Stereochemistry and Mechanism of the Ritter Reaction of Bromohydrins to Give 1-Amido-2-bromoalkanes and Ring Closure to Give 2-Oxazolines

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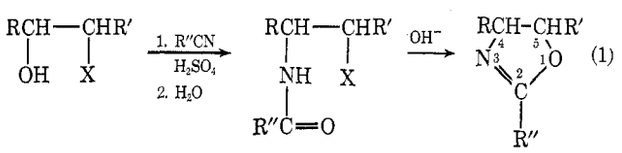
The stereochemistry of the Ritter reaction of bromohydrins has been investigated. It is shown that the reaction proceeds with complete retention, *e.g.*, *threo*-3-bromo-2-butanol (**1**) with acetonitrile or benzonitrile in the presence of sulfuric acid gave exclusively *threo*-2-acetamido-3-bromobutane (**3a**) and *threo*-2-benzamido-3-bromobutane (**3b**), respectively. Similarly, *erythro*-3-bromo-2-butanol (**2**) with acetonitrile and benzonitrile gave exclusively *erythro*-2-acetamido-3-bromobutane (**4a**) and *erythro*-2-benzamido-3-bromobutane (**4b**), respectively. The observed complete retention is explained by a mechanism over bridged bromonium ions. The bromoamides are not stable but ring close spontaneously to give the hydrobromide salts of the corresponding 2-oxazolines. The nmr spectra of the latter salts are discussed.

Ritter and Lusskin have reported the preparation of 1-amido-2-haloalkanes by the reaction of a halohydrin with a nitrile in the presence of concentrated sulfuric acid.[1,2] The resulting 1-amido-2-haloalkanes can with base be ring closed to give the corresponding 2-oxazolines (eq 1).[1,3] Owing to our interest in 2-oxazolines[4] we

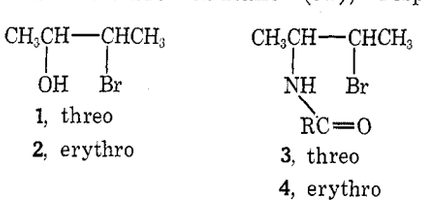


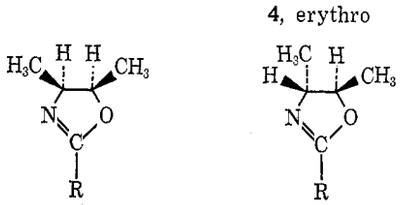
(1)

have investigated the stereochemistry of this reaction sequence.

Results

Using *threo*-3-bromo-2-butanol (**1**) as starting bromohydrin, reaction with acetonitrile and benzonitrile gave exclusively *threo*-2-acetamido-3-bromobutane (**3a**) and *threo*-2-benzamido-3-bromobutane (**3b**), respectively.





a, R = CH_3
b, R = C_6H_5

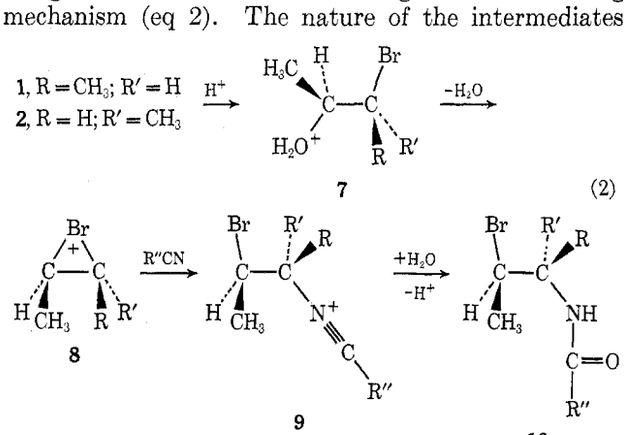
The stereochemistry of the bromoamides **3a** and **3b** was best demonstrated by their reaction with base to give exclusively *cis*-2,4,5-trimethyl-2-oxazoline (**5a**) and *cis*-4,5-dimethyl-2-phenyl-2-oxazoline (**5b**), respectively, in greater than 99% stereoisomeric purity as judged by gas-chromatographic analysis and comparison with the known compounds.[4] Since it is generally accepted that the ring-closure step forming the 2-oxazoline proceeds with Walden inversion,[5] the Ritter reaction step thus proceeds with complete retention.

