Anal. Calcd. for $C_6H_5O_3N$: N, 10.07. Found: N, 10.17, 10.22.

N-Substituted Coumalamides.—These compounds, described elsewhere, were prepared from the appropriate amine and coumalyl chloride by the procedure given above for coumalamide. Often the gummy solid obtained as the crude reaction product was washed by decantation prior to filtration. Most of the products were recrystallized from two different solvents or solvent pairs indicated. The N-(2-thiazolyl) amide also was purified by solution and reprecipitation from alkali.

5-(*p*-Methoxybenzoyl)-2-pyrone.—To a solution of 6.0 g. (0.038 mole) of coumalic acid chloride in 150 ml. of carbon disulfide was added 5.8 g. (0.054 mole) of anisole and 17.6 g. (0.132 mole) of aluminum chloride. The reaction mixture was warmed on a water-bath and held at 40° for 8 hours with stirring. Following the usual procedures, there was obtained 0.9 g. (10.3% of the theoretical amount) of crystals which after two recrystallizations from ethanol as white, needle-like crystals melted at 153–154.5°.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.83; H, 4.35. Found: C, 67.94, 67.68; H, 4.31, 4.51.

The ketone gives a solid derivative with 2,4-dinitrophenylhydrazine, m.p. 259–260°, which was not crystalline in appearance and was insoluble in the usual recrystallizing solvents. Oxidation of 0.1 g. (0.00043 mole) of the ketone with aqueous, alkaline potassium permanganate gave about 0.05 g. of crystals, m.p. 179–181°. A mixed melting point with an authentic sample of anisic acid showed no depression.

LOUISVILLE 8, KENTUCKY

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE BROOKHAVEN NATIONAL LABORATORY AND CORNELL UNIVERSITY]

The Acid-catalyzed Rearrangement of Cinenic Acid[1]

BY J. MEINWALD[2]

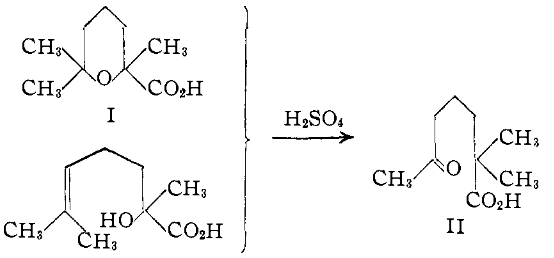
RECEIVED SEPTEMBER 15, 1954

Tracer studies reveal that the isomerization of α-cinenic acid (I) to geronic acid (II) involves carboxyl transfer rather than methyl migration. Some mechanistic implications of this finding are discussed.

The concept of the "1,2-shift" as the underlying mechanism of organic molecular rearrangements has been remarkably powerful. From its formulation in the 1920's to the present, it has shown itself capable of accommodating an astounding variety of molecular changes.[3] Although recent theoretical developments have led to a considerable refinement of detail, no fundamental modification of the concept has been necessary. In this context, those rearrangements which *cannot* be rationalized in terms of a 1,2-shift, or a short sequence of such shifts, are of special significance. One example of this type of reaction is the benzidine rearrangement; the large effort expended on this transformation[4] reflects the unusual interest in rearrangements of a "non-Whitmore" type.

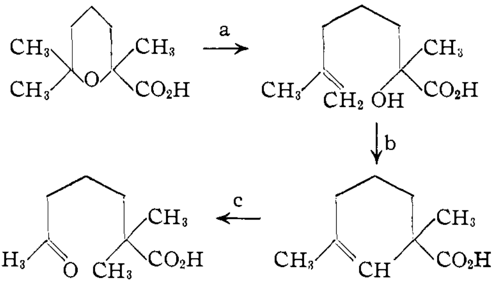
A less well known and less understood rearrangement has been mechanistically paradoxical for over forty years. This is the isomerization of α-cinenic acid (I) or β-cinenic acid (Ia) to geronic acid (II) represented in equation 1, which Rupe reported to occur in concentrated sulfuric acid solution.[5] In a fascinating summary of Rupe's life work, Dahn and Reichstein called attention to this mysterious observation, and pointed out that it seems to be *without analogy* in organic chemistry.[6,7] Rupe himself was concerned with the novelty of the rearrangement and offered two different explanations of the experimental facts. The first of these is represented in equation 2.[5] Since neither the cyclodehydration step (b) nor the hydration step (c) have any reasonable precedent, this series must be viewed with considerable doubt.

