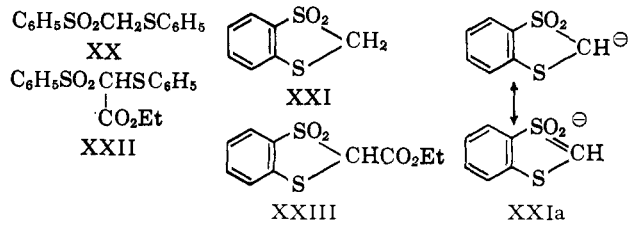
XX and XXII had very nearly the same dissociation constants as the cyclic analogs XXI and XXIII.



In the cyclic anion, the resonance indicated in XXIa would suggest a structure analogous to benzothiophene, but actually no enhanced stability is observed for XXIa, as measured by acidity, although the cyclic anions are colored, in contrast to the colorless anions from XX and XXII.

The difference in basicity between open-chain sulfur ylids, which remove protons from water, and the thiabenzene V which can be refluxed unchanged in acetic acid, on the other hand, supports our view of marked stabilization through cyclic conjugation in the thiabenzene ring. The marked stabilization of the latter is also supported by the resistance to desulfurization noted for II and V.

There are some significant differences between the anion XXIa and thiabenzenes, such as II or III. While the sulfonyl sulfur in XXIa and the "sulfonium" sulfur of II or III each have vacant 3d-orbitals to accommodate electrons, only the latter have unshared electrons on the sulfur. We have earlier suggested[22] that the much greater stabilization of a carbon free radical by a sulfide group than by a sulfonyl or silyl group may be due to use of 2p–3p orbitals for π-bonding, with promotion of an unshared electron on sulfide sulfur to a vacant 3d-orbital, and such a possibility was one of those we have already considered for thiabenzene.[2b]

The considerably greater stability of the four new thiabenzenes than of I could also be considered to support this view. Rehybridization of the usual p^3-structure of sulfonium salts[22c] to sp^2 would require that the S-phenyl group become coplanar with the thiabenzene ring. This would be considerably hindered by the bulk of the 2- and 6-phenyl groups in I, in contrast to the lesser hindrance in compounds II–V. It is thus possible that I utilizes p^3-orbitals for σ-bonding, retains its unshared pair in a 3s-orbital and uses one (or perhaps two) 3d-orbitals for cyclic conjugation, whereas compounds II–V utilize sp^2-orbitals for σ-bonding, the $3p_z$-orbital for cyclic conjugation and one (or more) 3d-orbitals for the unshared pair.[23]

The marked color of thiabenzenes, without any marked difference from the normal ultraviolet spectra of related benzenoid analogs, may also be relevant to the state of hybridization of the sulfur atom. If the unshared pair on sulfur is indeed promoted to a 3d-orbital in thiabenzenes, then the color may arise from atomic excitation of one of these electrons to another 3d-orbital of only slightly higher energy, without very great influence on the cyclic conjugated π-electron system. In normal sulfonium salts, with the unshared pair in a 3s-orbital, the excitation energy would be much greater, as indicated by ultraviolet absorption only at very short wave lengths.[22c]

Of many remaining unresolved questions, two are worthy of comment: One is the remarkable difference between coupling of thiopyrylium salts with phenyllithium and with phenylmagnesium bromide. Whereas we find virtually exclusive coupling on sulfur to give thiabenzenes by the former, every case of the latter so far studied couples on carbon to give isomeric thiopyrans. We have reported some examples earlier,[2] several more here, and Lüttringhaus, Engelhard and Kolb[24] report that X couples with the Grignard reagent to introduce a phenyl group at carbon 4. One possible explanation of this marked contrast may be that Grignard reagents coördinate on sulfur through the magnesium atom, blocking direct alkylation of sulfur, although this could not be complete, since we observed fleeting colors characteristic of thiabenzene[2b] during Grignard coupling.

Another preliminary observation, which may or may not be related to the mechanisms of coupling to form thiabenzenes, is that all reaction mixtures for formation of thiabenzenes I–V showed e.s.r. signals, some with remarkable fine structure—if measured before aqueous washing, but not after. The complete destruction of the e.s.r. signals by water suggests they may have arisen from some radical-ion, perhaps formed by electron transfer with phenyl anion. Some such radical-forming process might also be a logical explanation of the appreciable yield of dithioxanthyl (IVa) formed from XII along with the thiabenzene IV.

(22) (a) C. C. Price and J. Zomlefer, *J. Am. Chem. Soc.*, **72**, 14 (1950); (b) C. E. Scott and C. C. Price, *ibid.*, **81**, 2670 (1959); (c) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press Co., New York, N. Y., 1962.

(23) The puzzling reluctance of the thiabenzenes to crystallize, undoubtedly also related to their ready solubility and affinity for solvents, is, however, hard to reconcile with a planar sp^2 arrangement at sulfur. Perhaps freedom of motion between sp^2 and p^3 geometry retards crystallization.

(24) A. Lüttringhaus, N. Engelhard and A. Kolb, *Ann.*, **654**, 189 (1962).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.]

The Nature of Camphene Racemization[1,2]

BY WYMAN R. VAUGHAN, CHARLES T. GOETSCHEL, MARVIN H. GOODROW[3] AND CHARLOTTE L. WARREN

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Camphene-10-C^{14} has been prepared by a stereospecific synthesis. It has been diluted with unlabeled optically active camphene and subjected to racemization at 156° in acetonitrile–pyruvic acid for varying lengths of time, after which optical activity and isotope distribution have been measured. With the assistance of a newly developed set of kinetic equations applicable to the unique threefold racemization process, the extents of involvement of the three modes of racemization (*endo*-methyl shift, *exo*-methyl shift and 2,6-hydride shift) have been determined.

In 1953, two independent tracer studies[4,5] of the camphene racemization process demonstrated the operation of a methyl shift *and* a 2,6-hydride shift process in the course of racemization under a variety

(1) Work supported in part by the Michigan Memorial Phoenix Project and in part by a grant (CA 5406) from the National Cancer Institute to The University of Michigan.

(2) Abstracted in part from the Ph.D. Dissertation of Charles T. Goetschel, The University of Michigan, 1962. Presented before the Organic Division of the American Chemical Society, 144th National Meeting, Los Angeles, Calif., March 31–April 5, 1963.

(3) Michigan Memorial Phoenix Project Post-Doctoral Fellow, 1958–1959.

(4) J. D. Roberts and J. A. Yancey, *J. Am. Chem. Soc.*, **75**, 3165 (1953).

(5) W. R. Vaughan and R. Perry, Jr., *ibid.*, **75**, 3168 (1953).

of conditions. However, neither study unequivocally demonstrated involvement of *both endo* (10) and *exo* (9) methyl groups in the phenomenon, although one[4] purported to do so *if* one accepted the hypothesis that the statistical distribution of carbon-14 among the methyls and methylene group observed at equilibrium was the result only of competitive (and non-specific) methyl and hydride migrations neglecting all initial isotope rearrangement. The other study[5] suggested without proof an alternation of stereospecific methyl migration with hydride migration to account for the statistical isotope distribution.

The former study[4] was the more elegantly conceived to answer the question concerning the nature of the methyl migration, but unfortunately an over-simplified kinetic expression was adopted: specifically,one which treated the over-all racemization as two competing first-order processes which, to a first approximation, could be regarded as irreversible, or if reversible, as proceeding no farther than one migration in either direction. Consequently the numerical results, while qualitatively able to demonstrate different degrees of involvement of total methyl migration and hydride migration under differing conditions, quantitatively lack precision.

The latter study[5] was less elegantly conceived in that racemization occurred during the camphene hydrochloride–isobornyl chloride rearrangement rather than being restricted to camphene itself, and furthermore gave evidence only for the situation at equilibrium (complete racemization) and hence required an assumption regarding the sequence of events.

