Racemization of Camphor during π Sulfonation[1]

A. M. Tremaine Finch, Jr.,[2] and Wyman R. Vaughan[3]

Contribution from the Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48104. *Received November 1, 1968*

Abstract: (±)-Camphor-8-^{14}C was prepared by a reaction sequence involving ^{14}C-carbonation of 3-methylnorbornanone, reaction of the product with methylmagnesium iodide, followed by rearrangement of the β-hydroxy acid to 1,7-dimethylnorbornane-7-carbo-2-lactone. Reduction of the lactone to a glycol followed by selective oxidation of the secondary hydroxyl, replacement of the primary hydroxyl by bromine, and hydrogenolysis of the bromine completed the synthesis. Bartlett's use of 2-acetoxypropenonitrile as a dienophile in the synthesis of norbornanone was extended to 2-acetoxy-2-butenonitrile for the Diels–Alder synthesis of 3-methylnorbornanone, and explicit proof that camphor-π-sulfonic acid is the 9- or *anti*-sulfonic acid is provided. Racemization of camphor, with and without π sulfonation, is shown to involve two *exo*-methyl shifts, one before and one after sulfonation, and a 2,6-hydride shift in the actual racemization step. The consequence is an exchange of the 8- and 10-carbons when one enantiomer is converted to the other, the 9-carbon (sulfonated or not) remaining stationary. It appears that sulfonation accelerates the racemization step, and an explanation is offered for this.

The history of camphor (**1**) is possibly the longest and most involved of any natural product. It is mentioned in a chemical context by the alchemists as early as 1595,[4] and Boyle[5] first reported its recovery "unchanged" after dissolution in concentrated sulfuric acid. The first camphorsulfonic acid to be characterized was prepared in 1898 by Reychler,[6] who treated (+)-camphor with concentrated H_2SO_4 in acetic anhydride and obtained (+)-camphor-ω-sulfonic acid (**2**). Also, concurrently with Bredt's correct structural assignment for camphor,[7] Kipping and Pope[8] first prepared (±)-camphor-π-sulfonic acid (**3**) by sulfonation of (+)-camphor with fuming sulfuric acid or chlorosulfonic acid (see Chart I, **1**, for π, ω, 8, 9, and 10 assignments).

The structure of Reychler's ω-sulfonic acid was unequivocally established as (+)-camphor-10-sulfonic acid in 1923,[9] but even though there is ample evidence in the literature that Kipping and Pope's π-sulfonic acid is (±)-camphor-9-sulfonic acid, it has almost universally been assigned the C-7 epimeric structure (*i.e.*, the 8-sulfonic acid).[10-13] Since there is such persistent confusion, Corey,[14] for example, has found it necessary to point out resultant inconsistencies by calling attention to the fact that the π-bromocamphor (**4**) obtainable from the π-sulfonic acid differs from 8-bromocamphor (**5**), which he prepared.

Since we proposed to delineate the mode of racemization of camphor during π sulfonation,[8] we believe it appropriate, because of the existing confusion, to record at this point the salient evidence, and to reinforce it with our own, for the structure and configuration of the π-sulfonic acid as camphor-9-sulfonic acid (**3**). It was established as early as 1923[15] and confirmed in 1929[16] (and reconfirmed in the present study) that **3** can be converted into an "isoketopinic acid," mp 250° (**6**, 1,7-dimethyl-2-norbornanone-7-*anti*-carboxylic acid), whereas a second "isoketopinic acid," mp 272° (**7**, 1,7-dimethyl-2-norbornanone-7-*syn*-carboxylic acid), may be obtained by oxidation of 1,7-dimethylnorbornane-7-carbo-2-lactone (**8**).[16] This, too, is confirmed in the present study. Clearly neither of these is the well-characterized ketopinic acid, mp 234° (**9**, 7,7-dimethyl-2-norbornanone-1-carboxylic acid), which has been obtained from **2**.[9] Proof of the epimeric relationship between **6** and **7** rests on the conversion of (+)-**6** and (+)-**7** respectively to (−)- and (+)-dihydroteresantalic acids (**10**, 1,7-dimethylnorbornane-7-carboxylic acid).[17] Final confirmation provided by the present study is the conversion of **8** to camphor, outlined in the following section.

In order to provide a definitive description of the behavior of the (+)-camphor system during the sulfonation–racemization process leading to formation of (±)-camphor-9-sulfonic acid it was necessary to determine the identities of the 8-, 9-, and 10-carbons in the product (**3**) relative to their original positions in (+)-camphor (**1**). To this end it was necessary (1) to synthesize by an unambiguous pathway a ^{14}C-labeled camphor, (2) sulfonate it to **3** and degrade **3** by unambiguous methods permitting unequivocal identification of the positions in which the label appears in **3**.

Ideally optically pure (+)-**1** should contain the label, but failing this, racemic **1** may be labeled and diluted

(1) Abstracted from the Ph.D. Dissertation of A. M. T. Finch, Jr., The University of Michigan, 1965. Preliminary communication, A. M. T. Finch, Jr., and W. R. Vaughan, *J. Am. Chem. Soc.*, 87, 5520 (1965).

(2) Esso Research and Engineering Fellow, 1961–1962; Union Carbide Summer Fellow, 1962; Esso Research and Engineering Summer Fellow, 1963; University of Michigan Department of Chemistry Summer Fellow, 1964; University of Michigan Cancer Research Committee Fellow, 1964–1965.

(3) To whom inquiries should be addressed at the Department of Chemistry, The University of Connecticut, Storrs, Conn. 06268.

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(9) E. Wedekind, D. Schenk, and R. Stüsser, *Ber.*, **56**, 650 (1923).

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(11) 8-Camphorsulfonic acid: *Chemical Abstracts*, 6th Collective Index, Chemical Abstracts Service, Columbus, Ohio, 1957–1961, 2342*s*.

(12) R. H. Rodd, Ed., "Chemistry of Carbon Compounds," Vol. II, Elsevier Publishing Corp., Houston, Texas, 1953, pp 609–611.

(13) A. R. Pinder, "The Chemistry of the Terpenes," 1st ed, John Wiley & Sons, Inc., New York, N. Y., p 105.

(14) E. J. Corey, *J. Am. Chem. Soc.*, 81, 6305 (1959).

(15) E. Wedekind and R. Stüsser, *Ber.*, **56**, 1557 (1923).

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Table I. Degradation Data[a]

	Compd degraded	Basis for % radioactivity	Position	% radioactivity Run 1[b]	Run 2[c]	Run 3	Average[d]
1.	Camphor-8-^{14}C	Camphene	8 + 9[e]				98.5 ± 0.5
2.	(±)-Camphor-9-sulfonic acid	(±)-**6**	9[f]	1.89	1.85	0.95	1.56 ± 6
3.		(±)-**6**	8 + 10[g]	105	99	94	99.3 ± 6
4.		Camphene	10[h]	55.3	45.2	48.5	49.6 ± 6
5.		Camphene	8 + 9[e]	53.5	54.5	61.5	56.5 ± 6
6.		Calcd (8 + 10) − 10	8	49.7	53.8	45.5	49.7 ± 6
7.		Calcd (8 + 9) − 9	8	51.6	52.7	60.6	54.9 ± 6
8.		Calcd av	8	50.7	53.2	53.0	52.3 ± 6
9.		Calcd (C-8 av)	8 + 9 + 10	108	100	103	104 ± 6
10.	65.5% racemized camphor[i]	Camphene	10[h]	35			35
11.	61.5% racemized camphor[i]	Camphene	8 + 9[e]		67		67
12.	74.1% racemized camphor[i]	Camphene	8 + 9[e]			60	60
13.	(+)-Camphor-9-sulfonic acid[j]	Camphene	10[h,k]				25.9 ± 4.5
		Camphene	8 + 9[e]				81.5 ± 4.6

[a] For methods in degradation, see text. Total radioactivity in each case obtained by counting a pure intermediate in the degradation sequence, camphene or **6**. Bases for no. 6 and 7 are calculated by subtracting values for 4 from 3 and 2 from 5. Values for no. 8 obtained by averaging no. 6 and 7. Values for no. 9 obtained by adding no. 8, 2, and 4. [b] 98.9% racemized. [c] 99.2% racemized. [d] Includes appropriate error calculations for counting efficiency and number of samples actually counted. [e] As dimethylnorcampholide. [f] As benzoic acid. [g] As crude 7-bromo-1,7-dimethyl-2-norbornanone (see text). [h] As formaldehyde-dimethone derivative. [i] Recovered from corresponding sulfonation run. [j] Prepared from "resolved" (+)-camphor-8-^{14}C (81.5% ^{14}C as (+)-**1**). [k] The experimental value is high for the 10 position, this being unavoidable owing to the experimental procedure used, the low specific activity of the product counted, and the low counting efficiency inherent in these samples. It should be pointed out, however, that the parts, C-8 + C-9 + C-10 do add up to the whole within one standard deviation.

with (+)-**1** in order to provide a measure of the extent of racemization in **3** (essentially complete), or in recovered **1** (partial). Distribution of the label can readily be determined under these conditions, but only by establishing that the C-8 label in authentic (±)-**1** experiences a specific distribution after the sulfonation–racemization and appears in a particular position in (+)- *or* (−)-**3** as opposed to racemic **3** can the precise course of the process be established.

