

9.32(m) 9.55(ms) 9.82(s) 10.15(s) 10.90(vs) 11.38(m)
13.00–13.10(vs) 14.86(s) 15.02(ms).

1,1-Dibromo-2-vinylcyclopropane: 3.27(m) 3.37(mw)
3.43(m) 3.52(mw) 4.80(vw) 4.93(vw) 5.45(w) 5.81(vw)
6.13(m) 6.99(m) 7.05(m) 7.58(w) 7.73(mw) 8.24(m)
8.41(m) 9.03(vs) 9.55(ms) 9.89(s) 10.16(vs) 10.85–10.90(vs)
11.56(mw) 12.73(w) 13.93(vs).

1,1-Dichloro-2,2-dimethylcyclopropane: 3.37(ms) 3.40(s)
3.45(s) 3.50(m) 3.68(w) 6.30(w) 6.85(s) 6.92(ms) 6.97(s)
7.21(m) 7.27(ms) 7.52(vw) 7.62(w) 7.80(w) 7.94(mw) 8.22(w)
8.94(s) 9.06(s) 9.40(vs) 9.62(s) 9.96(ms) 10.34(m) 11.00(w)
11.20(w) 11.64(ms) 12.25(w) 12.70(m) 13.19(vs) 14.12(vw)
14.95(vw).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Confirmation of the Intramolecular Nature of the Hofmann "Haloamide" Reaction by Double Labeling

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Treatment of a mixture of *m*-DC₆H₄CONH₂ and C₆H₅CON¹⁵H₂ with sodium hypochlorite gave a mixture of *m*-DC₆H₄NH₂ and C₆H₅N¹⁵H₂ free of *m*-DC₆H₄N¹⁵H₂ as established by mass spectrometry. The degree of labeling of the substrates and the sensitivity of the analytical method are such that it can be stated with confidence that the Hofmann reaction is at least 96% intramolecular.

The reaction of an amide with hypohalite to give an amine or derivative thereof, *e.g.*, RCONH₂ + NaOBr → RNH₂ + CO₂ + NaBr, is known as the Hofmann haloamide reaction.^{1,2} This reaction, as well as several other related ones,³ has long been considered to be intramolecular. Evidence for this is entirely stereochemical and comes from the fact that amides in which the R-group is asymmetric at the point of attachment—such as C₆H₅-CH(CH₃)CONH₂—yield amines in which configuration is retained and optical activity almost completely preserved,⁴ even where activity is due to restricted rotation in a biphenyl system,⁵ and that geometric configuration of the R-group is also preserved⁶ in the rearrangement of R from carbon to nitrogen which must occur in the Hofmann haloamide reaction. Moreover, the reaction proceeds normally at bridgehead carbon atoms.⁷

While the stereochemical evidence for retention of configuration is thus overwhelming, it is not so convincing that this constitutes proof for the intramolecular nature of the rearrangement, especially in view of the fact that certain intermolecular reactions involving carbanion intermediates have recently been shown to involve retention of optical⁸

and geometrical⁹ configuration and that carbanion reactions may proceed normally at bridgehead carbon atoms.¹⁰ An independent proof of the intramolecular nature of the Hofmann haloamide reaction thus seemed desirable.

The most convincing evidence for the intramolecular nature of any reaction comes from study of the products obtained in the reaction when carried out on a mixture of two substrates A-B and A'-B'. If only products corresponding to A-B and A'-B' are obtained in a reaction involving rupture of the A-B bond, then the reaction is intramolecular; but if products corresponding to A-B' and A'-B are also obtained, then the reaction is at least in part intermolecular. In fact this criterion may well be considered an operational definition of the terms "intramolecular" and "intermolecular." In the case of the Hofmann haloamide reaction, an appropriate experiment would be to rearrange a mixture of RCONH₂ and R'CON¹⁵H₂, cleanly separate the two chemically distinct products RNH₂ and R'NH₂ (labeled or unlabeled), and demonstrate by conventional degradation to nitrogen gas and isotope ratio measurements of the latter¹¹ that RNH₂ contains no excess of the N¹⁵ isotope. There are, however, two difficulties with such a procedure. One is the need for rigorous purification of RNH₂, to eliminate the possibility of contamination with R'N¹⁵H₂. This difficulty can be obviated by carrying out the N¹⁵ analysis by direct mass spectrometry¹² of RNH₂ at reduced ionizing voltage¹³—provided RNH₂ and R'NH₂ are not isomeric. The second difficulty is concerned with the need of choosing RCONH₂ and R'CONH₂ so

(1) A. W. Hofmann, *Ber.*, **14**, 2725 (1881). We prefer to include the word "haloamide" since at least two other reactions—the alkylation of amines and the degradation of quaternary ammonium salts—are commonly associated with Hofmann's name.

