[Contribution from the Research Laboratories, Chemical Division, Merck & Co., Inc.]

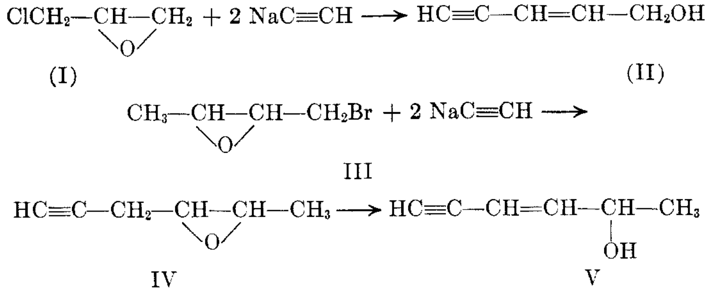
The Reaction of Epihalohydrins with Sodium Acetylide

CLAUDE F. HISKEY,* H. L. SLATES, AND N. L. WENDLER

Received December 19, 1955

3-Bromo-1,2-epoxybutane was converted by sodium acetylide in liquid ammonia to the same hex-3-en-5-yn-2-ol (V) as that previously obtained from the action of this reagent on 1-bromo-2,3-epoxybutane.[1] The apparent failure of configurational retention in the reductive removal of vinylic halogen in a system possessing a neighboring hydroxyl function was observed.

In 1947 Haynes, Heilbron, Jones, and Sondheimer[1] made the interesting observation that epichlorohydrin (I) was converted by sodium acetylide in liquid ammonia to pent-2-en-5-yn-1-ol (II). These authors further observed that 1-bromo-2,3-epoxybutane (III) with the same reagent gave hex-3-en-5-yn-2-ol (V). It was concluded therefrom that the initial phase of these reactions consists in substitution at the halogen-bearing center followed by eliminative opening of an intermediate ethynyl oxide (*e.g.*, IV) thus,

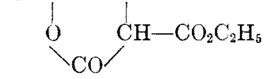


$$\underset{\text{(I)}}{\mathrm{ClCH_2{-}\underset{\diagdown O \diagup}{CH{-}CH_2}}} + 2\,\mathrm{NaC{\equiv}CH} \longrightarrow \underset{\text{(II)}}{\mathrm{HC{\equiv}C{-}CH{=}CH{-}CH_2OH}}$$

$$\underset{\text{III}}{\mathrm{CH_3{-}\underset{\diagdown O \diagup}{CH{-}CH}{-}CH_2Br}} + 2\,\mathrm{NaC{\equiv}CH} \longrightarrow$$

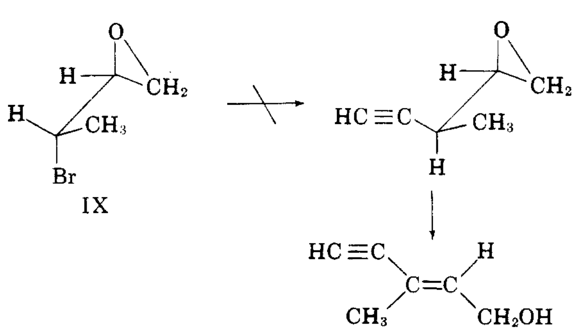
$$\underset{\text{IV}}{\mathrm{HC{\equiv}C{-}CH_2{-}\underset{\diagdown O \diagup}{CH{-}CH}{-}CH_3}} \longrightarrow \underset{\text{V}}{\mathrm{HC{\equiv}C{-}CH{=}CH{-}\underset{OH}{\underset{|}{CH}}{-}CH_3}}$$

These observations by themselves suggested that *threo*-3-bromo-1,2-epoxybutane (IX), obtained by stereoselective bromination and dehydrobromination of *trans*-crotyl alcohol (VI) (see below), should provide a stereospecific route to *trans*-3-methylpent-2-en-4-yn-1-ol (XVII), an important intermediate[2] in the synthesis of vitamin A. Despite the attractiveness of this approach to the synthesis of XVII there appeared to be reasons for doubting the generality of the interpretation proposed by the English authors[1] for this reaction type. In particular may be cited the established course of reaction of sodio-malonic ester with epichlorohydrin (I) to give the chlorolactonic ester (XVIII).[3] These reservations were eventually substantiated from the observation that *threo* 3-bromo-1,2-epoxybutane (IX) on reaction with sodium acetylide in liquid ammonia affords, in fact, one and the same hex-3-en-5-yn-2-ol as had been obtained under the same conditions from the isomeric 1-bromo-2,3-epoxybutane (III) by Haynes, Heilbron, Jones, and Sondheimer.[1] It therefore appears indicated that initial attack by acetylide ion on epihalohydrins is not restricted to the halogen-bearing center but instead is controlled by steric requirements and originates at the least substituted functional position.[4]



$$\mathrm{Cl{-}CH_2{-}\underset{\begin{array}{c}|\\ O\quad CH{-}CO_2C_2H_5\\ \diagdown CO \diagup\end{array}}{CH{-}CH_2}}$$

