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The Mechanism of the Rearrangement of Fenchone[1a]

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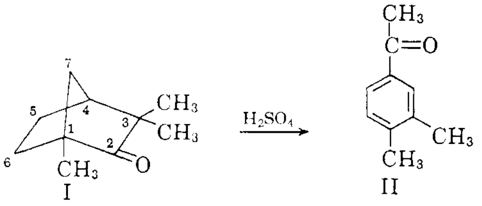
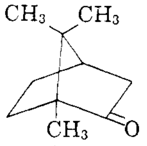
Fenchone labeled with ^{14}C in both methyl groups at the 3-position rearranges in concentrated sulfuric acid to 3,4-dimethylacetophenone in which the radioactivity is essentially equally distributed between the methyl group adjacent to the carbonyl and the one in the ring 4-position (see Fig. 4). A by-product of the rearrangement is camphor, which is likewise in part converted to fenchone in sulfuric acid. The mechanisms of these conversions are discussed.

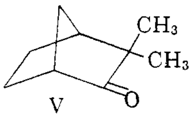
Introduction

The oxidative rearrangement of fenchone (I) in concentrated sulfuric acid at 80–100° affords 3,4-dimethylacetophenone (II) in about 45% yield.[2] Under similar conditions, camphor (III) furnishes 3,4-dimethylacetophenone in addition to carvenone (IV),[3] and camphenilone (V) rearranges to *p*-methylacetophenone (VI) in 15% yield.[4] Noyce[4] has rationalized the course of the reactions by a mechanism involving carbonium-ion intermediates interconverted by a series of more or less conventional 1,2-shifts, but in view of the profound skeletal rearrangements which accompany the carbonium-ion reactions of even the simplest bicyclic systems,[5] it seemed advisable to study these rearrangements using tracer techniques. For this purpose, we have carried out the rearrangement of fenchone labeled with carbon-14 in both methyl groups of the 3-position, and have determined the distribution of radioactivity in the resulting 3,4-dimethylacetophenone. In the course of this study, it was observed that fenchone and camphor are interconverted by the action of concentrated sulfuric acid.

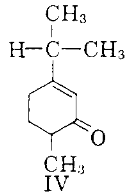




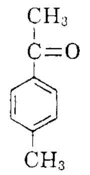
III



V



IV



VI

Synthesis and Rearrangement.—Radioactive fenchone was prepared as outlined in Fig. 1 by a procedure based on that of Beckmann and Schaber.[6] The final product after dilution with inactive fenchone had an activity of 12.3 ± 0.05 microcuries per millimole (μc./mmole) and was rearranged by heating at 90° for 30 minutes with ten times its weight of concentrated sulfuric acid. The reaction mixture was diluted with water and extracted with pentane to isolate the crude product, which was found by vapor-phase chromatography (v.p.c.) to contain about 70% of 3,4-dimethylacetophenone in addition to several other components whose identity is discussed later. Inactive 3,4-dimethylacetophenone was added to the mixture to facilitate isolation of the radioactive sample. The yield of radioactive material in the rearrangement was 44%.

Degradation Procedures.—Degradation of the radioactive 3,4-dimethylacetophenone and the activities of the degradation products are summarized in Fig. 2; the reaction yields are given in parentheses. The radioactive samples were not further diluted with inactive material in the degradation.

The sum of the activities of iodoform and 4-methoxybenzene-1,2-dicarboxylic acid was taken as 100%, and the radioactivity in the 4-methyl group was taken as the difference between the value for 4-methoxybenzene-1,2-dicarboxylic acid and that for 2,4-dibromo-5-methoxybenzoic acid. The carbon dioxide produced in the decarboxylation reaction was not isolated. The distribution of carbon-14 in the 3,4-dimethylacetophenone is shown in Fig. 3. If the radioactivity in the 4-position is actually significantly greater than 50%, it could be due to a small carbon isotope effect in the decarboxylation reaction. Isotope effects did not seem important in the rest of the degradation sequence, as indicated by the agreement between the activities of 3,4-dimethylbenzoic acid and 4-methoxybenzene-1,2-dicarboxylic acid.

Discussion

The results of the tracer experiment are essentially in agreement with the mechanism suggested by Noyce,[4] which is shown in Fig. 4 in a version slightly modified from the original formulation. Intermediates are shown for the purpose of

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[1] (a) Supported in part by the Petroleum Research Fund of the American Chemical Society. Grateful acknowledgment is made herewith to the Donors of this Fund. (b) United States Rubber Co. Foundation Fellow, 1960–1961.

[2] (a) J. E. Marsh, *J. Chem. Soc.*, **75**, 1058 (1899); (b) H. E. Zaugg, *J. Am. Chem. Soc.*, **67**, 1861 (1945).

[3] (a) H. E. Armstrong and F. S. Kipping, *J. Chem. Soc.*, **63**, 75 (1893); (b) J. Bredt, F. Rochussen and J. Monheim, *Ann.*, **314**, 369 (1901).

[4] D. S. Noyce, *J. Am. Chem. Soc.*, **72**, 924 (1950).

[5] J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *ibid.*, **76**, 4501 (1954).

[6] S. Beckmann and R. Schaber, *Ann.*, **585**, 154 (1954).