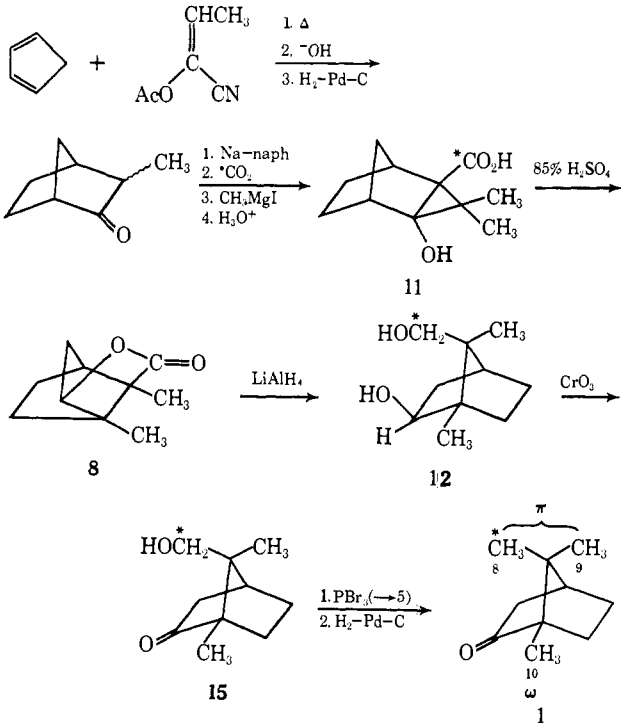
None of the various possible routes for synthesis of camphor with a particular labeled methyl group appeared to offer a feasible unambiguous method of producing an optically active product. Consequently it was decided to synthesize a labeled, racemic **1**, specifically camphor-8-^{14}C. This was then diluted with (+)-**1**, and for most of the work it was this substrate which was studied. However, for achieving the final goal, (−)-**1**-^{14}C was largely eliminated from this material by a modified resolution. And after sulfonation the resultant (±)-**3** was resolved prior to degradation.

With or without resolution (Table I, no. 13 or no. 2–9, respectively) **3** was subjected to two methods of degradation, one designed to remove the 9-carbon and the other the 10-carbon of **3**. It was shown in this manner that approximately half of the total C-8 label in **1** appears at C-8 and half at C-10 in (±)-**3**. Finally, in (+)-**3** the *per cent* of the label at C-8 is the same as the *per cent* at C-8 in (+)-**1**, and at C-10, the same as the *per cent* at C-8 in (−)-**1**. The obvious inference is that configurational (and optical) inversion involves exchange of C-8 and C-10. Details of synthesis, sulfonation, and degradations are given in the next three sections, and discussion of the mechanism follows them.

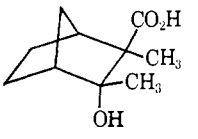
Synthesis of Camphor-8-^{14}C (Chart I)

In order to obviate ambiguity in the location of an isotopic label, it was introduced as a functional group whose integrity and position could not be questioned.

Chart I. Synthesis of (±)-Camphor-8-^{14}C (**1**)



Thus the enolate of 3-methylnorbornanone was carbonated with carbon dioxide-^{14}C, and the resultant salt was treated with methylmagnesium iodide to give 2,3-dimethyl-2-hydroxynorbornane-3-carboxylic acid (**11**). The configuration is assigned on the basis of preferred



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exo attack on the norbornane enolate system.[18] The large-scale synthesis of 3-methylnorbornanone was carried out analogously to Bartlett's novel synthesis of norbornanone:[19] reaction of cyclopentadiene with 2-acetoxy-2-butenonitrile, hydrolysis of the adduct to 3-methyl-5-norbornenone, and finally selective hydrogenation to the saturated ketone.

Treatment of **11** with 85% sulfuric acid afforded a readily separable mixture of acids and 1,7-dimethyl norbornane-7-carbo-2-lactone (**8**), which was also prepared (unlabeled) on a large scale by a reported method.[20]

Initially it was proposed to convert **8** to isoborneol *via* lithium aluminohydride reduction to 8-hydroxyisoborneol (**12**, 1,7-dimethyl-7-*syn*-hydroxymethyl-2-*exo*-norbornanol), selective tosylation of the primary alcohol group to give 8-toluenesulfonoxy-2-*exo*-bornanol (**13**), displacement of the tosylate group by propyl mercaptide, and hydrogenolysis of the propyl sulfide. However, the penultimate reaction afforded only 2,8-epoxybornane (**14**).

Instead, 8-hydroxycamphor (**15**) was prepared by oxidation of **12** with chromic anhydride (Jones' reagent) which provided some unreacted **12**, along with **8** which could be readily recovered and recycled. Conversion of **15** to 8-bromocamphor (**5**) was accomplished by a procedure used for preparation of neopentyl bromide from neopentyl alcohol: refluxing in bromobenzene with phosphorous tribromide and quinoline.[21] The hydrogenolysis of **5** to camphor-8-^{14}C (**1**) was effected over 5% palladium on charcoal in alcoholic potassium hydroxide solution. The product was identical in all respects with authentic racemic camphor. A total of 3 g of highly radioactive racemic camphor was prepared by this route and 1 g of this was diluted with 450 g of (+)-camphor and used in the initial racemization studies (Table I, no. 1–12).

Attempts to resolve (±)-camphor-8-^{14}C *via* the (−)-menthydrazone[22] were unsuccessful (*cf.* Experimental Section). Instead, a portion of radioactive camphor (1.8 g), diluted with 80 g of (+)-camphor was "counted" and converted to its menthydrazone (using (−) menthyl N-aminocarbamate[22]). The latter was repeatedly recrystallized, checking the radioactivity after each recrystallization, until only 61.5 ± 2.1% of the original specific activity remained. The product was reconverted to camphor and "counted" again, with the result that the theoretical number of "counts" per minute per millimole expected for complete "resolution" (*i.e.*, half the original value) was 81.5 ± 2.8% of the number observed. Thus the product is 81.5 ± 2.8% (+)-camphor-8-^{14}C. This material was again diluted with (+)-camphor for experiments requiring (+)-camphor-8-^{14}C (Table I, no. 13).

Sulfonation

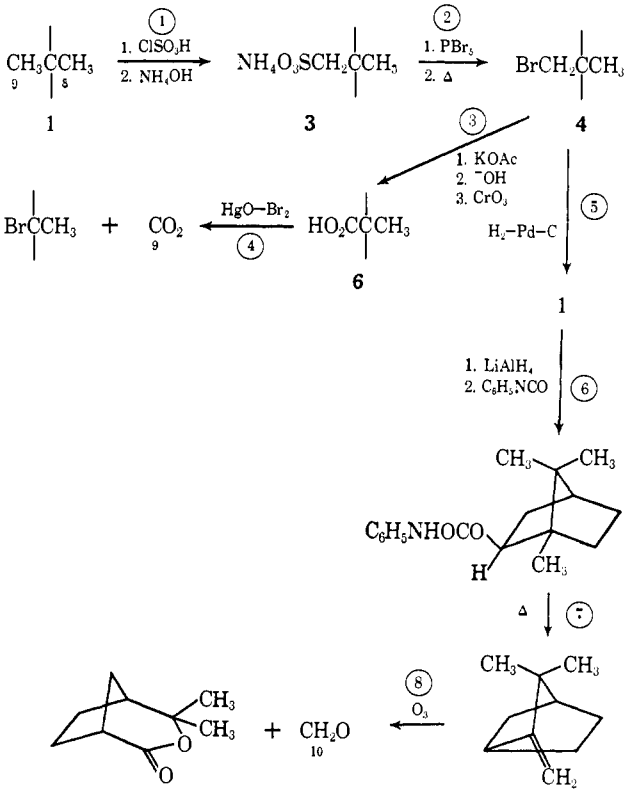
All sulfonation experiments were effected by means of chlorosulfonic acid, essentially as described by the original investigators.[23] Complete sulfonation can be effected by using a longer reaction time than we chose to employ, for by shortening the time we were able to recover partially racemized camphor, whereas (±)-**3** is essentially completely racemic. As in the original work, **3** was isolated as its ammonium salt.

