

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WASHINGTON SQUARE COLLEGE, NEW YORK UNIVERSITY]

Inactivation in the Camphene Series

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The inactivation of camphene (I, R = H) occurs comparatively rapidly in acid media, a fact not readily explainable on simple chemical grounds. Of the three asymmetric centers, carbon 2 alone is susceptible to optical alteration through simple chemical change. Lipp and Stutzinger² offered a reasonable theory of its mechanism in terms of well-established chemical transformations of camphene with the added assumption of a "second order" pinacol change in steps II-VII, summarized in formulas I-II-VII-VIII.

The present contribution deals with a further study of the Nametkin³ second order pinacol-pinacolone change in this series, employing camphenes carrying a substituent on carbon 8 (omega). It is evident from the accompanying formulas that the phenomena resulting in the inactivation of ordinary camphene should lead in the new series to structurally isomeric camphenes (VIII). It will be seen further that repetition of these changes on the part of VIII should yield its mirror image and inactivation with change of C-skeleton should result where an optically active hydrocarbon is the starting material.^{4,5}

Previously known methods for synthesis of omega-substituted camphenes⁶⁻¹⁰ were evidently cumbersome in practice or limited in scope, and in any case led to optically inactive products unsuited to our purpose. We succeeded in preparing a series of optically active omega-alkyl camphenes by condensation of omega-chloromethylcamphene with the Grignard reagents. Amyl- and benzylcamphenes were found to inactivate almost completely when heated with aniline hydrohalide in aniline solution, under the conditions which result in inactivation of camphene itself, apparently without formation of

isomers having different physical properties, contrary to expectation from the postulations of Lipp and Stutzinger. Our inability to secure solid derivatives of these hydrocarbons prevented our establishing conclusive evidence of the gross structural identity of the inactive and initially active hydrocarbons.

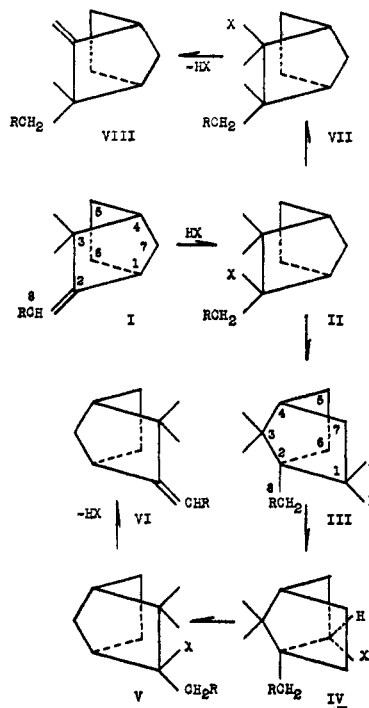


Fig. 1.

1-6 Pinacol exchange of H and X (III-IV), previously observed in the camphene series, was suggested originally by Nametkin and Brüssoff¹¹ to explain the transformation of fenchone to a camphor which was believed at first to be 6-methylcamphor. Nametkin later established its true identity as that of 4-methylcamphor, whose formation cannot be explained through 1-6 change but most simply through second order pinacol exchange.

The inactivation without change of C-skeleton in our own experiments seems most readily explained as the result of 1-6 exchange of H and X, following the path I-VI. The authors wish to emphasize the point that complete confirmation of

(1) Based upon a portion of the Dissertation submitted by George Vlases, Jr., to the Graduate Faculty of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy April, 1939. Original manuscript received June 27, 1941.

(2) Lipp and Stutzinger, *Ber.*, **65**, 241-250 (1932).

(3) Nametkin and Shavruigin, *J. Gen. Chem., U. S. S. R.*, **4**, 847-55 (1934).

(4) Houben and Pfankuch, *Ber.*, **65**, 491 (1932).

(5) Shavruigin, *J. Gen. Chem., U. S. S. R.*, **6**, 1314 (1936).

(6) Langlois, *Ann. chim.*, **12**, 193-363 (1919).