(2) For a review see E. S. Wallis and J. F. Lane in R. Adams, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, pp. 267–306.

(3) Cf. D. J. Cram in M. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 251–253.

(4) E. S. Wallis and S. C. Nagel, *THIS JOURNAL*, **53**, 2787 (1931); C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, 916 (1939).

(5) F. Bell, *ibid.*, 835 (1934); E. S. Wallis and W. W. Moyer, *THIS JOURNAL*, **55**, 2598 (1933).

(6) W. A. Noyes, *et al.*, *Am. Chem. J.*, **16**, 503 (1894); **24**, 290 (1900); **27**, 425 (1902); *THIS JOURNAL*, **32**, 1669 (1910); **36**, 118 (1914); **39**, 2692 (1917); J. Weir, *J. Chem. Soc.*, 99, 1270 (1911).

(7) P. D. Bartlett and L. H. Knox, *THIS JOURNAL*, **61**, 3184 (1939).

(8) R. L. Letsinger, *ibid.*, **72**, 4842 (1950); D. J. Cram, J. Allinger and L. Langemann, *Chemistry & Industry*, 919 (1955). The cases cited by A. N. Nesmeyanov, O. A. Reutov and S. S. Poddubnaya, *Doklady Akad. Nauk S.S.S.R.*, **88**, 479 (1953), *C. A.*, **48**, 2632b (1954), and S. Weinstein, T. G. Traylor and C. S. Garner, *THIS JOURNAL*, **77**, 3741 (1955), may or may not be pertinent here.

(9) Cf. E. Eliel in M. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 154–155.

(10) W. v. E. Doering and L. K. Levy, *THIS JOURNAL*, **77**, 509 (1955).

(11) D. W. Wilson, A. O. C. Nier and S. P. Reimann, "Preparation and Measurement of Isotopic Tracers," J. W. Edwards, Ann Arbor, Mich., 1946, pp. 20–22, 31–39.

(12) Cf. H. W. Washburn in W. G. Berl's "Physical Methods of Chemical Analysis," Vol. I, Academic Press, Inc., New York, N. Y., 1950, pp. 618–620; E. L. Eliel, T. J. Prosser and G. W. Young, *J. Chem. Ed.*, **34**, 72 (1957).

(13) D. P. Stevenson and C. D. Wagner, *THIS JOURNAL*, **72**, 5612 (1950).

that their rates of rearrangement are approximately the same; otherwise one might be completely rearranged before the other begins to react and no crossed products would result *even if* the reaction were intermolecular. Compliance with this condition usually requires considerable preliminary experimentation.

It occurred to us that a clear-cut experiment to distinguish intra- from intermolecular reaction paths would be to rearrange benzamide-*m-d* in the presence of benzamide-*N¹⁵*. These compounds must rearrange at approximately the same rate (except for the small isotope effect of the *N¹⁵*) so that, if the reaction is to any extent intermolecular, the product should contain some aniline-*m-d-N¹⁵*. This species can be easily detected mass spectrometrically, since its mass number is 95 whereas the mass-number of the intramolecular products aniline-*m-d* and aniline-*N¹⁵* is 94. Details of the calculations are given below; they show no evidence whatsoever for any intermolecular reaction and, given the limits of accuracy imposed by the isotopic purity of the substrates and the sensitivity of the analytical method, it can be stated with confidence that the Hofmann haloamide reaction is at least 96% intramolecular.¹⁴

The method used here to demonstrate the intramolecular nature of the Hofmann haloamide reaction commends itself to application in a wide variety of other reactions whose intra- or intermolecular nature is in doubt. The method should frequently be easy to apply, especially in view of the fact that the nature (*C¹³*, *N¹⁵* or *D*, but not *O¹⁸* whose degree of enrichment is insufficient for the purpose at hand) as well as the position of the tracer can be adapted, to a considerable extent, to the experimenter's convenience.¹⁵