When (+)-**1**-8-^{14}C was sulfonated, the crude ammonium salt was converted to an aqueous solution of the free acid by means of an ion-exchange column, and resolution of the racemic acid (Table I, no. 13) was effected by treatment of the solution with somewhat less than half an equivalent of strychnine, followed by recrystallizations, reconversion to the ammonium salt, and dilution with additional racemic ammonium salt (unlabeled). This procedure is infinitely simpler than the tedious strychnine resolution reported.[24] The absolute configuration of (+)-**3** follows from the π-sulfonation of (+)-α-bromocamphor, prepared from (+)-**1**, and reduction to (+)-**3**;[8,20] and our resolved **3** was in fact (+)-**3**.

Degradations

Methods were developed for removal of two of the pendent carbons from **3**, *i.e.*, the 9- and 10-carbons. The removal of the 10-methyl group involves regenerating camphor in the degradation scheme and therefore affords a method of splitting off the 10-methyl group of **1** also. For removal of either the 9- or 10-carbons, **3** was first converted to the sulfonyl bromide **17** *via* the ammonium salt[22] and then to 9-bromocamphor **4** by heating[23] (Chart II, step 2).

Chart II. Sulfonation and Degradation of **1**



(18) E. J. Corey, R. Hartmann, and R. A. Vatakencherry, *J. Am. Chem. Soc.*, **84**, 2611 (1962).
(19) P. D. Bartlett, *ibid.*, 78, 2473 (1956).
(20) S. Beckmann and H. Geiger, *Ber.*, **92**, 2411 (1959).
(21) L. H. Somer, H. D. Blackman, and P. C. Miller, *J. Am. Chem. Soc.*, **76**, 803 (1954).
(22) R. B. Woodward, T. P. Kohman, and G. C. Harris, *ibid.*, **63**, 120 (1941).
(23) F. A. Kipping and W. J. Pope, *J. Chem. Soc.*, **63**, 593 (1893); **87**, 628 (1905).
(24) W. J. Pope and J. Read, *ibid.*, **97**, 992 (1910).

If C-9 were then to be removed, **4** was converted to 9-hydroxycamphor (**16**) and then **16** was oxidized to *anti*-isoketopinic acid (**6**) which was "counted" as the basis for total radioactivity. The brominative decarboxylation (Hunsdiecker) reaction afforded C-9 as carbon dioxide, which was absorbed in excess phenylmagnesium bromide, and the resultant benzoic acid was isolated for radioactivity "counting." The other product of the decarboxylation reaction, 7-bromo-1-7-dimethyl-2-norbornanone, could only be obtained in moderate purity, but it, too, was "counted," representing C-8 plus C-10, chiefly as a check (Chart II, steps 3 and 4).

If C-10 were to be removed, **4** was hydrogenolyzed to camphor which then was reduced with lithium aluminohydride to isoborneol, which could be dehydrated to camphene without loss in optical integrity.[25] The optical purity of the camphor intermediate and of the camphene served as measures for the extent of racemization in **3**, and prior to removal of the original C-10 by ozonolysis of the camphene, the latter was "counted" as the basis for total radioactivity. As in earlier work[24] formaldehyde was isolated and "counted" as the dimethone derivative, and the residual dimethylnorcampholide was isolated and "counted," representing C-8 plus C-9 of **1** or **3** (Chart II, steps 5–8).

The results of radioactivity "counting" of the various degradation products are displayed in Table I in the form of mole percentages of the total radioactivity for the reference degradation compound, camphene or *anti*-isoketopinic acid (**6**), used in the particular experiment. In summary, it appears that for essentially complete racemization, the original label is about equally distributed between the 8 and 10 positions in racemic **3**, with a slight preference for C-8 reflecting the residual optical activity. In partially racemized camphor, recovered from sulfonation, optical inversion has progressed approximately one-third of the way (65% racemization), percentage migration of the label reflecting this. And finally the same percentage of the label which was initially present (at the 8 position) in (+)-camphor-^{14}C is found in the 8 position in (+)-camphor-9-sulfonic acid, while the same percentage originally at C-8 in (−)-camphor-8-^{14}C is found in the 10 position in (+)-camphor-9-sulfonic acid.

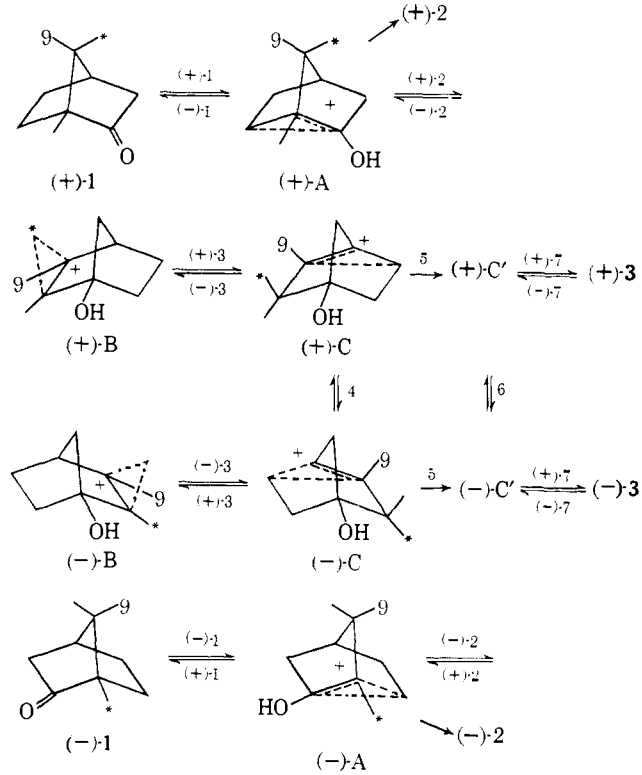
Sulfonation–Racemization Mechanism

Early attempts to account for both sulfonation and racemization include a ring-opening mechanism,[26] which would distribute the isotopic label equally between the 8 and 9 positions, and a direct sulfonation[27] which makes no provision for racemization and therefore cannot account for isotope distribution. A more rational mechanism has been proposed[28,29] which accounts satisfactorily for both 10- and 9-sulfonation but the racemization aspects of which have been experimentally ruled out by later study.[30] In this more recent work, which accounts for the isomerization of (+)-3,9-dihalocamphors into (−)-6,9-dihalocamphors, a rationale is provided for the resistance to racemization of α-halocamphors.[8,21]

Still another mechanism may be written for the sulfonation–racemization process, but it invokes, *inter alia*, both *endo*- and *exo*-methyl migrations. While one is tempted to rule out such a mechanism on the basis of Berson's arguments[31a] and the apparent requirement that an *endo* hydrogen become *exo* before it can experience 3,2 migration in the norbornane system,[31b] there is the possibility in the bornane system that purely *endo* hydrogen 2,3 migration can occur.[31c] There are, however, excellent grounds for excluding a combination of both *endo*- and *exo*-methyl migrations; such a mechanism necessarily leads to migration of the isotopic label from C-8 in (+)-camphor-8-^{14}C to C-10 in (+)-camphor-9-sulfonic acid, which is contrary to our observations. The mechanism which we favor is essentially that of the Japanese workers;[30] and while they left open the problem of *endo vs. exo* migration, we propose it as an essential feature of the racemization process. Thus the present investigation affords more support for the preference of exclusive *exo*-methyl migration in the norbornane series.[32]

The mechanism for the sulfonation–racemization process is most simply depicted in Chart III.