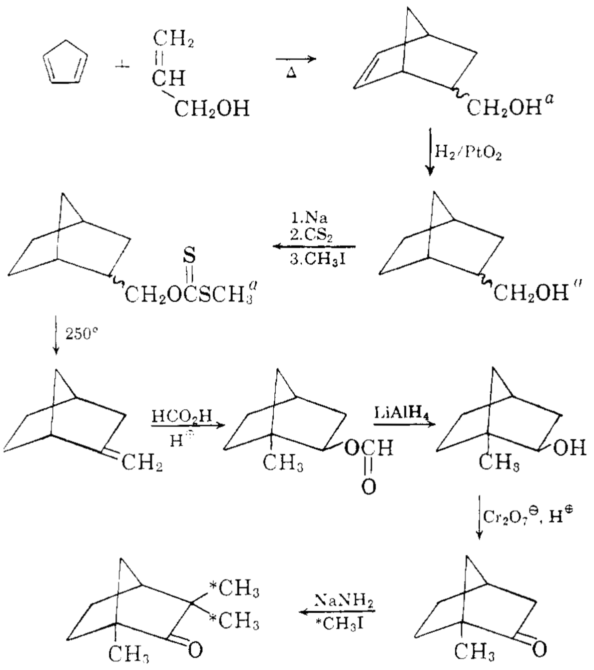
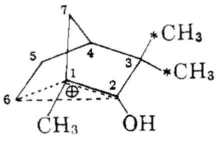


Fig. 1.—Synthesis of radioactive fenchone. [a] A mixture of the *exo* and *endo* products.

clarity as conventional carbonium ions, although all of the bicyclic ions discussed herein are probably more accurately represented as non-classical bridged structures[7] (*cf.* VIIa), whose properties impose certain restrictions on the possible courses of the rearrangement. The 1,2-methyl shift which converts VII to VIII very likely involves the *exo*-methyl group, since an examination of VIIa, the non-classical bridged counterpart of VII, reveals that migration of the corresponding *endo*-methyl group would be hindered by the partial bond between C-6 and C-2.



VIIa

The conversion of VIII to IX is depicted as an over-all migration of hydroxyl. That such a transformation can indeed take place is shown by the isotope-position rearrangement of ^{14}C-labeled benzopinacolone[8] (XII) under conditions similar to those employed for the rearrangement of fenchone. The labeled carbon atom loses the oxygen which was originally attached to it, but the exact mechanism of the transfer is not at all certain. Direct 1,2-migration of hydroxyl is one possibility. In terms of the mechanism proposed for the fenchone rearrangement, formation of IX from VIII would require the migration of an *endo*-hydroxyl group, but this should not be severely hindered by the partial bond between C-5 and C-3 in the appropriate bridged structure since this bond is weak (because it concentrates positive charge at the secondary

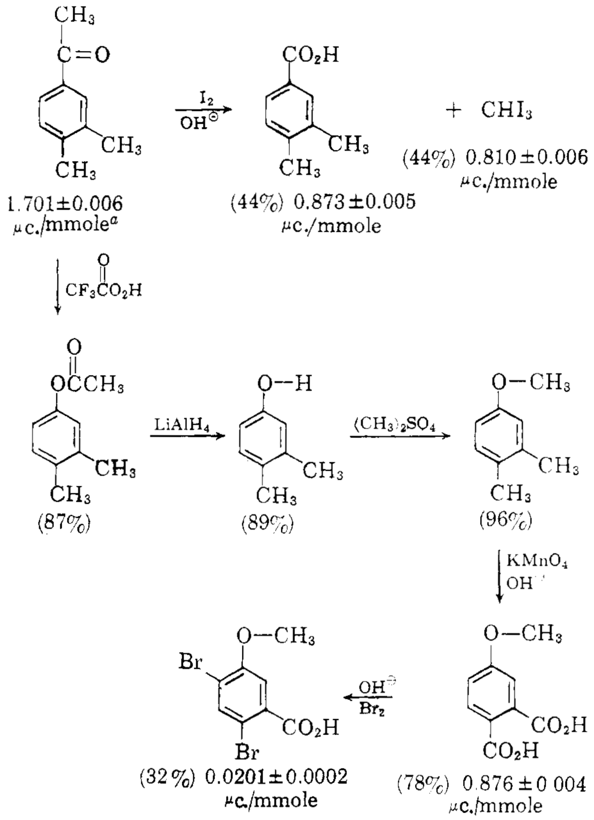


Fig. 2.—Degradation of radioactive 3,4-dimethylacetophenone. Activities are in microcuries per millimole (μc./mmole) and were determined by the vibrating-reed electrometer method as described by O. K. Neville, *J. Am. Chem. Soc.*, **70,** 3499 (1948). Errors are expressed as average deviations in the case of duplicate determinations or as standard deviations when three or more measurements were made (see Experimental). [a] Measured as the 2,4-dinitrophenylhydrazone; all other compounds whose activities are indicated were assayed directly.

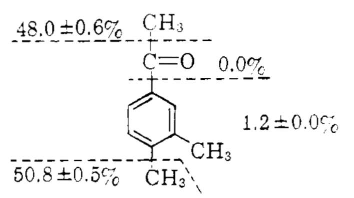
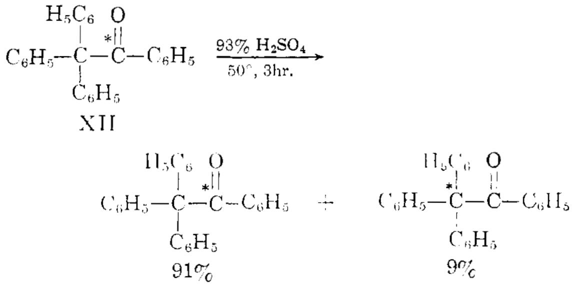


Fig. 3.



XII

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[7] For a mechanistically oriented discussion and review of the structures and rearrangements of bicyclic carbonium ions, see the chapter by J. A. Berson, "Carbonium-Ion Rearrangements in Bridged Bicyclic Systems," in "Molecular Rearrangements," P. de Mayo, Editor, Interscience Publishers, Inc., New York, N. Y., in press.

[8] A. Fry, W. L. Carrick and C. T. Adams, *J. Am. Chem. Soc.*, **80,** 4743 (1958).

