Mass Spectrometry in Structural and Stereochemical Problems. LXXXVIII.[1] Rearrangements of Simple Terpenes on Electron Impact[2]

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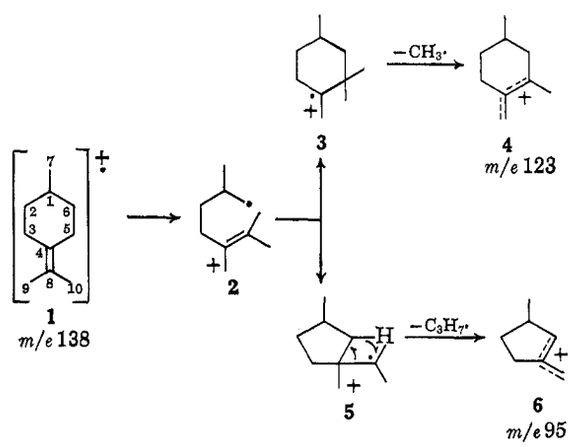
The mass spectra of $\Delta^{4(8)}$-menthene and camphor were studied as prototypes of simple cyclic monoterpenes, using both deuterium-labeling and high-resolution techniques. The results are at variance with earlier conclusions in the literature concerning the fragmentation of these terpenes and indicate that great caution must be exercised in interpreting the mass spectra of highly fused or substituted hydrocarbon nuclei lacking strong fragmentation-directing groups. Many of the fission reactions are best rationalized by postulating migrations of double bonds or alkyl groups.

The mass spectra of a variety of monocyclic and bicyclic terpenes have been published recently,[4-8] but the mechanisms of fragmentation postulated for most of the compounds examined have not been verified experimentally.

Since a positively charged molecular ion produced upon electron impact is both a carbonium ion and a free radical, and since many terpenes undergo carbonium ion or free-radical rearrangements with great facility, it is to be anticipated that even simple terpenes will exhibit unusually complicated electron-impact fragmentation reactions; consequently, it is important to employ high-resolution and deuterium-labeling techniques in the interpretation of the spectra of these compounds. We wish to report such a detailed analysis of the electron-impact fragmentation reactions of two representative terpenes, $\Delta^{4(8)}$-menthene and camphor, which demonstrates the complexity of the fragmentation behavior of simple terpenoids.

Discussion of Mass Spectra

$\Delta^{4(8)}$-Menthene.—Thomas and Willhalm[4] have published the spectra of a number of isomeric menthenes. They noted with surprise that elimination of a methyl group occurs as readily from $\Delta^{4(8)}$-menthene (**1**) as from the Δ^{3} isomer, although two of the three methyl groups present are attached to vinylic positions in the former, while two are attached to allylic positions in the latter. Equally as curious is the ease with which an isopropyl group is lost; the M − 43 fragment carries about the same fraction of total ion current in both the $\Delta^{4(8)}$ and Δ^{3} isomers. In order to account for this unusual behavior, they postulated[4] that initial cleavage of an allylic carbon–carbon bond in **1** is followed by recombination to give the rearranged intermediates **3** and **5**, which can lose a methyl group and an isopropyl group, respectively, to give **4** and **6**.[9]

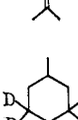
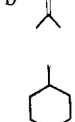
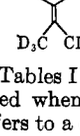


We have examined $\Delta^{4(8)}$-menthene substituted by deuterium at C-3 and C-5 and at C-9 and C-10 in order to determine the validity of these mechanisms. Our labeling results cast some doubt on the mechanism postulated for the formation of the *m/e* 123 fragment and invalidate the suggestion for the *m/e* 95 peak.

The mass spectrum of $\Delta^{4(8)}$-menthene as determined in our laboratory is reproduced in Figure 1; the primary mass spectral peaks of the parent compound and its deuterated analogs are listed in Table I and the fragmentation reactions are shown in Scheme I.

TABLE I[a]

PRINCIPAL MASS SPECTRA PEAKS OF $\Delta^{4(8)}$-MENTHENE AND DEUTERATED ANALOGS

Compound	Isotopic purity, %	*m/e* (% shift) M − 15	*m/e* (% shift) M − 43
		123	95
	70 d_4 20 d_3 5 d_2 5 d_1, d_0	127 (q)	98 (60–80) 99 (15–30)
	88 d_6 12 d_5	126 (82) 129 (18)	95 (80–90)

[a] Tables I and II show the per cent shift of the compounds discussed when specifically labeled with deuterium. The symbol *q* refers to a quantitative transfer (*i.e.*, >95%).