erythro-3-Bromo-2-butanol (**2**) similarly with acetonitrile or benzonitrile in the presence of sulfuric acid led to practically pure *erythro*-2-acetamido-3-bromobutane (**4a**) and *erythro*-2-benzamido-3-bromobutane (**4b**), respectively, which on ring closure with base gave the corresponding *trans*-2-oxazolines, **6a** and **6b**.

The bromoamides **3** and **4** are not stable at room temperature. In solution they spontaneously ring close within a few hours to give the hydrobromide salts of the corresponding 2-oxazolines. This conversion can conveniently be followed by nmr spectroscopy. In the solid state the conversion to the oxazoline salt is slower. The instability of 1-amido-2-halides with respect to ring closure to 2-oxazolines has been noted before.[1,5]

Discussion

The Ritter reaction step, as inferred from the observed complete retention, most likely proceeds over a bridged bromonium ion according to the following mechanism (eq 2). The nature of the intermediates



and products **8**–**10** are, as it turns out, identical with those encountered by Hassner, *et al.*, in the addition of bromine and nitriles to olefins in the presence of silver salts.[6]

(1) R. M. Lusskin and J. J. Ritter, *J. Amer. Chem. Soc.*, **72**, 5577 (1950).

(2) The reaction of carbenium centers with nitriles is known as the Ritter reaction. Original publications: J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045, 4048 (1948).

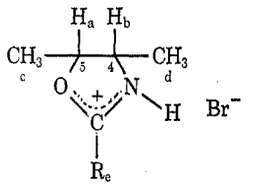
(3) For a recent review of oxazoline chemistry see J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).

(4) R. A. Wohl and J. Cannie, *J. Org. Chem.*, **38**, 1787 (1973).

(5) See also H. W. Heine, *J. Amer. Chem. Soc.*, **78**, 3708 (1956); **79**, 907 (1957); and ref 6.

(6) A. Hassner, L. A. Levy, and R. Gault, *Tetrahedron Lett.*, **No. 27**, 3119 (1966).

TABLE I
NMR SPECTRA OF 2-OXAZOLINE HYDROBROMIDES



2-Oxazoline hydrobromide	Chemical shifts, δ (CDCl₃)[a]				
	H_a (at C-5)	H_b (at C-4)	H_c (at C-5)	H_d (at C-4)	H_e
cis-2,4,5-Trimethyl- (**5a**)	5.64 (oct)	4.83 (pent)[b]	1.57 (d)	1.47 (d)	2.61 (s)
	[4.52 (m)]	[3.95 (m)]	[1.16 (d)]	[1.03 (d)]	[1.81 (d)]
	J_{ab} = 9.8	J_{ba} = 9.8	J_{ca} = 6.5	J_{db} = 6.4	(R = CH_3)
cis-4,5-Dimethyl-2-phenyl- (**5b**)	5.70 (oct)	4.98 (pent)[b]	1.61 (d)	1.56 (d)	7.34–7.97 (m) + 8.41 (m)
	[4.66 (oct)]	[4.14 (oct)]	[1.25 (d)]	[1.14 (d)]	[7.25 (m) + 7.83 (m)]
	J_{ab} = 9.5	J_{ba} = 9.5	J_{ca} = 6.4	J_{db} = 6.3	(R = CH_3)
trans-2,4,5-Trimethyl- (**6a**)	5.03 (pent)[b]	4.31 (pent)[b]	1.70 (d)	1.59 (d)	2.65 (s)
	[3.95 (pent)]	[3.43 (m)]	[1.27 (d)]	[1.15 (d)]	[1.83 (d)]
	$J_{ab} \cong 6.9$	J_{ba} = 6.9	K_{ca} = 7.9	J_{db} = 7.8	(R = C_6H_5]
trans-4,5-Dimethyl-2-phenyl- (**6b**)	5.07 (pent)[c]	4.40 (pent)[c]	1.71 (d)	1.71 (d)	7.33–8.04 (m) + 8.47 (m)
	[4.07 (pent)]	[3.64 (pent)]	[1.35 (d)]	[1.21 (d)]	[7.55 (m) + 7.83 (m)]
	J_{ab} = 7.9	J_{ba} = 7.9	J_{ca} = 6.4	J_{db} = 6.4	(R = C_6H_5)

