[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Stereochemistry of Elimination Reactions Involving Halohydrin Derivatives and Metals[1]

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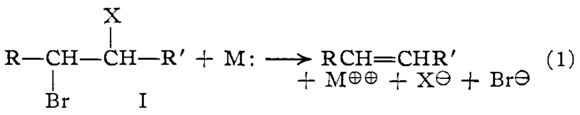
The *erythro* and *threo* isomers of 2,3-dibromobutane, 2-acetoxy-3-bromobutane, 2-bromo-3-methoxybutane, 4-bromo-5-methoxyoctane and 1-bromo-1,2-diphenyl-2-methoxyethane have been prepared and each compound was allowed to react with zinc in aqueous ethanol. With all compounds studied except the 2,3-dibromobutanes the elimination reaction was not stereospecific. The isomeric 2-bromo-3-methoxybutanes and 4-bromo-5-methoxyoctanes also were allowed to react with sodium in tetrahydrofuran: again the elimination reactions were not stereospecific. Possible mechanisms for eliminations with metals are discussed and a general hypothesis regarding the course of these eliminations is advanced.

The requirement of a *trans* coplanar transition state for bimolecular elimination (E 2) reactions has been shown to be applicable both to dehydrohalogenation and related reactions[3,4] and to the elimination reaction which results when vicinal dihalides are treated with iodide ion.[5-7] For a third class of bimolecular (or at least not intramolecular) elimination reactions, including the reactions of vicinal dibromides, halohydrins or halohydrin derivatives with metals such as magnesium, zinc, lithium or sodium (equation 1 where X = a halogen atom, OH, OR or OCOR),[8] the stereochemical requirements are less well known.

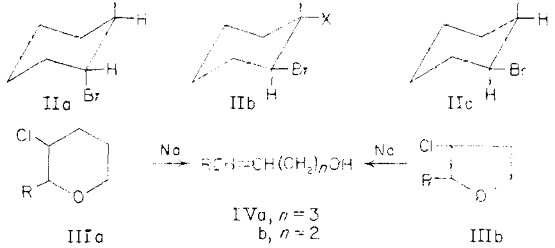


$$\underset{\displaystyle\text{Br}}{\text{R—}\underset{|}{\text{CH}}}\text{—}\overset{\displaystyle\text{X}}{\overset{|}{\text{CH}}}\text{—R}' + \text{M:} \longrightarrow \text{RCH=CHR}' + \text{M}^{\oplus\oplus} + \text{X}^{\ominus} + \text{Br}^{\ominus} \qquad (1)$$

I

The stereochemical consequences of elimination reactions effected by metals have been most thoroughly studied with vicinal dibromides.[9] These studies have demonstrated that reaction of either zinc or magnesium with dibromides of the type I (X = Br) where R and R′ are *n*-alkyl groups results in a stereospecific *trans* elimination.[9c-e] However, if the groups R and R′ of the dibromide I (X = Br) are either large (*e.g.*, R = R′ = C_6H_5) or polar (*e.g.*, R = R′ = COO^- or COOR), the elimination is no longer stereospecific, the *trans*-olefin being obtained from either diastereoisomeric dibromide.[9a,b,e] Furthermore, in all cases studied, reaction of the dibromide I (X = Br) with sodium was not stereospecific, similar olefin mixtures containing excess *trans*-olefin being obtained with each pair of diastereoisomeric dibromides I (X = Br) used.[9e]

The stereochemistry of elimination reactions with metals and halohydrins or their derivatives have been investigated in only a few instances,[3,10,11] all of which have involved cyclic systems (*i.e.*, II and III). In the examples of the reactions of bromohydrins II (X = OH) with zinc which have been studied[3,11] elimination has occurred readily with both the *cis* (IIc) and *trans* (IIa and IIb) isomers. Furthermore, studies[11] of bromohydrins in the sterol series have indicated that elimination occurs readily with both the axial–axial (IIa) and the equatorial–equatorial (IIb) conformations of the *trans* isomer. These results are in marked contrast to the observations made with other types of bimolecular elimination reactions.[5] Similarly, studies[10] of the reaction of the cyclic β-chloro ethers III with sodium have shown that both diastereoisomeric configurations of the tetrahydropyran derivative IIIa afford the *trans*-olefin IVa. In the tetrahydrofuran series IIIb the *trans*-β-halo ether afford an olefin mixture IVb containing 80–87% of the *trans*-olefin and the olefin mixture IVb obtained from the *cis*-β-halo ether contained 56–57% of the *trans*-olefin. These results raise the question as to whether the elimination reaction which occurs when halohydrin derivatives are treated with metals is ever a stereospecific process even with molecules whose conformations are not constrained by the presence of one or more rings. This paper reports the results of a study designed to answer this question.



The *erythro* and *threo* isomers of compounds V, VI and VII have been prepared and each compound was allowed to react with a suspension of zinc in aqueous ethanol. In addition the β-bromo ethers

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[1] Presented at the 132nd Meeting of the American Chemical Society, New York, N. Y., Sept. 8 to 13, 1957.

[2] Alfred P. Sloan postdoctoral fellow, 1957.

[3] S. J. Cristol, Abstracts of Papers presented at the 14th Symposium of the Organic Division of the American Chemical Society, Lafayette, Ind., June 13 to 16, 1955, pp. 6–12.

[4] D. J. Cram in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 314–346.

[5] D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950).

[6] S. Winstein, D. Pressman and W. G. Young, *ibid.*, **61**, 1645 (1939).

[7] S. J. Cristol, J. Q. Weber and M. C. Brindell, *ibid.*, **78**, 598 (1956).