A double-labeling method of the above type has apparently been used only once before¹⁶ in a demonstration of the intermolecular nature of hydride exchange between (CH₃)₂CD and (CH₃)₂-CHC¹³H₃. Double-labeling with a somewhat different purpose has been used in biochemical studies.¹⁷

Experimental¹⁸

Benzamide-*N¹⁵*.—Labeled ammonia was generated¹⁹ from ammonium-*N¹⁵* nitrate²⁰ containing 33.4 atom % *N¹⁵* and converted to benzamide-*N¹⁵* by treatment with benzoyl

chloride in ether.²¹ Recrystallized from water the product was obtained in well-formed crystals (79%) which, however, melted over a range²² 124–129°.

Toluene-*m-d* was prepared from *m*-tolylmagnesium bromide and deuterium oxide (99.5+ %) as previously described.²³ Preliminary experiments indicated that removal of the bulk of the ether prior to addition of the deuterium oxide²⁴ was necessary to ensure adequate isotopic purity of the product.²⁵ When DCl and CH₃COOD (used in preference to heavy water alone in view of the difficulties reported in ref. 25) was added to *etheral m*-tolylmagnesium bromide, isotopic purity of the resulting toluene-*m-d* was about 10% less than when the method of Weldon and Wilson²⁵ was used, even though the product was removed from the reaction vessel by vacuum distillation without ever coming in contact with ordinary water or acid. Toluene-*m-d* boiled at 106–108°, *n*_D²⁰ 1.4960, and was obtained in 69% yield (lit.²⁶ for toluene, b.p. 110.6° (760 mm.), *n*_D²⁰ 1.4968).

*Anal.*²⁹ toluene-*d*, 96.0%; unlabeled toluene, 4.0%.

Benzamide-*m-d*.—Toluene-*m-d* was converted to benzoic-*m-d* acid in 73% yield by oxidation with alkaline permanganate essentially as described for the *o-d* compound.²⁷ Treatment of the acid, m.p. 121–125°, with thionyl chloride²⁷ gave benzoyl-*m-d* chloride, b.p. 79–83.5° (16 mm.), in 90% yield. This chloride with concentrated aqueous ammonia yielded benzamide-*m-d*, m.p. 125–129°, in 81% yield.

Anal. Calcd. for C₇H₆DNO: D, 14.28 atom %. Found: D, 13.55 atom % corresponding to an isotopic purity of 94.9%.

Anilines.—The Hofmann haloamide reaction of the benzamides was carried out by means of freshly prepared sodium hypochlorite as described before.²¹ Benzamide-*m-d* gave aniline-*m-d*, b.p. 82–82.5° (20 mm.), *n*_D²⁰ 1.5858 (lit.²⁸ b.p. 85.8° (24.1 mm.), *n*_D²⁰ 1.5863 for aniline) in 70% yield.

*Anal.*²⁹ aniline-*d*, 95.8%; unlabeled aniline, 4.2%.

Benzamide-*N¹⁵* similarly yielded aniline-*N¹⁵*, b.p. 84–85° (24 mm.), *n*_D²⁰ 1.5841, in 72% yield. *Anal.*²⁹ labeled, 31.9%; unlabeled, 68.1%.

A mixture of 2.02 g. of benzamide-*m-d* and 1.98 g. of benzamide-*N¹⁵* similarly yielded 2.16 g. (70.1%) of mixed aniline, b.p. 83.5–84.0° (22–23 mm.), *n*_D²⁰ 1.5845. The composition of this mixture is discussed below.

Mass Spectra and Calculations.—The mass spectra were recorded on a Consolidated 21-103A instrument at reduced ionizing voltage. Each spectrum was recorded three times. Below are shown the individual and average patterns for aniline, the peak heights and patterns for aniline-*m-d* and aniline-*N¹⁵* and the peak heights and treatment of same for the three spectra of the mixture. The spectra of aniline-*m-d* and aniline-*N¹⁵* were handled as follows: The 93-peak was assumed to be due entirely to light aniline (since the aniline spectrum showed no 92-peak). The contribution of light aniline to 94 and 95 was then calculated from the aniline pattern and deducted from the 94- and 95-peaks in the spectra of the labeled compounds.³⁰ The remaining 94- and

(21) W. S. Fones and J. White, *Arch. Biochem.*, **20**, 118 (1949).