(1) Paper LXXXVII: M. Fischer and C. Djerassi, *Chem. Ber.*, in press.

(2) We are indebted to the National Institutes of Health of the U. S. Public Health Service for financial support (Grants No. GM-06840 and AM-04257).

(3) National Institutes of Health Postdoctoral Fellow, 1964–1965.

(4) A. F. Thomas and B. Willhalm, *Helv. Chim. Acta*, **47**, 475 (1964).

(5) R. Ryhage and E. von Sydow, *Acta Chem. Scand.*, **17**, 2025 (1963).

(6) (a) E. von Sydow, *ibid.*, **17**, 2504 (1963); (b) *ibid.*, **18**, 1099 (1964); (c) *ibid.*, **18**, 1791 (1964).

(7) B. Willhalm, A. F. Thomas, and M. Stoll, *ibid.*, **18**, 1573 (1964).

(8) (a) R. I. Reed, "Ion Production by Electron Impact," Academic Press Inc., New York, N. Y., 1962, pp. 204–206; (b) R. I. Reed, "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter 13.

(9) For symbolism employed throughout the present article, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day, Inc., San Francisco, Calif., 1964, pp. 1–3, as well as J. S. Shannon, *Proc. Roy. Austral. Chem. Inst.*, 323 (1964).

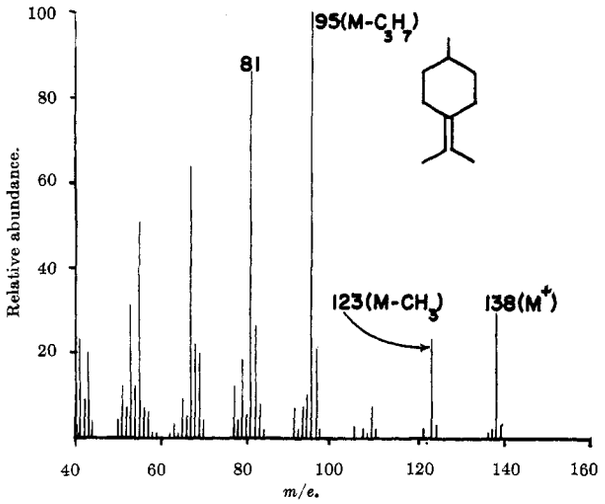


Figure 1.

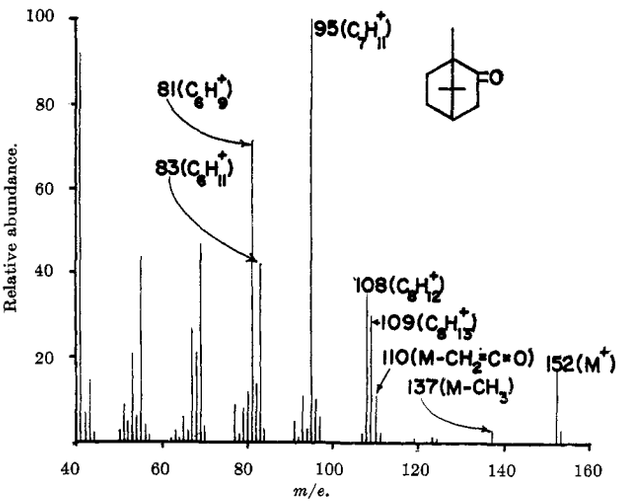
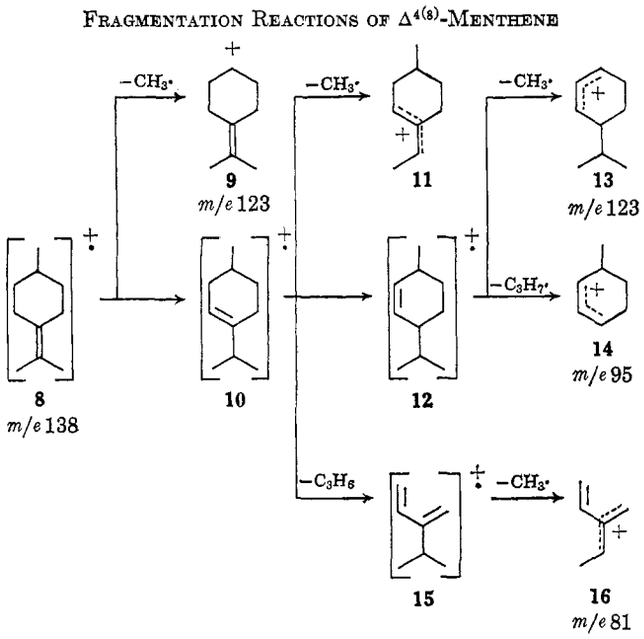


Figure 2.