[8] Throughout this discussion M: is used to represent either one atom of a divalent metal (*e.g.*, zinc or magnesium) or two atoms of a monovalent metal (*e.g.*, sodium or lithium) which occupy part of the surface of the metal.

[9] (a) R. Otto and F. Stoffel, *Ber.*, **30**, 1799 (1897); (b) A. Michael and O. Schultess, *J. prakt. Chem.*, **43**, 587 (1891); (c) W. G. Young, Z. Jasaitis and L. Levanas, THIS JOURNAL, **59**, 403 (1937); (d) H. J. Lucas, M. J. Schlatter and R. C. Jones, *ibid.*, **63**, 22 (1941); (e) W. M. Schubert, B. S. Rabinovitch, N. R. Larson and V. A. Sims, *ibid.*, **74**, 4590 (1952).

[10] L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1707, 1715 (1950); L. Crombie, J. Gold, S. H. Harper and B. J. Stokes, *ibid.*, 136 (1956).

[11] D. R. James, R. W. Rees and C. W. Shoppee, *ibid.*, 1370 (1955), and references cited therein.

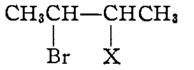
Va and VI were treated with a suspension of sodium in tetrahydrofuran. In each instance the olefin mixture produced was analyzed. The results of this study are summarized in Table I. From these results it is apparent that none of the studied reactions of the diastereoisomeric bromohydrin derivatives with metals afforded olefinic products consistent with a concerted *trans* elimination process.[12] Furthermore, it will be noted that the composition of the olefin mixture obtained in each system was approximately the same irrespective of whether the *erythro* or *threo* diastereoisomer was used. This observation suggests that at some stage in the reaction equilibration of the possible configurations occurred.[13]

TABLE I

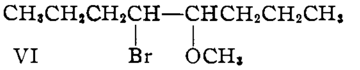
RESULTS OF ELIMINATION REACTIONS INVOLVING BROMOHYDRIN DERIVATIVES AND METALS

Reactant	Reaction conditions	Reacn. time, hr.	Recovered reactant, %	Yield of olefin, %	Composition of olefin, % *trans*	*cis*
erythro-Va	Zn in H_2O–	4	..	74	50	50
	EtOH	4.5	..	70	49	51
	Na in C_4H_8O	3	..	70	53	47
		3.5	..	70	52	48
threo-Va	Zn in H_2O–	3	..	70	45	55
	EtOH	3.5	..	68	44	56
	Na in C_4H_8O	2	..	70	55	45
		2.5	..	65	55	45
erythro-VI	Zn in H_2O–	3	35[a]	26	45	55
	EtOH	6	..	70	44	56
	Na in C_4H_8O	6	..	75	58	42
threo-VI	Zn in H_2O–	3	40[a]	24	41	59
	EtOH	6	..	71	45	55
	Na in C_4H_8O	6	..	76	56	44
erythro-VII	Zn in H_2O–	90	..	53[c]	100	0[b]
	EtOH	23	23	..	..	..
threo-VII	Zn in H_2O–	47	..	51[c]	100	0[b]
	EtOH	24	..	36[c]	100	0[b]
erythro-Vb	Zn in H_2O–	3	..	99	55	45
	EtOH	4	..	90	56	44
threo-Vb	Zn in H_2O–	3	..	82	52	48
	EtOH	3.5	..	80	51	49
		0.2	50[a]	..	..	..
erythro-Vc	Zn in H_2O–	0.8	..	85	96	4
	EtOH	1	..	83	97	3
threo-Vc	Zn in H_2O–	0.75	..	89	4	96
	EtOH	0.75	..	85	4	96

[a] No diastereoisomeric impurity was detected in the recovered starting material. [b] No *cis*-stilbene was detected. The maximum amount of this isomer which would have escaped detection is estimated to be 4%. [c] These yields are based on the amount of crude *trans*-stilbene isolated.



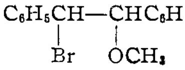
$$CH_3\underset{Br}{\underset{|}{C}}H—\underset{X}{\underset{|}{C}}HCH_3$$



$$CH_3CH_2CH_2\underset{Br}{\underset{|}{C}}H—\underset{OCH_3}{\underset{|}{C}}HCH_2CH_2CH_3$$

VI

Va, X = OCH_3
b, X = $OCOCH_3$
c, X = Br



$$C_6H_5\underset{Br}{\underset{|}{C}}H—\underset{OCH_3}{\underset{|}{C}}HC_6H_5$$

VII

Although the absence of stereospecificity observed in the elimination reactions described here could be ascribed to non-concerted elimination process, the possibilities also existed that either the starting bromohydrin derivatives I were being partially epimerized by reaction with the bromide ion formed in the reaction mixture or the olefinic products were being partially isomerized under the conditions of the reaction. However, both of the latter possibilities have been excluded. To ensure that the bromohydrin derivatives I were not being partially epimerized in the reaction mixtures, the unchanged bromo ethers *erythro*-VI and *threo*-VI and the bromo acetate *threo*-Vb were recovered from their reaction mixtures. In each case we were unable to detect the presence of a diastereoisomeric impurity as would be required if partial epimerization had occurred. In the case of 1,2-diphenylethane derivatives VII the possibility of the interconversion of the *threo* and *erythro* isomers could not be either excluded or verified since the recovered bromo ethers VII were seriously contaminated with other products, presumably from partial solvolysis of the bromo ether VII in the reaction mixture.