(7) Prins, *C. A.*, **14**, 1662 (1920).

(8) Lipp, Kuppers and Hall, *Ber.*, **60**, 1575 (1927).

(9) Lipp and Quaedvlieg, *ibid.*, **62**, 2311 (1929).

(10) Lipp, Dessauer, and Wolf, *Ann.*, **525**, 271 (1936).

(11) Nametkin and Brüssoff, *ibid.*, **459**, 144 (1927).

TABLE I

Compound.....	ω -Benzyl-camphene	ω -Ethyl-camphene	ω -Amyl-camphene	ω -Cyclohexylmethyl-camphene
Yield, %	81	34	51	45
B. p. { °C. Mm.	138-140 5	104-106 45	124 15	133 4
d	0.9656 (25°)	0.8738 (20°)	0.8668 (20°)	0.9205 (20°)
n_D^{25}	1.537	1.476	1.474	1.500
$[\alpha]_D$	0.66° (25°)	16.4° (20°)	17.8° (20°)	16.5° (20°)
% C (calcd.)	90.19	87.72	87.29	87.85
% C (found)	90.19	87.56	87.31	87.93
% H (calcd.)	9.81	12.28	12.71	12.15
% H (found)	9.90	12.10	12.44	11.88
d^{25} Hydrochloride	(m. p. 58-60°)	0.999	0.963	1.013
n_D^{25} Hydrochloride		1.49	1.48	1.50
% Cl Hydrochloride (calcd.)	13.50	17.67	14.64	13.20
% Cl Hydrochloride (found)	13.17	17.13	14.04	12.79
Bromine addition	+	+	+	+
Molecular weight	214 (benzene)			

the tentative conclusions drawn herein must await unequivocal establishment by chemical means of the identities of the hydrocarbons under discussion.

Experimental

Materials.—The camphene used for the synthesis of ω -benzylcamphene was prepared by treatment of isobornyl chloride with aniline by the procedure of Lipp and Stutzinger² yielding the "primary camphene." The other hydrocarbons were prepared from camphene of much higher specific rotation, secured through the courtesy of E. I. du Pont de Nemours and Co. of Wilmington, Delaware.

Acetate of ω -Hydroxymethylcamphene.—This compound was prepared from camphene, $[\alpha]^{25}_D +25.5^\circ$, by the method of Langlois²; yield of ester 53%; b. p. 130-138° (20 mm.); n_D^{25} 1.480; d^{20} 0.9977; $[\alpha]^{20}_D +18.9^\circ$ (*c*, 99.77). *Anal.* 97.9% ester, mol. wt. 208.0.

ω -Hydroxymethylcamphene was prepared from the ester, $[\alpha]^{25}_D +18.9^\circ$, by Langlois' method. The product was recovered from the reaction mixture by dilution with salt solution and extraction with petroleum ether. The alcohol, b. p. 120-125° (10 mm.), was obtained in 85% yield, n_D^{25} 1.501; d^{20} 0.9841; $[\alpha]^{20}_D +24.0^\circ$ (*c*, 98.41). *Anal.* Calcd. for $C_{11}H_{18}O$: C, 79.50; H, 10.80. Found: C, 79.32; H, 10.85.

ω -Chloromethylcamphene.— ω -Hydroxymethylcamphene (141 g., 0.84 mole; $[\alpha]^{20}_D +24.0^\circ$) was placed in a dry one-liter three-necked flask provided with a dropping funnel, reflux condenser, and a mechanical stirrer with a mercury seal. The dropping-funnel and reflux condenser were fitted with calcium chloride tubes. Dry petroleum ether (50 cc.) was added and the solution cooled in an ice-salt-bath. Phosphorus trichloride (45 g., 0.33 mole) was then added dropwise with stirring over a period of two hours, and the mixture allowed to stand overnight. Sirupy phosphorous acid and red phosphorus separated in the bottom layer. Since distillation of a similar mixture is reported to have resulted in an explosion,¹² more petroleum ether was added and the mixture washed with cold water, and then with cold dilute sodium carbonate solution until the petroleum ether layer was clear. The latter was sepa-