Chart III. Racemization of Camphor (**1**)



In Chart III the 9 position of (+)-**1** clearly remains the 9 position in (−)-**1** while the original C-8 label experiences *exo* migration to become C-10 in (−)-**1** and the original C-10 experiences *exo* migration to become C-8

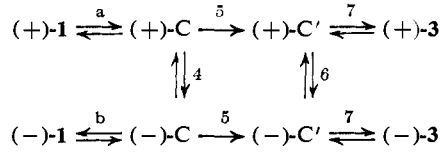
(25) W. R. Vaughan, C. T. Goetschel, M. H. Goodrow, and C. L. Warren, *J. Am. Chem. Soc.*, **85**, 2282 (1963).
(26) H. E. Armstrong and T. M. Lowry, *J. Chem. Soc.*, 81, 1469 (1902).
(27) A. Windaus and E. Kuhr, *Ann.*, **532**, 52 (1935).
(28) Y. Asahina, *Proc. Imp. Acad. Tokyo*, **13**, 38 (1937).
(29) P. Lipp and H. Knapp, *Ber.*, **73**, 915 (1940).
(30) T. Miki, M. Nishikawa, and P. H. Hagiwara, *Proc. Japan Acad.*, **31**, 718 (1955).
(31) (a) J. A. Berson, R. G. Bergmann, J. H. Hammons, A. W. McRowe, A. Remanic, and D. Houston, *J. Am. Chem. Soc.*, 87, 3246 (1965); (b) G. J. Collins, Z. K. Cheema, R. G. Werth, and B. M. Franklin, *ibid.*, **86**, 4913 (1964); (c) A. W. Bushnell and P. Wilder, Jr., *ibid.*, **89**, 5721 (1967).
(32) A. M. T. Finch, Jr., and W. R. Vaughan, *ibid.*, 87, 5520 (1965).

in (−)-**1**. Racemization involves a 2,6-hydride migration (reaction 4). The ions, (±)-C′, are C-9 sulfonated (±)-C. Step 7 involves the rearrangement of (±)-C′ *via* (±)-B′ and (±)-A′ (analogous to (±)-B and (±)-A) to (+)-**3**. The processes represented account for all of the reported isotope distributions and related optical activities: those in which the label is initially present as (±)-**1**-8-^{14}C in (+)-**1** and appears 50% as (±)-**3**-8-^{14}C and 50% as (±)-**3**-10-^{14}C in (±)-**3**, those in which it is initially present as (±)-**1**-8-^{14}C in (+)-**1** and appears as 65% (±)-**1**-8-^{14}C in 65% racemized (+)-**1**, and those in which it is initially present as (+)-**1**-8-^{14}C in (+)-**1** and appears as (+)-**3**-8-^{14}C in (+)-**3**.

The reaction, (+)-A → (+)-**2**, represents 10-sulfonation, which evidently is suppressed under conditions leading to 9-sulfonation, for we attempted without success to convert (+)-**2** to **3** or derivatives thereof under our sulfonation conditions. Consequently, it would appear that 10-sulfonation is not reversible. We have proposed that 9-sulfonation occurs on ions C (or the conjugate bases) by analogy with 10-sulfonation occurring on ion (+)-A (or its conjugate base), which formally resembles them. And by further analogy, we suggest that 9-sulfonation is also irreversible.

For purposes of the following discussion the reactions in Chart I may be condensed with a single equilibrium pictured between **1** and C as shown in Chart IV.

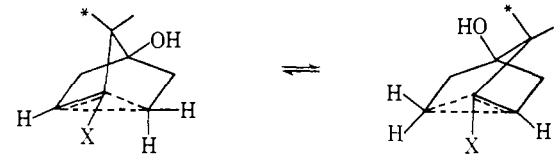
Chart IV



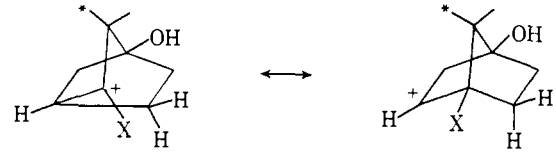
The salient facts which must be taken into account are: (1) the **3** produced is essentially completely racemic, and (2) the **1** recovered is but partially racemized, and furthermore, partial racemization of (+)-**1** can be effected simply by standing in sulfuric acid. These mean that **3** must be formed from a completely racemic intermediate (*i.e.*, (±)-C or (±)-C′) which cannot lead to (−)-**1** at a rate greater than that involved in the production of (−)-**3**. This rules out sulfonation (reaction 5) as the slowest step in the whole sequence, for were this so, **1** could achieve complete racemization well *before* substantially complete sulfonation obtained.

However, since sulfonation is at least a bimolecular process, it seems only reasonable to assume that it is the slowest step in the sequences leading from (+)-**1** to (±)-**3**. This additional condition imposes two furthers ones: (1) reactions 6, 7, and −7 are a great deal faster than reaction 5 (*i.e.*, all reactions following 5 attain effective equilibrium, coupled with the obvious fact that neither (+)-**3** nor (−)-**3** is thermodynamically favored), or alternatively that reaction 6 be followed by at least one irreversible step (7) which is appreciably slower, to account for the production of completely racemic **3**; and (2) that reaction 4 involves the highest energy barrier in the whole system, in keeping with the relatively very low rate of sulfuric acid induced racemization and in order to account for the failure to produce completely racemic **1** too early in the reaction sequence. It should be noted that (±)-**3** can be produced from (+)-C without involving reaction 4.

Thus from two experimental facts and one reasonable assumption there follows the conclusion that (+)-C′ racemizes more rapidly than does (+)-C.



A possible explanation for this situation may be adduced from a consideration of the two canonical contributors to the hybrid ions



where X = methyl, the camphene-hydro ion (tertiary) should be more stable than the isobornyl ion (secondary); but where X = methylenesulfonic acid, the effect of the electron-attracting substituent would lead to destabilization of the tertiary ion to the advantage of the secondary ion. And it is the secondary ion which is constitutionally better able to experience the 2,6-hydride shift essential for racemization. One may either disregard the double-headed arrow and consider the two classical ions as an equilibrating pair, or one may argue that the sulfonic acid group more effectively delocalizes the positive charge in the hybrid, thus facilitating the hydride shift. In either case the result is the same: greater lability for the appropriate 2-hydrogen.

The situation is not without precedents of a sort. Thus 8-phenylcamphene appears to racemize *via* the 2,6-hydride shift without the usual concomitant methyl shifts,[33] which suggests enhancement of the hydride shift reaction, and, conversely, α-bromocamphor fails to racemize during 9-sulfonation,[8,21] a fact which may be attributed to destabilization of the above secondary ion by the bromine on the adjacent carbon.[30]

In summary, we have presented experimental evidence for the manner in which camphor racemizes, with or without sulfonation: two *exo*-methyl shifts are essential, one before sulfonation can occur and one after sulfonation, and a 2,6-hydride migration is involved in the actual racemization step. The behavior is entirely consistent with that of camphene.[25,34] The consequence is an exchange of the 8- and 10-carbons in going from (+)- to (−)-camphor, and sulfonation, when it occurs, takes place on the stationary 9-carbon, *anti* to the carbonyl group. From the experimental evidence we have argued for more rapid racemization of a sulfonated intermediate ion than of the corresponding unsulfonated one, and we have explained this in terms of charge delocalization by the sulfonic acid substituent.

Experimental Section[35]

2-Acetoxy-1-butenonitrile. Phosphorous tribromide, 360 g (1.36 mol) was slowly added *via* a dropping funnel to 300 g (4.05 mol)

(33) J. J. Ritter and G. Vlases, *J. Am. Chem. Soc.*, **64**, 583 (1942).
(34) P. Hirsjarvi, K. Heinonen, and L. Pirila, *Suomen Kemistilehti*, **B37**, 77 (1964).
(35) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra obtained as Nujol mulls of solids or films of liquids using a Perkin–Elmer Model 21 spectrometer.

of propanoic acid in a three-necked flask equipped with a magnetic stirrer and reflux condenser. After the addition, the solution was refluxed for 1 hr and cooled and the top layer decanted off. This material was carefully distilled, and the fraction boiling at 99–110° was collected. The propionyl bromide, 303 g (2.21 mol), was added, together with three drops of phosphorous tribromide, to 188 g (2.1 mol) of powdered cuprous cyanide in a 5-l., three-necked, round-bottomed flask equipped with mechanical stirrer, heating mantle, reflux condenser, and dropping funnel.

