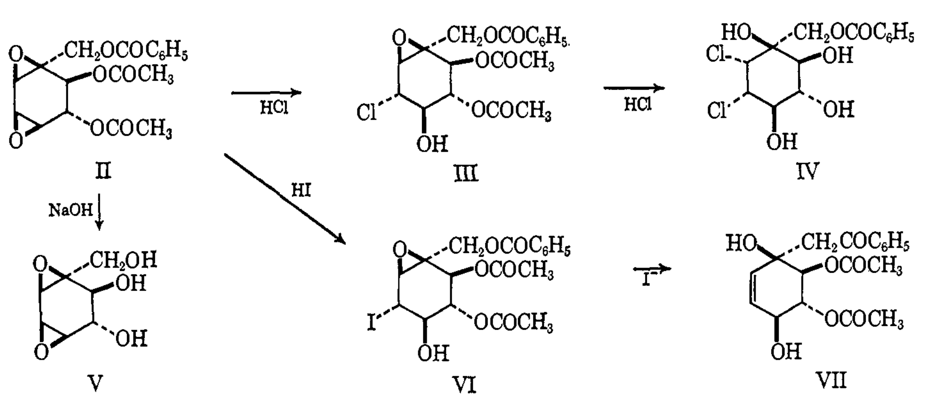


reagent yielded an oil, with spectral characteristics of an α,β-unsaturated ketone, and hydrogenation of the oil yielded the saturated ketone ($C_{18}H_{20}O_8$; mp 117–118°; $[\alpha]^{24}D$ $-3°$ (c 1.00, $CHCl_3$).

Crotepoxide iodohydrin crystallized from ether in the monoclinic system, space group $P2_1$, with two molecules of $C_{18}H_{19}IO_8$ in a cell of dimensions a = 5.21, b = 15.85, c = 12.18 Å; β = 100° 42′. The X-ray reflections were recorded on equiinclination Weissenberg photographs of the $0kl$ through $4kl$ layers, and visual estimation of the intensities gave a total of 1150 $|F_o|$ values. The coordinates of the iodine atom were derived from a Patterson synthesis, and the carbon and oxygen atoms were located in three-dimensional electron-density distributions calculated with weighted Fourier coefficients.[6] The initial maps were complicated by the pseudo-symmetry associated with the space group $P2_1$. The approximate atomic coordinates are now being refined by least-squares calculations, and the present value of R is 16%. The absolute configuration of the molecule was determined by Bijvoet's anomalous-dispersion method.[7]

The results of the X-ray analysis establish that the iodohydrin has the constitution and absolute stereochemistry VI. The ring adopts a half-chair conformation in the crystal, with the neighboring hydroxyl and acetyl substituents oriented equatorially. That the compound is in this stable conformation in solution as well is indicated by the magnitude of the coupling constants for the protons on the carbons bearing the relevant functional groups. It may be concluded that the epoxide opening proceeded in a *trans*-diaxial fashion and that crotepoxide has structure II. The coupling constants derived from the nmr spectra are in good accord with structure II. It is apparent that initial *trans*-diaxial opening of the epoxide, to an intermediate in an unfavorable boat conformation, is followed by inversion to the half-chair form with the neighboring iodine and hydroxyl group in equatorial conformations.[8]

Crotepoxide belongs to a small group of naturally occurring highly oxygenated cyclohexane derivatives, other members of which are terreic acid,[9] epoxydone,[10] senepoxyde and seneol,[11] and shikimic acid. However, crotepoxide is the only member of this group which possesses the diepoxide functionality. This function has been shown earlier to confer tumor-inhibitory activity on other classes of synthetic compounds.[12]

Investigations are in progress to determine the significance of various structural features in relation to the tumor-inhibitory activity of crotepoxide.

---

(6) G. A. Sim in "Computing Methods and the Phase Problem in X-ray Crystal Analysis," R. Pepinsky, J. M. Robertson, and J. C. Peakman, Ed., Pergamon Press, Ltd., Oxford, 1961, p 227.

(7) J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature*, **168**, 271 (1951).

(8) *Cf.* D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 2907 (1957).

(9) J. C. Sheehan, W. B. Lawson, and R. J. Gaul, *J. Am. Chem. Soc.*, **80**, 5536 (1958).