rated, dried over calcium chloride, decanted and fractionated after removal of the petroleum ether at ordinary pressure; 110 g. (71%) of ω -chloromethylcamphene was obtained; b. p. 109-111° (15 mm.); n_D^{25} 1.503; d^{15} 1.0205; d^{20} 1.0187; $[\alpha]^{20}_D +18.5^\circ$, (*c*, 101.87). Langlois reported: b. p. 110° (15 mm.); d^{15} 1.020; Cl, 18.47. *Anal.*¹³ Calcd. for $C_{11}H_{17}Cl$: Cl, 19.24. Found: Cl, 18.73.

ω -Substituted Camphenes: General Method.—An ether solution of the Grignard reagent, prepared in the usual manner using 0.5 mole of halide, 0.5 mole magnesium turnings, and 225 cc. dry ether, was cooled and 79 g. (0.43 mole) of ω -chloromethylcamphene $[\alpha]^{20}_D +18.5^\circ$, in 125 cc. of anhydrous ether added with stirring at a rate to maintain gentle reflux. After about half the material was added, a solid, probably magnesium halide, separated. About one-half hour was usually required to complete the addition; refluxing and stirring were continued for an hour longer. The reaction mixture was allowed to stand overnight and then decomposed by cautious addition of about 20 cc. of concentrated hydrochloric acid in 100 cc. of water with external cooling and stirring. The precipitated magnesium compounds dissolved and the ether layer was washed with cold water, 10% sodium hydroxide, and then again with water. The washings were extracted with ether which was added to the main portion. The combined extracts were dried over calcium chloride and the ether removed. Sodium metal (3 g.) was added and the material heated at 140° for two hours. After cooling, the hydrocarbon was removed from the sodium, with the aid of dry ether, the ether distilled, and the residue fractionated at reduced pressure.

Addition of Hydrogen Chloride.—The gas was passed into a solution of 2 g. of the hydrocarbon in 6-8 cc. of anhydrous ether for one-half hour at 5-10°, and one-half hour at 10-15°, and the solution was then allowed to stand in a stoppered flask for two days at room temperature. The ether and excess hydrogen chloride were distilled off, and the residue dried for one-half hour at 100°. Further purification was not attempted because of the instability of these compounds. They are soluble in 95% alcohol, and in ether. The data for the various preparations are given in Table I.

(13) Halogen determinations on all compounds reported were carried out with a modified Volhard method using alcohol as solvent.

(12) Bancroft, *This Journal*, **41**, 427 (1919).

Hydrogen Bromide ω -Benzylcamphene.—A continuous stream of dry bromine-free hydrogen bromide, generated by the action of dry bromine on naphthalene, was passed into a solution of 7 g. (0.03 mole) of ω -benzylcamphene in 25 cc. of anhydrous ether for two hours at 15°. About 9 g. of a reddish-brown liquid was obtained after removal of the ether. This was dried over calcium chloride: d^{25} 1.194; n_D^{25} 1.55; decomposed on attempted distillation at 1 mm. into a hydrocarbon having the physical properties of ω -benzylcamphene and hydrogen bromide. *Anal.* Calcd. for $C_{17}H_{23}Br$: Br, 26.03. Found: Br, 25.83.

Inactivation Procedures: (a) ω -Amylcamphene.— ω -Amylcamphene (35.5 g., 0.17 mole, $[\alpha]^{20}_D +17.8$) was dissolved in anhydrous ether (100 cc.) and treated with dry hydrogen chloride. After two hours at 5–10°, and two additional hours at 10–15°, the saturate was stoppered securely and allowed to stand in a refrigerator for twelve hours; chlorine content, ca. 14% based upon the ether-free material. The ether was removed, 60 g. (0.64 mole) of aniline added, and the mixture refluxed for eighteen hours. Washing of the cool mass with ether left 22 g. of aniline hydrochloride as crystalline residue. The ether extract was dried, the ether removed and the liquid residue distilled (15 mm.) after addition of 5 g. of aniline hydrochloride. The two fractions (55 g. at 124°, and 12 g. at 124–126°) thus secured were dissolved separately in petroleum ether and extracted with 5% hydrochloric acid. The two portions were combined, washed, dried, and freed of petroleum ether. Final distillation yielded ω -amylcamphene (26 g.); b. p. 124–125° (15 mm.); d^{20} 0.8672; n_D^{20} 1.475; $[\alpha]^{20}_D +0.20^\circ$ (c, 86.72).