The stability of the olefins under the conditions of the reaction was demonstrated in two ways. The configurational stability of the 2-butenes[14] follows from the formation of essentially pure *cis*- and *trans*-2-butene from the diastereoisomeric dibromides Vc under comparable reaction conditions. In a more rigorous test of the olefin stabilities *cis*-stilbene was subjected to the conditions of the elimination reaction; no *trans*-stilbene could be detected in the recovered hydrocarbon. Therefore, we are forced to conclude that the elimination reactions themselves are not stereospecific.

The intervention of a free-radical intermediate X (equation 2) which has been suggested for certain dibromide–metal eliminations[9e] and β-halo ether–metal eliminations[15,16] provides an adequate explanation for the lack of stereospecificity observed in these elimination reactions. However, a radical intermediate is less attractive in other respects. As noted by Crombie and Harper,[10] the elimination reactions appear to be free from the usual side reactions (*e.g.*, coupling, disproportionation, solvent attack) expected with a radical intermediate.[17]

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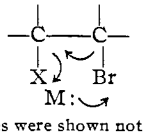
[12] The reaction of the *erythro* and *threo* diastereoisomers of 2,3-dibromobutane (Vc) with zinc in aqueous ethanol was included in this study in order to be certain that our reaction conditions and analytical methods were comparable to those previously reported by Schubert and co-workers (ref. 9e).

[13] The fact that this apparent equilibration occurred with every bromohydrin derivative studied argues strongly against an alternative explanation requiring the simultaneous occurrence of a concerted *trans* elimination and a concerted *cis* elimination. Although we know of no instance in which this latter process has been established, the possibility that a cyclic process of the type (a), may be realized cannot be excluded.



(a)

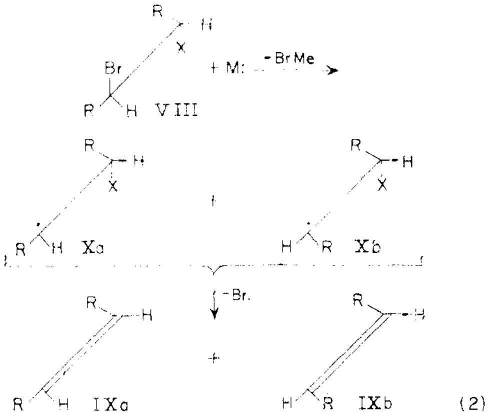
[14] The butene mixtures were shown not to contain either 1-butene or isobutylene. The conditions required to equilibrate the isomeric butenes have been studied by A. M. Eastham, THIS JOURNAL, **78**, 6040 (1956).

[15] E. D. Amstutz, *J. Org. Chem.*, **9**, 310 (1944).

[16] R. Paul, *Bull. soc. chim. France*, [5] **2**, 745 (1935).

[17] This argument may be overcome if a very short lifetime is postulated for the radical intermediate X.

A more serious objection to a radical intermediate, previously recognized by Schubert and co-workers,[9e] is whether or not a radical of the type X would spontaneously eliminate a bromine atom or alkoxy radical (*i.e.*, X → IX) since the reverse reaction appears to occur readily as one step in the peroxide-catalyzed addition of hydrogen bromide to olefins.[18] Also, the peroxide-initiated bromination of α-bromobibenzyl with N-bromosuccinimide to form α,α'-dibromobibenzyl appears to involve the formation of a radical of the type X (X = Br) without subsequent elimination.[19] Similar arguments can be presented against an elimination of the type X → IX where the group X is an alkoxy group. Thus the (presumably free-radical) bromination of γ-tetrahydropyrone with N-bromosuccinimide yielded α,α'-dibromo-γ-tetrahydropyrone.[20] Also, the Kolbe electrolysis of β-amyloxypropionic acid[21] and β,β-diethoxypropionic acid[22] afforded the corresponding coupling products in good yield although radicals of the type X (X = OR) were presumably involved.[23] Although an elimination of the type X → IX cannot be rigorously excluded by these data, the combined arguments have led us to believe that equation 2 does not represent a probable reaction path for the elimination reactions discussed here. These data have no bearing on the possibility that a radical such as X may be involved as an intermediate in the reaction of the halide VIII with the metal to form a carbanionic or organometallic intermediate of the type subsequently discussed. The intervention of a carbonium ion as an intermediate in the elimination seems to be improbable for the reasons stated by Shoppee and co-workers.[11]



Consequently, the non-stereospecific elimination reactions may be supposed to proceed *via* organometallic or carbanionic intermediates (equation 3).[11,24–26] Both the failure to detect such intermediates[15,27] and the fact that the elimination is not accompanied by a significant amount of reduction of the carbon–bromine bond when the reaction is run in hydroxylic solvents require the lifetime of a carbanionic or organometallic intermediate to be short. However, the supposition of such intermediates does provide a rational explanation for the difference in behavior of vicinal dibromides and halohydrin derivatives. The first stage in the reaction may be represented by XI, a nucleophilic attack on the halogen atom by the metal. If simultaneous loss of the group X occurs, the elimination is a concerted *trans* process as is observed with simple vicinal dihalides. However, if the group X is not lost at this stage XI, the reaction with the metal may be supposed to proceed further to form organometallic intermediates XII which may then dissociate to yield carbanionic intermediates XIII. There is ample evidence that the configuration of the carbon atom bound to bromine would not be maintained in proceeding from the first stage XI of the reaction to the organometallic intermediates XII.[28] Thus, if reaction of the halide VIII with the metal does not result in elimination in the first stage XI of the reaction, the subsequent elimination would be expected not to be stereospecific.