(10) A. Closse, R. Mauli, and H. P. Sigg, *Helv. Chim. Acta*, **49**, 204 (1966).

(11) R. Hollands, D. Becher, A. Gaudemer, J. Polonsky, and N. Ricroch, *Tetrahedron*, **24**, 1633 (1968).

(12) J. L. Everett and G. A. R. Kon., *J. Chem. Soc.*, 3131 (1950).

S. Morris Kupchan, Richard J. Hemingway
Department of Pharmaceutical Chemistry
University of Wisconsin, Madison, Wisconsin 53706

P. Coggon, A. T. McPhail, G. A. Sim
Chemical Laboratory, University of Sussex, Brighton
Sussex, England

Received March 9, 1968

A Randomly Labeled Tropylium Ion in the Mass Spectrum of Toluene-α,1-$^{13}C_2$[1]

Sir:

Toluene has been shown to fragment under electron impact by the sequence shown in eq 1.[2,3] Considerable evidence has accumulated[4,5] which demonstrates that the $C_7H_7^+$ ion is not a simple benzyl ion (I) but that its fragmentations can be explained by a tropylium ion structure (II).[4] Other isomeric hydrocarbons and α-substituted toluenes fragment *via* a $C_7H_7^+$ ion of similar properties. Much of the earlier evidence for a tropylium ion structure rests on isotope-labeling data, perhaps the most significant being that derived from the spectrum of toluene-α-^{13}C,[3] in which nearly random loss of ^{13}C occurred in the $C_7H_7^+ \rightarrow C_5H_5^+$ transition. However, the earlier data do not allow one to distinguish between a tropylium ion arising from simple 1,2 insertion of the methyl (α) carbon (path a) and a tropylium ion formed in some way by random insertion of the α carbon between any carbon–carbon bond in the benzene ring (path b). We present here evidence which indicates

$$\begin{array}{lccccccc} & C_7H_8{}^{+} & \xrightarrow{-H\cdot} & C_7H_7{}^+ & \xrightarrow{-C_2H_2} & C_5H_5{}^+ & \xrightarrow{-C_2H_2} & C_3H_3{}^+ \\ m/e & 92 & & 91 & & 65 & & 39 \end{array} \qquad (1)$$

---

(1) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstracts, S85.

(2) P. N. Rylander, S. Meyerson, and H. M. Grubb, *J. Am. Chem. Soc.*, **79**, 842 (1957).

(3) S. Meyerson and P. N. Rylander, *J. Chem. Phys.*, **27**, 901 (1957).

(4) H. M. Grubb and S. Meyerson in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter 10.

(5) S. Meyerson, *Record Chem. Progr.*, **26**, 257 (1965).

Table I. Mass Spectral Peaks (Low Resolution)

	Relative abundance^{a-c}			
m/e	Toluene^{d}	Toluene-α-$^{13}C^{e,f}$	Toluene-1-$^{13}C^{e,g}$	Toluene-α,1-$^{13}C_2^{e,h}$
61	0.053	0.021	0.030	
62	0.115	0.065	0.081	0.033
63	0.267	0.161	0.157	0.102
64	0.052	0.185	0.186	0.169
65	0.482	0.184	0.201	0.245
66	0.028	0.371	0.333	0.204
67	0.005	0.013	0.013	0.250

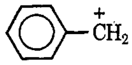
[a] Σ_{61-67} = 1.000. [b] Corrected for naturally abundant ^{13}C. [c] Average of at least three runs. [d] Commercial sample, purified by glpc. [e] Calculated for 100% isotopic enrichment. [f] Sample contained 49.6% excess ^{13}C. [g] Sample contained 57.0% excess ^{13}C. [h] Sample contained 22.9% unlabeled toluene, 22.2% toluene-α-^{13}C, and 27.9% toluene-1-^{13}C.