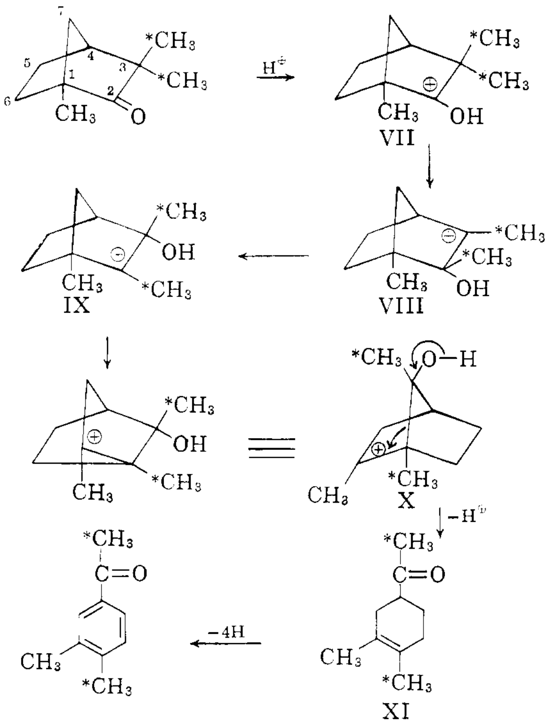
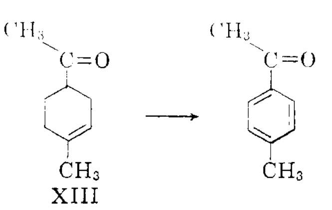


Fig. 4.

center, C-4) with respect to the partial bond between C-5 and C-4 (which concentrates the charge at a tertiary center, C-3). Other possible pathways involve epoxide, protonated epoxide, dihydroxy or sulfate intermediates.

A conventional Wagner–Meerwein rearrangement converts IX to X. Formation of XI occurs by a fragmentation of a type frequently encountered in the carbonium-ion reactions of bicyclic compounds.[9] The nature of the final aromatization reaction is uncertain, but it could involve abstraction of hydride from the ring by $^{\oplus}SO_3H$ followed by loss of a proton.[10] The sulfurous acid by-product would decompose to water and sulfur dioxide; the latter is in fact evolved in the course of the rearrangement. The reality of an intermediate corresponding to XI is made plausible by the observation that 1-methyl-4-acetylcyclohex-1-ene (XIII) is converted to *p*-methylacetophenone by heating with concentrated sulfuric acid, the reaction being accompanied by evolution of sulfur dioxide.[11]



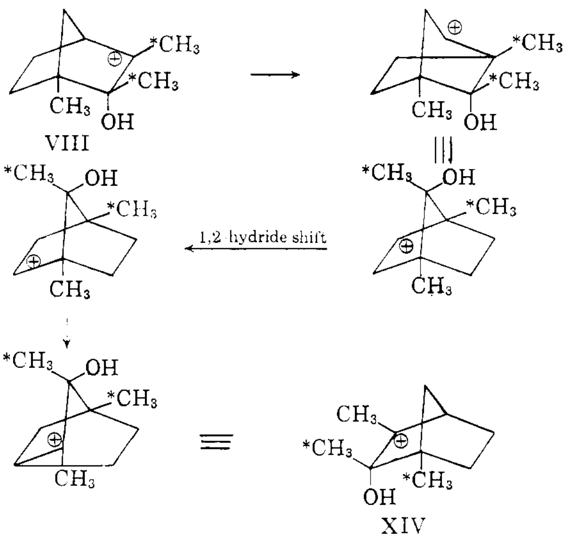
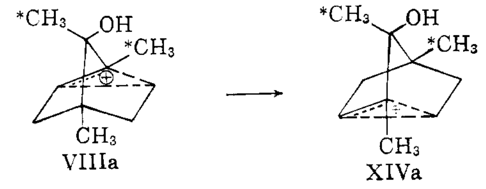
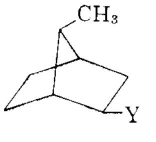


Fig. 5.

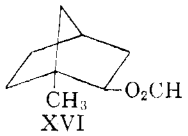
The approximately 4% of reaction which puts radioactive carbon at the 3-methyl of 3,4-dimethylacetophenone at the expense of the methyl group adjacent to the carbonyl may be rationalized by the sequence of steps shown in Fig. 5. Intermediate VIII is converted to its mirror image (except for ^{14}C) XIV which would then go to product in the same manner as suggested for VIII. In terms of the bridged-ion description, the transformation is from VIIIa to XIVa. To account for the observed radioactivity distribution, this equilibration must be slow with respect to succeeding product-forming steps.



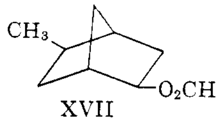
1,2-Hydride shifts are rarely encountered in the carbonium-ion reactions of bicycloheptane derivatives, but such a shift apparently is required to explain the production of 1-methyl-2-*exo*-norbornyl formate (XVI) in the formolysis of *syn*-7-methyl-2 *exo*-norbornyl acid phthalate (XV).[12] A second product, 5-*exo*-methyl-2-*exo*-norbornyl formate (XVII), may be derived by the conventional combination of Wagner–Meerwein rearrangement and 1,3-hydride shift; a plausible route for formation



XV, Y = acid phthalate



XVI



XVII

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(9) Exemplified by the conversion of camphor to carvenone, discussed in a later section.

(10) As suggested by W. von E. Doering and F. M. Beringer, *J. Am. Chem. Soc.*, **71**, 2221 (1949).

(11) O. Wallach and O. Rahn, *Ann.*, **324**, 79 (1902).

(12) S. Beckmann and G. Eder, *Chem. Ber.*, **91**, 2878 (1958).

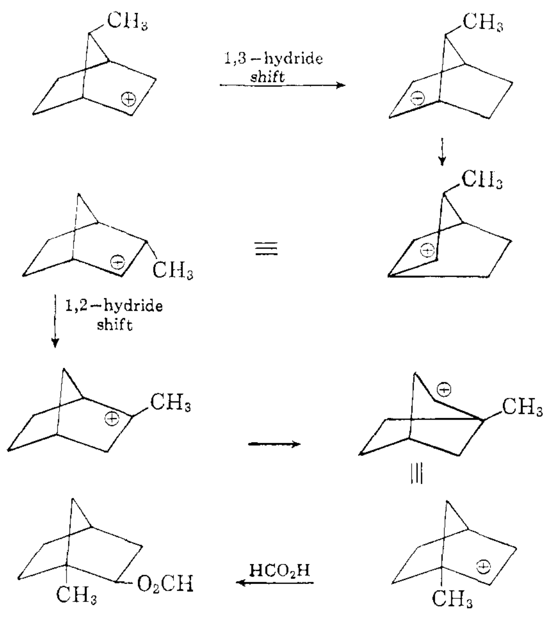


Fig. 6.

of the 1-substituted derivative has been suggested by Berson[7,13] and is given in Fig. 6.