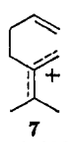
SCHEME I[a]

FRAGMENTATION REACTIONS OF $\Delta^{4(8)}$-MENTHENE



[a] For the sake of clarity, Schemes I and II depict the reactions as proceeding in a stepwise manner and do not imply that concerted reactions do not occur nor that a given species is in fact a common precursor of several fragments.

Peak *m/e* 123 (M − 15) must be formed by loss of one of the original methyl groups since the peak shifts quantitatively to *m/e* 127 in the d_4 species. A shift of 82% of *m/e* 123 to *m/e* 126 and 18% to *m/e* 129 in the d_6 analog shows that the methyl groups at C-8 are lost 4.5 times as readily as the one at C-1, in agreement with the qualitative prediction made by Thomas and Willhalm.[4] However, if the first step (**1** → **2**) of their mechanism is correct, it is difficult to understand why the C-1 methyl group is not lost preferentially from **2** to give the stable species **7**.



7
m/e 123

With this in mind and in view of the mode of formation of the *m/e* 95 fragment described below, we suggest that a better representation of the mechanism is allylic migration of a hydrogen atom from C-3 (or C-5) to C-8 to give **10**, followed by allylic cleavage of a methyl group to give **11** as shown in Scheme I. Loss of the C-1 methyl group would then occur by simple cleavage or by cleavage of **12**, formed by a second allylic rearrangement. The postulated allylic migrations must be relatively slow since the loss of methyl is not random; this conclusion is supported by the fact that deuterium scrambling in the allylically rearranged precursor of the *m/e* 95 fragment does not occur to a significant extent and that the mass spectra of the isomeric menthenes, although similar, are not identical.[4]

At least 80–90% of the *m/e* 95 (M − 43) peak remains at *m/e* 95 in the d_6 analog suggesting that the peak is formed by the loss of the isopropylidene group plus one additional hydrogen atom. Since only 15–30% of the peak shifts to *m/e* 99 while 60–80% of it shifts to *m/e* 98 in the d_4 species, the primary source of this hydrogen must be C-3 and C-5. These results show clearly that the mechanism (**5** → **6**) postulated by Thomas and Willhalm[4] is not the principal fragmentation mechanism since it requires that at least 50% of the C-2 hydrogen be eliminated with the isopropylidene group. Therefore, we propose that two allylic hydrogen transfers occur in the molecular ion to give **12**, which then cleaves to give the allyl cation **14** and an isopropyl radical. This behavior is consistent with the allylic hydrogen transfers postulated for unsaturated esters[10] and constitutes additional evidence for the mobility of some double bonds under electron impact conditions.

Qualitatively, a large portion of the *m/e* 81 (M − 57) peak appears to be evenly partitioned between *m/e* 81 and 84 in the d_6 species. Although the large number of peaks in the *m/e* 81 range in the nondeuterated species make it impossible to state without qualification that all of the *m/e* 84 peak in the spectrum of the d_6 species corresponds to *m/e* 81 in Figure 1, that portion which does arise in this manner can be rationalized by invoking a reverse Diels–Alder reaction of **10**, giving **15**, followed by methyl elimination to give **16**.

(10) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 83, 84, and references cited therein.