(22) V. Grignard, *Traité de Chimie Organique*, **13**, 438 (1941), reports that benzamide is dimorphic, the labile form melting at 128° and the stable at 115°.

(23) J. Turkevich, H. A. McKenzie, L. Friedman and R. Spurr, *THIS JOURNAL*, **71**, 4045 (1949).

(24) From Stuart Oxygen Co., San Francisco, Calif.

(25) Cf. L. H. P. Weldon and C. L. Wilson, *J. Chem. Soc.*, 235 (1946).

(26) A. F. Forziati, A. R. Glasgow, C. B. Willingham and F. D. Rossini, *J. Research Natl. Bur. Standards*, **36**, 129 (1940).

(27) C. D. Hurd and J. Azorlosa, *THIS JOURNAL*, **73**, 37 (1951).

(28) W. Ramsay and S. Young, *J. Chem. Soc.*, **47**, 648 (1885); R. Weegmann, *Z. physik. Chem.*, **2**, 229 (1888).

(29) By mass spectrometry at reduced ionizing voltage.

(30) This procedure is not entirely justified theoretically, since in deducting the 94 contribution of aniline, one deducts not only the contribution due to 6 × 1.1% *C¹³* but also that due to 0.38% *N¹⁵* and 7 × 0.02% *D* caused by naturally occurring heavy isotopes. The error is insignificant in the case of aniline-*d* but affects the 95-pattern of aniline-*N¹⁵* to the extent of about 6%. However, even if this error carried entirely into the mixture spectrum, it would affect the 95 residual only to the extent of 0.25 scale division. Actually the effect tends to cancel altogether, since the mixture spectrum is treated in the same way as the aniline-*N¹⁵* spectrum.

(14) If 95+ % *N¹⁵* had been used in this investigation, this limit could have been as high as 99%. High-purity nitrogen-15 is now available: *Chem. Eng. News*, **34**, 5324 (1956).

(15) The nature and position of the tracer must be such that it is not subject to exchange in the course of the reaction studied and preparation of the substrates. This is why benzamide-*m-d* was chosen in this work in preference to the *o-d* or *p-d* isomer: Aniline is known to undergo exchange of ring-hydrogen atoms in the *ortho* and *para* positions in acid media: M. Harada and T. Titani, *Bull. Chem. Soc. Japan*, **11**, 554 (1938).

(16) O. Beeck, J. W. Otvos, D. P. Stevenson and C. D. Wagner, *J. Chem. Phys.*, **17**, 418, 419 (1949).

(17) E.g., V. du Vigneaud, J. R. Rachele and A. M. White, *THIS JOURNAL*, **78**, 5131 (1956).

(18) Mass spectra by Mr. George W. Young with the exception of those used in the analyses of aniline-*m-d* and aniline-*N¹⁵* which were performed by Mr. Seymour Meyerson of the Standard Oil Company (Indiana). Deuterium analysis by combustion and falling drop method by Mr. Jozsef Nemeth, University of Illinois.

(19) R. Schoenheimer and S. Ratner, *J. Biol. Chem.*, **127**, 301 (1939).

(20) Purchased from Eastman Kodak Co., Rochester, N. Y.

ANILINE PATTERN					
<i>m/e</i>	1	2	3	Average	
92	0	0	0	0	
93	100	100	100	100	
94	7.50	7.51	7.43	7.48	
95	0.24	0.24	0.24	0.24	

ANILINE- <i>m-d</i> (THREE SPECTRA)					
<i>m/e</i>	Peak height	Contribution		Pattern	
		Aniline	Aniline- <i>m-d</i>		
93	30.0; 30.5; 30.3	30.0; 30.5; 30.3	0	0	
94	377.0; 368.0; 358.0	2.24; 2.28; 2.27	374.8; 365.7; 355.7	100	
95	27.3; 25.5; 26.1	0.1; 0.1; 0.1	27.2; 25.4; 26.0	7.28; 6.97; 7.34 (7.31) ^c	