The principal by-product of the rearrangement of fenchone was camphor, identified by a comparison of its infrared spectrum and v.p.c. retention time with those of an authentic sample. The complete v.p.c. spectrum is reproduced in Fig. 7A. Treatment of camphor with concentrated sulfuric acid under conditions comparable to those employed for the rearrangement of fenchone yielded a mixture whose v.p.c. spectrum (Fig. 7B) showed that the same components, although in different proportions, were produced in both rearrangements. The principal product of the camphor rearrangement in addition to 3,4-dimethylacetophenone is known to be carvenone (IV)[3b]; the peaks so designated in the v.p.c. spectra were assigned on that basis. It is seen that camphor is also partially converted to fenchone.[14]

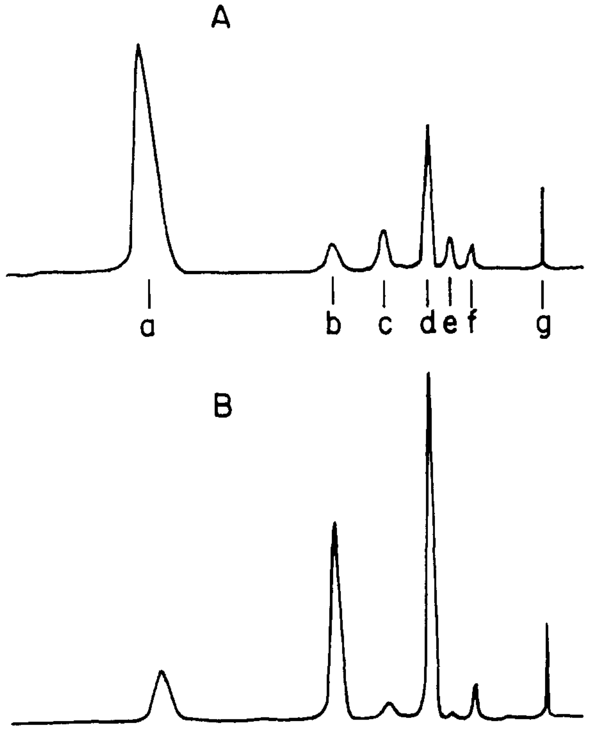
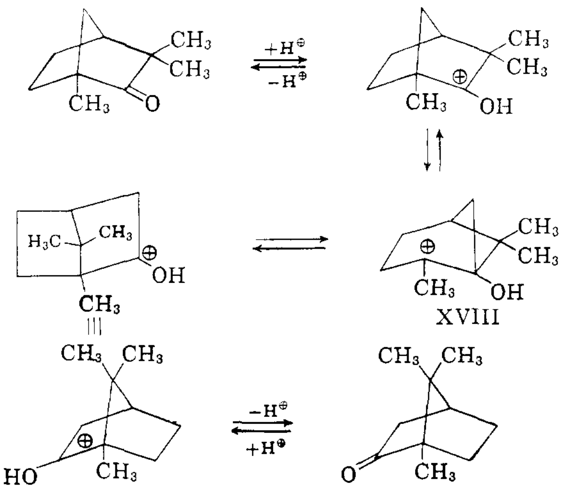
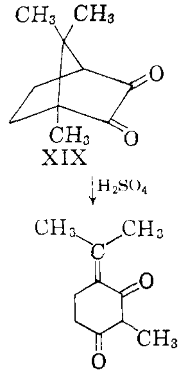


Fig. 7.—Vapor-phase chromatograms of rearrangement product mixtures analyzed at 190° using polyethylene glycol (Carbowax 1500) on a diatomaceous earth support. The indicated peaks represent the following compounds: a, 3,4-dimethylacetophenone; b, carvenone; c, unidentified; d, camphor; e, unidentified; f, fenchone; g, solvent. The distance between a and g on the time scale is 17 min. (A) Rearrangement of fenchone at 90° for 30 min.; (B) rearrangement of camphor at 90° for 1 hr.; the same mixture, except for relative proportions, was obtained after 30 min. at 90°.

The interconversion of fenchone and camphor is most readily rationalized by a process involving the four-membered-ring intermediate XVIII. Analogous intermediates have been proposed to account for the conversion of camphorquinone (XIX) to isocamphorquinone (XX),[15] and for the formation of α-terpineol (XXII) as a minor product in the nitrous-acid deamination of *endo*-fenchylamine (XXI).[4,16]

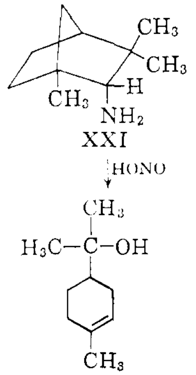


XVIII



XIX

XX



XXI

XXII

The most reasonable pathway for the conversion of camphor to 3,4-dimethylacetophenone then ap-

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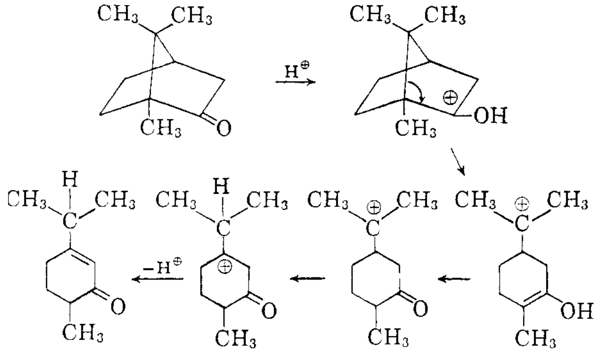
[13] This route is different from that suggested in ref. 12.

[14] Based on the identity of v.p.c. retention times.

[15] S. G. Levine, *J. Am. Chem. Soc.*, **82**, 2556 (1960).