(1)



I, Ia, II

(2)



Rupe's second suggestion, transcribed into currently acceptable notation in equation 3, deserves more serious consideration.[8] Here the key step is visualized as a *direct transfer of one of the C_6-methyl groups to a site five atoms removed.* Once more this type of change is totally without analogy. Besides the unprecedented 1,5-shift of methyl, the initial cleavage of the tetrahydropyran ring is in a direction which would be unexpected, since it results in placing a formal positive charge adjacent to an

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[1] Research carried out in part under the auspices of the U. S. Atomic Energy Commission.

[2] All work involving radioactivity was carried out during the tenure of an appointment as Associate in Chemistry at the Brookhaven National Laboratory.

[3] For an intersting historical survey of the development of this concept, as well as a review of its scope, see C. K. Ingold," Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 473–529.

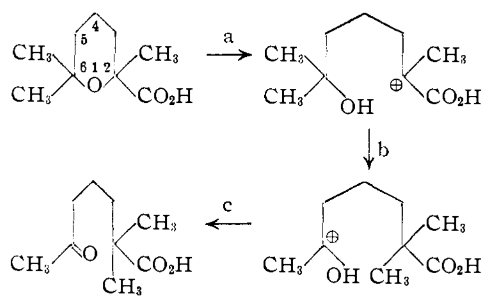
[4] Reference 3, pp. 631–642.

[5] H. Rupe and C. Liechtenhan, *Ber.*, **41**, 1278 (1908).

[6] H. Dahn and T. Reichstein, *Helv. Chim. Acta*, **35**, 1 (1952).

[7] In a preliminary investigation of this reaction, carried out at Cornell University, Mr. Richard Burrows was able to confirm Rupe's findings in detail. The 2,4-dinitrophenylhydrazone of the rearrangement product was identical with an authentic sample of geronic acid 2,4-dinitrophenylhydrazone.

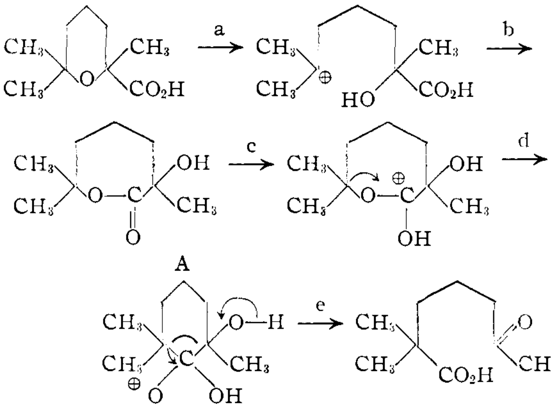
[8] H. Rupe and H. Hirschmann, *Helv. Chim. Acta*, **16**, 505 (1933).

(3)


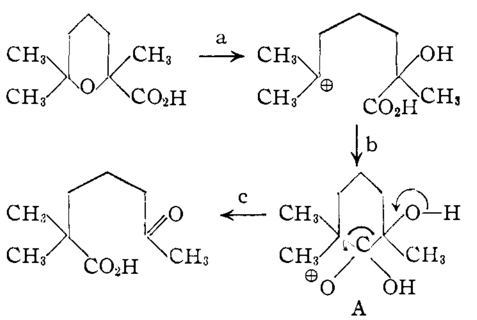
already positive center. The relatively radical nature of both these proposals is attributable to the inherent difficulty in devising any series of classical steps which accomplishes the desired methyl migration.