Taken together these studies give unequivocal evidence for both methyl and hydride migration, but neither is intrinsically able to provide evidence concerning the extent to which either or both methyl groups may be involved in the methyl shift process, even when an appropriate kinetic expression is applied. The reason for this situation is attributable to the fact that expedience dictated methylene (8) labeling and isotope distribution analysis by measurement of carbon-14 concentration at C-8 (and/or at C-9 *plus* C-10). Thus ozonative degradation can at best determine *total* carbon-14 at C-8, and this is present in an indeterminable mixture of two enantiomers for any except zero time, since a 2,6-hydride migration provides only the enantiomer of the original while methyl migration provides either or both of two optical enantiomers which are isotopic structural isomers. And while measurements at very short initial racemization times might give a fair indication of the extent of isotope rearrangement *vs.* hydride migration, measurements at any appreciable time intervals become valueless, since further rearrangement leads to regeneration of the original configuration and still further isotope redistribution with reappearance of the label at C-8 with either (+)- or (−)-rotation or both in indeterminate amounts. The development of appropriate kinetic equations, which are applicable experimentally only in their simplified approximate forms (see below), clearly reveals the undesirability of a label solely at C-8, if information as to relative involvement of *endo*- and *exo*-methyl migrations is to be estimated. On the other hand, labeling at C-8 is ideal for estimation of relative involvement of hydride and total methyl migration. Thus any solution of the problem must involve data from both C-8 labeled camphene and camphene with carbon-14 at either C-9 or C-10, unless a method for determining the isotope concentration at *each* of the three positions becomes available.

Since the experimental difficulties in such an analysis were evident, it was decided to rely on the distribution data of Roberts and Yancey[4] for the total methyl *vs.* hydride migration and to investigate the individual methyl migrations by labeling at C-9 or C-10. To this end a general method of synthesis for such labeled camphene was laid out.

Two syntheses were investigated, both providing the label at the desired position by the same stereospecific path and both capable of placing it either at C-9 or C-10. The 10-position was selected for two reasons: synthesis of the starting material, citraconic anhydride, was experimentally easier, and it was thought that if exclusive *endo*-methyl migration were occurring, this might be most readily detected qualitatively if the migrating group were labeled and thus would not show up at C-8 in the early stages of racemization.

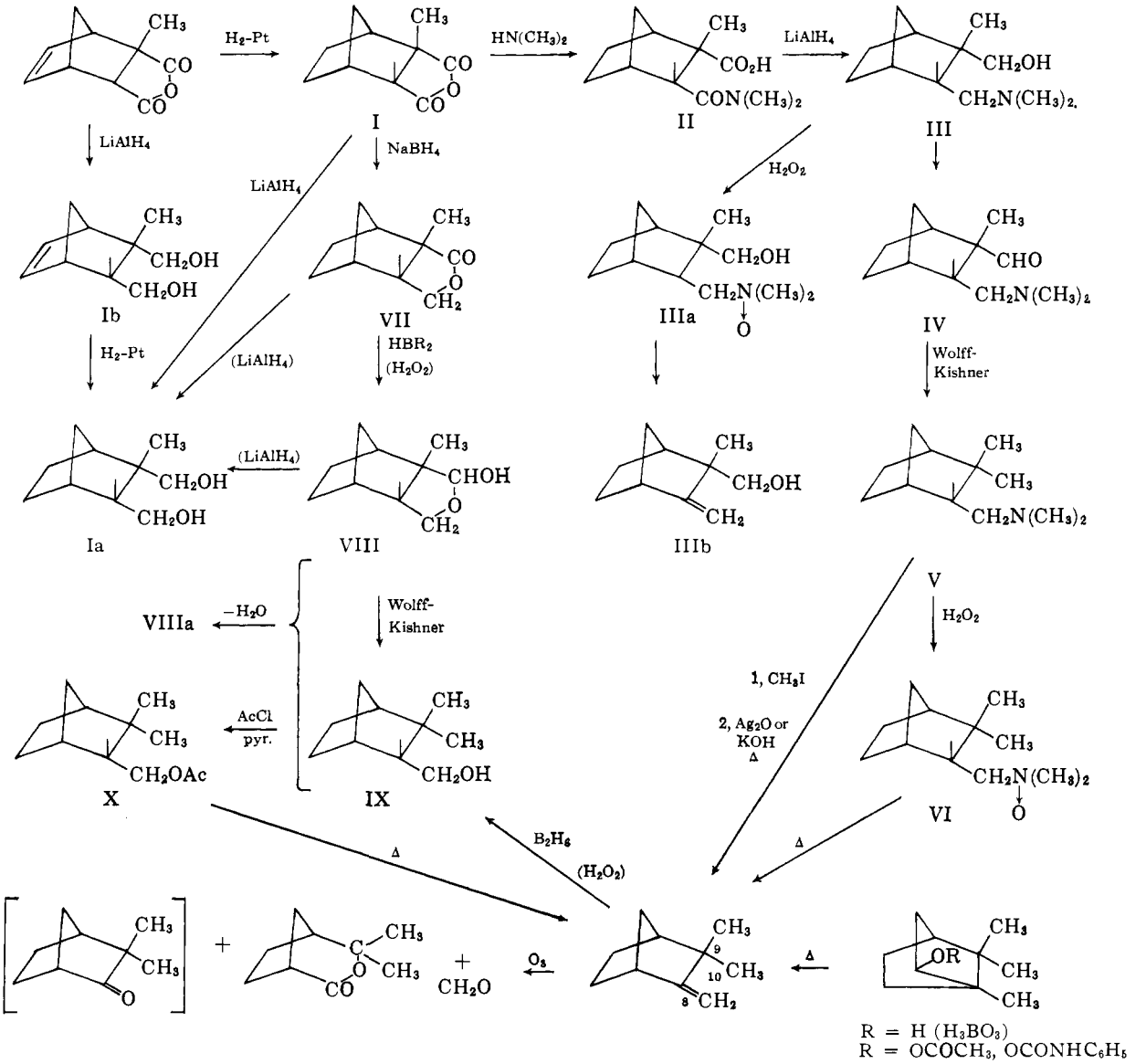
The method for construction of the C-10 labeled carbon skeleton involved the Diels–Alder reaction of citraconic anhydride with cyclopentadiene, followed by hydrogenation of the exclusively *endo* adduct.[6] The labeled citraconic anhydride was prepared from ethyl acetoacetate and sodium cyanide-C^{14} by known procedures.[7-9] Thus the citraconic anhydride possessed carbon-14 in the carbonyl group α to the methyl, and ultimate conversion of the hydrogenated Diels–Alder adduct I to camphene required conversion of the α-*endo*-carbonyl to methyl and conversion of the β-*endo*-carbonyl to methylene under conditions such that no alteration in the gross skeleton could occur. Specifically the latter condition requires that the introduction of the methylenic double bond be the ultimate step and be effected under conditions not allowing acid-catalyzed rearrangement of the product.

Both synthetic routes (Chart I) took cognizance of this requirement and both involved conversion of the labeled carbonyl of the anhydride to an aldehyde (lacking α-hydrogen and hence insensitive to epimerization). The original route involved conversion of the anhydride I to the N,N-dimethyl half-amide II, a process which proved to be stereospecific owing to the α-methyl adjacent to the labeled carbonyl. Lithium aluminohydride reduction of II afforded the aminoalcohol III in good yield, but all attempts to replace the hydroxyl on the labeled carbon with hydrogen proved impracticable in terms of yield, the strategically placed tertiary amino group appearing to interfere with all obvious reactions. Consequently the conversion of the primary alcohol to aldehyde IV was carried out, and the aldehyde was then reduced to methyl *via* the Wolff–Kishner reaction (V). Finally the tertiary amine was converted to the amine oxide VI and decomposed *via* the Cope elimination to give camphene. However, lack of reproducibility and general experimental difficulties with the oxidation of III to IV led us to investigate a more tractable route from I to camphene.

It was discovered that the selective reduction of I by sodium borohydride to 2-methylnorcamphane-*endo*-(3-methyl-2-carbo-3a-lactone) (VII) could be accomplished in excellent yields, and that VII could be further reduced to the cyclic hemi-acetal VIII by means of bis-3-methyl-2-butylborane.[10] Unfortunately VIII provided no solid derivatives except for the acetal (formed during the subsequent reaction by dehydration) VIIIa, nor could it be satisfactorily purified except by vapor phase chromatography. Consequently, conditions were worked out for *in situ* hydrazone formation followed without isolation by Wolff–Kishner reduction

(6) K. Alder, F. Brochagen, C. Kaiser and W. Roth, *Ann.*, **593**, 1 (1955).
(7) L. Bouveault and F. Levallois, *Ann. chim. phys.*, [8] **21**, 422 (1910).
(8) D. T. Mowry and A. G. Rossow, *J. Am. Chem. Soc.*, **67**, 926 (1945).
(9) J. Volhard, *Ann.*, **268**, 255 (1892).
(10) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 3222 (1960); H. C. Brown and D. B. Bigley, *ibid.*, **83**, 486 (1961).