[16] W. Hückel and U. Ströle, *Ann.*, **585**, 182 (1954).

pears to be through the intermediate formation of fenchone, as suggested by Noyce. Likewise, the production of carvenone in the rearrangement of fenchone probably involves camphor by the straightforward route shown below.



Experimental

The synthesis of labeled fenchone, summarized in Fig. 1, was based on procedures either given or referred to by Beckmann and Schaber.[6] The experimental details will be reported here only for reactions involving radioactive materials.

In the procedure of Beckmann and Schaber, 1-methyl-*exo*-norborneol was prepared by the sulfuric acid-catalyzed addition of acetic acid to norcamphene followed by saponification of the acetate with methanolic potassium hydroxide. In the present work, it was found that reduction of the acetate with lithium aluminum hydride yielded a mixture which was shown by v.p.c. (column K,[17] 144°) to contain about 65% of 1-methyl-*exo*-norborneol and 35% of the isomeric 2-methyl-2-hydroxynorbornane. The structure of the latter was assigned on the basis of its acid-catalyzed equilibration with 1-methyl-*exo*-norborneol. Variations in the experimental conditions for the preparation of the acetate effected only minor changes in the proportion of the two products, but a mixture containing about 95% of 1-methyl-*exo*-norborneol could be obtained by preparation and reduction of the formate ester. The formate was obtained by the addition of formic acid catalyzed by fluoroboric acid, and reduction with lithium aluminum hydride was carried out by the usual procedure.

Radioactive Fenchone from 1-Methylnorcamphor.—To an ice-cold magnetically stirred suspension of sodamide in 50 ml. of ether, prepared by the procedure described by Vogel[18] from liquid ammonia and 3.1 g. (0.13 mole) of metallic sodium, was added 4.5 g. (0.036 mole) of 1-methylnorcamphor. The mixture was heated at reflux for 1.5 hr., cooled in an ice-bath, and 7.0 g. (0.049 mole) of radioactive methyl iodide[19] (about 16 μc./mmole) was added all at once, causing the immediate precipitation of a white solid. The mixture was heated at reflux for 1 hr., the coolant (ice-water) then drained out of the reflux condenser, and the ether and excess methyl iodide were allowed to distil over to be collected at −78°. The last of the low-boiling liquids was brought over under reduced pressure. In a pilot reaction prior to this particular run, a sample of the residue remaining after removal of ether and methyl iodide was quenched with water and the ketone mixture isolated by extraction with pentane and removal of the solvent. Analysis by v.p.c. (column C,[17] 162°) showed that it contained about 40% of fenchone, 60% of fenchosantenone (1,3-dimethylbicyclo[2.2.1]heptan-2-one) and a trace of 1-methylnorcamphor.

The residue was cooled in ice, and a freshly prepared suspension of sodamide [from 3.1 g. (0.13 mole) of sodium] in 50 ml. of ether added. The mixture was refluxed for 1.5 hr., then cooled in ice; 4.4 g. (0.031 mole) of the radioactive methyl iodide was added and reflux continued for an additional 30 min. At this point was added 15 g. of a 17% (by weight) solution of radioactive methyl iodide (2.6 g., 0.018 mole) in ether; this solution was recovered from a previous preparation of radioactive fenchone and was used as such, since it was found impractical to separate the methyl iodide from the solvent ether. Reflux was continued for 1 hr., then the ether and excess methyl iodide were removed as before.

The excess sodamide was cautiously decomposed by the dropwise addition of water, and the mixture acidified with 10% sulfuric acid (until the 100-ml. reaction vessel was almost full) followed by the dropwise addition of concentrated sulfuric acid. The organic layer was examined by v.p.c. (column A,[17] 167°) and found to contain about 75% of fenchone, 13% of 1-methylnorcamphor and 12% of what are believed to be *exo*- and *endo*-fenchosantenones.

Inactive fenchone[20] (4.5 g.) was added to the reaction mixture and the total continuously extracted for 28 hr. with pentane. The pentane was removed by distillation, and the residue set aside for 45 hr. in 30 ml. of methanol containing the semicarbazide acetate prepared by triturating 4.5 g. of semicarbazide hydrochloride with 6.8 g. of anhydrous sodium acetate. (Fenchone forms the semicarbazone very slowly, whereas 1-methylnorcamphor and fenchosantenone react readily.) The solution was diluted with 100 ml. of water, extracted with two 40-ml. portions of pentane and continuously extracted for 48 hr. with pentane. The pentane solution containing the principal sample of product was filtered to remove semicarbazone which had separated out within 1 day, dried over anhydrous sodium sulfate and distilled to remove solvent. The crude fenchone was distilled through a short Vigreux column to yield 0.20 g. of forecut, 6.75 g. boiling at 69–72° (11 mm.) and 0.15 g. which was distilled using the full pump vacuum with strong heating of the pot and column. Analysis by v.p.c. (column A,[17] 168°) indicated that the forerun contained about 10% of low-boiling impurities and that the other fractions contained less than 1% of impurities.

The pentane solution from the continuous extraction was separated from precipitated semicarbazones, dried and distilled; the residue, found by v.p.c. to contain a large proportion of impurities, was treated as before with semicarbazide acetate. The fenchone which was isolated and distilled (0.40 g.) contained less than 1% of impurities. The combined weights of all the fenchone fractions represent a yield of 55% for the methylation reaction if it is assumed that the inactive fenchone added to the crude product mixture was recovered quantitatively.

The oxime of the radioactive fenchone was prepared in 86% yield by heating a sample, quantitatively diluted with inactive fenchone, with hydroxylamine hydrochloride in pyridine solution on the steam-bath for 8 hr., and sublimation of the crude product; m.p. 159–160° (sealed capillary; lit.[6,21] m.p. of the α-oxime, 158–160°). Radioactivity analysis (duplicate) indicated an activity for the undiluted fenchone of 12.3 ± 0.05 μc./mmole.