Having arrived at an impasse, a critical examination of the implicit assumption *that a methyl migration is occurring* seems desirable. Brief consideration of structures I and II reveals that although methyl migration would account for the observed isomerization, *transfer of the carboxyl in the opposite direction would achieve the same end.* This hitherto unrecognized possibility may be made attractive by consideration of two new pathways presented below. The interesting point is that no analog of these can be written for methyl transfer.

The first of the new mechanisms is presented in equation 4. Steps (a), (b) and (c) are straightforward and require no special comment. The key step (d) is pictured as a 1,2-shift which is unique, however, in that it generates an electron-deficient oxygen rather than a carbonium ion.[9] The final step (e) is isoelectronic with the acid cleavage of 1,3-diols to yield an olefin and a carbonyl compound.[10]

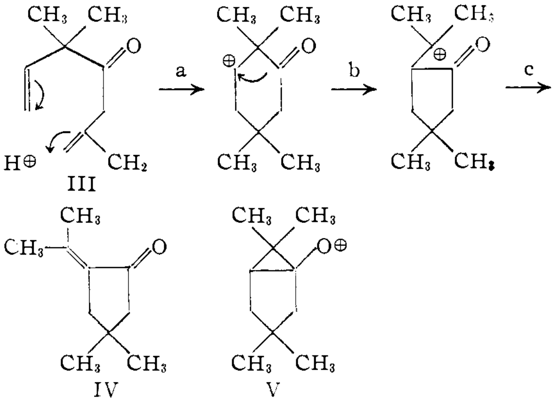
4)


A second possibility may be imagined which has the virtue of greater simplicity. This is demonstrated in equation 5, which is in some respects merely a telescoped version of equation 4, in that it postulates direct addition of the initially generated carbonium ion to the carbon of the carboxyl group, thus avoiding formation of a seven-membered ring and subsequent rearrangement.

(5)


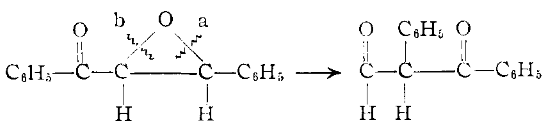
It should be noted that the same cyclic intermediate (A) would arise by either of these paths.

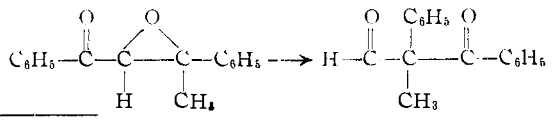
Reactions in which a carbonyl function appears to be attacked by a carbonium ion have been observed in the past. For example, the acid cyclization of artemisia ketone (III) to cycloartemisia ketone (IV) is rationalized readily in terms of carbonyl migration to a positive center,[11] as shown in equation 6.

(6)


It is even possible that a bridged intermediate, such as that represented by V, in which the π-electrons of the carbonyl group help distribute the positive charge, plays some role in the reaction. In that case there would be a striking resemblance to the intermediate (A) postulated for the cinenic acid rearrangement.

A more clear-cut case of attack of a carbonyl group by a carbonium ion is provided by the acid-catalyzed conversion of α-ketoepoxides into β-dicarbonyl compounds. Although the original example of this reaction did not allow distinguishing between two alternate paths (cleavage at "a" followed by benzoyl migration or cleavage at "b" followed by phenyl migration in equation 7,[12a] cases are now available which definitely require benzoyl migra-

(7)


(8)


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(9) Electron-deficient oxygen is generally conceded to play a role in several types of organic reaction, including the Baeyer–Villiger oxidation of ketones to esters by peracids. For a recent contribution to the mechanism of this reaction, see W. von E. Doering and E. Dorfman, THIS JOURNAL, **75**, 5595 (1953).