CHART I: CAMPHENE SYNTHESES AND RELATED REACTIONS



to *endo*-camphenilanol (IX). This reduction product was identified by acid phthalate formation and *p*-nitrobenzoate formation,[11,12] both derivatives proving to be identical with authentic samples and different from the corresponding derivatives of the *exo* isomer.[11,13] Conversion of IX to camphene was by way of pyrolysis of the acetate (X) of IX, the identity of X being checked by comparison of infrared spectra and v.p.c. retention times with those of authentic samples. Thus an unequivocal route to camphene-10-C^{14} has been established, and the only difficult step is the conversion of VII to VIII, which is extremely sensitive to the amount of hydrogen peroxide used in the work-up of the hydroboration product. The yields are excellent throughout, and the integrity of the labeled position is assured.

In order to study racemization concurrently with isotope distribution it was essential to have a convenient source of optically active camphene and, since published procedures were inconvenient for various reasons, a new method of preparation was devised. It was found that reduction of natural camphor by lithium aluminohydride (but *not* by sodium borohydride) afforded 89% pure isoborneol. Professor C. A. Bunton[14] assured the authors that pyrolytic decomposition of isobornyl esters leads to unracemized camphene, and this was shown to be true for the acetate XI. In addition, results of catalytic dehydration of isoborneol have recently appeared elsewhere[15] and thus a very convenient source of optically active camphene was at hand. Boric acid dehydration of isoborneol and pyrolysis of isobornylphenylurethan were also investigated. The former is accompanied by racemization (partial), the latter is not.

It only remained to dilute the racemic 10-labeled camphene with a suitable quantity of optically active camphene for study of the racemization and isotope distribution as a function of time. Accordingly, a macro sample was prepared and was shown to be free of carbon-14 at C-8 by ozonolysis and examination of the resultant formaldehyde (counted as the methone derivative). The specific activity of the concurrently formed dimethylnorcampholide[5] was used as a standard for

(11) R. Dulou and Y. Chretien-Bessière, *Bull. soc. chim. France*, 1362 (1959).

(12) W. Hückel and H. Schultze, *Ann.*, **575**, 32 (1951).

(13) It should be noted that a previous publication (W. R. Vaughan and R. Perry, Jr., *J. Am. Chem. Soc.*, **74**, 5355 (1952)) purporting to prove the configuration of "isocamphenilanol" has been shown to be in error (K. Alder and W. Roth, *Chem. Ber.*, **90**, 1830 (1957)). Configurational assignments in the present work agree with recent conclusive configurational assignments (ref. 12.).

(14) Private communication.

(15) K. Watanabe, C. N. Pillai and H. Pines, *J. Am. Chem. Soc.*, **84**, 3934 (1962).

counting the same material obtained on ozonolysis after several partial racemizations of labeled camphene, these being carried out so as to duplicate as nearly as possible the conditions established by Roberts and Yancey[4] so as to provide maximum methyl migration. Precise temperature control and exact reaction times could not be achieved since the racemization involves heating a solution of camphene in acetonitrile–pyruvic acid in a sealed tube above the boiling point of the system. But by assuming that racemization is a strictly first-order process so long as the relative concentrations of the three components is constant, it is possible to establish effective reaction times by calculating first-order racemization rate constants from optical activities of pure camphene samples isolated after suitable time intervals, initial concentrations being identical and temperature control being at 156 ± 2°, with heating and cooling operations being conducted as reproducibly as possible. Thus a useful apparent first-order rate constant for racemization (k_{rac}) becomes available and, by isotope analysis, mole fractions of camphene-8-C^{14} become available for the same time intervals as measurements of optical activity. Pertinent data are collected in Table I.

TABLE I

RACEMIZATION AND COUNTING DATA

Time, hr.[a]	$[\alpha]^{25}D$[b]	kt	Radioactivity,[c] d./min./mmole	Z/X_0[d]
0.0000	+42.3°	0.000	81.7	0.000
0.575	36.3	.0795	80.2	.0184 ± 0.048
1.485	28.4	.199	76.0	.0698 ± .044
2.575	20.7	.357	65.1	.203 ± .040

[a] Reactions run in sealed tubes in vapor bath at 156 ± 2°; tubes placed in bath at room temperature. Camphene = 1.10 *M* in acetonitrile–pyruvic acid[4] at reaction temperature. "Zero time" calculated from kinetic plot for optical activity: $k = k_{rac} = 0.134$ hr.$^{-1}$. [b] *Cf.* footnote 17. [c] Corrected for background and appropriate standard[20]; values reliable to ±5%. [d] 1 − measured mole fraction of camphene-8-C^{14} isolated as dimethylnorcampholide.[5]

Once the isotope rearrangement data were available it became apparent that our hope of having the label at C-10 would qualitatively permit demonstration of exclusive *endo*-methyl migration was naïve. Consequently it became necessary to derive kinetic expressions which could be used in conjunction with the earlier data[4] to provide the desired answer as to the extent of involvement of both *endo*- and *exo*-methyl migration. The system can most simply be described (Fig. 1) by the letters A through F, where each letter represents one of the six isotopic isomers of camphene (three ± pairs), and where each form has the opposite sign of rotation to that of its immediately adjacent and directly opposite neighbors. The numbers refer to the modes of interconversion: (1) *endo*-methyl shift, (2) 2,6-hydride shift, (3) *exo*-methyl shift.

Thus at zero time only one of the isotopic isomers is present, and at any appreciable time interval thereafter all six are present, concentration becoming equal at equilibrium (infinite time). If isotope distribution is to be measured by ozonative degradation, it is possible only to measure the *sum* of the mole fractions of (+)- and (−)-camphene-8-C^{14} after any given time interval, regardless of the position of the original label. But in addition it is possible to measure the concentrations of A + C + E and B + D + F by making use of optical activities, since within each group the specific rotations are identical and opposite to those of the other group. Moreover, $k_{rac} = k_1 + k_2 + k_3$, and k_{rac} can be obtained from optical activity measurements.

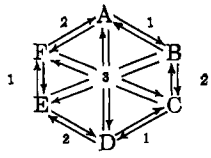


Figure 1.

Furthermore, all processes are strictly first order so long as initial concentrations of camphene and members of the solvent pair are identical, and each of the individual rate constants can be expressed as a fraction of the total racemization rate constant; thus k_1 can be replaced by αk_{rac}, k_2 by $(1 - \alpha - \beta)k_{rac}$ and k_3 by βk_{rac}, where α and β represent the fractions racemizing by *endo*- and *exo*-methyl shifts, respectively.