TABLE II

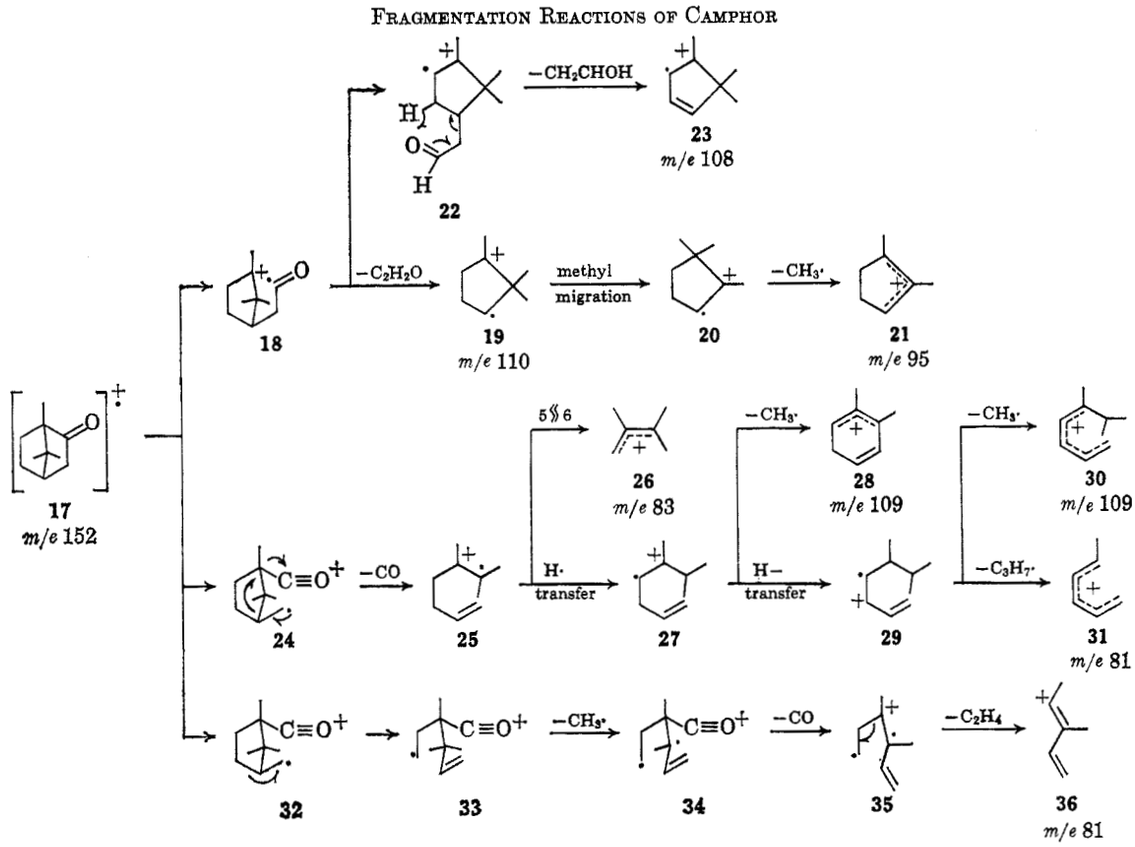
PRINCIPAL MASS SPECTRA PEAKS OF CAMPHOR AND DEUTERATED ANALOGS[a]

Compound	Isotopic purity, %	m/e (% shift) M − 15	M − 42	M − 43	M − 57	M − 57	M − 69	M − 71
		137	110	109	108	95	83	81
	92 d_1 8 d_0	138 (66) 137 (33)	111 (q)	109 (35) 110 (65)	109 (q)	95 (44) 96 (56)	84 (q)	82 (93)
	95 d_2 5 d_1	139 (q)	110 (q)	109 (12) 111 (88)	108 (q)	95 (q)	83 (q)	83 (80–90)

[a] See footnote *a*, Table I.

SCHEME II

FRAGMENTATION REACTIONS OF CAMPHOR



The portion that remains at 81 must have lost the isopropylidene radical plus an additional methyl group and hydrogen atom, but a mechanism can not be proposed in the absence of further isotopic labeling.

Camphor.—Both Reed[8] and von Sydow[6b] have examined recently the mass spectrum of camphor. Reed[8] has offered a highly speculative explanation of the breakdown of camphor on electron impact, but none of his conclusions are substantiated by our labeling and high-resolution results, demonstrating once again the dangers inherent in predicting mass spectroscopic fragmentation mechanisms on purely pragmatic grounds.

The deuterated camphor derivatives employed in this study were camphor-10-d_1[11] and camphor-3,3-d_2; the mass spectrum of camphor as determined in our laboratory is represented in Figure 2, the principal mass spectral fragmentation peaks of camphor and its deuterated analogs are listed in Table II, and the corresponding fragmentation reactions are shown in Scheme II. The elemental compositions of the *m/e* 109, 108, 95, 83, and 81 peaks have been confirmed by high resolution measurements.

The shift of two-thirds of the *m/e* 137 (M − 15) peak to *m/e* 138 in the d_1 analog and all of the peak to *m/e* 139 in the d_2 compound suggests that a methyl group is lost statistically from the molecular ion.