(10) J. English, Jr., and F. V. Brutcher, Jr., *ibid.*, **74**, 4279 (1952).

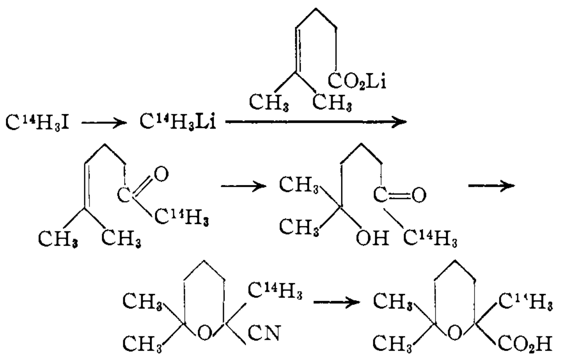
(11) A. Eschenmoser, H. Schinz, R. Fischer and J. Colonge, *Helv. Chim. Acta*, **34**, 2329 (1951).

(12) (a) J. Algar and J. McKenna, *Proc. Royal Irish Acad.*, **49**, 225 (1944); *C. A.*, **38**, 5502 (1944); (b) H. O. House, THIS JOURNAL, **76**, 1235 (1954).

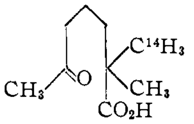
tion[12b] (eq. 8). Here again, the formation of a bridged intermediate, similar to those already suggested, may be involved.[13]

Before the details of any of the mechanisms are investigated, it would be desirable to decide whether the gross change consists in fact of the newly suggested carboxyl transfer. Although analogous molecules could be constructed which upon rearrangement might give information on this point,[14] the most direct approach to the question seemed to be the application of isotopic tracer techniques. Toward this end, α-cinenic acid-(2-methyl)-C^{14} was synthesized using the reaction sequence shown in equation 9.[15]

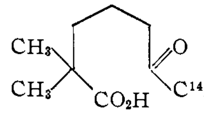
(9)



The over-all yield from methyl iodide-C^{14} [16] was 32%. Isomerization of the final product in concentrated sulfuric acid gave a 41% yield of geronic acid whose specific activity was equal to that of its precursor (2.66 mμc./mg. C). Comparing mechanisms 2 and 3 with 4 and 5, it is obvious that the former pair should yield geronic acid-(2-methyl)-C^{14} (VI), while the latter should give rise to geronic acid-(7-methyl)-C^{14} (VII).



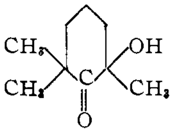
VI



VII

Haloform degradation offered a simple means of distinguishing between these two possibilities. The active geronic acid was treated with excess potassium iodide and Clorox,[17] which produced iodoform in 75% yield. This iodoform had just nine times the specific activity (24.0 mμc./mg. C) of the acid precursor, which must therefore have possessed structure VII. *This result provides unambiguous evidence for a carboxyl transfer mechanism.*

Experiments which would help decide between mechanisms 4 and 5 are designed easily. Thus 4 requires a carboxyl specifically, while 5 should proceed with comparable ease with almost any carbonyl function. Furthermore, it should be possible to arrive at the postulated cyclic intermediate (A) by an entirely independent route: the treatment of 2,2,6-trimethyl-6-hydroxycyclohexanone (VIII) with a peracid. This would then be predicted to yield geronic acid. Research suggested by these speculations is now in progress.



VIII

Experimental[18]

Synthesis and Rearrangement of α-Cinenic Acid.—α-Cinenic acid was prepared from natural methylheptenone as described by Rupe.[5] It was then rearranged in concentrated sulfuric acid, and the acidic product converted into a 2,4-dinitrophenylhydrazone. This derivative was purified by chromatography on silica gel, using 1% methanol in chloroform, and finally by recrystallization from ethyl acetate–cyclohexane mixtures. The final product was compared with an authentic sample of geronic acid 2,4-dinitrophenylhydrazone,[19] purified in the same way; rearrangement product, m.p. 135–138°; authentic geronic acid 2,4-dinitrophenylhydrazone, m.p. 135–137°[20]; mixture m.p. 135–138°. The infrared spectra of Nujol mulls of the two solids were indistinguishable.

