclobutane derivatives in a 3:7 ratio. The major component had the vinylidene structure in this instance. The acid mixture was characterized in the same manner as the other pyrolysate.

Pinanic acid (VII). The above acid mixture (13 g., 0.076 mole) was hydrogenated with Adams catalyst in methanol; one equivalent of hydrogen was absorbed. Removal of catalyst and solvent followed by distillation *in vacuo* yielded a quantitative amount of pinanic acid, b.p. 138–91°/10 mm., $n^{20}D$ 1.4493. Characterization was established by comparison of the refractive index and infrared spectrum with authentic samples of *cis-* and *trans*-pinanic acid prepared by Schmidt and Fisher.[11] The composition of the acid mixture established by separation by vapor phase chromatography of its methyl ester mixture, was predominately (75%) the *trans* isomer.

Degradative oxidation of pyrolysate from VI. The methyl ester of the pinenic acid mixture was ozonized in accordance with the procedure reported by King and Farber.[16] A

(15) R. V. Lemiux and E. Von Rudloff, *Can. J. Chem.* **33**, 1701 (1955).

(16) L. C. King and H. Farber, *J. Org. Chem.*, **26**, 326 (1961).

sample of methyl ester (12 g. 0.066 mole) as dissolved in 150 ml. methanol and ozonized at −70°. When no more ozone was absorbed the solution was warmed at −10° and diluted with 100 ml. of water. Chlorine was slowly added at 0° until saturated. After standing overnight, the crude oxidate was isolated by washing, and removing the solvent. The residue, 6.8 g., was dissolved in ether, extracted with sodium bicarbonate solution to remove the soluble acids. Removal of the ether from the bicarbonate insoluble material gave a residue (4.5 g., 58%) (based on a 3:7 ratio of isomers), which was distilled, b.p. 104–106°/2 mm. By infrared spectral and vapor phase chromatographic analysis, the acid moiety, a keto acid, was identical to that obtained from the oxidation of the pinenic mixture obtained from pyrolysis of pinolic acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Ivalin, a New Sesquiterpene Lactone[1]

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The structure of ivalin, a new sesquiterpene lactone from *Iva microcephala* Nutt. and *Iva imbricata* Walt., is shown to be I.

The interesting connection which we established recently[2] between some sesquiterpene lactones of *Ambrosia* and *Parthenium* species made it desirable to investigate other genera related to *Ambrosia*. In the following, we report on the isolation and structure of a new sesquiterpene lactone from two *Iva* (marsh elder) species.

Extraction of flowers and leaves of *Iva microcephala* Nutt., an annual weed found in the Southern coastal plain, gave in 1.9% yield[3] a crystalline compound $C_{15}H_{20}O_3$, m.p. 130–132°, $[\alpha]^{23}D$ + 142°, which appeared to be new and which we have named ivalin. Ivalin was also obtained in somewhat lower yield from *Iva imbricata* Walt., but not from *Iva frutescens* L.

Ivalin (I) had a hydroxyl group (infrared bands at 3700 and 3500 cm.$^{-1}$, formation of an acetate, II) and two double bonds (infrared bands at 1600 and 1645 cm.$^{-1}$, hydrogenation). The remaining two oxygen atoms were presumably present as a γ-lactone (infrared band at 1750 cm.$^{-1}$) conjugated with one of the double bonds (λ_{max} 208 mμ, ϵ 11000). Ivalin is therefore bicyclic.

The nature of the two double bonds was inferred from the following. Ozonolysis of ivalin gave a 94% yield of formaldehyde, indicating the possibility of more than one exocyclic methylene group.[4] Partial hydrogenation of ivalin (palladium-on-calcium carbonate in ethanol) gave dihydroivalin (III) which still had one exocyclic methylene group (liberation of formaldehyde on ozonolysis, infrared band at 1645 cm.$^{-1}$), but no longer exhibited conjugation in the ultraviolet and whose lactone frequency had moved to 1770 cm.$^{-1}$ Hence ivalin contained two exocyclic methylene groups, one unconjugated and one conjugated with the lactone ring. This was also shown by the formation of a pyrazoline on treatment of ivalin with diazomethane. Hydrogenation of ivalin in acetic acid furnished tetrahydroivalin (V) which resisted ozonolysis and exhibited no double bond frequencies in the infrared.

The NMR spectra[5] of I, III, and V and their acetates completely verified these conclusions. I had two low-field doublets (367.4 and 336.7 c.p.s., J ~ 1.6 c.p.s.), each representing one proton, characteristic of the methylene group conjugated with a lactone.[6] These were absent in III and V. A second pair of doublets at somewhat higher field (291 and 271[7] c.p.s., J ~ 1.5–unconjugated >C=CH_2) was found in the spectra of I and III, but not in that of V. On the other hand, I had only one sharp signal at 57 c.p.s., (intensity three protons, tertiary methyl group). III exhibited this signal at 48 c.p.s. and had a new methyl doublet at 70 and 77 c.p.s. (methyl alpha to lactone). V had two split methyl signals (56, 64.5 and 73, 80 c.p.s.) one

(1) Supported in part by grants from the National Science Foundation (NSF G-14396) and the Eli Lilly Company.

(2) W. Herz and G. Högenauer, *J. Org. Chem.*, 26, 5011 (1961).

(3) The high yield of ivalin appears to be due to a fortuitous combination of circumstances, perhaps because of time and location of collection (see Experimental). This problem and the phytochemistry of other *Iva* species are being investigated further.

(4) The yields of formaldehyde, precipitated as the dinitrophenylhydrazone or dimedone derivative, generally are 30–50% per exocyclic methylene group in compounds of this type).

(5) Spectra were run by Mr. Fred Boerwinkle in deuteriochloroform solution at 60 mc., on a Varian HR-60 instrument, with tetramethylsilane as internal standard. Frequencies were determined by the side band technique.

(6) W. Herz, M. Miyazaki, and Y. Kishida, *Tetrahedron Letters*, 82 (1961).

(7) In the NMR spectrum of ivalin, this doublet was superimposed on the signal of the C-8 lactonic hydrogen (*vide infra*).