Six rate equations may be written, one for each constituent (A–F) being reversibly converted to each of three antipodes as shown in Fig. 1. By selecting and adding appropriate pairs of these equations, so that one such sum represents the pair with the C-8 label, three sets of equations for the appearance (or disappearance) of pairs of camphene radioisotopes are produced

$$dX/dt = -(k_1 + k_2)X + k_1Y + k_3Z \quad (1a)$$
A = (+)- or (−)-8-C^{14}

$$-(k_1 + k_2)X + k_1Y + k_2Z \quad (1b)$$
A = (+)- or (−)-9-C^{14}

$$-(k_2 + k_3)X + k_2Y + k_3Z \quad (1c)$$
A = (+)- or (−)-10-C^{14}

$$dY/dt = k_1X - (k_1 + k_2)Y + k_2Z \quad (2a)$$
A = (+)- or (−)-8-C^{14}

$$k_1X - (k_1 + k_3)Y + k_3Z \quad (2b)$$
A = (+)- or (−)-9-C^{14}

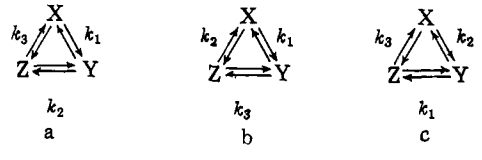
$$k_2X - (k_1 + k_2)Y + k_1Z \quad (2c)$$
A = (+)- or (−)-10-C^{14}

$$dZ/dt = k_3X + k_2Y - (k_2 + k_3)Z \quad (3a)$$
A = (+)- or (−)-8-C^{14}

$$k_2X + k_3Y - (k_2 + k_3)Z \quad (3b)$$
A = (+)- or (−)-9-C^{14}

$$k_3X + k_1Y - (k_1 + k_3)Z \quad (3c)$$
A = (+)- or (−)-10-C^{14}

These sets of equations (1a, 2a, 3a, etc.) are equivalent to the rate equations for the simpler systems a, b, and c



wherein X, Y and Z replace the appropriate pairs (true enantiomers, *i.e.*, with identical positions labeled) of camphene radioisotopes; and the mole fractions of camphene-8-C^{14} (a, X/X_0; b, Y/X_0; c, Z/X_0) are measurable by ozonative degradation. Now a related reaction system, $A_1 \rightleftarrows A_2 \rightleftarrows A_3$ has been explicitly treated,[16] and by using an identical method of derivation, expressions for X, Y and Z as functions of time and the racemization rate constant can be established. The present system is simpler in that the forward and reverse rate constants are identical because of the enantiomeric relationships, and hence there are involved but three instead of six constants (or four in the system treated[16]). But the present system is unique in that it is a closed cycle.

(16) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 160–164. We are indebted to Dr. Carl David and Mr. Melvyn Feinberg for calling this relationship to our attention.

The integrated forms of the rate equations are (*cf.* method in ref. 16)

$$\frac{X}{X_0} = 1/3 + \frac{e^{-kt}}{6}\left[\frac{q}{p}M + 2N\right] \quad (4)$$

$$\frac{Y}{X_0} = 1/3 + \frac{e^{-kt}}{6}\left[\frac{r}{p}M - N\right] \quad (5)$$

$$\frac{Z}{X_0} = 1/3 + \frac{e^{-kt}}{6}\left[\frac{s}{p}M - N\right] \quad (6)$$

k = racemization rate constant
t = time
$p = [1 - 3(\alpha + \beta - \alpha\beta - \alpha^2 - \beta^2)]^{1/2}$
$M = (e^{ktp} - e^{-ktp}) = \sinh(ktp)$
$N = (e^{ktp} - e^{-ktp}) = \cosh(ktp)$

a series: $q = 2 - 3\alpha - 3\beta$; $r = 3\alpha - 1$; $s = 3\beta - 1$
A = (+)- or (−)-8-C^{14}

b series: $q = 3\beta - 1$; $r = 3\alpha - 1$; $s = 2 - 3\alpha - 3\beta$
A = (+)- or (−)-9-C^{14}

c series: $q = 3\alpha - 1$; $r = 2 - 3\alpha - 3\beta$; $s = 3\beta - 1$
A = (+)- or (−)-10-C^{14}

α = fraction racemizing *via endo*-methyl shift
β = fraction racemizing *via exo*-methyl shift
$1 - \alpha - \beta$ = fraction racemizing *via* 2,6-hydride shift

It is clear that eq. 4a is applicable to the work of Roberts and Yancey[4] while eq. 6c is applicable to the present work. Thus from the former work a value for $\alpha + \beta$ can be obtained while from the present work β can be evaluated. Furthermore it must be noted that if the expression (ktp) is sufficiently small, these equations may be considerably simplified and thus permit solution, since the indeterminable value p disappears, eq. 4a and 6c, respectively, reducing to eq. 7 and 8.

$$\alpha + \beta = 1/3\left[2 + \frac{2 - (3X/X_0 - 1)e^{kt}}{kt}\right] \quad (7)$$

$$\beta = 1/3\left[1 + \frac{1 + (3Z/X_0 - 1)3^{kt}}{kt}\right] \quad (8)$$

Introduction of Roberts' and Yancey's data[4] for the run (Table II last run) most nearly corresponding to those of the present investigation into eq. 7 gives $\alpha + \beta = 0.8$, or 20% hydride migration accompanied by 80% total methyl migration. Substitution in eq. 8 of the data of Table I gives $\beta = 0.58$ to 0.68. Thus *exo*-methyl migration accounts for 58 to 68% of total racemization, and when this is combined with the information from the earlier work,[4] *endo*-methyl migration is seen to account for 22 to 12% of total racemization. The differences observed in extent of hydride migration under differing conditions must in part be attributed to probable differences in the dependence of the individual activation parameters on temperature and in part to possible gross differences in transition states for the individual processes when they are actuated by the different reagent and/or solvent systems employed in the earlier work.[4] Corrected values for the methyl–hydride shift processes calculated from the earlier experimental data[4] are collected in Table II.

TABLE II

RACEMIZATION OF CAMPHENE UNDER VARIOUS CONDITIONS[a]

System[a]	Temp., °C.[a]	t, min.[a]	kt[b]	X/X_0[c]	$(\alpha + \beta)$[d]
$TiO_2(H_2O)_x$	100	210	0.45	0.96	0
$TiO_2(H_2O)_x$	160	1.3	.74	.80	0.24
$C_6H_5NH_3Cl$ in $C_6H_5NH_2$	180	13	.38	.88	.31
CH_3COCO_2H in CH_3CN	156 ± 2	330	.34	.78	.78

[a] Ref. 4. [b] Calculated from t and rotation data of ref. 4. [c] 1 − "% rearranged" (from ref. 4). [d] Calculated from eq. 7.

Experimental[17–20]

Ethyl Acetoacetate Cyanohydrin-C-14.—To 286.3 g. (2.2 moles) of ethyl acetoacetate (redistilled, b.p. 70° (6.0 mm.)) and 50 ml. of water was added, with gentle stirring, 11.13 mg. (0.226 millicuries) of sodium cyanide (C-14), 103.9 g. (2.0 moles) of 95% sodium cyanide and 250 g. of finely crushed ice. The mixture was cooled in an ice-bath, and with rapid stirring a solution of 264.3 g. (2.5 moles) of sodium bisulfite in 400 ml. of water was added dropwise over a period of 0.5 hr. After addition, the mixture was stirred with continued cooling for 15 min., then allowed to warm to room temperature and stirred for an additional hour. The mixture was allowed to settle for 20 min., and as much of the liquid decanted from the salts as possible (about 400 ml.). Next, 300 ml. of water was added to the salts; and repeated ether extraction followed (1 × 200 ml., 8 × 100 ml.). The original decanted solution was separated and the water layer extracted with ether (2 × 100 ml.). The ether solution was dried by first shaking for 3 min. with anhydrous sodium sulfate followed by standing for 12 hr. over anhydrous magnesium sulfate. The ether was removed (*in vacuo*) leaving a straw-colored residue weighing 264.8 g. (84.5% crude). The residue was vacuum distilled giving a colorless liquid: 198 g., b.p. 104–112° (6 mm.), $n^{24}D$ 1.4302; reported[8] b.p. 120–124° (13 mm.), $n^{25}D$ 1.4298. Yields ranged from 63–81%.

***cis*- and *trans*-β-Cyano-C-14-crotonates.**—A solution of 189 g. (1.20 moles) of ethyl acetoacetate cyanohydrin and 192 g. (2.40 moles) of dry pyridine was cooled in an ice-bath, and 160 g. (1.34 moles) of thionyl chloride was added dropwise at a rate of about 80 drops per min. Following the addition, stirring was continued until the mixture solidified (about 0.5 hr.). The solid was broken up by addition of 200 ml. of dry ether, and the mixture was poured over 400 g. of ice. The water and ether layers were separated and the water layer repeatedly extracted with ether (1 × 200 ml., 8 × 100 ml.). The ether extracts were combined and washed with 10% aqueous sodium carbonate (2 × 100 ml.), followed by water (2 × 100 ml.), then dried (anhydrous sodium sulfate followed by anhydrous magnesium sulfate). Distillation of the residue (162 g., 97%) after removal of ether gave a yellow liquid: 143.7 g. (86%); b.p. 84° (7.0 mm.); $n^{19}D$ 1.4520. After dissolving this yellow product in 100 ml. of ether, washing with 5% aqueous sodium bisulfite (2 × 20 ml.), 5% aqueous sodium carbonate (2 × 20 ml.), 2% aqueous hydrochloric acid (2 × 20 ml.), water (2 × 20 ml.), and drying over anhydrous magnesium sulfate, it was again distilled. A colorless liquid was obtained: 129.1 g. (77.6%); b.p. 75–97° (6.0 mm.) (redistilled 100–125° (24 mm.)); $n^{19}D$ 1.4500; reported[8]: *trans:* b.p. 93–94° (24 mm., $n^{25}D$ 1.4494); *cis:* b.p. 119–120° (24 mm.), $n^{25}D$ 1.4518. Yields ranged from 77–91%.