Lithium 4-Methyl-hex-3-enoate.—A mixture of 13.2 g. of 4-methyl-hex-3-enoic acid[21] (containing about 20% of the corresponding lactone) and a small amount of water was neutralized with an aqueous solution of lithium hydroxide, using phenolphthalein as an indicator. The resultant solution was evaporated to dryness, the white residue washed several times with ether to remove the lactone, and finally dried to constant weight at 100°. The theoretical yield (11 g.) was obtained.

Lithium Methyl-C^{14}.[22]—A 3-necked, round-bottom flask equipped with an exit stopcock at its base was provided with a mechanical stirrer, reflux condenser and dropping funnel. A small plug of glass wool was placed in the exit tube, above the stopcock, so that the product could be filtered as it was drawn out at the end of the reaction. The entire system was swept out with dry nitrogen. Approximately 2.5 g. of lithium ribbon, cut into small pieces, was placed in the flask and covered with *ca.* 50 ml. of dry ether. A small portion of a solution of 17 g. of methyl iodide-C^{14} (108 ± 5 mμc./mg. C) in 150 ml. of dry ether was then run in, and the stirring started. Refluxing began in about a minute. The remainder of the methyl

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[13] A Referee has called attention to the elegant tracer work carried out by J. D. Roberts, D. R. Smith and C. C. Lee, THIS JOURNAL, **73**, 618 (1951), on the decarbonylation of diphenyltriketone. This reaction provides an unequivocal example of acyl migration toward a positive center, although the analogy to the cinenic acid rearrangement is weakened by the fact that the decarbonylation requires cupric acetate, aluminum chloride or sodium hydroxide as catalyst, and is reported to fail with sulfuric or phosphoric acids.

[14] The synthesis and rearrangement of molecules related to α-cinenic acid is now being studied; the results will be presented in a subsequent communication.

[15] The synthesis is essentially the same as the path originally used by Rupe; see reference 5.

[16] The author is grateful to Dr. David Christman, Brookhaven National Laboratory, for the preparation of the radioactive methyl iodide.

[17] This technique, described in R. Adams and J. R. Johnson, "Laboratory Experiments in Organic Chemistry," The Macmillan Company, N. Y., 4th Ed., 1949, p. 259, seemed to work particularly smoothly compared to others tried.

[18] The analyses reported below were performed by Dr. David R. Christman and Miss Patricia R. Hansell. Samples were oxidized to CO$_2$ on a standard micro-combustion train, and the gaseous CO$_2$ counted in gas counting tubes with a proportional counter. For a description of this technique, see R. Christian Anderson, Y. Delabarre and Aksel A. Bothner-By, *Anal. Chem.*, **24**, 1298 (1952).

[19] The author is indebted to Dr. A. D. Mebane of the Ortho Research Foundation, Raritan, N. J., for an authentic sample of geronic acid 2,4-dinitrophenylhydrazone.

[20] H. H. Strain, THIS JOURNAL, **57**, 758 (1935).

[21] This acid was prepared by Mr. John T. Ouderkirk, according to the procedure described by R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 580 (1933) (*cf.* H. Staudinger, W. Kreis and W. Schilt, *Helv. Chim. Acta*, **5**, 743 (1922)). Efforts to use haloform degradation of the readily available methylheptenone were unrewarding.

[22] The procedure described is essentially that of D. A. van Dorp and J. E. Ahrens, *Rec. trav. chim.*, **65**, 338 (1946). The yield is somewhat better than that obtained by W. G. Dauben and C. W. Vaughan, Jr., THIS JOURNAL, **75**, 4651 (1953), using a large excess of lithium.

iodide solution was then run in at a rate which maintained comfortable refluxing. When the addition was complete, the mixture was stirred for an additional hour, and then filtered directly into a dropping funnel.