Among the factors which might oppose a concerted elimination at stage XI, one of the more important is the nature of the leaving group X. The ease with which various groups are eliminated, by analogy with the behavior of various groups in nucleophilic displacement reactions, would be expected to decrease in the following order: X = Br and OTs > OCOR > OR and OH. In agreement with this hypothesis, the ratios of elimination rates for the reaction of the *cis*-(IIc) and *trans*-(IIa or IIb)-cyclohexene bromohydrin derivatives with zinc have varied with the group X in the following way: X = OTs, $k_{trans}/k_{cis} = 10$; X = OCOCH$_3$, $k_{trans}/k_{cis} = 2$; X = OH, $k_{trans}/k_{cis} = 1$.[3] Thus, the reaction of the halide VIII with a metal apparently receives little, if any, aid by the simultaneous formation of a carbon–carbon double bond and loss of the group X when X is an acyloxy, alkoxyl or hydroxyl group. If the reaction of the halide VIII with the metal to form XII or XIII were made energetically more favorable by use of a more reactive metal, then the elimination reaction would not be expected to occur as a concerted proc-

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[18] F. R. Mayo and C. Walling, *Chem. Revs.*, **27**, 351 (1940).

[19] F. D. Greene, W. A. Remers and J. W. Wilson, THIS JOURNAL, **79**, 1416 (1957). The possibility that the radical intermediate in this reaction undergoes elimination of the type X → IX followed by addition of bromine to the resultant olefin has not yet been rigorously excluded.

[20] E. Sorkin, W. Krähenbuhl and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 65 (1948).

[21] J. Hamonet, *Bull. soc. chim. France*, [3] **33**, 513 (1905).

[22] S. Sugasawa, *J. Pharm. Soc. Japan*, No. **545**, 551 (1927); *C. A.*, **21**, 3601 (1927).

[23] The results of these electrolyses are not conclusive evidence for the stability of radicals with β-alkoxyl substituents since the entire coupling process may occur before the radicals (or perhaps some other type of intermediate) have dissociated from the surface of the anode.

[24] L. C. Swallen and C. E. Boord, THIS JOURNAL, **52**, 651 (1930).

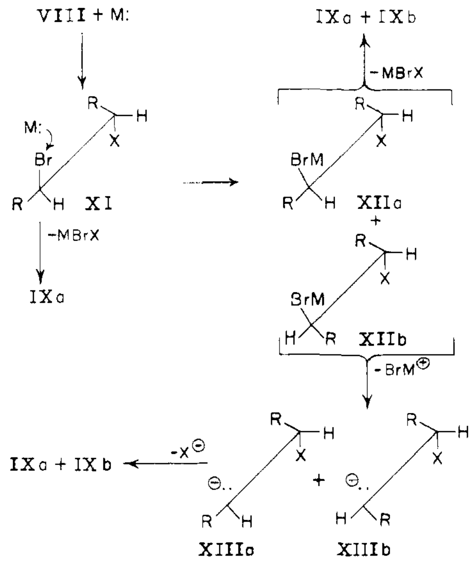
[25] R. Paul, *Bull. soc. chim. France*, [4] **53**, 421 (1933).

[26] M. Tallman, THIS JOURNAL, **56**, 126 (1934).

[27] R. Robinson and L. H. Smith, *J. Chem. Soc.*, 195 (1936).

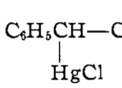
[28] For a survey of the attempts to produce optically active organometallic compounds and a description of the formation of an optically active organolithium compound, see R. L. Letsinger, THIS JOURNAL, **72**, 4842 (1950). The evidence currently available does not permit a reliable choice to be made among the possible mechanisms for the racemization of organometallic intermediates. Although the formation of the organometallic substance may well be accompanied by racemization (*e.g.*, as the result of intermediate radical formation as previously mentioned), we have tentatively adopted the viewpoint that the organometallic intermediate is formed with retention of configuration and undergoes subsequent racemization. This viewpoint appears to be more nearly consistent with the work of Letsinger and with the numerous observations that substituted vinyllithium compounds are formed from the corresponding halides with retention of configuration.

ess (*i.e.*, XI) even with a favorable leaving group X. This line of reasoning provides a convenient explanation for the non-stereospecific eliminations which have been observed when either halohydrin derivatives (Table I) or vicinal dibromides[9e] are treated with sodium. Another factor which would be expected to oppose a concerted elimination of the type XI is delocalization of the partial negative charge imposed on the carbon atom beta to the group X by attack of the metal on the halogen atom. Such delocalization of charge would be anticipated if the adjoining group R of structure XI was a phenyl, carbalkoxyl or keto group. A concerted elimination (*i.e.*, XI) would also be unfavorable if the groups R, which would be partially eclipsed in the transition state leading to *cis*-olefin,[29] were either large or repelled each other electrostatically.

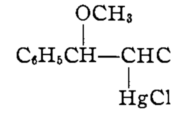


(3)

It will be noted in Table I that the reaction of the bromo ethers Va and VII with zinc produced olefin mixtures which contained a slight excess of the thermodynamically less stable *cis* isomer[30] while reaction of the same bromo ethers with sodium produced olefin mixtures richer in the *trans* isomer. A tempting explanation of these results postulates that the reactions with zinc involve elimination from the organometallic intermediates XII whereas the reactions with sodium form the carbanionic intermediates XIII (or perhaps as ion pairs) before elimination occurs. Such an explanation presumes that the size of the metal-containing substituent MBr is sufficiently great to favor structure XIIa,[30a] that equilibration of structures XIIa and XIIb has occurred before elimination and that the groups MBr and X are oriented *trans* to one another when elimination occurs. In regard to the elimination of the groups MBr and X from the organometallic intermediate XII, it is of interest that the stability of such intermediates apparently is enhanced greatly if the carbon–metal bond has little ionic character. For example, structures of the types XIV and XV could