[a] With respect to tetramethylsilane as internal standard. Chemical shifts in brackets are the values for the free 2-oxazoline bases in CCl_4 from ref 4. *J* values are observed splitting values in hertz. [b] Major splitting pattern in actually higher multiplet. [c] Predominating splitting pattern. Actually two overlapping quartets.

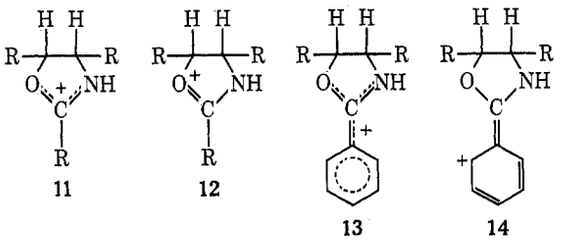
The 2,3-butylenebromonium ions **8** have also been discussed in the reaction of the bromohydrins **1** and **2** with HBr to give the corresponding 2,3-dibromobutanes,[7] in the reaction of 2-acetoxy-3-bromobutanes and 2,3-dibromobutanes with silver acetate in acetic acid,[8] and in the addition of bromine azide to *cis*- and *trans*-2-butene.[9] Recently they have been observed by Olah, *et al.*, by means of nmr spectroscopy in antimony pentafluoride–sulfur dioxide solution at low temperature.[10]

2-Oxazolines are of possible synthetic utility because they can be readily hydrolyzed to the corresponding amino alcohols. In the case of cyclic bromohydrins the resulting amino alcohols will possess the otherwise not readily available cis configuration.[6]

Nmr Spectra.—The nmr data of the hydrobromide salts of the 2-oxazolines are summarized in Table I. The general appearance of the spectra is very similar to that of the free 2-oxazoline bases.[4] The cis salts **5a** and **5b** have a vinical coupling constant J_{ab} of about 9.7 cps, and the trans compounds **6a** and **6b** have a coupling constant of 7–8 cps. Thus, as usual in more or less planar rings, cis-proton coupling is larger than trans-proton coupling.[4,11–13] The magnitude of the vicinal coupling contant J_{ab} is 1–2 Hz larger as compared to the values in the free oxazoline bases.[4]

The 4 and 5 methyl groups absorb at approximately 0.1 ppm higher field in the cis salts than in the corresponding trans isomers, whereas the 4 and 5 methine protons absorb at approximately 0.5 ppm lower field in the cis salts than in the trans compounds as is found in many cis–trans isomer pairs of planar three- to five-membered ring compounds.[4,14]

All protons appear in the hydrobromide salts as expected at lower field as compared with the same protons in the corresponding free 2-oxazolines. It is very interesting to note, however, that this downfield shift is very similar in magnitude for both the 4 and 5 substituents in spite of the fact that the 4 carbon atom is neighboring the protonated nitrogen atom. Actually the 5-methine proton which is neighboring the oxygen atom suffers a larger shift downfield than the 4-methine proton. In order to account for these data the resonance hybrid **11** may be invoked with the canonical



11 **12** **13** **14**

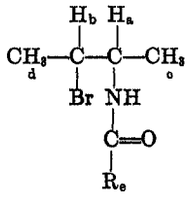
form **12** as an important contributor, *i.e.*, the positive charge is delocalized over both heteroatoms. The above assignment and conclusions agree with those by Pittman and coworkers, which are based on a large number of oxazolinium cations observed in sulfuric acid solution.[15]

In the case of the 2-phenyloxazolines **5b** and **6b** the positive charge is further delocalized into the aromatic ring according to the resonance hybrid **13**. The canonical form **14** and the canonical form with the positive charge in the other ortho position explain the observation that the two ortho hydrogen atoms of the phenyl group show the by far the largest shift downfield (*ca.* 0.6 ppm) of the aromatic protons as compared to their chemical shifts in the free bases.