After the addition, the stirred mixture was refluxed for 1 hr, cooled, and filtered and the cuprous bromide washed with ether. The ether wash and the original filtrate were combined, and the ether was removed (*in vacuo*).

The remaining liquid was fractionally distilled and the portion boiling at 48–50° (19 mm) collected. This material was redistilled at 108–110° (760 mm) (lit.[36] bp 108–110° (760 mm)).

Propionyl cyanide, 105 g (1.26 mol), was dissolved in 250 ml of isopropenyl acetate with 2 g of *p*-toluenesulfonic acid monohydrate.

The solution was refluxed using a spinning-band column, and 80 g (1.3 mol) of acetone was distilled out over a 2-day period.

The remaining solution was diluted with 100 ml of ether and washed with 5% potassium hydroxide solution until it no longer tested acid. Then it was washed with water and dried over anhydrous magnesium sulfate. Fractional distillation yielded 82 g (16%) of a clear colorless liquid boiling at 95–101° (33 mm). This material gave infrared peaks at 2240, 1780, and 1668 cm^{-1} and a satisfactory nmr spectrum

Anal. Calcd for $C_6H_7O_2N$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.68; H, 5.74; N, 11.28.

3-Methylnorboranone (3-Methylbicyclo[2.2.1]heptan-2-one). 2-Acetoxy-1-butenonitrile, 40 g (0.32 mol), and freshly cracked cyclopentadiene, 50 g (0.76 mol), were placed in a Pyrex tube, cooled with a Dry Ice–chloroform bath, and sealed. The tube was heated in an oven at 180° for 8 hr, cooled, and opened and the material poured into 300 ml of 15% potassium hydroxide ethanol–water (1:1) solution and refluxed for 4 hr. The mixture was cooled, 200 ml of water added, and extracted with ether.

The ether solution was washed with water and dried over anhydrous magnesium sulfate and the ether distilled off. The remaining liquid was fractionally distilled and the fraction boiling at 65–72° (20 mm) collected.

This was hydrogenated in ethyl acetate over 5% palladium on charcoal in a Parr shaker. The ethyl acetate was removed and fractional distillation gave 15 g (38%) of a clear colorless liquid, bp 72–75° (20 mm) (lit.[37] bp 67° (14 mm)). This material had the identical infrared spectrum, vpc (6-ft silicone gum rubber column) retention time, and nmr spectrum as samples made by the methods of Corey[18] and van Tamelen.[37]

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.20; H, 9.84.

2,3-Dimethyl-3-hydroxynorbornane-2-carboxylic Acid (11). Naphthalene, 88.5 g (0.69 mol), was dissolved in 750 ml of tetrahydrofuran in a 3-l., three-necked flask equipped with a magnetic stirrer and reflux condenser. To this stirred solution, 14.95 g (0.65 g-atom) of sodium, cut into small pieces, was added and the mixture allowed to stir until all the sodium had dissolved (a dark green color developed upon first addition of sodium). During the approximately 12 hr needed for dissolution, the flask was cooled with a water bath.

The flask was then fitted with a dropping funnel, and 3-methylnorbornanone, 74.6 g (0.6 mol), in 20 ml of THF was added at *ca.* 50 drops/min. The dark green color disappeared at the end of the addition.

The solution was stirred at room temperature for 5 min, the dropping funnel replaced by a delivery tube connected to a carbon dioxide generator, and carbon dioxide bubbled in slowly. When all the carbon dioxide had been produced, the system was flushed with dry nitrogen.

The carbon dioxide generator was a 500-ml, three-necked flask equipped with magnetic stirrer, dropping funnel, and delivery tube. Barium carbonate, 90 g (0.045 mol), as an aqueous slurry was placed in the flask and concentrated sulfuric acid used to liberate the carbon dioxide.

Methylmagnesium bromide in ether, (300 ml of a 2.17 *M* solution) was added slowly *via* a dropping funnel to the THF which contained the sodium 3-methylnorbornanone-3-carboxylate and the mixture stirred for 0.5 hr. The excess Grignard reagent was destroyed with water and a cold 15% hydrochloric acid solution used to acidify the mixture. The ether–tetrahydrofuran solution was separated, concentrated to 150 ml, and extracted with cold 10% potassium hydroxide solution. The basic solution, containing the potassium salt of the hydroxy acid, was extracted twice with ether to remove all nonacidic material and acidified with cold 10% hydrochloric acid. The hydroxy acid was removed by extraction with chloroform, washed with a little water, dried over anhydrous magnesium sulfate, and treated with Norit and the solvent removed (*in vacuo*).

This left 70 g (82%) of a white solid, which was used for preparation of **8** (procedure 2) *without further purification.*

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.62; H, 8.38.

1,7-Dimethylnorbornane-7-carbo-2-lactone (8). Two procedures were used to synthesize this compound.

Procedure 1. This is a modification of the method used by Beckmann and Geiger.[20] Tiglic acid, 50 g (0.5 mol), and freshly cracked cyclopentadiene, 500 g (7.6 mol), were placed in a 200-ml, round-bottomed flask equipped with a reflux condenser. The solution was heated in an oil bath, slowly raising the temperature so that the bath temperature reached 180° after 6 hr. It was held at 180° for an additional 8 hr.

The hot solution was poured into 500 ml of 10% potassium hydroxide solution, the lumps were crushed, and the mixture was stirred vigorously for 2.5 hr. It was suction filtered, and the basic solution extracted with ether and acidified with cold concentrated hydrochloric acid, and this acidific solution extracted with ether. The extract was dried over anhydrous magnesium sulfate and the ether removed (*in vacuo*) leaving a dark oil which was fractionally distilled; the mixture of *endo* and *exo* adducts, bp 145–155° (28 mm) (lit.[38] bp 145–148° (12 mm)) was collected.

The mixture of adducts was dissolved in a 1 *M* solution of sodium bicarbonate and titrated with a 1 *M* sodium iodide–iodine solution until the red color persisted.

The white iodolactone, formed from the *endo* adduct, separated out and was extracted with ether. The aqueous layer, containing the sodium salt of the *exo* adduct, was acidified with hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and the ether evaporated leaving 8.5 g of a white solid.

The white solid was dissolved with cooling in 100 ml of cold 85% sulfuric acid and allowed to stand at room temperature for 17 hr. The solution was then poured over 300 g of crushed ice and extracted with ether. The ether solution was washed with two portions of cold 5% potassium hydroxide solution, water, dried over anhydrous magnesium sulfate, and treated with Norit and the ether evaporated leaving a white solid which was recrystallized from ether–heptane: yield 8.0 g (9.5%), mp 192–193° (lit.[20] mp 192–194°). Its infrared spectrum was identical with that given.[20]

Procedure 2. Cold 85% sulfuric acid (400 ml) was added slowly, with stirring, to a flask containing 2,3-dimethyl-3-hydroxynorbornane-2-carboxylic acid (**11**), 70 g (0.38 mol), in an ice bath. The yellow solution was allowed to stand at room temperature for 17 hr (it became dark red), then poured over 500 g of crushed ice.

The aqueous mixture was extracted with ether (three 150-ml portions) and the ether concentrated to about 100 ml. It was then washed twice with 50 ml of cold 5% potassium hydroxide solution, dried over anhydrous magnesium sulfate, and treated with Norit and the ether removed (*in vacuo*). This left 35 g (55%) of a white solid which was recrystallized once from ether–heptane, mp 192–193° (lit. mp[20] 192–194°). It had an identical infrared spectrum and vpc retention time (6-ft silicone gum rubber column) with the lactone from procedure 1. A mixture melting point with the lactone from procedure 1 showed no depression.

8-Hydroxyisoborneol (12). 1,7-Dimethylnorbornane-7-carbo-2-lactone (**8**), 25 g (0.15 mol), was dissolved in 50 ml of dry ether and added *via* a dropping funnel to a stirred slurry of 5.7 g (0.5 mol) of lithium aluminum hydride in 150 ml of dry ether in a 1-l., round-bottomed flask equipped with a good reflux condenser. The slurry was stirred at room temperature for 6 hr.

The excess lithium aluminum hydride was carefully destroyed with

(36) W. Tschelinzeff and W. Schmidt, *Ber.*, **62**, 2211 (1929).