Table II. Mass Spectral Peaks (High Resolution)

		Relative abundance^{a-c}			Abundance ratios,^{b,c} $^{13}C_nC_{5-n}H_5/(C_5H_5 + {}^{13}CC_4H_5 + {}^{13}C_2C_3H_5)$		
m/e	Composition	Toluene-α-$^{13}C^{d}$	Toluene-1-$^{13}C^{e}$	Toluene-α,1-$^{13}C_2^{f}$	Toluene-α-$^{13}C^{d}$	Toluene-1-$^{13}C^{e}$	Toluene-α,1-$^{13}C_2^{f}$
65	C_5H_5	13.33	15.07	2.48	0.308	0.334	0.060
	$^{13}CC_4H_4$	6.07	4.52	2.07			
	$^{13}C_2C_3H_3$			19.29			
66	C_5H_6	3.99	3.43	0.41			
	$^{13}CC_4H_5$	29.99	30.02	18.88	0.692	0.666	0.457
	$^{13}C_2C_3H_4$			4.52			
67	C_5H_7			1.70			
	$^{13}CC_4H_5$	2.01	2.28	2.30			
	$^{13}C_2C_3H_5$			19.99			0.483

[a] Σ_{61-67} = 100. [b] Corrected for naturally abundant ^{13}C. [c] Calculated for 100% isotopic enrichment. [d] Sample contained 49.6% excess ^{13}C. [e] Sample contained 57.0% excess ^{13}C. [f] Sample contained 22.9% unlabeled toluene, 22.2% toluene-α-^{13}C, and 27.9% toluene-1-^{13}C.

that the $C_7H_7^+$ ion can be satisfactorily represented as a tropylium ion in which the carbon atoms have lost all positional identity related to their toluene origin, *i.e.*, that the tropylium ion is formed by path b.



I

II

IIa

IIb

We have prepared toluene-α,1-$^{13}C_2$. The tropylium ions arising from this compound by paths a and b would have structures IIa and IIb, respectively. Loss of C_2H_2 from IIa would give $^1/_7$ (0.143) C_5H_5, $^2/_7$ (0.286) $^{13}CC_4H_5$, and $^4/_7$ (0.572) $^{13}C_2C_3H_5$, while loss of C_2H_2 from IIb would give $^1/_{21}$ (0.048) C_5H_5, $^{10}/_{21}$ (0.476) $^{13}CC_4H_5$, and $^{10}/_{21}$ (0.476) $^{13}C_2C_3H_5$. Synthesis of toluene-α,1-$^{13}C_2$ proceeded from methyl-^{13}C iodide and barium carbonate-^{13}C *via* a Grignard reaction to sodium acetate-1,2-$^{13}C_2$ and esterification[6] with dimethyl sulfate to methyl acetate-α,1-$^{13}C_2$,[7,8] which was converted, successively, by the procedure of Rieker, *et al.*,[9] to 1-methylcyclohexanol-α,1-$^{13}C_2$[7,8] and 1-methylcyclohexene-α,1-$^{13}C_2$.[7,8] The latter compound was dehydrogenated over palladium–charcoal to toluene-α,1-$^{13}C_2$.[7] Since neither the methyl iodide nor the barium carbonate was isotopically pure, it was necessary to synthesize also toluene-1-^{13}C and toluene-α-^{13}C as model compounds. The former was prepared by the same sequence employed for the dilabeled compound starting with sodium acetate-1-^{13}C, the latter from phenyllithium and methyl-^{13}C iodide.

Low-resolution mass spectra were determined with an Atlas CH4 mass spectrometer; employing wide slits, flat top peaks were measured. Data for unlabeled, α-labeled, 1-labeled, and dilabeled toluenes are presented in Table I. Spectra of the unlabeled and α-labeled compounds compare favorably with those reported earlier.[4] Each nominal mass peak in spectra of the labeled compounds contains isobaric ions whose relative abundance was measured on a CEC 21-110 mass spectrometer at a resolution of 20,000 and averaged for 20–30 scans. Peak-intensity ratios for the isobaric sets at m/e 65, 66, and 67 are presented in Table II. Retention of label by the $C_5H_5^+$ ion in the spectra of toluene-1-^{13}C and -α-^{13}C is very nearly the same for the two compounds (and agrees with the earlier data for the latter compound).[3] These spectra of the monolabeled compounds thus support the hypothesis of a tropylium ion, though they do not define its mode of formation. The intensities of the C_5H_5, $^{13}CC_4H_5$, and $^{13}C_2C_3H_5$ ions in the spectrum of toluene-α,1-$^{13}C_2$ fit closely to the distribution expected (0.048, 0.476, and 0.476) for their formation from a tropylium ion (IIb) whose carbon atoms have been completely randomized; they do not agree with the distribution expected (0.143, 0.286, and 0.572) for a tropylium ion (IIa) containing two adjacent ^{13}C atoms.