Methylheptenone-1-C^{14}.[23]—Two hundred ml. of dry ether was used to suspend 16.5 g. of lithium 4-methyl-hex-3-enoate in a round-bottom flask swept by dry nitrogen. The filtered solution of lithium methyl-C^{14} prepared above was added slowly with stirring. After the addition, the mixture was refluxed for six hours, at the end of which time a clear solution had formed. This was worked up in standard fashion by pouring onto ice, washing the ether layer until neutral, drying over magnesium sulfate, evaporating the ether, and distilling the product. A 10.1 g. yield of methylheptenone-1-C^{14}, b.p. 81–84° (36 mm.), corresponding to 74% of theory for the two steps, was obtained. The infrared spectrum of this material was identical with that of a sample of distilled authentic, natural methylheptenone.

Anal. Calcd. for $C_8H_{14}O$: C, 76.1; H, 11.1. Found: C, 76.2; H, 11.1; specific activity, 14.3 mμc./mg. C.

Hydration of Methylheptenone-1-C^{14}.—A mixture of 4.2 g. of methylheptenone-1-C^{14} and 45 g. of 35% sulfuric acid was shaken under nitrogen at room temperature for 9 hours. It was then placed in the refrigerator overnight, diluted with ice and water, and carefully neutralized by cautious addition of aqueous sodium hydroxide. The temperature was kept below 5° at all times by means of an ice–salt-bath. The neutral mixture was placed in a continuous extractor and extracted exhaustively with ether. The ether extract, after drying over potassium carbonate, was evaporated and the residue (4.9 g.) distilled. In this way 4.1 g. of the desired tertiary alcohol b.p. 100–102° (7 mm.) was obtained, corresponding to 85% of theory.

Anal.[24] Calcd. for $C_8H_{16}O_2$: C, 66.7; H, 11.1. Found: C, 66.8; H, 10.84; specific activity, 14.1 mμc./mg. C.

α-Cinenic Nitrile-(2-methyl)-C^{14}.—A mixture of 4.0 g. of the hydrated methylheptenone-1-C^{14} and an equal volume of anhydrous hydrogen cyanide was heated in a sealed glass tube at 55° for 36 hours. The bomb was then cooled in Dry Ice, opened, and the excess hydrogen cyanide evaporated. The yellow residue was taken up in ether, washed with aqueous sodium hydroxide and then with water till neutral. The aqueous layers were re-extracted with ether, and the combined ether solutions dried over magnesium sulfate. Distillation yielded 2.77 g. of product,[25] b.p. 71–73° (10 mm.), whose infrared spectrum was indistinguishable from that of an authentic sample of α-cinenic nitrile. The yield corresponds to 65%.

Anal. Calcd. for $C_9H_{15}ON$: C, 70.6; H, 9.8; specific activity expected, $8/9 \times 14.1 = 12.5$ mμc./mg. C. Found: C, 70.3; H. 10.2; specific activity, 12.6 mμc./mg. C.

α-Cinenic Acid-(2-methyl)-C^{14}.—A solution containing 2.67 g. of α-cinenic nitrile-(2-methyl)-C^{14}, 1 g. of potassium hydroxide, 2 ml. of methanol, 3 ml. of ethanol and 3 ml. of water was refluxed for 24 hours. At the end of this time, ammonia was still being evolved. A solution of 1 g. of potassium hydroxide in 2 ml. of water was added and refluxing continued for an additional 24 hours. Ammonia evolution had now stopped. The reflux condenser was removed and a few ml. of solvent allowed to distil out. The mixture was then cooled, extracted twice with ether to remove neutral material and acidified with hydrochloric acid. At this point an oil separated which crystallized within a few minutes. The crude α-cinenic acid was extracted thrice with ether, the ether washed with water, dried over magnesium sulfate, and evaporated. In this way 2.96 g. of crude product, m.p. 81–82°, was obtained. To this was added 10.03 g. of pure, synthetic α-cinenic acid. The mixture was taken up in hot cyclohexane, concentrated to *ca.* 50 ml., and allowed to crystallize overnight. The first crop of crystals weighed 10.2 g., and an additional 1.9 g. was obtained by concentration of the mother liquors. The yield of α-cinenic acid-(2-methyl)-C^{14}, based on the specific activity of the final product, was 89%.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.8; H, 9.30. Found: C, 62.4; H, 9.55; specific activity, 2.66 mμc./mg. C.