Rearrangement of Radioactive Fenchone.—A sample of radioactive fenchone (6.52 g., 0.0429 mole) was added all at once to 35 ml. of 95.5–96.5% sulfuric acid maintained at 90° and the mixture was magnetically stirred and heated at 90° for 30 min.; during this period sulfur dioxide was evolved. The dark-brown reaction mixture, containing a considerable amount of charred material, was cooled to room temperature, poured over crushed ice, diluted to about 400 ml., and continuously extracted with pentane for 24 hr. A sample of the extract was withdrawn, the solvent removed, and the residue examined by v.p.c. (column K,[17] 192°; see Fig. 7-A). The boiler was replaced with a flask of fresh pentane, 5.0 g. of inactive 3,4-dimethylacetophenone was added to the extraction vessel, and extraction continued for an additional 36 hr. The pentane solution from the first extraction was filtered through a bed of anhydrous magnesium sulfate mixed with anhydrous sodium carbonate; the solution from the second extraction was filtered through the

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[17] Analyses were made with a Perkin–Elmer vapor fractometer. The column designations refer to the following stationary phases: column A, diisodecyl phthalate; column C, dimethylsiloxane polymer (silicone oil DC-200); column K, polyethylene glycol (Carbowax 1500).

[18] A. I. Vogel, "Practical Organic Chemistry," Third Edition, Longmans, Green and Co., Inc., New York, N. Y., 1956, p. 197.

[19] Prepared in 89% yield by distilling the iodide out of the mixture obtained from radioactive methanol and a large excess of 55–58% hydroiodic acid, followed by drying and distillation from phosphorus pentoxide.

[20] Obtained by the careful fractional distillation of commercial fenchone and shown by v.p.c., using several different columns, to be >99% pure.

[21] O. Wallach, *Ann.*, **272**, 99 (1893); for the β-oxime, see M. Delepine, *Bull. soc. chim., France*, **35**, 1330 (1924).

same bed, followed by 1.0 g. of inactive 3,4-dimethylacetophenone to flush out the radioactive material.

The combined filtrates and washings were distilled to remove solvent, an additional 7.0 g. of inactive 3,4-dimethylacetophenone was added to the residue, and distillation continued (using a 30-cm. wire-spiral-packed column) to yield 1.2 g. of material boiling at 31–71° (0.1 mm.). This fraction contained the by-products of the rearrangement, the principal one of which was shown to be camphor by a comparison of its v.p.c. retention time and infrared spectrum with those of an authentic sample. The camphor solidified in the head and condenser during distillation and was remelted with a small flame. The column was then washed down with 1.0 g. of inactive 3,4-dimethylacetophenone, and 1.1 g. of a mixture of inactive by-products obtained from the rearrangement of inactive fenchone was added to the boiler. Distillation was continued using a 22-cm. heated vacuum-jacketed Vigreux column equipped with a fractionating head; the fractions were examined by v.p.c. (column K,[17] 200°) as they were collected. Ten fractions (4.4 g.) were taken before the principal one [13.7 g., 57.8–59° (0.3 mm.)]. When as much of the product as possible had been collected, 1.0 g. of inactive 3,4-dimethylacetophenone was added to the residue and distilled to yield 1.1 g. of sample which was combined with the main fraction. Fractions 5–10 were combined and redistilled to yield, in addition to forefractions, 3.6 g. of acceptably pure material which was added to the main sample (18.4 g.), which was then diluted to 20.0 g. with inactive 3,4-dimethylacetophenone.

The 2,4-dinitrophenylhydrazone was prepared in 97% yield by heating on the steam-bath for 20 min. 108 mg. (0.729 mmole) of the final diluted product with 10% excess of a 0.15 F stock methanolic solution (0.3 F in sulfuric acid) of 2,4-dinitrophenylhydrazine. The dried product was recrystallized three times from dioxane and vacuum dried; m.p. 256–257° (Kofler block, with some pre-melting at 253°). Duplicate radioactivity analyses gave the value 1.701 ± 0.006 μc./mmole. The radioactivity yield in the rearrangement was 44%.

Degradation of Radioactive 3,4-Dimethylacetophenone. Haloform Reaction of 3,4-Dimethylacetophenone.—The procedure used was an adaptation of that given in Shriner, Fuson and Curtin.[22] A sample of the radioactive 3,4-dimethylacetophenone (501 mg., 3.38 mmoles) was dissolved in 15 ml. of dioxane, and 5 ml. of 10% sodium hydroxide was added. To the magnetically stirred suspension was added all at once 23 ml. of a solution prepared by dissolving 10 g. of iodine and 20 g. of potassium iodide in 80 ml. of water. After 1.5 min., sufficient 10% sodium hydroxide (about 2 ml.) was added to react with the excess iodine and most of the sample was poured into 110 ml. of water. The remaining yellow-brown sticky globules were dissolved in a little dioxane, and a few drops of 10% sodium hydroxide was added to destroy the dark coloration. The solution was added to the main aqueous mixture and placed in a refrigerator overnight.

The iodoform was collected and air-dried (586 mg., 44%) then recrystallized three times from 95% ethanol and vacuum-dried (149 mg., m.p. 123° dec., Kofler block). Radioactivity analyses in quadruplicate gave 0.810 ± 0.006 μc./mmole for this material.

The aqueous filtrate from above was evaporated to near dryness on the steam-bath under reduced pressure (rotary evaporator); the residue was redissolved in 20 ml. of water, filtered, and acidified with 15 ml. of 10% hydrochloric acid. The resulting precipitate was suction-filtered from the iodine-colored solution, washed well with water and air-dried (221 mg., 44% yield). It was recrystallized three times from 60% (vol.) aqueous acetic acid, but since the product was still cream-colored, it was redissolved in the combined mother liquors and heated with two separate portions of activated charcoal. About 1 ml. of water was added to the hot solution; the 3,4-dimethylbenzoic acid was allowed to crystallize slowly to yield a clean white product which was collected and dried under reduced pressure (71 mg., m.p. 165–166°, sealed capillary; lit.[23] m.p. 166.5°). Radioactivity analyses in triplicate gave for the pure material 0.873 ± 0.005 μc./mmole.