(7) S. Winstein and H. J. Lucas, *J. Amer. Chem. Soc.*, **61**, 2845 (1939).
(8) S. Winstein and R. E. Buckles, *J. Amer. Chem. Soc.*, **64**, 2780, 2787 (1942).
(9) A. Hassner and F. Boerwinkle, *J. Amer. Chem. Soc.*, **90**, 216 (1968).
(10) G. A. Olah, J. M. Bollinger, and J. Brinich, *J. Amer. Chem. Soc.*, **90**, 2587 (1968).
(11) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969.
(12) Reference 11, p 286 ff.
(13) S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969).
(14) Reference 11, p 234 ff.
(15) C. U. Pittman, Jr., S. P. McManus, and J. W. Larsen, *Chem. Rev.*, **72**, 357, 420 (1972), and references cited therein.

TABLE II

NMR SPECTRA OF 2-AMIDO-3-BROMOBUTANES



2-Amido-3-bromobutane	Chemical shifts, δ (CDCl₃)[a]				
	H_a	H_b	H_c	H_d	H_e
3a (threo)	← 4.25 (m) →		1.67 (d) J_{ca} = 6.8	1.25 (d) J_{db} = 6.4	2.06 (s) (R = CH_3)
3b (threo)	← 4.35 (m) →		1.73 (d) J_{ca} = 7.0	1.34 (d) J_{db} = 6.6	6.49 + 7.82 (m) (R = C_6H_5)
4a (erythro)	4.40 (oct) J_{ab} = 3.2	4.03 (m) J_{ba} = 3.2	1.67 (d) J_{ca} = 6.9	1.19 (d) J_{db} = 6.4	2.01 (s) (R = CH_3)
4b (erythro)	4.49 (oct) J_{ab} = 3.0	4.12 (m) J_{ba} = 3.0	1.17 (d) J_{ca} = 6.5	1.29 (d) J_{db} = 6.2	7.47 + 7.82 (m) (R = C_6H_5)

[a] With respect to tetramethylsilane as internal standard. J values are observed splitting values in hertz.

The 2-methyl group in the salts **5a** and **6a** appears essentially as a singlet, whereas in the free 2-oxazolines it couples with the 4-methine proton with a long-range coupling constant of approximately 1.5 cps.[4,16] The long-range coupling is, if present at all, much smaller in the salts as expected owing to the decreased double bond character of the C=N bond.[17]

The spectrum of a hydrobromide salt could be converted gradually into the spectrum of the free 2-oxazoline base by adding slightly moist potassium carbonate in small portions to the nmr tube.

Experimental Section

General Procedures.—Infrared spectra were taken on a Perkin-Elmer Model 137 sodium chloride spectrophotometer. Methylene chloride was used as a solvent. Nmr spectra were taken on a Varian T-60 nuclear magnetic resonance spectrometer. Gas chromatography was done on a Varian Model 90P gas chromatograph. Acetonitrile was distilled over phosphorous pentoxide. Benzonitrile was dried over molecular sieves 3A.

2-Amido-3-bromobutanes.—The method of Lusskin and Ritter was essentially followed.[1] To 0.3 mol of the nitrile, which was cooled in ice and stirred magnetically, 70 g of concentrated sulfuric acid was added slowly. After stirring for another 0.5 hr, 0.1 mol of the bromohydrin was slowly added in about 30 min. The solution was allowed to warm up to room temperature, kept for 3 hr at 35°, and then poured into 300 g of ice and water; 20 g of sodium carbonate was added in portions; and the solution was stirred for another 5–10 min. The individual halo amides were then isolated as described below.