(37) E. E. van Tamelen and R. J. Thiede, *J. Am. Chem. Soc.*, **74**, 2615 (1952).

(38) K. Alder and H. F. Rickert, *Ann.*, **543**,1 (1939).

water and cold 5% hydrochloric acid was added until the aqueous layer tested acid. The layers were separated and the aqueous layer extracted with chloroform. The chloroform and ether solutions were combined, washed with bicarbonate and then water, and dried over anhydrous magnesium sulfate, and the solvent was evaporated (*in vacuo*), leaving 24 g (93%) of a white solid whose infrared spectrum showed a hydroxyl peak at 3300 cm^{-1} (broad) and no carbonyl peak. A small portion was recrystallized from ether, mp 275–276°. *Anal.* Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.35; H, 10.58.

2,8-Epoxybornane (14). A sample of 8-hydroxyisoborneol (**12**), 3.0 g (0.018 mol), was converted to the monotosylate by treatment with 1 equiv (3.4 g) of *p*-toluenesulfonyl chloride in 10 ml of dry pyridine and stirring for 10 hr at room temperature. A 50-ml portion of cold 5% hydrochloric acid was added and the mixture stirred at 0° for 0.5 hr. It was then transferred to a separatory funnel and extracted with ether. The extract was washed with 10% aqueous sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and the solvent removed (*in vacuo*) leaving a thick oil whose infrared spectrum showed hydroxyl (3440 cm^{-1}) and tosylate (1615 and 665 cm^{-1}) peaks.

The oil was dissolved in 20 ml of dry ether and added to a slurry of 50 ml of ether and 0.65 g (0.017 mol) of lithium aluminum hydride. The excess hydride was destroyed with water, 20 ml of cold 5% hydrochloric acid solution was added, and the aqueous layer extracted with ether. The ether portions were combined, washed with 10% aqueous sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and the solvent removed (*in vacuo*). A vpc analysis showed 5% isoborneol, 11% diol, 84% another compound. Recrystallization from ethanol–water, then ether–pentane gave 0.8 g (30%) of a white solid, mp 164–167°, showing no peak in its infrared spectrum corresponding to hydroxyl or tosylate. It analyzed for 2,8-epoxybornane.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.03; H, 10.60.

8-Hydroxycamphor (15). 8-Hydroxyisoborneol, 8.0 g (0.047 mol), was dissolved in 100 ml of acetone and cooled to 0° in an ice–water bath. To this solution 11.8 ml of 2.67 *M* Jones' reagent was added with vigorous stirring at such a rate that the temperature remained between 8 and 12°.

The acetone was decanted from the green salts and evaporated (*in vacuo*), until only *ca.* 20 ml remained. Then 50 ml of water was added to the acetone and 50 ml to the chromic salts. The aqueous solutions were combined and extracted with ether; the extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated leaving an oil. An infrared spectrum showed carbonyl peaks at 1750 and 1785 cm^{-1}.

The oil was dissolved in 100 ml of 10% alcoholic potassium hydroxide and refluxed for 2 hr. Water (100 ml) was added and the basic solution extracted with ether; the ether was washed with water, dried over anhydrous magnesium sulfate, and evaporated (*in vacuo*). The residue was recrystallized three times from pentane giving 1.9 g (23%) of a white solid, mp 232–233° (lit.[39] mp 233°), which had an infrared spectrum showing a carbonyl peak at 1750 and an hydroxyl peak at 3440 cm^{-1}.

8-Bromocamphor (5). 8-Hydroxycamphor (**15**), 1.9 g (7.7 mmol), was dissolved in 4 ml of bromobenzene containing 1.3 g (10.0 mmol) of quinoline in a 50-ml, round-bottomed flask.[21] To this solution, cooled in an ice bath, phosphorous tribromide, 2.2 g (8.1 mmol) was added slowly with stirring.

The mixture was refluxed with stirring at 180–190° for 24 hr. At the end of this period it was poured into 50 ml of 5% hydrochloric acid and the solution stirred for 0.5 hr, after which it was extracted with ether, the ether solution washed with water, dried over anhydrous magnesium sulfate, and treated with Norit and the ether removed using a water pump.

The remaining bromobenzene was evaporated using an oil pump leaving 1.4 g (83%) of an oil which showed a carbonyl peak at 1755 cm^{-1} but no hydroxyl peak in the infrared.

After standing in the refrigerator for a day it became crystalline, and a small portion was recrystallized from ethanol–water, then pentane, mp 120–122° (lit.[14] mp 121.5–122.5°).

Camphor (1). A sample of 8-bromocamphor (**5**), 1.5 g (6.5 mmol), dissolved in 20 ml of ethanol, was added to a slurry of 7 g of 5% palladium on charcoal in 5 ml of water containing 0.37 g (6.7 mmol) of potassium hydroxide in a Parr bottle. This was shaken under 3 atm of hydrogen for approximately 6 hr.

(39) Y. Asahina and M. Ishidate, *Ber.*, **67**, 71 (1934).

The bottle was flushed with nitrogen, the solution removed from the shaker, and the catalyst filtered off. Water (100 ml) was added and the aqueous alcohol solution extracted with pentane.

The pentane was washed with water and dried over anhydrous magnesium sulfate and the solvent carefully removed in order to keep loss of camphor due to sublimation at a minimum. This left a viscous oil which was sublimed at 100° (760 mm) giving a white solid 0.9 g (92%), mp 176–178° (lit.[40] mp 178.0–178.5°). Its infrared spectrum was identical with camphor and a mixture melting point showed no depression.

Ammonium Camphor-9-sulfonate (3-Ammonium Salt). According to the procedure of Kipping and Pope,[41] dry powdered camphor (**1**), 100 g (0.65 mol), was dissolved in 70 g (0.6 mol) of redistilled chlorosulfonic acid in a 3-l. flask equipped with an air condenser. The dark red solution was heated on the steam bath for 20 min with occasional shaking, then removed and allowed to cool for 5 min.

Another portion of chlorosulfonic acid, 80 g (0.69 mol), was added *via* the condenser and the flask allowed to stand for 10 min, then returned to the steam bath and heated with shaking until most of the camphor had reacted (*ca.* 30 min). This could be determined by adding a drop of the reaction solution to cold water and observing the amount of camphor which separated out. If recovery of camphor was desired, the entire sulfonation procedure (including cooling) was shortened to *ca.* 50 min: first addition, wait 5 min, steam bath 20 min, cool 5 min; second addition, heat 20 min, cool. If complete sulfonation was desired, the final heating was prolonged until no camphor appeared on dilution.

The thick black material was poured over 1000 g of crushed ice and stirred until it had dissolved. Calcium hydroxide was added until the mixture tested basic. The calcium sulfate and unreacted camphor were filtered off, and the basic solution was washed with ethanol and ether and extracted with ether to remove all nonacidic products. The organic washings and extracts were combined, dried, and evaporated to dryness (32 g). From this *ca.* 12 g of camphor was recovered by sublimation.

An excess of ammonium sulfate was added to the basic filtrate and the calcium sulfate formed filtered off again. The basic solution containing the ammonium salt of camphor-9-sulfonic acid and excess ammonium sulfate was treated with Norit several times, poured into a large evaporating dish, and heated on the steam bath, while passing air over it, for several days.

When almost all of the water had evaporated, leaving a thick dark brown paste, it was taken up in absolute ethanol, warmed on the steam bath, and filtered. The ammonium sulfate residue was again triturated with absolute ethanol and filtered. The two alcoholic portions containing the ammonium salt of camphor-9-sulfonic acid were combined and treated with Norit until it was yellow, then poured into an evaporating dish and heated on the steam bath.

When most of the ethanol had evaporated and a light brown paste remained, the evaporating dish was transferred to a large vacuum desiccator and most of the remaining solvent removed *via* a water aspirator. The solid was broken up and ground to a powder with a mortar and pestle, then returned to the desiccator and the last traces of solvent removed using an oil pump. It was stored over anhydrous calcium sulfate, yield 70–80%.

Camphor-9-sulfonyl Bromide. Ammonium camphor-9-sulfonate (**3**), 50 g (0.20 mol), of dry powdered material, was triturated with 108 g (0.25 mol) of phosphorus pentabromide (made by pouring phosphorous tribromide and bromine together in a cooled mortar) in a large mortar placed in an ice bath. After 10 min, the bath was removed and the trituration continued until it began to liquefy. Then it was allowed to stand with occasional stirring for *ca.* 40 min.