Carbon atoms 2 and 3 are lost as ketene (**17** → **18** → **19**) to give a hydrocarbon peak, *m/e* 110 (M − 42), which is shifted to *m/e* 111 in the d_1 analog and not at all in the d_2 compound. This result is in agreement with the prediction made by von Sydow[6b] and is reminiscent of the behavior of *trans*-8-methylhydrindan-2-one (**37**).[12]

(11) We are grateful to Dr. R. McCrindle of The University, Glasgow, for a sample of this compound. [See J. D. Connolly and R. McCrindle, *Chem. Ind.*, 379 (1965).]

(12) J. Karliner, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 580 (1965).

A hydrocarbon ion composes 95% of the *m/e* 109 (M − 43) peak, which shifts almost completely to *m/e* 111 in the d_2 analog and 65% to *m/e* 110 in the d_1 species. Its origin is quite different from that of *m/e* 110 or 108 and must result from the loss of carbon monoxide and a methyl group. It is difficult to understand why a C-1 methyl group is lost as frequently as a C-7 methyl, since two bonds to C-1 must be broken, unless the fragmentation occurs after a rearrangement of the molecular ion. A convenient rationalization is provided by the sequence of reactions shown in Scheme II. Rearrangement of **24** to **25** is followed by allylic rearrangements and cleavages as described above for $\Delta^{4(8)}$-menthene (Scheme I). Intermediate **25** is particularly attractive because it correctly predicts (see below) the deuterium content of *m/e* 83, which is formed by simple allylic cleavage and *m/e* 81, which would be formed from **25** in the same manner as *m/e* 95 is formed from the molecular ion in the spectrum of $\Delta^{4(8)}$-menthene.

The *m/e* 108 (M − 44) peak exhibits the same type of shifts upon deuteration as indicated for the *m/e* 110 species. However a metastable peak at 71.8[6b] indicates that at least a portion of this hydrocarbon fragment arises directly from the molecular ion, rather than by the elimination of molecular hydrogen from *m/e* 110. The mechanism (**18** → **22** → **23**) indicated in Scheme II must be considered to be tentative, since the source of the hydrogen was not determined, but Dreiding models indicate that both hydrogen abstractions are sterically favorable.

The *m/e* 95 (M − 57) peak is the base peak in the spectrum; high-resolution measurements demonstrate that it is a hydrocarbon fragment, contrary to Reed's hypothesis.[8] The peak does not shift in the d_2 analog and accordingly ketene and a methyl group must be lost. Once again it is difficult to justify the facility with which the C-1 methyl group is eliminated (44% of *m/e* 95 does not shift in the d_1 analog) since two bonds to C-1 must be broken. Either one must postulate that loss of a methyl radical or carbon monoxide from a positively charged site occurs readily, contrary to stability considerations,[13] or that a rearrangement occurs. We favor the latter in which migration of the C-7 methyl group in **19** to C-1 produces **20**, which can then lose either methyl group at C-1 to give the stable species **21**. The loss of the migrating C-7 methyl must be slightly favored since it is expelled 56% of the time.

Deuterium labeling (Table 2) shows that the hydrocarbon fragment *m/e* 83 (M − 69) retains all of the deuterium in the d_1 analog while all that in the d_2 analog is lost. Sequence **24** → **26** shown in Scheme II accounts nicely for the observed deuterium shifts.

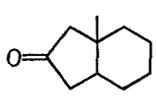
The deuterium labeling results (Table II) imply that both C-2 and C-10 are predominantly retained in the hydrocarbon species *m/e* 81 (M − 71). The sequence **24** → **31** involving hydrogen radical and hydride ion transfers[10] must be considered highly tentative; the alternative sequence shown in Scheme II (**32** → **36**) should also be considered, although it suffers from the disadvantage that bond fission adjacent to a positively charged center is implicated.

(13) F. H. Field and J. L. Franklin, "Electron Impact Phenomena," Academic Press Inc., New York, N. Y., 1957, Chapter 4.

Conclusion

The electron-impact fragmentation reactions of $\Delta^{4(8)}$-menthene and camphor demonstrate that relatively simple terpenes can undergo quite complicated fragmentations in their compact and highly substituted hydrocarbon framework in the absence of powerful directing groups. It is necessary to postulate allylic rearrangements and methyl migrations to rationalize the fragmentation reactions using principles which have been shown to be so useful in ground-state reactions of organic compounds; the fragmentations are not predictable on purely pragmatic grounds and postulated mechanisms must be supported by high-resolution and deuterium-labeling data.