The nmr spectra of all halo amides are summarized in Table II. On prolonged standing of the solid or a solution all 2-amido-3-bromobutanes converted to the hydrobromide salts of the corresponding 2-oxazolines.

threo-**2-Acetamido-3-bromobutane** (**3a**)—The following work-up was done as rapidly as possible and with the temperature not exceeding room temperature. The aqueous reaction mixture, in which no precipitate had formed, was extracted three times with ether. After drying with magnesium sulfate, evaporation yielded 15.7 g (81%) of a colorless oil, which eventually solidified to an extremely hygroscopic solid.

threo-**2-Benzamido-3-bromobutane** (**3b**).—The precipitate formed in the aqueous reaction mixture was isolated by filtration and washed with 10% sodium carbonate solution, water, and pentane; 50 g of white crystals were obtained containing substantial amounts of benzamide. The material was not purified further for conversion to the 2-oxazoline **5b**.

erythro-**2-Acetamido-3-bromobutane** (**4a**).—The following work-up was done as rapidly as possible and with the temperature not exceeding room temperature. The aqueous reaction mixture, in which no precipitate had formed, was extracted three times with ether. After drying with magnesium sulfate, evaporation of the ether yielded 14.2 g (73%) of a colorless oil which solidified to an extremely hygroscopic solid.

erythro-**2-Benzamido-3-bromobutane** (**4b**).—The precipitate formed in the aqueous reaction mixture was isolated by filtration and washed successively with 10% sodium carbonate solution, water, and pentane; 44 g of white crystals were obtained which contained substantial amounts of benzamide. The material was not further purified for conversion to the 2-oxazoline **6b**. A much purer sample was obtained by rapidly treating the crude material with boiling water in order to extract the benzamide. This sample, which contained practically no benzamide, melted at 132–135°.

General Procedure for 2-Oxazolines.—A 50-mmol portion of the crude 2-amido-3-bromobutane was treated with 40 ml of 2 *N* sodium hydroxide solution and then steam distilled. The 4,5-dimethyl-2-phenyl-2-oxazolines **5b** and **6b** were isolated by extracting three times with ether, drying the combined ether phases with magnesium sulfate, and evaporating the ether. The 2,4,5-trimethyl-2-oxazolines **5a** and **6a** were isolated by extracting the steam distillate with ether in a Kutscher–Steudel apparatus, then drying the ether with magnesium sulfate and evaporating the ether through a short Vigreux column. Table III shows the yields. The gas chromatographic separations were performed on a 6-ft column of 15% Carbowax 20M on Gas-Chrom P with a flow rate of 90 ml/min. Column temperature was 104° for the *trans*- and *cis*-2,4,5-trimethyl-2-oxazolines **6a** and **5a**, which had retention times of 2.5 and 3 min, respectively. Column temperature was 215° for the *trans*- and *cis*-2-phenyl-2-oxazolines **6b** and **5b**, which had retention times of 2.7 and 3.7 min, respectively. The stereoisomeric purity of all 2-oxazolines exceeded 99%.

TABLE III

YIELDS OF 2-OXAZOLINES

2-Oxazoline	Yield, %[a]
cis-2,4,5-Trimethyl-2-oxazoline (**5a**)	33
trans-2,4,5-Trimethyl-2-oxazoline (**6a**)	31
cis-4,5-Dimethyl-2-phenyl-2-oxazoline (**5b**)	94
trans-4,5-Dimethyl-2-phenyl-2-oxazoline (**6b**)	87

[a] Crude weight yield based on initial bromohydrin. The isolated oxazolines are essentially pure as judged by their ir and nmr spectra and gas chromatograms.

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Registry No.—**1**, 19773-41-2; **2**, 19773 40-1; **3a**, 40891-89-2; **3b**, 40891-90-5; **4a**, 40891-91-6; **4b**, 40891-92-7; **5a**, 23236-41-1; **5b**, 36746-57-3; **6a**, 23336-75-6; **6b**, 38898-95-2.

(16) J. Roggero and J. Metzger, *Bull. Soc. Chim. Fr.*, 1715 (1964).

(17) See, however, the comments pertaining to footnote 361 in ref 15.