Mesaconic Acid-1-C^{14}.—To 750 ml. of water and 118 g. (2.96 moles) of sodium hydroxide was added 128.1 g. (0.740 mole) of *cis*- and *trans*-ethyl β-cyanocrotonates, and the solution was heated under reflux for 40 hr.; then it was distilled to one-half its original volume. The concentrated solution was neutralized to congo red with concd. hydrochloric acid. The resultant mixture was continuously extracted for 60 hr. with ether, after which the extract was dried and the ether removed. The residual yellow liquid solidified upon cooling: 85.0 g. (88.5%), m.p. 203.0–203.5°; reported[21a] m.p. 203–205°. Recrystallization was effected from water. Yields ranged from 88–93%.

Citraconic Anhydride-1-C^{14}.—An intimate mixture of 44.5 g. (0.340 mole) of mesaconic acid and 48.6 g. (0.340 mole) of phosphorous pentoxide, was heated in an oil-bath while being evacuated with a water aspirator. Citraconic anhydride began to distil over when the oil-bath reached 140–150° (*cf.* ref. 21b), the reaction being complete after 2 hr.; clear colorless liquid, 40 g. (90%), $n^{25}D$ 1.4692. Yields ranged from 85–90%.

***exo*-2-Methylnorborn-5-ene-*endo*-2,3-dicarboxylic Anhydride-2a-C^{14}.**—To a solution of 40 g. (0.36 mole) of citraconic anhydride and 30 ml. of reagent benzene was added dropwise (60 drops/min.) 24.2 g. (0.38 mole) of cyclopentadiene (twice distilled from iron powder and used immediately, b.p. 40°), while stirring at room temperature. Following the addition (25 min.) the clear colorless solution was stirred for 2.5 hr. at room temperature, then allowed to stand for 21 hr. The benzene was removed leaving a snow-white solid; 63.8 g. (99.6%), m.p. 131–132°. Yields ranged from 87–99%. Recrystallization was effected from ethyl acetate–petroleum ether (b.p. 40–60°); m.p. 137–138°, reported[22] 138°.

(17) Melting points and boiling points are uncorrected. All rotations taken in a 1-dm. tube are correct to ±0.10°.

(18) Infrared spectra were taken on a Perkin-Elmer model 21 spectrometer as Nujol mulls for solids and and as pure compounds for liquids.

(19) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., unless marked *, in which case they are by Mrs. Anna Griffin, to whom we express our appreciation.

(20) Radioactivity measurements obtained with a Tri-Carb liquid scintillation counter, toluene solvent, with internal standard. (*Cf.* R. T. Overman and H. M. Clark, "Radioisotope Techniques," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp. 31–38, 187–191.)

(21) (a) R. L. Shriner, S. G. Ford and L. J. Roll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 382; (b) R. L. Shriner, S. G. Ford and L. J. Roll, *ibid.*, p. 140.

(22) O. Diels and K. Alder, *Ann.*, **460**, 98 (1928).

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.40, H, 5.66. Found: C, 67.37; H, 5.83.

***exo*-2-Methylnorbornane-*endo*-2,3-dicarboxylic Anhydride-2a-C^{14} (I).**—A solution of 63.8 g. (0.358 mole) of *exo*-2-methylnorborn-5-ene-*endo*-2,3-dicarboxylic anhydride-2a-C^{14} in 200 ml. of reagent grade ethyl acetate was hydrogenated at 3 atm. (300 mg. of Adams catalyst). After Norit treatment and solvent removal, a snow-white solid remained; 63 g. (98%), m.p. 131.0–131.5° (reported[23] 132°). This material may be recrystallized from an ethyl acetate–petroleum ether (b.p. 40–60°) solution.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65, H, 6.71. Found: C, 66.59, H, 6.66.

***exo*-2-Methyl-*endo*-3-carbamidonorbornane-*endo*-2-carboxylic Acid. (II).**[24]—To a mixture of 36.0 g. (0.20 mole) of I in 20 ml. of benzene and 80 ml. of dry ether there was added as rapidly as possible 25 ml. (17 g., 0.38 mole) of anhydrous dimethylamine (−2°, Dry Ice reflux condenser). After complete addition, the mixture, now containing a precipitate, was allowed to stand at room temperature overnight, after which it was filtered and the residue washed with ether; 42.4 g. (94%), m.p. 134–136° (sealed capillary). The product was recrystallized 4 times from ethyl acetate without change in m.p.

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 64.09*; H, 8.79*; N, 6.22.

***exo*-2-Methyl-*endo*-2-hydroxymethyl-*endo*-3,N,N-dimethylaminomethylnorbornane (III).**[24]—To a slurry of 10.2 g. (0.27 mole) of lithium aluminohydride and 50 ml. of dry tetrahydrofuran (THF) there was added 40.5 g. (0.18 mole) of II in 400 ml. of dry THF over a 2-hr. period; then the mixture was vigorously refluxed for 1 hr. and decomposed with 20.4 ml. of water followed by 16.3 ml. of 10% sodium hydroxide. It was filtered after standing overnight. The residue was slurried with THF (24 hr.), refiltered and the combined THF solutions evaporated at the aspirator; 31.2 g. (88%). Distillation *in vacuo* afforded 23.61 g. (67%), b.p. 90–100° (0.02 mm.). Redistillation at 90° (0.02 mm.) gave an analytical sample, $n^{25}D$ 1.4905.

Anal. Calcd. for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.78*; H, 11.51*; N, 7.07.

The amine (picrate, m.p. 133–135°; hydrochloride, m.p. 207.5–208.5°) was converted to the amine oxide IIIa[24] (procedure similar to one described below), subl. 68°, m.p. 166.0–166.5° (block). A picrate of the amine oxide was prepared for analysis, m.p. 131–132°.

Anal. Calcd. for $C_{18}H_{26}N_4O_9$: C, 48.86; H, 5.92; N, 12.67. Found: C, 49.01*; H, 6.03*; N, 12.65.

All attempts to prepare reducible esters (*e.g.*, tosylates) or halides from the original aminoalcohol failed.

10-Hydroxycamphene (IIIb).—A 6.00-g. (0.0282 mole) sample of crude IIIa was powdered and heated at 20 mm. in a short-path distillation apparatus by means of an oil-bath. The temperature was slowly raised from 100°, the product distilling from 160–172° (bath temperature). There was obtained 5.10 g. (85%) of a semisolid substance showing terminal methylene absorption in the infrared (1660, 885 cm.$^{-1}$). The crude distillate was taken up in ether and washed with 5% sodium hydroxide and water (until neutral), and the solution then was dried (sodium sulfate followed by Drierite). Upon filtration and evaporation of the solvent 3.55 g. (83%) of IIIb was recovered as a transparent oil which solidified on being seeded with a crystal of previously prepared material (m.p. 88.0–91.5°). An additional 0.16 g. of IIIb was recovered from the distillation apparatus (87% total yield). A sample was sublimed for analysis, m.p. 92.0–93.5°.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.85; H, 10.46.