$C_6H_5CH(HgCl)-CH(OCH_3)CH_3$

XIV


$C_6H_5CH(HgCl)-CH(OCH_3)CH_3$

XV

be isolated and apparently were not subject either to ready elimination or rapid epimerization.[31]

Experimental[32]

Preparation of the 2-Butene Derivatives V.—The 2,3-dibromobutanes (Vc) were prepared as previously described.[33-35] The *meso*-dibromide, b.p. 72° (50–51 mm.), n^{27}D 1.5080 [lit.[34] b.p. 73.2° (50 mm.), n^{25}D 1.5090] was shown by vapor-phase chromatographic analysis to contain less than 1% of the racemic isomer. The racemic dibromide, b.p. 76–77° (50 mm.), n^{27}D 1.5112 [lit.[34] b.p. 76.4° (50 mm.), n^{25}D 1.5125], was shown similarly to contain less than 1% of the *meso* isomer. The 2-bromo-3-hydroxybutanes were prepared and acetylated as previously described[34] except that the N-bromoacetamide used in the original preparation was replaced by N-bromosuccinimide.[36] The *erythro*-bromide acetate Vb, b.p. 61–62° (9 mm.), n^{27}D 1.4480 [lit.[34] b.p. 67.2° (13 mm.), n^{25}D 1.4489], was shown by vapor-phase chromatographic analysis to contain less than 1% of the *threo* isomer. In the case of the *threo*-bromo acetate Vb, b.p. 64° (8 mm.), n^{27}D 1.4478 [lit.[34] b.p. 70.1° (13 mm.), n^{25}D 1.4490], the vapor-phase chromatographic analysis was less valuable since the peak from the *erythro* isomer overlapped the front of the peak corresponding to the *threo* isomer. As a result the *threo* isomer could have contained up to 7% of the *erythro* isomer which would have gone undetected. The infrared spectra of the two samples were too similar to permit a more reliable estimate of the amount of the *erythro* isomer which was actually present.

The 2-bromo-3-methoxybutanes (Va) were prepared as previously described[37] except that the N-bromoacetamide used in the original preparation was replaced by N-bromosuccinimide. Since the *erythro* isomer, b.p. 67–69° (58–63 mm.), n^{27}D 1.4478 [lit.[37] 55.7–56.2° (40 mm.), n^{25}D 1.4483], and the *threo* isomer, b.p. 67–70° (69–73 mm.), n^{27}D 1.4464 [lit.[37] 55.6–55.7° (40 mm.), n^{25}D 1.4478], were not resolved by vapor-phase chromatography, alternate analytical methods were investigated. The infrared spectra of the two isomers were not sufficiently different to permit reliable estimates of purity. Consequently each bromo ether was treated with silver acetate in acetic acid and the resulting crude 2-acetoxy-3-methoxybutanes were saponified, the entire procedure being that previously employed by Winstein and Henderson.[37] The crude 2-hydroxy-3-methoxybutane samples produced from each of the bromo ethers Va were partially purified by distillation through a

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[29] For a discussion of this point see D. J. Cram, F. D. Greene and C. H. Depuy, THIS JOURNAL, **78**, 790 (1956).

[30] In the case of the 2-butenes the greater stability of the *trans* isomer has been established unequivocally by equilibration studies (ref. 20).

[30a] For a discussion of this point see D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 48–49 (1956).

[31] W. R. R. Park and G. F. Wright, *J. Org. Chem.*, **19**, 1435 (1954).

[32] All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined either with a Baird, model B, or a Perkin-Elmer, model 21, double beam infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, model 11 MS. The microanalyses were performed by Dr. S. M. Nagy and his associates. The vapor-phase chromatographic analyses were obtained with a 8 mm. × 215 cm. column packed either with di-(2-ethylhexyl) sebacate or with ethyl N,N-dimethyloxamate suspended on 50–80 mesh firebrick. The fractions from the chromatogram, eluted with helium, were detected with a thermal conductivity cell.

[33] W. G. Young, R. T. Dillon and H. J. Lucas, THIS JOURNAL, **51**, 2528 (1929).

[34] S. Winstein and H. J. Lucas, *ibid.*, **61**, 1576 (1939).

[35] The *cis*- and *trans*-2-butenes were purchased from Phillips Petroleum Co. as 99 mole % pure. The composition of the *trans* isomer was 95% *trans*-2-butene, 1% *cis*-2-butene and 4% 1-butene and isobutylene. The composition of the *cis* isomer was 85% *cis*-2-butene, 5% *trans*-2-butene and 10% 1-butene and isobutylene.

[36] C. O. Guss and R. Rosenthal, THIS JOURNAL, **77**, 2549 (1955).

[37] S. Winstein and R. B. Henderson, *ibid.*, **65**, 2196 (1943).

short-path still and then analyzed by vapor-phase chromatography. The lower boiling methoxy alcohol (previously assigned the *threo* configuration[37] obtained from the *threo*-bromo ether Va, was contaminated with 3% of the higher boiling diastereoisomer. The higher boiling methoxy alcohol (assigned the *erythro* configuration[37]), obtained from the *erythro* bromo ether Va, contained 15% of the lower boiling diastereoisomer. Consequently, the maximum contamination of either of the isomeric bromo ethers Va by the other diastereoisomer was 15%.