ANILINE-N ¹⁵ (THREE SPECTRA)					
<i>m/e</i>	Peak height	Contribution		Pattern	
		Aniline	Aniline-N ¹⁵		
93	173.7; 168.6; 163.8	173.7; 168.6; 163.8	0		
94	94.8; 92.4; 88.5	13.0; 12.6; 12.3	81.8; 79.8; 76.2	100	
95	6.0; 6.0; 5.8	0.4; 0.4; 0.4	5.6; 5.6; 5.4	6.85; 7.01; 7.09 (6.98) ^d	

MIXTURE (THREE SPECTRA)						
<i>m/e</i>	Peak height	Contribution			Residue	
		Aniline	Labeled ^a	Aniline- <i>m-d</i> ^b	Aniline-N ¹⁵ ^b	
1st	93	123.3	0	0	0	0
	94	248.4	239.2(100)	184.0	55.2	0
	95	17.4	17.1(7.15)	13.45	3.85	-0.2
2nd	93	120.3	0	0	0	0
	94	242.4	233.4(100)	179.5	53.9	0
	95	17.0	16.7(7.16)	13.12	3.76	-0.2
3rd	93	117.9	0	0	0	0
	94	237.3	228.5(100)	175.8	52.7	0
	95	16.7	16.4(7.18)	12.85	3.68	-0.1

^a Total labeled material (pattern in parentheses). ^b Contribution to 94-peak calculated on the assumption that $^{10}/_{13}$ of this peak is due to aniline-*m-d* and $^9/_{13}$ to aniline-N¹⁵. Contribution to 95-peak calculated from assumed 94-peak and appropriate pattern. ^c Average of first and third values. ^d Average.

95-peaks were used to calculate patterns for aniline-*m-d* and aniline-N¹⁵ and the three patterns for each compound were averaged.

The mixture spectrum was handled as follows: The 93-peak was again taken to be due to aniline and the contribution of aniline to the 94- and 95-peaks was deducted.³⁰ The residual 94-peaks are due to aniline-*m-d* and aniline-N¹⁵. Since the patterns at 95 of these two species are very similar, only a rough apportionment between the two species is necessary and this was obtained by assuming that *ca.* $^9/_{13}$ of the labeled material bore the N¹⁵-label and $^{10}/_{13}$ the D-label.³¹ The residual 95 peak was then calculated and found insignificant in all three spectra.

Sensitivity of Method.—In setting an upper limit to the amount of intermolecular reaction giving rise to aniline-N¹⁵-*m-d* which might escape detection, one has to make an assumption on the minimum height of the 95 residual which can be clearly detected. Since the total height of the 95-peak is only about 17 divisions, the assumption that a residual of at least one scale division can be clearly detected is certainly a most conservative one. Since the sum of the peak heights at the parent peaks due to aniline (at 93) and the labeled anilines (at 94) is about 350 scale divisions, one division at 95 would correspond to about 1 part doubly

labeled aniline in 350 or about 0.3% (making the reasonable assumption that the sensitivities for unlabeled, singly labeled and doubly labeled species at the parent peak are roughly equal).

It can be calculated that about 4% intermolecular reaction suffices to produce 0.3% doubly labeled material; thus 4% is the maximum of intermolecular reaction that might have escaped detection. The 4% figure is arrived at as follows: Out of 200 parts of a 50-50 mixture of aniline-N¹⁵ and aniline-*m-d*, according to the above analyses 95.8 parts will be deuterated, 31.9 parts will contain N¹⁵ (neglecting natural deuterium and N¹⁵) and the rest will be unlabeled. If there is 4% of intermolecular reaction, then 8 parts of the above mixture, containing 3.83 parts deuterium and 1.28 parts N¹⁵ will be subject to random recombination (neglecting any isotope effects), giving rise to 0.61 part in 200 or *ca.* 0.3% of doubly labeled material.

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(31) Making the rough assumption that all of the 50% deuterated material was labeled but only 30% of the 50% N¹⁵ material was labeled. The calculations are in no way sensitive to this assumption. For example, in the first mixture spectrum, if all the labeled material was assumed to be aniline-*m-d*, the residue would be -0.4 and if all labeled material was assumed to be aniline N¹⁵, the residue at 95 would be +0.4.