***exo*-2-Methyl-*endo*-3-N,N-dimethylaminomethyl-*endo*-2-formylnorbornane (IV).**—To a stirred and ice-cooled mixture of 3.73 g. (0.0373 mole) of chromic anhydride in 30 ml. of 10 volume per cent acetic anhydride in glacial acetic acid was added 10.0 g. (0.0508 mole) of III, and the mixture was stirred at room temperature for 5 hr. Upon adding alkali (to pH 10) a gel formed, so the mixture was diluted to 1 l. and then was continuously extracted for 10 hr. The extract afforded 9.93 g. of crude IV as a light yellow oil which was converted directly to the semicarbazone, the procedure being critical. Relatively pure aminoaldehyde was obtained by tedious fractional distillation, b.p. 62–66° (0.2 mm.), $n^{27}D$ 1.4870. Crude IV was added to a solution of 10.0 g. of semicarbazide hydrochloride and 15.0 g. of sodium acetate trihydrate in 50 ml. of water. Solution occurred upon shaking. The solution was then twice heated in a boiling water-bath with spontaneous cooling to room temperature after each heating. Upon standing overnight the pH was brought to 10 with 10% potassium hydroxide. Addition of ether assisted the crystallization of the extremely insoluble semicarbazone, 7.2 g. (56%), m.p. 177–178°. Recrystallization from ethyl acetate afforded the analytical sample, m.p. 177.0–177.5° (cor.); picrate m.p. 178.5–180.5°; hydrochloride, m.p. 180–182°.

Anal. Calcd. for $C_{13}H_{24}N_4O$: C, 61.87; H, 9.59; N, 22.20. Found: C, 61.71; H, 9.64; N, 22.19.

2,2-Dimethyl-*endo*-3-N,N-dimethylaminomethylnorbornane (V).—To a solution of 7.00 g. of the semicarbazone of IV in 30 ml. of diethylene glycol was added 15 g. of 50% aq. potassium hydroxide, and the mixture was refluxed (oil-bath 140–150°) for 2 hr. The water was then distilled off (to 210°) and refluxing was continued for 5 hr. After cooling, the mixture was steam distilled (200 ml. distillate), and the distillate was extracted with ether. The extract afforded 4.14 g. (82%) of V, b.p. 82–84° (5 mm.), $n^{27}D$ 1.4702.

Anal. Calcd. for $C_{12}H_{23}N$: C, 79.49; H, 12.78. Found: C, 79.85; H, 12.87.

The amine picrate, m.p. 179–180°, was prepared.

Anal. Calcd. for $C_{18}H_{26}N_4O_7$: C, 52.67; H, 6.39; N, 13.65. Found: C, 52.95; H, 6.54; N, 13.54.

The amine methiodide, m.p. 303.0–303.5° dec., was also obtained.

2,2-Dimethyl-*endo*-3,N,N-dimethylaminomethylnorbornane oxide (VI).—A mixture of 1.00 g. (0.0055 mole) of V, 5 ml. of methanol and 1.8 ml. (0.018 mole) of 30% hydrogen peroxide was stirred for 13 hr. at room temperature, after which 10 mg. of Adams catalyst was added and stirring continued overnight. Filtration and concentration of the filtrate afforded 1.33 g. of crude VI. A picrate was formed in hot aqueous picric acid: m.p. 169–171°. Recrystallization from ethanol provided an analytical sample, m.p. 174.5–175.6°.

Anal. Calcd. for $C_{18}H_{26}N_4O_8$: C, 50.70; H, 6.15; N, 13.14. Found: C, 50.87; H, 6.21; N, 13.22.

Camphene from Decomposition of VI and Methiodide of V.—Exploratory thermal decomposition of VI (150°) and exhaustive methylation of V (methyl iodide) followed by treatment with silver oxide or potassium hydroxide with strong heating both afforded camphene, along with several unidentified products in addition to those expected. The camphene was identified by infrared analysis. Conditions for optimal reaction were not worked out, attention being turned to the more promising route, below.

***exo*-2-Methylnorbornane-*endo*-(3-methyl-2-carbo-3a-lactone) (Camphenolide) (VII).**—A mixture of 300 ml. of reagent isopropyl alcohol and 8.9 g. (0.23 mole) of powdered sodium borohydride was stirred rapidly for 30 min. at room temperature, and then a solution of 30 g. (0.17 mole) of 2-methylnorbornane-2,3-*endo*-dicarboxylic acid anhydride in 100 ml. of reagent isopropyl alcohol was added dropwise over 30 min. The reaction mixture became fairly warm during the addition but cooled to room temperature shortly thereafter, whereupon stirring was continued for 36 hr. at room temperature. The solvent was then removed (*in vacuo*) and the white solid residue hydrolyzed by adding it to a mixture of 75 ml. of concd. hydrochloric acid in 200 g. of ice. The hydrolyzed mixture was stirred for 1 hr., heated gently on the steam-bath for 30 min. followed by stirring 3 hr. longer, after which it was extracted with ether (3 × 200 ml.). The ether extracts were combined, washed with 10% aqueous sodium bicarbonate (3 × 75 ml.), water (3 × 75 ml.), and dried over anhydrous magnesium sulfate for 12 hr. The ether was removed (*in vacuo*) leaving a white solid: 23.0 g. (83%), m.p. 136–137°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.25; H, 8.53.

***exo*-2-Methyl-2a,3a-epoxy-2a-hydroxy-*endo*-2,3-dimethylnorbornane (Dihydrocamphenolide) (VIII).**—A mixture of 4.95 g. (0.129 mole) of powdered sodium borohydride and 200 ml. of purified tetrahydrofuran was stirred at room temperature for 20 min. then cooled in an ice-bath. To the cooled mixture was added, all at once, 25.5 g. (0.36 mole) of 2-methyl-2-butene. Then 25.5 g. (0.177 mole) of boron trifluoride etherate (redistilled using water aspirator) was added dropwise at a rate of 15–20 drops/min. over a 70-min. period. After the addition, stirring was continued at 0° for 2 hr., followed by stirring at room temperature for 1 hr.[10] The hydride concentration was then determined by adding an aliquot of the reaction mixture to ethylene glycol and collecting the hydrogen gas evolved (0.68 *M* in hydride). To the reaction mixture was added, over a 5-min. period, a solution of 10.0 g. (0.06 mole) of camphenolide in 35 ml. of purified tetrahydrofuran. The mixture was heated in an oil-bath at 75° for 22 hr. After cooling in an ice bath, 7.20 g. (0.177 mole) of sodium hydroxide in 57 ml. of water was added slowly, followed by adding dropwise 30.8 g. (0.268 mole) of 30%

(23) S. Beckmann and R. Schaber, *Ann.*, **585**, 159 (1954).

(24) These compounds (II, III and IIIa) were submitted to Dr. G. I. Poos of the McNeil Laboratories, Inc. (Philadelphia) for pharmacological testing. The following results were obtained: II. $LD_{50} \sim 1$ g./kg. (in mice), no interesting pharmacological behavior; III. $LD_{50} = 240$ mg./kg. (IP in mice), 1.280 g./kg. (orally in mice); below these doses some signs of CNS stimulation are seen, but it does not appear useful. A moderate hypertension is produced at very high doses; IIIa. $LD_{50} > 1.280$ g./kg. (IP in mice); no particular CNS or cardiovascular activity.

hydrogen peroxide.[25] After stirring at 0° for 1 hr., the reaction mixture was stirred at room temperature for 2 hr. Then 60 ml. of 10% aqueous sodium hydroxide was added and stirring continued an additional 30 min. The layers were separated and the water layer extracted with ether (3 × 100 ml.). The ether extracts and original organic layer were combined and dried by shaking 5 min. with anhydrous sodium sulfate followed by drying 12 hr. over anhydrous magnesium sulfate. The solvent was removed (*in vacuo*) leaving an oily residue: 9.8 g. (97% crude). The infrared spectrum showed no carbonyl absorption but did have hydroxyl absorption (3400 cm.$^{-1}$). A spectrum of known diol (see next experiment) corresponding to complete reduction was not the same.

***endo*-2,3-Bis-hydroxymethyl-*exo*-2-methylnorbornane (Ia).**—A sample of I was reduced with lithium aluminohydride in ether and worked up with dilute hydrochloric acid. From 18.00 g. (0.10 mole) of I, reduced with 5.30 g. of LAH in a total of 260 ml. of ether, there was obtained 16.9 g. (99%) of diol, m.p. 142.0–143.5° (sealed capillary and Koffler block) (ethyl acetate).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.47; H, 10.59.