The 4-Bromo-5-methoxyoctanes (VI).—*cis*-4-Octene, b.p. 48° (62 mm.), $n^{27}\mathrm{D}$ 1.4117 [lit.[38a] b.p. 121.7° (739 mm.), $n^{25}\mathrm{D}$ 1.4113, $n^{20}\mathrm{D}$ 1.4151[38c]] and *trans*-4-octene, b.p. 48–48.5° (63 mm.), $n^{27}\mathrm{D}$ 1.4078 [lit.[38a] b.p. 121.4° (739 mm.), $n^{25}\mathrm{D}$ 1.4091, $n^{20}\mathrm{D}$ 1.4122[38c]] were prepared by the appropriate reductions of 4-octyne, b.p. 64° (73 mm.), $n^{24}\mathrm{D}$ 1.4222–1.4236 [lit.[38c] b.p. 85.1° (169 mm.), $n^{25}\mathrm{D}$ 1.4225] as previously described.[38a] Each of the olefin samples contained less than 2% of the other isomer. The infrared spectra[39,40] of the two olefin samples were consistent with these analytical results. The vapor-phase chromatograms of the isomer 4-octenes excluded the possibility that either isomer could have been contaminated with appreciable amounts of either *n*-octane or 4-octyne.

erythro-4-Bromo-5-methoxyoctane (VII) was prepared by stirring a mixture of 22.4 g. (0.2 mole) of *trans*-4-octene, 35.6 g. (0.2 mole) of N-bromosuccinimide, 3 drops of concentrated sulfuric acid and 128 g. (4 moles) of methanol for 30 min. at 0–5°. The *erythro*-bromo ether, isolated as described[37] for the 2-bromo-3-methoxybutanes, was collected at 50–50.5° (1 mm.), $n^{25}\mathrm{D}$ 1.4542, yield 32 g. (71%).

Anal. Calcd. for $C_9H_{19}BrO$: C, 48.43; H, 8.58; Br, 35.81. Found: C, 48.34; H, 8.44; Br, 35.93.

Similarly, 22.4 g. (0.2 mole) of *cis*-4-octene afforded 35 g. (78%) of *threo*-4-bromo-5-methoxyoctane, b.p. 47° (0.8 mm.), $n^{27}\mathrm{D}$ 1.4518.

Anal. Calcd. for $C_9H_{19}BrO$: C, 48.43; H, 8.58; Br, 35.81. Found: C, 48.20; H, 8.76; Br, 35.71.

Although the vapor-phase chromatograms of the two isomers established that neither isomer was contaminated with significant quantities of higher or lower boiling impurities, the two diastereoisomers were not resolved by this method. The infrared spectra[39,41] of the two samples established that the two products were not identical. The spectrum[41] of the *erythro*-isomer has bands at 965 and 930 cm.$^{-1}$ which are not present in the spectrum of *threo* isomer and the spectrum[41] of the *threo* isomer has bands at 950, 920 and 705 cm.$^{-1}$ not present in the spectrum of the *erythro* isomer. Unfortunately, an accurate estimate of the amount of diastereoisomeric contamination in each sample was not possible.

The 1-Bromo-1,2-diphenyl-2-methoxyethanes (VII).—A solution of 1.80 g. (0.01 mole) of *cis*-stilbene [b.p. 94–102° (1 mm.), $n^{25}\mathrm{D}$ 1.6193], 3.56 g. (0.02 mole) of N-bromosuccinimide, 1 ml. of acetic acid and 10 ml. of acetone in 100 ml. of methanol was allowed to stand for 2.5 hr. and then concentrated, diluted with water and extracted with ether. The ether extract was washed first with water and then with aqueous sodium bicarbonate solution and then dried over magnesium sulfate and concentrated. A solution of the residual oil in petroleum ether deposited the crude bromo ether. Recrystallization afforded 2.0 g. (69%) of *threo*-1-bromo-1,2-diphenyl-2-methoxyethane as white plates, m.p. 85.5–87.5°. An additional recrystallization sharpened the melting point to 86–87.5°.

Anal. Calcd. for $C_{15}H_{15}BrO$: C, 61.86; H, 5.19; Br, 27.45. Found: C, 61.61; H, 5.18; Br, 27.60.

Similarly 1.80 g. (0.01 mole) of *trans*-stilbene afforded 2.1 g. (72%) of *erythro*-1-bromo-1,2-diphenyl-2-methoxyethane as white prisms, m.p. 116–118°. An additional crystallization from pentane sharpened the melting point to 117–118° (lit.[42] 115–116°).

Anal. Calcd. for $C_{15}H_{15}BrO$: C, 61.86; H, 5.19; Br, 27.45. Found: C, 61.97; H, 5.50; Br, 27.61.

The infrared spectra[39] of the two isomers differ only in the presence of a band at 1215 cm.$^{-1}$ in the spectrum of the *threo* isomer which is absent in the spectrum of the *erythro* isomer.

Reaction of the 2-Butene Derivatives V with Metals. A. Reaction with Zinc.—A mixture of 0.01 mole of the 2-butene derivative, 2.6 g. (0.04 gram-atom) of zinc powder (Mallinckrodt, analytical reagent) 10 ml. of ethanol and 1 ml. of water was boiled under reflux with stirring for the specified reaction time (Table I). In the case of the dibromides Vc the reaction mixtures were cooled to −10° before the zinc was added to avoid the loss of gaseous products accompanying the vigorous reaction which occurred when the reactants were mixed at room temperature. The gaseous reaction products, entrained in a slow stream of nitrogen, were passed first through a trap cooled in ice, then through a tube packed with Drierite and finally collected in a trap cooled in a Dry Ice-acetone-bath. The cold trap containing the butene mixture was connected to gas buret, evacuated and then allowed to warm to room temperature. The total volume of the gaseous products was measured and then the gas mixtures in the trap and the gas buret were allowed to mix until the composition of the gas samples in the trap and the gas buret were the same.[43] The butene analyses (Table I) were obtained at room temperature with a vapor-phase chromatographic column packed with ethyl N,N-dimethyloxamate on ground firebrick. Neither 1-butene or isobutylene could be detected in the products analyzed. Since the experimentally determined response factor for *cis*- and *trans*-2-butene was found to be 1.00, the relative peak areas from the chromatograms served as a direct measure of the composition of the 2-butene mixtures. For the purpose of yield calculations, the 2-butenes were assumed to behave as ideal gases.