This note of caution is obviously applicable to other members of this class of natural products and it seems that *at this stage* mass spectrometry will show its principal utility for analytical and "fingerprinting" purposes rather than for the structure elucidation of unknown cyclic monoterpenes. In this connection, it is relevant to point out that camphor (**17**) and *trans*-8-methylhydrindan-2-one (**37**),[12] which are isomeric but possess grossly different structures, display very similar mass spectra over the range *m/e* 50–152, the principal differences residing in the relative intensity of certain peaks.



37

m/e 152

Experimental Section[14]

Triphenylisopropylphosphonium Bromide.—Equivalent quantities of isopropyl bromide and triphenylphosphine were heated at 125° in a sealed tube for 5 days. The product was dissolved in ethanol, precipitated by ether, collected, and dried, m.p. 240–242° (lit.[15] m.p. 239–241°).

$\Delta^{4(8)}$-Menthene.—Corey's modification[16,17] of the Wittig synthesis of methylenecyclohexane was employed in the preparation of $\Delta^{4(8)}$-menthene from 4-methylcyclohexanone and triphenylisopropylphosphonium bromide. The final reaction mixture was allowed to stand for 36 hr. at room temperature and poured into a 10-fold excess of water; the suspension was filtered, the filtrate was extracted with an equal volume of pentane, and the organic extract was dried over anhydrous magnesium sulfate. The solution was filtered and the filtrate was concentrated under a Vigreux column. The concentrate was purified by a bulb-to-bulb distillation in a closed system at 1 torr and the product was isolated by vapor phase chromatography using a 10-ft. 20% silver nitrate–polypropylene glycol on Chromosorb W column. The mass spectrum (Figure 1) of the product was consistent with the data reported by Thomas and Willhalm for an authentic sample[4] and the n.m.r. spectrum confirmed the absence of olefinic protons.

$\Delta^{4(8)}$-Menthene-3,3,5,5-d_4.—The Wittig reaction was repeated with dimethyl-d_6 sulfoxide substituted for the unlabeled solvent. Deuterium exchange of the ketone was much faster than reac-

(14) Melting points are uncorrected. The low-resolution spectra were obtained by Mr. John W. Smith with a C.E.C. mass spectrometer, Model No. 21-103C, using an all-glass inlet system heated to 200°. The ionizing energy was maintained at 70 e.v. and the ionizing current at 50 μa. The high-resolution spectra were recorded by Dr. Dieter Becher on an A.E.I. MS-9 double-focusing mass spectrometer with an apparent resolution of 12,000.

(15) M. Schlosser, *Chem. Ber.*, **97**, 3219 (1964).

(16) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(17) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).

tion with the ylide and a product containing 70% d_4, 20% d_3, 5% d_2, 3% d_1, and 2% d_0 was obtained.

$\Delta^{4(8)}$-Menthene-9,9,9,10,10,10-d_6.—This product was prepared using the same procedure described for the nondeuterated analog except that appropriately labeled triphenylisopropylphosphonium bromide was employed. The product contained 88% d_6 and 12% d_5.

Camphor-3,3-d_2.—A solution of camphor (0.01 mole), trifluorodeuterioacetic acid (0.10 mole) and deuterium oxide (0.495 mole) was heated at 130° in a sealed tube for 9 days. The reaction mixture was basified with anhydrous potassium carbonate and extracted with pentane. The extract was dried and filtered, and the solvent was removed. The residue was recrystallized from hexane and sublimed: m.p. 179.5–180.5° (unlabeled camphor, m.p. 179.5–180.5°). The difficulty in introducing more than one atom of deuterium experience by Thomas and Willhalm[18] was avoided under these conditions, and a product containing 95% d_2 and 5% d_1 was obtained after one exchange.

(18) A. F. Thomas and B. Willhalm, *Tetrahedron Letters*, 1309 (1965).