A ditosylate was prepared using *p*-toluenesulfonyl chloride and pyridine; m.p. 105.5–106.2° (absolute ethanol–petroleum ether 30–60°). The infrared spectrum lacked hydroxyl bands and showed tosylate absorption at 1355 and 1175 cm.$^{-1}$. The dimethanesulfonate had m.p. 180–183°.

A bis-*p*-nitrobenzoate was also prepared, m.p. 155.3–155.7°.

Anal. Calcd. for $C_{24}H_{16}N_2O_8$: C, 62.61; H, 3.50; N, 6.09. Found: C, 62.40; H, 4.02; N, 6.01.

***endo*-2,3-Bis-hydroxymethyl-*exo*-2-methylnorborn-5-ene (Ib).**—The procedure and yield (95%) were the same as for the saturated analog, the starting material being the precursor to I; m.p. 146.5–147.5° (sealed capillary) (ethyl acetate).

A dimesylate of Ib was prepared using methanesulfonyl chloride and pyridine; m.p. 72.0–73.5° (95% ethanol).

Anal. Calcd. for $C_{12}H_{20}O_6S_2$: C, 44.43; H, 6.21. Found: C, 44.43; H, 6.37.

Catalytic hydrogenation of Ib afforded Ia, 96% yield, m.p. 142.0–143.5°. The product had the same infrared spectrum as in the preceding experiment.

***endo*-3-Hydroxymethyl-2,2-dimethylnorbornane (*endo*-Camphenilanol) (IX) (Wolff–Kishner–Huang-Minlon Procedure).**—A solution of 90 ml. of technical diethylene glycol, 10.0 g. (0.06 mole) of dihydrocamphenolide and 10 ml. (0.20 mol.) of hydrazine hydrate (99–100%) was heated in an oil-bath at 140° for 30 hr. (A 200-ml. flask equipped with a Dean–Stark water trap was employed.) The solution was then cooled to room temperature, 11.2 g. (0.20 mole) of potassium hydroxide added, and this mixture heated at 215° for 3 hr. After cooling, the reaction mixture was added to 500 ml. of water, and this mixture extracted with ether (4 × 100 ml.). The ether extracts were combined, washed with water (3 × 50 ml.) and dried by shaking with anhydrous sodium sulfate followed by standing over anhydrous magnesium sulfate 12 hr. The ether was removed (*in vacuo*) leaving a semisolid residue weighing 8.0 g. (88%); acid phthalate, m.p. 144–145°, reported 143.5–144.5°,[12] 141–142°[11]; *p*-nitrobenzoate, m.p. 91.3–91.7°, reported[11] 88–89° (93°). Mixture melting point determinations with authentic samples[11] showed no depression and microanalyses were satisfactory.

In a later run in other hands this procedure afforded, in addition to *endo*-camphenilanol, a crystalline by-product (VIIIa) which apparently sublimed from the Wolff–Kishner reaction vessel. Its infrared spectrum lacked both hydroxyl and carbonyl bands. From 3.3 g. of dihydrocamphenolide there was obtained approximately 1 g., m.p. 86–87° (ethanol–water).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; mol. wt., 304. Found: C, 78.94, 78.82; H, 10.70, 10.63. mol. wt. (Rast), 293.

***endo*-3-Acetoxymethyl-2,2-dimethylnorbornane (*endo*-Camphenilanyl Acetate) (X).**—To a solution of 80 ml. of dry pyridine and 31.0 g. (0.2 mole) of *endo*-camphenilanol cooled to 0° was added, dropwise and with stirring, 16.6 g. (0.21 mole) of acetyl chloride over a 15-min. period. Stirring was continued for 3 hr. at 0° followed by stirring 10 hr. at room temperature. The mixture was then added to 400 ml. of 18% hydrochloric acid, cooled in an ice-bath, and stirred 1 hr. This mixture was extracted with ether (3 × 100 ml.). The ether extracts were combined, washed with 10% aqueous sodium bicarbonate (2 × 50 ml.), water (2 × 50 ml.), and dried over anhydrous magnesium sulfate. The ether was removed (*in vacuo*) leaving a light yellow oil, 36 g. (90% crude). Vacuum distillation yielded a colorless liquid, 32 g. (82%), b.p. 79° (8.0 mm.). The infrared spectrum is identical with an authentic sample prepared from authentic *endo*-camphenilanol.[11]

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43, H, 10.27. Found: C, 73.65; H, 10.42.

Camphene-10-C^{14} (Pyrolysis of *endo*-Camphenilanyl Acetate).—The pyrolysis of X was carried out using a vertical glass pyrolysis tube of total length of 75 cm. The top and bottom thirds of the tube were 1.2 cm. outside diameter while the middle third was 2.5 cm. outside diameter. The top two-thirds of the tube was filled with glass beads (about 40 g.) and heated in a vertical furnace to 526°. A solution of 10 g. (0.05 mole) of *endo*-camphenilanyl acetate in 3 ml. of hexane was passed, along with nitrogen gas, through the pyrolysis tube at a flow rate of 6 ml. per hr. The liquid passing from the bottom of the tube was collected in a water-cooled flask and added to an aqueous solution of sodium carbonate. The organic layer was removed and the water layer extracted with hexane. The organic layer and hexane extracts were combined and dried over anhydrous sodium carbonate. After removing the hexane, a yellowish oil remained, 7.0 g. (91%). Chromatography on neutral alumina and elution with pentane gave good recovery and high purity camphene (>95%) as shown by the infrared spectrum and vapor phase chromatography.

(−)-Isoborneol.—A solution of 91.2 g. (0.6 mole) of (+)-camphor in 900 ml. of purified tetrahydrofuran was cooled under nitrogen to below 0°, and to it was added dropwise, with stirring, 214 ml. of a 0.704 *M* solution of lithium aluminohydride (0.18 mole) in tetrahydrofuran over a period of 1.5 hr. Following the addition, the solution was stirred below 0° for 30 min. followed by stirring at room temperature for 1.5 hr. The hydride was decomposed by adding 6.9 ml. of 10% aqueous sodium hydroxide followed by 6.9 ml. of water. The mixture was stirred for 1 hr., filtered, and the residue washed well with ether. Combining the ether washings and filtrate and removing the solvent (*in vacuo*) gave a white solid, 85.7 g. (93% crude), m.p. 211–212°, $[\alpha]^{25}D$ −28.0° (absolute alcohol, 8 g./100 ml. l = 1 dm.); reported[26] m.p. 214°, $[\alpha]D$ −34.09° (ethanol).

(+)-Camphene *via* Boric Acid Pyrolysis.[27]—A mixture of 10.0 g. (0.065 mole) of (−)-isoborneol, $[\alpha]D$ −28.0°, and 4.0 g. (0.065 mole) of boric acid was placed in a 500-ml. flask equipped with a simple vacuum distillation apparatus and heated at 110° for 6 hr. The temperature was then raised to 250–280° and a slight vacuum (80 mm.) applied to the system. The receiver was cooled in an ice-bath throughout the pyrolysis. After 2 hr. at 80 mm., the vacuum was reduced to 1.0 mm. and pyrolysis continued an additional hour. The semisolid distillate, consisting of camphene and water, was dissolved in ether, the water separated, and the ether layer dried over anhydrous magnesium sulfate for 12 hr. The ether was removed leaving a colorless solid, 8.0 g. (91%), analyzing for pure camphene by vapor phase chromatography; $[\alpha]^{25}D$ +53.5° (benzene, 5 g./100 ml. l = 1 dm.), reported,[28] $[\alpha]D$ +107° (benzene).

(−)-Isobornylphenylurethan.—A mixture of 11.3 g. (0.07 mole) of isoborneol, 9.5 g. (0.08 mole) of phenyl isocyanate, and enough carbon tetrachloride to give a solution of the materials (about 2 ml.) was heated for 10 min. on a steam-bath. The solution was shaken frequently; the reactants were protected from moisture. The solution was cooled and crystallization induced upon scratching. A white solid precipitated quantitatively. Recrystallization from petroleum ether (90–100°) gave colorless needles, 11.4 g. (60%), m.p. 131.0–131.5°, reported[29] m.p. 138–139°.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48, N, 5.12. Found: C, 74.56; H, 8.20; N, 5.16.