(b) ω -Benzylcamphene.— ω -Benzylcamphene ($[\alpha]^{25}_D +0.66^\circ$, 75.4 g., 0.33 mole), aniline (93 g., 1 mole) and aniline hydrobromide (58 g., 0.33 mole) were refluxed for twenty-two hours. The resulting hydrocarbon and excess aniline were distilled directly from the reaction mixture, and isolation of the hydrocarbon effected substantially as under (a) recovered ω -benzylcamphene, 58 g.: b. p. 138–140° (5 mm.); d^{25} 0.9668; n_D^{25} 1.538; $[\alpha]^{25}_D +0.10^\circ$ (c, 96.68).

Action of Trichloroacetic Acid on ω -Amylcamphene.— ω -Amylcamphene, 23 g. (0.11 mole), was heated with 90 g. (0.55 mole) of trichloroacetic acid at 40° for several days. The product was dissolved in ether (100 cc.), neutralized and distilled to remove ether, leaving 40 g. of ester (8 amyliisobornyl trichloroacetate, III). The ester (34 g.) was hydrolyzed with a solution of 25 g. of potassium hydroxide in 180 cc. of 95% alcohol and 50 cc. of water by refluxing for four hours, yielding 9 g. of amyliisoborneol, b. p. 105–120° (1 mm.). This product solidified in part on standing for two weeks. Dried on a porous plate, it melted at 63–64°.

Anal. Calcd. for $C_{15}H_{23}O$: C, 80.29; H, 12.58. Found: C, 80.17; H, 12.80.

This procedure is substantially that of Lipp and Lausberg¹⁴ for the transformation of ω -bromocamphene to an ester through trichloroacetic acid addition.

Summary

1. A method has been developed that has led to the synthesis of new optically active ω -substituted camphenes in good yield.
2. The character and structure of these ω -substituted camphenes has been shown by their synthesis from compounds of known structure, by their behavior with halogen and hydrogen halides, and by the action of trichloroacetic acid.
3. ω -Chloromethylcamphene has been prepared in improved yield by a method which involves a minimum of racemization.
4. Inactivation has been accomplished in this series without any apparent alteration of the carbon skeleton.

(14) Lipp and Lausberg, *Ann.*, **436**, 280 (1924).

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Probable Structure of a Crystalline Substance Derived from Starches Oxidized with Periodate

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The oxidation of corn starch with periodic acid was first performed by Jackson and Hudson,^{2a} who afterward hydrolyzed the product with aqueous acid and isolated derivatives of glyoxal and *d*-erythrose in yields of 33 and 22%, respectively.^{2b}

(1) This article is based on a thesis submitted by J. H. Michell to the Faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the Degree of Doctor of Science, 1941.

(2) Jackson and Hudson, *THIS JOURNAL*, (a) **59**, 2049 (1937); (b) **60**, 989 (1938).

These and similar results,³ together with the known behavior of 1,2 glycols toward oxidation with aqueous periodate,⁴ justified the conclusion that most or all of the oxidized starch had the structure I.

Jackson and Hudson observed that acid methanol changed the oxidized starch to a soluble, non-reducing, levorotatory sirup^{2a} from which an un-

(3) Caldwell and Hixon, *J. Biol. Chem.*, **123**, 595 (1938).

(4) Malaprade, *Bull. soc. chim.*, [5] **1**, 833 (1934).