Investigation on the Sodium–Liquid Ammonia Cleavage of a Tosyl Protecting Group of Tosylamino Acids and Peptides[1]

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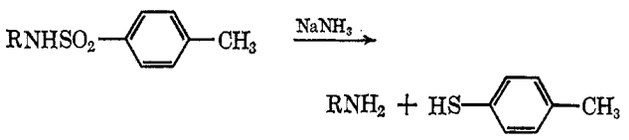
The major reaction product of the sodium–liquid ammonia cleavage of tosyl protecting groups of tosylamino acids and peptides is not thiocresol, as it is presented in the literature, but sulfite and toluene. The reaction can be best represented as two parallel reactions: (a) the major course of reaction involves carbon–sulfur cleavage giving sulfite and toluene, in addition to the amino acid or peptide; and (b) the minor path is sulfur–nitrogen cleavage giving sulfinic acid which again undergoes two types of reaction leading primarily to *p*-thiocresol through reduction and to sulfite and toluene by carbon–sulfur cleavage.

The removal of a tosyl protecting group of tosylamino acids was reported first by Fischer in 1915 using a warm phosphonium iodide–hydriodic acid mixture.[2] This quite drastic procedure was applied by Schönheimer[3] in 1926 to generate the free peptide from the tosyl derivatives. In 1937 du Vigneaud[4] demonstrated that a tosyl protecting group can be cleaved under very mild conditions using sodium–liquid ammonia. Since then the tosyl protecting group has become an important tool in peptide chemistry.

However, not much information was available regarding the fate of the *p*-toluenesulfonyl group in such reactions. The over-all reaction has been represented by Birch[5] in his reveiw on metal–amine reduction as follows. In connection with the synthesis of



some peptides using a tosyl protecting group we found a considerable quantity of sulfite instead of *p*-thiocresol during sodium–ammonia cleavage, which led us to investigate the details of this reaction.

The sodium–liquid ammonia cleavage of *p*-toluenesulfonamide, which was selected as the simplest model compound, gave 70 to 81% of sulfite along with 10 to 14% of *p*-thiocresol when 3.5 g.-atoms of sodium was used. The results are compiled in Table I. When a lesser amount of sodium was used, *i.e.*, 2.5 g.-atoms/mole, again a considerable amount of sulfite (58 to 65%) formed, along with traces of *p*-thiocresol.

For further investigations simple tosylamino acids were selected and the results are shown in Table I (expt. 3–7). The major part of the cleavage was sulfite again. The hydrocarbon part of the cleavage reaction, that is toluene, was not obtained in a quantitative yield since its major part evaporated with the ammonia. In the case of tosyl-L-glutamic acid and tosyl-DL-alanine using modified experimental techniques, it was possible to isolate about 24–25% toluene using vapor phase chromatography. This value was corrected to about 60%, counting the approximate loss observed during isolation of toluene in a control experiment.

Results of cleavage reactions of tosyl peptides are similar to that of tosylamino acids and are summarized in Table I (expt. 8–12).

p-Toluenesulfinic acid was considered first as an intermediate in this reaction, which undergoes further cleavage to sulfur dioxide and toluene or is reduced to thiocresol. Sodium–liquid ammonia reaction of *p*-toulenesulfinic acid as shown in Table I (expt. 13) yielded 49–50% of thiocresol and 21–23% of sulfite, *i.e.*, the major part of the reaction is reduction, along with some carbon–sulfur bond cleavage. The ratio of cleavage to reduction is about 1:2. Similar results were observed with benzenesulfinic acid (expt. 14, Table I).

These results show that *p*-toluenesulfinic acid cannot be the major intermediate in cleavage reactions; if this were the case, then *p*-thiocresol rather than sulfite would be the major cleavage product of tosylamino acids and peptides.

This led to the conclusion that the cleavage reaction can be best represented as shown in Scheme I.

Path a represents the major course of reaction involving carbon–sulfur cleavage leading to sulfur dioxide and toluene. Path b is the minor course of reaction which indicates sulfur–nitrogen cleavage giving sulfinic acid. Sulfinic acid again undergoes two types of reaction leading primarily to thiocresol through

(1) This investigation was presented at the Metropolitan Regional Meeting of the New York and New Jersey Sections of the American Chemical Society, 1963; a part of the results was communicated in *Chem. Ind.* (London), 913 (1963).

(2) E. Fischer, *Ber.*, **48**, 93 (1915).

(3) R. Schönheimer, *Z. Physiol. Chem.*, **154**, 203 (1926).

(4) V. du Vigneaud and O. K. Behrens, *J. Biol. Chem.*, **117**, 27 (1937).

(5) A. J. Birch and H. Smith, *Quart. Rev.* (London), **12**, 17 (1958).