(+)-Camphene *via* (−)-Isobornylphenylurethan.[30]—In a 50-ml. round-bottom flask was placed 7.0 g. (0.026 mole) of isobornylphenylurethan. The flask, equipped with a simple distillation apparatus, was heated in a wax-bath at 220° for 7 hr. During this time, the vapor temperature fluctuated with the maximum temperature being 150°. The colorless distillate, 4.5 g., was dissolved in 2 ml. of pentane and passed through a chromatography column filled with 30 g. of neutral alumina. Elution with pentane gave a colorless oil which after subliming yielded a solid weighing 2.6 g. (75%), m.p. 50–51°, $[\alpha]^{25}D$ +107° (benzene, 5 g./100 ml., l = 1 dm.). Gas chromatography indicated pure camphene; reported[28] m.p. 51–52°, $[\alpha]D$ +107° (benzene).

(25) In later runs in other hands, using a new batch of camphenolide, it was found necessary to use 40.7 g. of 30% hydrogen peroxide (0.354 mole), added at 30–40°. Stirring was continued for 2 hr. at room temperature, after which the solution was saturated with potassium carbonate and then extracted with ether. A v.p.c. analysis of the product showed only solvent, product and expected secondary alcohol (from the dialkylborane). We are indebted to Prof. H. C. Brown of Purdue University for suggesting these procedural modifications.

(26) R. H. Pickard and W. O. Littlebury, *J. Chem. Soc.*, **91**, 1973 (1907).

(27) W. Brandenberg and A. Galat, *J. Am. Chem. Soc.*, **72**, 3275 (1950); G. L. O'Connor and H. R. Nace, *ibid.*, **77**, 1578 (1955); D. M. Young and C. D. Anderson, *J. Org. Chem.*, **26**, 2158 (1961).

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(29) J. Bertram and H. Walbaum, *J. prakt. Chem.*, [ii] **49**, 1 (1894).

(30) Kindly suggested by Prof. Bunton, ref. 14.

Ozonolysis of Original (+)-Camphene-10-C^{14} and Formaldehyde Isolation.—This procedure was that of Roberts and Yancey.[4] The crystalline formaldehyde methone was collected and recrystallized twice from methanol–water; m.p. 192–193°. This material was "counted" at zero disintegrations/min.[20]

Partial Racemization of (+)-Camphene-10-C^{14}.—The procedure used was that of Roberts and Yancey.[4] A mixture of 7.3 g. of (+)-camphene-10-C^{14}, $[\alpha]_D$ +42.3° (benzene), 1.5 ml. of redistilled (*in vacuo*) pyruvic acid and 30 ml. of acetonitrile[31] was heated in a sealed tube immersed in refluxing bromobenzene vapor, b.p. 156°. The time of heating varied from 1–3 hr. The mixture was cooled, added to 200 ml. of water, neutralized with 20 ml. of 10% aqueous sodium carbonate and extracted with ether (3 × 100 ml.). The ether extracts were combined, dried over magnesium sulfate and the ether distilled. The residue was sublimed at 10 mm. affording 4.1 g. (56%) of camphene.

Ozonolysis of Camphene.—This procedure was the same as that of Harries.[32] The crystals of dimethylnorcampholide were dissolved in ether and allowed to crystallize, giving snow-white crystals, m.p. 95–96°; reported 96.0–96.5°,[32] 95–96°.[33]

Acknowledgment.—The senior author is indebted to the Michigan Memorial Phoenix Project for a grant which enabled Dr. Goodrow to undertake the initial extensive research on this problem in 1957.

(31) Eastman Organic Chemicals, yellow label, No. P-488, purified by refluxing with phosphorus pentoxide and distilling.

(32) C. Harries and B. J. Palmen, *Ber.*, **43**, 1432 (1910); *cf.* ref. 5.

(33) F. W. Semmler, *ibid.*, **42**, 246 (1909).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

Application of Mass Spectrometry to Structure Problems. XIV.[1] Acetates of Partially Methylated Pentoses and Hexoses

BY DON C. DE JONGH AND K. BIEMANN

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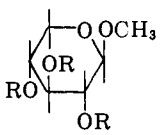
The mass spectra of the acetates of various mono-, di-, tri- and tetra-O-methyl derivatives of xylose, glucose and mannose are presented and interpreted. It is possible to relate the characteristics of the spectra to the number and position of the methoxyl groups in these molecules and to distinguish between pyranoses and furanoses. Some of the perdeuterioacetates have been prepared to corroborate the assignments; a convenient procedure for the preparation of sugar acetates on a 1 mg. scale is described.

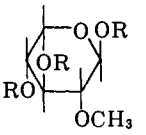
Recently[1] we have shown that the mass spectra of the polyacetates of hexoses and pentoses can be interpreted in terms of the structural characteristics of these compounds—such as molecular size, ring size and variation in the degree of the substitution—but not so much in terms of the stereochemistry. Because of the role which partially methylated sugars play in the determination of the structure of polysaccharides and derivatives of monosaccharides,[2] in addition to naturally occurring methyl sugars, it was of interest to explore the possibility of locating mass spectrometrically a methoxyl group within a sugar molecule.

Fully acetylated derivatives (*e.g.*, of monomethylxyloses, monomethylglucoses and monomethylmannoses) were chosen because of their volatility, thermal stability and ease of preparation on a micro scale. The separability of these derivatives from each other and the acetylating reagents by gas chromatography makes it possible to prepare a sample for mass spectrometry using as little as 1 mg. of the O-methyl sugar, a technique which might also prove useful in working up a mixture of acetylated O-methyl sugars without prior separation into the individual components.

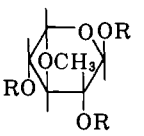
The availability of four of the five possible monomethylxyloses, namely, Ia, IIa, IIIa and IVa, provided a rather complete series of compounds differing in the position of the methoxyl group and in one case (IVa) also differing in the ring size. Of these, the 1-O-methyl derivative was expected to behave on electron impact quite differently from the others as the methoxyl group is a glycosidic one rather than an ordinary methyl ether, as in the 2-O-methyl and 3-O-methyl isomers. Furthermore, 5-O-methylxylose as a furanose differs in ring size and should also give rise to a very different spectrum in analogy to the previously reported acetates of pyranoses and furanoses.[1] However, even the most closely related compounds of this series, the 2-O-methyl and 3-O-methyl derivatives, also exhibit very different mass spectra, indicating that the position of the substituent at the ring can be established mass spectrometrically.



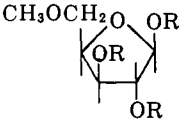
Ia, R = H
Ib, R = CH_3CO



IIa, R = H
b, R = CH_3CO



IIIa, R = H
b, R = CH_3CO



IVa, R = H
b, R = CH_3CO
c, R = CD_3CO

The presence of a peak at *m/e* 259 (M-31) in the spectrum (Fig. 1) of methyl β-D-xylopyranoside triacetate (Ib), a peak absent in the spectra of the other isomers (Fig. 2 through 4), is due to the loss of the glycosidic methoxyl group from C-1, a process leading to a secondary carbonium ion next to an ether oxygen which provides considerable stabilization. Loss of the methoxyl in the isomers IIb, IIIb, IVb would lead instead to a simple secondary or primary carbonium ion lacking any additional stabilization, and is thus not able to compete with the loss of the acetoxyl group from C-1; the latter process gives rise to the M-59 peak in those isomers, which is in turn absent in the spectrum of Ib. This observation is in agreement with the earlier one, namely, that the 1-acetoxyl group is exclusively lost from polyacetates of pentoses or hexoses on electron impact.[1]

The remaining part of the spectrum of Ib, with the exception of the peaks at mass 171, 230, 291 and 333, is very similar to the spectrum of α-D-xylopyranose tetraacetate (the similar spectrum of the epimeric ribose derivative has been published previously[1]). In most of the significant fragments of sugar acetates, the substituent at C-1, or that entire carbon atom, is

(1) Part XIII: K. Biemann, D. C. De Jongh and H. K. Schnoes, *J. Am. Chem. Soc.*, **85**, 1763 (1963).

(2) (a) H. O. Bouveng and B. Lindberg, *Advan. Carbohydrate Chem.*, **15**, 53 (1960); (b) W. Pigman, "The Carbohydrates," Academic Press, Inc., New York, N. Y., 1960.