3,4-Dimethylphenyl Acetate.—The procedure was adapted from that of Emmons and Lucas.[24] Peroxytrifluoroacetic acid was prepared by the dropwise addition (over a period of 1 hr.) of 48.5 g. (0.231 mole) of freshly distilled trifluoroacetic anhydride (38–40°) to an ice-cooled suspension of 6.5 g. (0.19 mole) of hydrogen peroxide (as a 90% solution) in 40 ml. of dichloromethane. The resulting water-clear solution was added dropwise over 1 hr. to 18.5 g. (0.125 mole) of radioactive 3,4-dimethylacetophenone in 160 ml. of dichloromethane containing 83 g. (0.58 mole) of finely powdered disodium hydrogen phosphate; the solvent refluxed from the exothermic reaction, and efficient stirring of the viscous mass was required to keep the reaction under control. The mixture was stirred and heated at reflux for 1 hr. after the completion of addition.

The solids were filtered out with suction and washed with 200 ml. of dichloromethane, and the filtrate and washings were extracted with 75 ml. of 6% sodium carbonate and dried over anhydrous magnesium sulfate. The aqueous layer was washed with a little dichloromethane which was added to the main body of solution; the solvent was removed by distillation. The crude material was distilled through a 22-cm. heated vacuum-jacketed Vigreux column to yield 0.4 g. of bright yellow forerun of b.p. 52–59° (0.6 mm.) and 16.7 g. of pale yellow liquid boiling at 62–65° (0.6–0.7 mm.). Flash distillation of the residue using a semi-micro apparatus afforded an additional 0.8 g. of sample. The infrared spectra of the first two fractions were virtually identical with that of an authentic water-clear sample of 3,4-dimethylphenyl acetate. The spectrum of the third fraction indicated that it was mainly the desired product contaminated by easily detectable impurities. The combined weights of the three fractions represented an 87% yield.

3,4-Dimethylphenol.—A solution of 17.8 g. (0.108 mole) of radioactive 3,4-dimethylphenyl acetate in 150 ml. of anhydrous ether was added dropwise, at a rate sufficient to maintain a moderate reflux, to 4.0 g. (0.11 mole) of lithium aluminum hydride suspended with stirring in 30 ml. of ether. Stirring at room temperature was continued for 1 hr. and 15 min. after the completion of addition. The excess lithium aluminum hydride was decomposed with water and the mixture acidified with 130 ml. of 10% sulfuric acid. The aqueous layer was separated, further acidified with 20 ml. of 10% sulfuric acid and extracted with 40 ml. of fresh ether. The aqueous layer was again acidified with 20 ml. of the dilute acid and continuously extracted with ether for 12 hr.

The combined ether solutions were dried over anhydrous magnesium sulfate and distilled through a 30-cm. wire-spiral-packed column to remove solvent. The boiler contents were transferred to a smaller flask, and distillation was continued with a bath temperature up to 165° to yield 1.5 g. of ethanol (70–77.5°). The residue, which solidified when refrigerated, was recrystallized from *n*-hexane, and the mother liquors repeatedly concentrated until no more 3,4-dimethylphenol could be obtained; the combined air-dried samples weighed 11.7 g. (89% yield).

3,4-Dimethylphenyl 3,5-Dinitrobenzoate.—A portion of the radioactive 3,4-dimethylphenol was recrystallized once more from *n*-hexane; 104 mg. (0.852 mmole) of the recrystallized material was mixed intimately with 0.25 g. (1.1 mmoles) of 3,5-dinitrobenzoyl chloride and heated on the steam-bath until most of the mixture had liquefied. Pyridine (1 ml.) was added to dissolve the sample completely, and the solution heated on the steam-bath for 10 min. The solution was cooled to room temperature, 6 ml. of 5% sodium carbonate solution was added, and the resulting precipitate was collected by suction filtration, washed with water and vacuum dried (131 mg., 49% yield). The sample was twice recrystallized from 95% ethanol (activated charcoal was used in the first recrystallization) and dried for 3 hr. at 60° (< 1 mm.); m.p. 181–182° (Kofler block), with some peripheral melting at 171–174° followed by resolidification (lit.[25] m.p. 181.6°). Duplicate ^{14}C analyses gave 0.868 ± 0.001 μc./mmole. Further recrystallization of this derivative might have brought the radioactivity into closer agreement with the values for 3,4-dimethylbenzoic acid and 4-methoxybenzene-1,2-dicarboxylic acid (see below). In view of the agreement between the latter two, no further purification and analysis of the 3,5-dinitrobenzoate was carried out.

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(22) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Fourth Edition, John Wiley and Sons, Inc., New York, N. Y., 1960, p. 156.

(23) S. Coffey, *Rec. trav. chim.*, **42**, 387 (1923).

(24) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(25) M. Phillips and G. L. Keenan, *ibid.*, **53**, 1924 (1931).

3,4-Dimethylanisole.—The procedures for the preparation and oxidation of 3,4-dimethylanisole were adapted from those given by King.[26] The radioactive 3,4-dimethylphenol (11.5 g., 0.0942 mole) as a solution in 55 ml. of 2 *F* sodium hydroxide was stirred magnetically and heated to 95° in a 300-ml. flask equipped with two dropping funnels and a reflux condenser. The temperature was maintained at 92–97° during the simultaneous dropwise addition (over a period of 10 min.) of 55 ml. of 2 *F* sodium hydroxide and 18 ml. (about 14 g., 0.11 mole) of methyl sulfate, and for 30 min. after the completion of addition.

The mixture was cooled to room temperature and extracted with 70 ml. of ether in two portions; the aqueous layer was then extracted continuously with ether for 30 hr. The combined ether solutions were dried over anhydrous magnesium sulfate and distilled to remove the solvent. The crude product was distilled through a 22-cm. vacuum-jacketed heated Vigreux column to yield 0.3 g. of product boiling at 66–69° (5 mm.) and 12.0 g. boiling at 68.5–69° (5 mm.; full vacuum was used to bring over the last of the product), with 0.3 g. of undistilled residue. The weight of the combined fractions represents a 96% yield.