It should be noted in conclusion that, while the present data are in accord with a randomized tropylium ion structure for the $C_7H_7^+$ ion, they do not indicate the intermediates involved in its formation. Speculation on this topic and discussion of the other ions in the m/e 61–67 region [C_5H_n (n = 0–4, 6, 7)] must await the full paper.[10]

---

[6] W. Sakami, W. E. Evans, and S. Gurin, *J. Am. Chem. Soc.*, **69**, 1110 (1947).

[7] Pure by glpc analysis.

[8] Mass spectra of the labeled intermediates will be discussed in the full paper.

[9] A. Rieker, K. Scheffler, and E. Mueller, *Ann. Chem.*, **260**, 23 (1963).

Acknowledgment. This research was supported by a grant (No. AI 04769) from the National Institute of Allergy and Infectious Diseases. We thank Dr. M. F. Grostic, Upjohn Co., for assistance in determining the high-resolution mass spectra.

(10) We have recently shown, for example, that the $C_5H_3^+$ ion is derived at least in part from the $C_7H_5^+$ ion (89 → 63; m^* 44.59; Calcd 44.60).

(11) National Institutes of Health Predoctoral Fellow, Allied Chemical Co. Fellow.

(12) National Institutes of Health Postdoctoral Trainee in Biophysical Chemistry (Training Grant No. 2TI GM722).

(13) Undergraduate Research Participant supported by a grant (No. 8/410-2492) from the National Science Foundation.

Kenneth L. Rinehart, Jr., Allan C. Buchholz[11]
George E. Van Lear,[12] **Herbert L. Cantrill**[13]
Department of Chemistry and Chemical Engineering
University of Illinois, Urbana, Illinois 61801

Received March 11, 1968

Stereochemistry at Trivalent Nitrogen. II. Diastereomers Which Differ in Configuration at Nitrogen[1]

Sir:

Although the isolation of stereoisomers which differ in configuration at trisubstituted nitrogen has remained a goal of organic chemists for many years, attempts to isolate such stereoisomers have for the most part been frustrated by the low barriers to pyramidal inversion which obtain in ammonia and most of its derivatives. The recent isolation of *cis* and *trans* diastereomers of 1-chloro-2-methylaziridine[2,2a] prompts us to disclose the isolation of one of a pair of diastereomers which differ in configuration at nitrogen in an acyclic trivalent nitrogen compound, N-trichloromethanesulfenyl-N-(1-phenylethyl)benzenesulfonamide, ($C_6H_5SO_2N(SCCl_3)$-$CH(CH_3)C_6H_5$, **1**), and to report on its configurational stability.

Reaction of *dl*-N-(1-phenylethyl)benzenesulfonamide with *n*-butyllithium followed by trichloromethanesulfenyl chloride affords **1**[3] in high yield[4] (54%). As the nmr spectrum (Figure 1A) clearly indicates, solutions of **1** at room temperature are composed of mixtures of two diastereomers. Thus two methyl doublets almost equal in intensity (1.05:1.00) are observed at δ 1.27 and 1.78. These two diastereomers are interconverted by epimerization at a chiral center which is configurationally labile as indicated by the nmr spectra observed at elevated temperatures. As the temperature is raised above 55°, the two doublets broaden, coalesce (T_c = 68°), and finally sharpen until one doublet is observed at temperatures at which epimerization is rapid on the nmr time scale. Although, strictly speaking, equal population of sites does not apply, the near equality of the mole fractions of the two diastereomers permits a reasonable approximation to the rate constant at T_c to be obtained by application of the Gutowsky–Holm equation.[5] The rate constant was used in the Eyring equation to calculate the approximate free energy of activation ($\Delta\nu_{\max}$ 31 Hz, T_c +68°, $\Delta G^{\ddagger} \approx$ 17.2 kcal/mol at 68°; solvent bromobenzene).