At the end of this time, an ice–water mixture was added and the mixture stirred until the phosphorus oxybromide decomposed (the solution bubbles vigorously for approximately 10 sec). Chloroform was added to dissolve the remaining brown oil and the layers separated. The aqueous layer was extracted with chloroform and the organic portions combined. This was dried over anhydrous magnesium sulfate and treated with Norit until it was light yellow. The chloroform was removed (*in vacuo*) and the remaining oil crystallized from ether yielding 13.7 g (23%) of a white solid, mp 121–135°. A small portion was recrystallized from ethyl acetate, mp 142–145° (lit.[42] mp 145°).

(40) G. Komppa, *ibid.*, **41**, 4470 (1908).

(41) F. A. Kipping and W. J. Pope, *J. Chem. Soc.*, **63**, 593 (1893); **67**, 155 (1895).

(42) R. C. Guha and S. C. Bhattacharyya, *J. Indian Chem. Soc.*, **21**, 261 (1944).

9-Bromocamphor (4). In accordance with the procedure of Kipping and Pope,[41] camphor-9-sulfonyl bromide was divided into 3-g portions in 250-ml erlenmeyer flasks. Each flask was covered with a watch glass holding a small piece of ice and heated in an oil bath maintained at 145–155°. The acid bromide melted, then decomposed giving off sulfur dioxide and some hydrogen bromide.

When the material had stopped bubbling (approximately 10 min), it was removed from the oil bath and cooled and the residue dissolved in ether. The ether solutions were combined, dried over anhydrous magnesium sulfate, and treated with Norit. The ether was removed (*in vacuo*) leaving a white solid (91% crude) which was recrystallized from ether–heptane, mp 92–93° (lit.[41] mp 93–94°).

9-Hydroxycamphor (16). A sample of 9-bromocamphor (**4**), 10 g (0.043 mol), was added to a mixture of 25 g (0.30 mol) of potassium acetate and 25 g (0.42 mol) of glacial acetic acid in a 100-ml, round-bottomed flask equipped with magnetic stirrer and reflux condenser with drying tube. The flask was heated in an oil bath whose temperature was held at 180° for 30 hr; then, while still hot, it was poured into 100 ml of water. The aqueous mixture was made basic with potassium hydroxide and extracted with ether.

The ether was removed *in vacuo* and the light yellow oil dissolved in 100 ml of 10% alcoholic potassium hydroxide solution and refluxed for 2.5 hr. Water (100 ml) was added and the aqueous alcohol solution extracted with ether. The ether was washed once with water, dried over anhydrous magnesium sulfate, and treated with Norit. The solvent was evaporated (*in vacuo*) leaving a white solid. Recrystallization from ether–pentane gave a crystalline solid, mp 233–234° (lit.[39,42] mp 233°), yield 5.9 g (81%).

1,7-Dimethyl-2-oxonorbornane-7-*syn*-carboxylic Acid (7). A sample of 1,7-dimethylnorbornane-7-carbo-2-lactone (**8**), 2 g (0.012 mol), was added to 25 ml of 10% potassium hydroxide solution and refluxed for 2 hr. Next, it was placed in an ice bath and slowly acidified with cold 5% hydrochloric acid solution. It was then extracted with chloroform; the chloroform solution was washed with water and dried over anhydrous magnesium sulfate and the solvent very carefully evaporated (*in vacuo*) leaving a white solid, 1,7-*anti*-dimethyl-2-*endo*-hydroxynorbornane-7-*syn*-carboxylic acid, mp 194–196° (lit.[17] 196°).

This was dissolved in 15 ml of reagent acetone, cooled to 0°, and Jones' reagent slowly added until the red color persisted. The acetone was decanted from the chromic salts and evaporated (*in vacuo*). Water (25 ml) was added to both the residue and the chromic salts, and the combined aqueous solutions were extracted with chloroform. The chloroform solution was washed with water and dried over anhydrous magnesium sulfate and the chloroform evaporated (*in vacuo*). Recrystallization from ether gave 1.4 g (78%) of a white solid, mp 273–275° (lit.[17] mp 270°).

1,7-Dimethyl-2-oxonorbornane-7-*anti*-carboxylic Acid (6). A sample of 9-hydroxycamphor (**16**), 5 g (0.029 mol), was dissolved in 75 ml of reagent acetone in a 250-ml erlenmeyer flask. To this flask Jones' reagent was added slowly with stirring until the orange color persisted.

The acetone was decanted from the green chromic salts and evaporated (*in vacuo*). Water (50 ml) was added to the residue and the original chromic salts. These two aqueous portions were combined and extracted with chloroform.

The chloroform solution was dried over anhydrous magnesium sulfate and the solvent removed. The remaining white solid was dissolved in cold 5% potassium hydroxide solution and extracted with ether to remove any nonacidic material. It was then acidified with hydrochloric acid and extracted with chloroform. The chloroform was dried over anhydrous magnesium sulfate and removed (*in vacuo*) leaving 4.2 g (80% crude) of a white solid which was recrystallized from ether, mp 250–251° (lit.[17] 250°).

Camphor (1). A sample of 9-bromocamphor (**16**), 2 g (9.6 mmol), was dissolved in 20 ml of ethanol and added to a slurry of 7 g of 5% palladium on charcoal in 5 ml of water containing 0.55 g (9.8 mmol) of potassium hydroxide in a Parr bottle. This was shaken under hydrogen (3 atm).

At the end of a 5-hr period, the bottle was flushed with nitrogen, the solution removed from the shaker and the catalyst removed by filtration. Water (50 ml) was added and the aqueous alcohol solution extracted with pentane. The pentane solution was washed with water and dried over anhydrous magnesium sulfate and the pentane carefully evaporated (*in vacuo*).

This left a thick oil which was sublimed at 100° (760 mm) yielding 1.36 g (93%) of a white solid, mp 177.0–178.5° (lit.[40] mp 178.5–179°). A mixture melting point with authentic racemic camphor showed no depression.

Isoborneol. Camphor (**1**), 10 g (0.066 mol), dissolved in 25 ml of dry ether was slowly added *via* a dropping funnel to a slurry of 1.5 g (0.04 mol) of lithium aluminum hydride and 100 ml of dry ether in a 300-ml flask equipped with reflux condenser and magnetic stirrer. It was stirred at room temperature for 3 hr and the excess hydride carefully destroyed with 10 ml of water. With cooling, 50 ml of cold 5% HCl was added and the contents transferred to a separatory funnel; the layers were separated. The aqueous layer was extracted with ether; the original ethereal layer and extracts were combined, washed with water, and dried over anhydrous $MgSO_4$, and the solvent was removed (*in vacuo*) leaving a white solid, 8.7 g (93%), mp 209–213°. Recrystallization from ethanol–water gave isoborneol, mp 213–214° (lit.[43] mp 214°).

Benzoic Acid *via* Hunsdieker Reaction.[44] A slurry of 4.32 g (0.02 mol) of red mercury oxide and 60 ml of carbon tetrachloride was made up in a 200-ml, two-necked flask, fitted with a dropping funnel and reflux condenser (capped with a drying tube containing potassium hydroxide and anhydrous calcium sulfate). The apparatus was previously flame-dried and was continually flushed with dry nitrogen.

To this slurry 2.0 g (0.011 mol) of 1,7-dimethyl-2-oxonorbornane-7-*anti*-carboxylic acid (**6**) was added and the mixture refluxed in an oil bath with stirring for 0.5 hr. It was cooled, the drying tube removed, and a delivery tube attached which led from the top of the condenser into and beneath the surface of a 200-ml flask equipped with reflux condenser and magnetic stirrer and containing an excess of phenyl magnesium bromide in ether. This apparatus had been flame dried and swept out and kept under dry nitrogen.

Bromine, 3.36 g (0.021 mol), was slowly added *via* the dropping funnel and the mixture refluxed for 15 min. Carbon dioxide was evolved and collected in the phenylmagnesium bromide. The mixture was cooled and allowed to stand for 10 min in order to ensure that all carbon dioxide was carried over by the nitrogen.