4-Methoxybenzene-1,2-dicarboxylic Acid.—Eleven grams (0.0808 mole) of the radioactive 3,4-dimethylanisole was suspended in 30 ml. of 10% sodium hydroxide in a 2-l. flask equipped with a stirrer, reflux condenser and dropping funnel. It was heated on the steam-bath while a solution of 80 g. (0.51 mole) of potassium permanganate in 1100 ml. of water was added dropwise over 6 hr. Heating was continued for 2.5 hr. after the completion of addition.

The hot mixture was suction filtered and the solids washed with 130 ml. of 1% sodium hydroxide; the combined filtrate and washings (still permanganate-colored) were cooled to room temperature, acidified with 40 ml. of concentrated hydrochloric acid (which destroyed the excess permanganate) and refrigerated overnight. The mixture was filtered to remove 0.2 g. of 2-methyl-4-methoxybenzoic acid; the filtrate was concentrated under reduced pressure on the steam-bath (rotary evaporator) until crystallization began (about 200 ml.), and then cooled slowly to room temperature and refrigerated overnight. The precipitate was collected by suction filtration, washed with ice-water, and vacuum dried to yield 12.9 g. of material which, when recrystallized from water, yielded three crops weighing 7.9 g., 1.2 g., and 0.4 g. No more acid could be obtained from the mother liquor, indicating that the original 12.9 g. of precipitate probably contained inorganic salts.

The filtrate was extracted continuously for 30 hr. with ether, and the extract was evaporated to dryness in a stream of nitrogen to yield 2.9 g. of a solid whose infrared spectrum as a mineral-oil mull was similar to that of the recrystallized acid, but which contained an additional broad band at 3500 cm.$^{-1}$. The combined weights of the three recrystallized samples and the residue from the ether extraction represent a yield of 78%. Melting points were not determined since the acid readily forms the anhydride on heating.

A sample of crop 1 from above was recrystallized twice from ethyl acetate and vacuum-dried overnight at room temperature. Radioactivity assay in quadruplicate showed the activity to be 0.876 ± 0.004 μc./mmole.

Brominative Decarboxylation of 4-Methoxybenzene-1,2-dicarboxylic Acid.—The procedure was based on that given by Berman and Price[27] for the decarboxylation of 4-methoxybenzoic acid. Three grams (0.015 mole) of radioactive 4-methoxybenzene-1,2-dicarboxylic acid (from crop 1 of the above preparation) was dissolved in 30 ml. of 10% sodium hydroxide, and 50 ml. of water was added. The solution was stirred magnetically and heated to about 55°, then 4.8 g. (0.030 mole) of bromine was added dropwise over the period of a few minutes. The resulting turbid solution was heated at 55–60° for 15 min., and acidified while still hot with a solution of 25 ml. of concentrated hydrochloric acid in an equal volume of water. Some carbon dioxide was evolved and a dense precipitate formed. The mixture was heated on the steam-bath for 45 min., and filtered hot to collect the 2,4-dibromo-5-methoxybenzoic acid, which was washed with hot water and vacuum dried; 1.5 g. (32% yield), m.p. 197–202° (Kofler block) with peripheral melting from 176°. A portion of the acid was recrystallized from 50% aqueous ethanol and twice more from chloroform; m.p. 205° (Kofler block preheated to 195°, lit.[28] m.p. 203°).

Anal. Calcd. for $C_8H_6O_3Br_2$: C, 31.00; H, 1.95; Br, 51.56; neut. equiv., 310. Found: C, 30.92; H, 2.06; Br, 51.60; neut. equiv., 314.

The n.m.r. spectrum of the acid in acetone showed the two ring-proton resonances as well separated singlets, consistent with the structure of 2,4-dibromo-5-methoxybenzoic acid. Duplicate radioactivity analyses of a vacuum-dried sample showed the ^{14}C activity to be 0.0201 ± 0.0002 μc./mmole.

The original filtrate from above deposited a second crop of crystals when allowed to cool to room temperature; 0.4 g., m.p. 135–165°. The filtrate was then chilled in ice for several hours to precipitate 4-methoxy-5-bromobenzene-1,2-dicarboxylic acid which was collected and dried; 1.5 g., 36% yield. A sample was recrystallized twice from water (it was treated with activated charcoal in the first recrystallization) and vacuum dried over phosphorus pentoxide; m.p. 201–201.5° (Kofler block preheated to 195°). The acid forms the anhydride on heating and the melting point depends on the rate of heating. Faltis, *et al.*,[29] observed foaming at 192° and melting at 195.5°.

Anal. Calcd. for $C_9H_7O_5Br$: C, 39.30; H, 2.57; Br, 29.05. Found: C, 39.16; H, 2.49; Br, 29.14.

A potentiometric titration showed a distinct inflection point at one-half the end-point. The ring-proton resonances in the n.m.r. spectrum of the acid in methanol appeared as well separated singlets. Both of these observations are consistent with the structure of 4-methoxy-5-bromobenzene-1,2-dicarboxylic acid.

Rearrangement of Camphor.—One gram of resublimed camphor, shown by v.p.c. (column K,[17] 192°) to be > 99% pure, was added to 6 ml. (about 11 g.) of 95.5–96.5% sulfuric acid maintained at 90°. Samples were withdrawn periodically, quenched with water and extracted with pentane. The solvent was pumped off under reduced pressure and the residue examined by v.p.c. (column K,[17] 192°). The vapor-phase chromatogram of the product of rearrangement for 1 hr. is given in Fig. 7-B; earlier samples showed the same constituents in different proportions. The main product was designated as carvenone on the basis of the known behavior of camphor in sulfuric acid.[3] Carvacrol (2-methyl-5-isopropylphenol) and *p*-cymene, which might also be formed under the conditions of the rearrangement,[30] were examined by v.p.c., but could not be correlated with any of the unidentified products. Carvacrol apparently reacted with the column packing, since only a few small broad peaks appeared in the analysis of a relatively large sample. It is obvious from a comparison of vapor-phase chromatograms (Figs. 7-A and 7-B) that the same mixture of components, with different proportions, is produced in the rearrangements of both camphor and fenchone.

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