Rearrangement of α-Cinenic Acid-(2-methyl)-C^{14}.—Thirty-five ml. of concd. sulfuric acid was cooled to 5° in an ice-bath, and 5.97 g. of finely powdered α-cinenic acid-(2-methyl)-C^{14} added slowly. The resultant clear, colorless solution was covered with dry nitrogen, protected with a calcium chloride tube and allowed to stand at room temperature for 21 hours, at the end of which time it was the color of light honey. The reaction mixture was poured onto ice, diluted to 400 ml., and continuously extracted with ether. The ether phase was extracted with several portions of aqueous sodium bicarbonate. The combined aqueous washings were then acidified with dilute sulfuric acid and extracted thrice with ether. The ether layer was finally washed twice with water, dried over magnesium sulfate, and evaporated to yield 3.39 g. of acidic residue. Distillation yielded 2.47 g. of geronic acid,[26] b.p. ca. 135° (25 mm.), corresponding to 41% of theory.

Anal.[24] Calcd. for $C_9H_{16}O_3$: C, 62.8; H, 9.30. Found: C, 62.3; H, 9.27; specific activity, 2.67 mμc./mg. C.

Iodoform Degradation of Radioactive Geronic Acid.—A solution of 623 mg. of geronic acid obtained in the above experiment was prepared using a small amount of aqueous sodium carbonate. Excess potassium iodide was added (*ca.* 3 g.), and Clorox was allowed to run in dropwise until no further iodoform was produced. (This point was discerned by addition of Clorox to filtered samples of the reaction mixture.) The iodoform was then filtered, washed with water, and dried in a vacuum desiccator. In this way 1.07 g. (75%) of crude iodoform was obtained. This material was purified by two successive vacuum sublimations (50° (0.1 mm.)), which produced brilliant, lemon-yellow hexagons of iodoform with only negligible loss of material; specific activity of crude CHI_3, 24.0 mμc./mg. C; specific activity of resublimed CHI_3, 24.1 mμc./mg. C; specific activity calculated on basis of carboxyl transfer, $9 \times 2.67 = 24.0$ mμc./mg. C (specific activity calculated on basis of methyl migration, 0 mμc./mg. C).

Acknowledgment.—The author is deeply grateful to the members of the Chemistry Department of Brookhaven National Laboratory for providing the facilities and encouragement which have made this work possible.

UPTON, LONG ISLAND, N. Y.

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(23) *Cf.* J. Baddiley, G. Ehrensvard and H. Nilsson, *J. Biol. Chem.*, **178**, 399 (1949).

(24) Elementary analysis by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

(25) A crystalline material, m.p. 90–91°, which is actually a by-product from the hydration of methylheptenone, remains in the residue during this distillation. It has the composition $C_8H_{16}O_2$ (*Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.7; H, 11.11. Found: C, 66.8; H, 11.45) and seems to be a ditertiary alcohol. This material, possibly the product of an internal Prins type reaction, will be discussed in a subsequent communication.

(26) The infrared spectrum of this acid, indistinguishable from that of geronic acid obtained in preliminary "cold" runs, showed two strong bands in the double bond region. The boiling point is approximate because the final product was distilled rapidly. Geronic acid froze to silky, white needles in the refrigerator.