The delivery tube was removed and replaced by a dropping funnel containing carbon dioxide free water and the excess phenylmagnesium bromide destroyed. Then cold 5% HCl solution was added until it was acidic, and the material was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with ether. The original ethereal layer and the extracts were combined and d : anhydrous $MgSO_4$, and the solvent was carefully removed *o*), leaving a crystalline white solid, 0.23 g (51%), mp 118–1 was sublimed and gave long colorless needles, mp 121–122°.

1,7-Dimethyl-7-bromonorbornan-2-one. The carbon tetrachloride solution (preceding experiment) was combined with 100 ml of *n*-pentane and filtered and the solvent removed (*in vacuo*). The remaining oil was mixed with 50 ml of cold 5% sodium hydroxide solution and extracted with *n*-pentane. The pentane solution was treated with Norit and dried over anhydrous magnesium sulfate and the solvent removed (*in vacuo*) leaving a white solid which was recrystallized twice from ethanol–water and three times from pentane (Dry Ice). This gave 1.1 g (25%) of a crystalline white compound, mp 160–180°.

Anal. Calcd for $C_9H_{13}OBr$: C, 49.81; H, 6.04; Br, 36.81. Found: C, 47.46; H, 5.67; Br, 39.46.

Racemization of Camphor in Concentrated Sulfuric Acid. A 50-g (0.33 mol) sample of camphor, mp 177–178°, $[\alpha]_D$ +45.5° (*c* 12.7, absolute alcohol), was placed in a 1000-ml flask and immersed in an ice bath and 250 ml of cold concentrated sulfuric acid added slowly. The yellow solution was allowed to warm to room temperature and stand for 1 week. During this period its color changed to dark red.

At the end of a week it was poured onto cracked ice and extracted with ether; the ether solution was washed with 5% sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, treated with Norit, and ether evaporated (*in vacuo*). This left a white solid which was recrystallized several times from 50% ethanol–water giving 32.4 g (64.5%) of camphor, mp 177–178°; $[\alpha]_D$ +37.7° (*c* 12.2, absolute alcohol) (lit.[40] mp 178.5–179°), $[\alpha]_D$ +43.6° (*c* 5, absolute alcohol), $[\alpha]_D$ +44.8° (*c* 20, absolute alcohol), $[\alpha]_D$ +44.8° (*c* 20, absolute alcohol).

Attempted Rearrangement of (+)-Camphor-10-sulfonic Acid (2). A 20-g sample of (+)-camphor-10-sulfonic acid was dissolved in 15 ml of cold chlorosulfonic acid. It was heated up and blackened, poured over ice, and treated with calcium hydroxide until basic

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(44) S. J. Cristol and W. J. Firth, *J. Org. Chem.*, **26**, 280 (1961).

and the mixture filtered. Then ammonium sulfate was added and the mixture filtered. It was evaporated to dryness, taken up in absolute methanol, filtered, treated with Norit until light yellow, and again evaporated to dryness, and the last traces of moisture were removed at the oil pump.

The residue was triturated with phosphorus pentabromide, as previously described, the resulting "sulfonyl bromide" decomposed to the bromide by boiling in *o*-xylene. (This same procedure was used to make the 10- and 9-bromocamphor used in the vpc analysis.)

The small residue was subjected to vpc analysis (6-ft silicone gum rubber column) and it failed to give a peak corresponding to either the 10- or 9-bromocamphor.

Another 15-g sample of (+)-camphor-10-sulfonic acid was dissolved in 50 ml of concentrated sulfuric acid. The solution was heated on the steam bath for 1 hr and the acid worked up as the ammonium salt as described above.

The "ammonium salt" was triturated with phosphorus pentabromide and the "sulfonyl bromide" decomposed in boiling *o*-xylene.

A vpc analysis (6-ft silicone gum rubber column) did not show peaks corresponding to either 9- or 10-bromocamphor.

Attempted Resolution of (±)-Camphor. Following a reported procedure,[22] the (−)-menthydrazone was prepared from racemic camphor and was repeatedly recrystallized to give the reported constants: mp 193–194°, $[\alpha]^{20}D$ −101°. Camphor regenerated from this product invariably had $[\alpha]D$ −12.3° (63.5% (−)-camphor).

The (−)-menthydrazone was then prepared from 80.8% (−)-camphor and was twice recrystallized: mp 193–197°, $[\alpha]D$ −54.7°. Camphor regenerated from this product had $[\alpha]D$ −35.8° (90% (−)-camphor).

Next the (−)-menthydrazone was prepared from pure (+)-camphor: mp 183–185°, [M]D −252° (lit.[22] mp 177–178°, [M]D 236°). Pure (+)-camphor, $[\alpha]D$ 44.5°, could be recovered from this product.

Using these data, calculations suggest a value of [M]D −33° for pure (−)-camphor-(−)-menthydrazone, or about one-third the reported value.

Since we were unable to effect further purification of the 63.5% (−)-camphor-(−)-menthydrazone by exhaustive recrystallizations we abandoned this attempt at resolution in favor of that reported in the next section.

Partial Resolution of (±)-Camphor-8-^{14}C (1). (+)-Camphor-8-^{14}C. A sample of 1.9 g of extremely radioactive (±)-camphor-8-^{14}C was diluted with 80 g of (+)-camphor and this mixture, mp 177–179°, $[\alpha]D$ +44.3° (*c* 8.1, absolute alcohol), 425,112 ± 650 cpm/mmol, was converted to the (−)-menthydrazone as previously described. The hydrazone was recrystallized five times from 95% ethanol and the radioactivity examined after each recrystallization. After the fifth recrystallization it counted 261,081 ± 510 cpm/mmol or 61.5 ± 2.1% of the original activity was present and the yield was 70 g (38%).

The hydrazone was decomposed and gave 25 g (82.5% recovery) of camphor, mp 177–179°; $[\alpha]D$ +44.5° (*c* 9.1, absolute alcohol), 259,994 ± 510 cpm/mmol (lit.[40] mp 178.5–179°, $[\alpha]D$ +44.8° (*c* 20, absolute alcohol)).

Resolution of Camphor-9-sulfonic Acid. (+)-Camphor-9-sulfonic Acid (3). A 100-g (0.66 mol) sample of camphor was treated with chlorosulfonic acid as previously described and worked up as the ammonium salt, 160 g (0.64 mol). This material was dissolved in 1.0 l. of distilled water and 433 g of Mallinckrodt's Amberlite 1R 120 HCP medium porosity (strong acid ion exchange resin) added and the mixture stirred vigorously for 6 hr. It was filtered and the exchange resin washed with 300 ml of distilled water.

The combined aqueous portions were treated with 90 g (0.27 mol) of strychnine and heated on the steam bath for 10 min and then cooled in the refrigerator whereupon a flocculent precipitate came down. It was filtered off and then dissolved in boiling water and treated with Norit until colorless.

The colorless solution was cooled and the crystals filtered. After repeated recrystallization a small amount of optically pure strychnine (+)-camphor-9-sulfonate was obtained.

In the meantime, the original filtrate was allowed to evaporate slowly and a new crop of crystals separated.

The same procedure was followed, and all mother liquors were saved, combined, and evaporated and the resulting crystals recrystallized from boiling water.

This entire process was continually repeated until 20 g (0.35 mol) of optically pure strychnine (+)-camphor-9-sulfonate was obtained: $[\alpha]D$ +22.8° (*c* 1.0, chloroform) (lit.[24] $[\alpha]D$ +22.6° (*c* 0.43, chloroform)). The ammonium salt was regenerated by treating the strychnine salt with an excess of ammonia, filtering off the strychnine, extracting the last traces of strychnine with benzene, and evaporating to dryness, using the water pump and then the oil pump to remove the last traces of moisture. This left 8.4 g (5.1%) of ammonium (+)-camphor-9-sulfonate, $[\alpha]D$ +69° (*c* 2, water) (lit.[24] $[\alpha]D$ 68° (*c* 2, water)).

The procedures, sulfonation and removal of the 9- and 10-methyl groups, were carried out starting with (±)-camphor-8-^{14}C diluted with (+)-camphor. In addition the removal of the 10-methyl group (camphor → camphene → ozonization) was carried out on the (±)-camphor-8-^{14}C and the labeled camphor recovered from the sulfonation.

The resolved camphor-8-^{14}C was sulfonated, the product, camphor-9-sulfonic acid, resolved, and the 10-methyl group removed as described above.

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