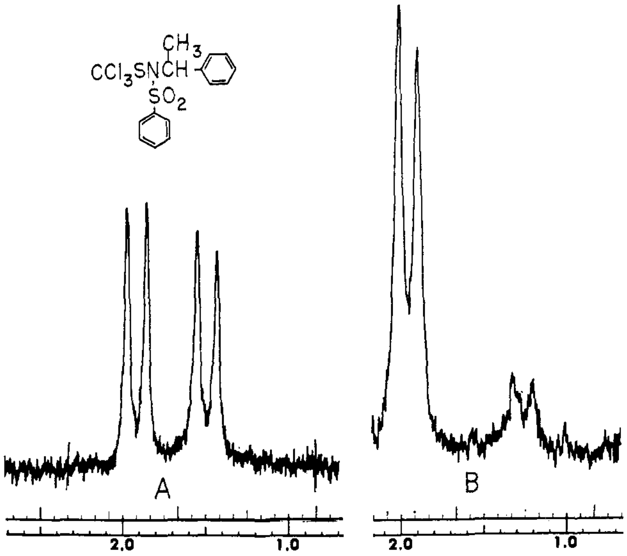


Figure 1. Nmr spectrum of **1**: (A) room temperature, nearly equal mixture of diastereomers; (B) low temperature (−70°), predominantly one diastereomer.

Crystallization of **1** from cyclohexane or methanol proceeds with concomitant second-order asymmetric transformation,[6] resulting in crystals which are diastereomerically homogeneous. This event is manifest not only in the narrow melting range observed, 84–85.5°, but also in the nmr spectra of solutions prepared at low temperatures. When **1** is dissolved in dichloromethane at temperatures below −70°, the nmr spectrum observed (Figure 1B) is not that of a nearly equal mixture of diastereomers but rather indicates the preponderance of a single diastereomer which corresponds to the low-field doublet observed in the room-temperature spectrum.[7] At these temperatures **1** *is configurationally stable at nitrogen on the isolation time scale.* When the temperature is raised to −61° epimerization occurs at a measurable rate and the doublet at higher field begins to grow at the expense of the low-field signal. Although the spectral changes at high temperatures are reversible, those that occur on raising the temperature from −70° to above −60° are irreversible, indicative of a change in the composition of the sample from a nearly pure diastereomer to a nearly equal mixture of diastereomers.

Although the nmr data do not permit a definitive assignment of the rate process which results in epimerization at nitrogen, two alternative rationalizations suggest themselves. The explanation most in agreement with precedent attributes the epimerization to inversion of the nitrogen pyramid. It is now firmly established[2,8]

---

(1) Part I: M. Raban, *Chem. Commun.*, 1017 (1967).

(2) S. J. Brois, *J. Am. Chem. Soc.*, 90, 508 (1968).

(2a) Note Added in Proof. "Invertomers" of 7-chloro-7-azabicyclo[4.1.0]heptane have also been isolated: D. Felix and A. Eschenmoser, *Angew. Chem.*, 80, 197 (1968).

(3) Satisfactory elemental analyses were obtained for all new compounds. Nmr spectra were measured on a Varian A-60A spectrometer equipped with a variable-temperature accessory. Probe temperatures were obtained by examination of methanol spectra in the usual way.

(4) N-(Trichloromethanesulfenyl)benzenesulfonamide has been prepared in low yield (5%) by reaction of benzenesulfonamide with trichloromethanesulfenyl chloride in dry benzene: A. Senning, *Acta Chem. Scand.*, 21, 1567 (1967).

(5) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 25, 1228 (1956).

(6) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 42.

(7) A small, variable amount of the high-field diastereomer was observed as the result of momentary warming of the sample during its transfer into the spectrometer probe.

(8) (a) S. J. Brois, *J. Am. Chem. Soc.*, 90, 506 (1968); (b) A. Mannschreck, R. Radeglia, E. Gründemann, and R. Ohme, *Chem. Ber.*, 100, 1778 (1967); E. Fahr, W. Fischer, A. Jung, L. Sauer, and A. Mannschreck, *Tetrahedron Letters*, 161 (1967); (c) J. E. Anderson and J. M.