In another experiment a mixture of 3 g. (0.015 mole) of *erythro*-2-acetoxy-3-bromobutane, 7.8 g. (0.12 gram-atom) of zinc powder, 30 ml. of ethanol and 3 ml. of water was boiled with stirring for 10 min., cooled, filtered, diluted with water and extracted with ether. After the ether extract had been dried over magnesium sulfate, the ether was removed by distillation through a 6-ft. Vigreux column. The residual oil, analyzed by vapor-phase chromatography, was found to contain ether and the unchanged *erythro*-bromoacetate Vb (1.5 g. or 50% recovery). The recovered *erythro*-bromoacetate contained less than 1% of the *threo* isomer.

B. **Reaction with Sodium.**—A mixture of 0.01 mole of the bromo ether, 1 g. (0.04 gram-atom) of sodium (cut into small pieces) and 10 ml. of tetrahydrofuran (distilled from sodium) was boiled under reflux for the specified time (Table I). The 2-butene mixtures were collected and analyzed (Table I) as previously described.

Reaction of the 4-Bromo-5-methoxyoctanes with Metals. A. Reaction with Zinc.—A mixture of 9 g. (0.04 mole) of the bromo ether, 5.2 g. (0.08 gram-atom) of zinc powder, 40 ml. of ethanol and 4 ml. of water was boiled under reflux with stirring for 3 hr., filtered, diluted with 300 ml. of water and extracted with three 150-ml. portions of ether. After the extracts had been dried over magnesium sulfate, the ether was removed by distillation through a 6-ft. Vigreux column (no 4-octene could be detected in the ether). The vapor-phase chromatograms of the residues in each instance indicated the presence of ether, *cis*- and *trans*-4-octene and the unchanged bromo ether. The olefinic products were isolated by distillation, the products being collected in the range 43–49° (53–62 mm.), and analyzed at 60° with the same vapor-phase chromatographic column used for the 2-butene analyses. The experimentally determined response factor (*i.e.*, area of *cis*-4-octene peak/area of *trans*-4-octene peak for an equimolar mixture) was 1.045. The percentage compositions reported in Table I are corrected for this factor. In two instances the 4-octene analyses obtained (Table I) were checked by an independent analytical method based on the infrared spectra[40] of the 4-octene mixtures. The higher-boiling material isolated from each

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[38] (a) K. N. Campbell and L. T. Eby, THIS JOURNAL, **63**, 216 (1941); (b) E. A. Bried and G. F. Hennion, *ibid.*, **59**, 1310 (1937); (c) M. C. Hoff, K. W. Greenlee and C. E. Boord, *ibid.*, **73**, 3329 (1951).

[39] Determined in carbon tetrachloride solution.

[40] Determined in carbon disulfide solution.

[41] Determined as a pure liquid.

[42] (a) E. L. Jackson, THIS JOURNAL, **48**, 2166 (1926). The product prepared in this study apparently was contaminated with 1,2-dimethoxy-1,2-diphenylethane. (b) P. D. Bartlett and D. S. Tarbell, *ibid.*, **58**, 466 (1936).

[43] A period of about 12 hr. usually was required for complete mixing. This procedure was found to be very important since the initial compositions of gas samples in the trap and the gas buret frequently differed by more than 10%.

reaction mixture was shown to be the unchanged bromo ether by comparison of both the vapor-phase chromatograms and the infrared spectra[41] of the samples. In each instance the infrared spectra of the pure bromo ether and the recovered sample were superimposable, indicating that significant epimerization of the bromo ether had not occurred.

In subsequent experiments, where no bromo ether was recovered, mixtures of 4.5 g. (0.02 mole) of the bromo ether, 5.2 g. (0.08 gram-atom) of zinc powder, 20 ml. of ethanol and 2 ml. of water were refluxed with stirring for 6 hr. The octene mixtures were isolated and analyzed as previously described.

B. **Reaction with Sodium.**—Mixtures of 4.5 g. (0.02 mole) of the bromo ether, 1 g. (0.04 gram-atom) of sodium (cut into small pieces) and 20 ml. of tetrahydrofuran (distilled from sodium) were refluxed with stirring for 6 hr., filtered and distilled. The 4-octene mixtures were collected and analyzed as previously described. A small forerun obtained in each distillation consisted of a mixture of the 4-octenes (not included in the yield reported) and tetrahydrofuran. Since the composition of the olefin mixtures in the foreruns was essentially the same (within ±1%) as the composition of the olefin mixtures isolated, no error in olefin composition was introduced by this procedure.

Reaction of the 1-Bromo-1,2-diphenyl-2-methoxyethanes with Zinc.—Mixtures of 291 mg. (0.001 mole) of the bromo ether, 654 mg. (0.01 gram-atom) of zinc powder, 24 ml. of ethanol and 1 ml. of water were refluxed with stirring for the specified times (Table I), poured into aqueous ammonium chloride and extracted with ether. After the ether extract had been dried over magnesium sulfate and concentrated, a solution of the residue in petroleum ether was chromatographed on Merck acid-washed alumina. The hydrocarbon fractions, eluted with petroleum ether, were combined and the infrared spectrum[39] of the crude product was determined. These spectra were compared with spectra[39] of *cis*- and *trans*-stilbene which have distinctive bands at 920 and 965 cm.$^{-1}$, respectively. In no case could *cis*-stilbene be detected in the product; the maximum amount of *cis*-stilbene which would escape detection by this method was estimated to be 4%. The olefin yields reported in Table I represent the amount of crude *trans*-stilbene, melting within the range 117–124°, which was isolated from each hydrocarbon fraction. The later fractions from the chromatogram proved to be oils. In one reaction of the *erythro*-bromo ether VII (Table I) a small amount of the crude *erythro*-bromo ether VII, m.p. 110–117°, was recovered. Also, in one reaction of the *threo*-bromo ether the infrared spectrum of the crude oil from the later fractions of the chromatogram was obtained. No *cis*-stilbene could be detected in the oil whose spectrum would be consistent with presence of the *erythro*-bromo ether VII. Thus, the possibility that partial epimerization of the bromo ethers VII occurs prior to elimination is not excluded.

As a control experiment to establish that *cis*-stilbene is not isomerized to *trans*-stilbene under the conditions of the reaction, a mixture of 180 mg. (0.001 mole) of *cis*-stilbene, 167 mg. (0.001 mole) of *threo*-2-bromo-3-methoxybutane, 654 mg. (0.01 gram-atom) of zinc powder, 24 ml. of ethanol and 1 ml. of water was refluxed for 70.5 hr. and worked up as described above. The infrared spectrum[39] of crude hydrocarbon fraction (242 mg.) from the chromatogram was very similar to the spectrum of *cis*-stilbene. The maximum amount of *trans*-stilbene which could have been present in the mixture was estimated to be 2%.

CAMBRIDGE 39, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE FLORIDA STATE UNIVERSITY]

Chemical Effects of the Trifluoromethyl Group.[1,2] V. Reactions of Ethyl β-Trifluoromethylglycidate; the Synthesis of 2-Amino-3-hydroxy-4,4,4-trifluorobutyric Acid

BY H. M. WALBORSKY AND M. E. BAUM

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2-Amino-3-hydroxy-4,4,4-trifluorobutyric acid (III) was synthesized by reducing the phenylhydrazone of 2-keto-3-hydroxy-4,4,4-trifluorobutyric acid (II). Ammonolysis of ethyl β-trifluoromethylglycidate (VI) gave as the sole product the amide of III. This is in direct contrast to the products obtained by ammonolysis of other glycidic ester derivatives. This reversal of ring opening is due to the strong electron-withdrawing power of the CF_3 group. $LiAlH_4$ reduction of VI did not lead to a mixture of glycols but yielded exclusively 4,4,4-trifluorobutan-1,3-diol.

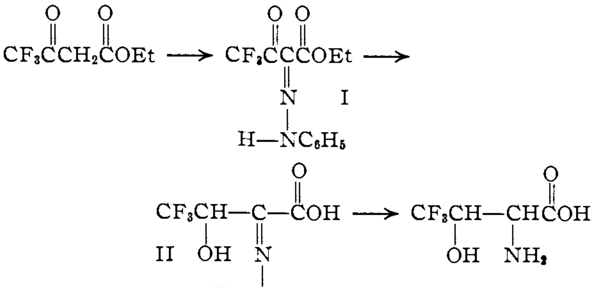
Introduction

Because of the potential antimetabolic activity[3] of amino acids containing the CF_3 group a number of these acids have been prepared.[2–4] In the course of their syntheses some unique chemical effects attributable to the CF_3 group have been observed and discussed.[2–4]

In continuation of these studies the synthesis of the CF_3 analog of threonine has been attempted. Owing to the strong electron-withdrawing power of the CF_3 group, the preparation of 2-amino-3-hydroxy-4,4,4-trifluorobutyric acid (III) by ammonolysis of ethyl β-trifluoromethylglycidate was made possible. In the present paper, the synthesis of III is described and the effect of the CF_3 group is discussed.

Results and Discussion

Syntheses of 2-Amino-3-hydroxy-4,4,4-trifluorobutyric Acid (III). Method A.—Ethyl trifluoroacetoacetate was diazotized with benzenediazonium chloride in 62% yield. The crude material contained a small amount of red impurity



$$CF_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt \longrightarrow CF_3\overset{O}{\overset{\|}{C}}\underset{NHC_6H_5}{\underset{\|}{\underset{N}{C}}}\overset{O}{\overset{\|}{C}}OEt \ (\mathrm{I}) \longrightarrow$$

$$(\mathrm{II})\ CF_3\underset{OH}{\underset{|}{C}H}-\underset{NHC_6H_5}{\underset{\|}{\underset{N}{C}}}-\overset{O}{\overset{\|}{C}}OH \longrightarrow CF_3\underset{OH}{\underset{|}{C}H}-\underset{NH_2}{\underset{|}{C}H}\overset{O}{\overset{\|}{C}}OH\ (\mathrm{III})$$

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[2] (a) Presented in part before the Division of Organic Chemistry at the 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956; (b) Paper IV of this series: H. M. Walborsky and J. Lang, THIS JOURNAL, **78**, 4314 (1956).

[3] H. M. Walborsky, M. Baum and D. F. Loncrini, *ibid.*, **77**, 3637 (1955).

[4] H. M. Walborsky and M. Schwarz, *ibid.*, **75**, 3241 (1953); H. M. Walborsky and M. E. Baum, *J. Org. Chem.*, **21**, 538 (1956).