XVIII



IX

XVII

trans-Crotyl alcohol (VI) was prepared by the reduction of crotonaldehyde with lithium aluminum hydride[5] and brominated according to the method of Charon[6] to afford crystalline 2,3-dibrombutanol-1 (VIII).

---

*Present Address: 605 So. Irving Blvd., Los Angeles, Calif.

(1) J. Haynes, I. Heilbron, E. R. H. Jones, and F. Sondheimer, *J. Chem. Soc.*, 1583 (1947).

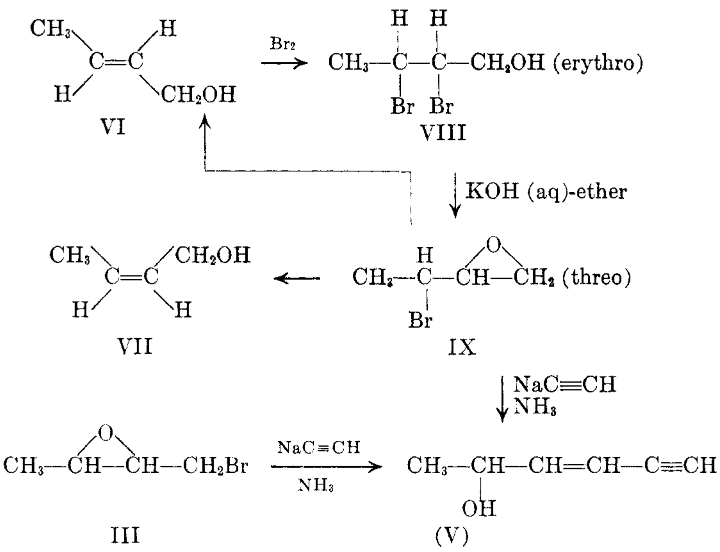
(2) O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947).

(3) H. Leuchs, *Ber.*, **38**, 1937 (1905).

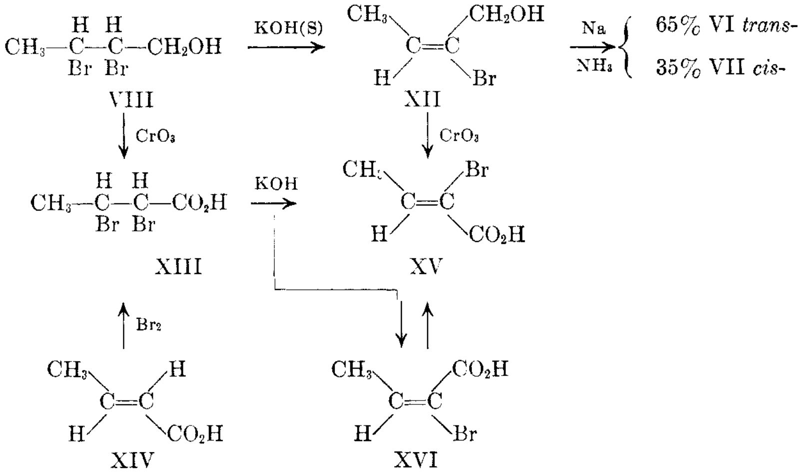
(4) After this work had been completed an article appeared by R. C. Waters and C. A. van der Werf [*J. Am. Chem. Soc.*, **76**, 709 (1954)] in which these authors independently arrived at similar conclusions based on the observed reaction course of 3-bromo-1,2-epoxybutane and 1-bromo-2,3-epoxybutane with sodium methoxide in methanol.

(5) (a) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 1197 (1947); (b) L. Hatch and S. S. Nesbitt, *J. Am. Chem. Soc.*, **72**, 727 (1950).

(6) E. Charon, *Ann. chim.*, [7], **17**, 226 (1889).



Treatment of the dibromo alcohol VIII in ether solution with an equivalent of normal alkali converted it smoothly and in excellent yield to 3-bromo-1,2-epoxybutane (IX). The latter had previously been converted by Petrov[7] to 1-bromo-2,3-epoxybutane (III). The latter substance in turn afforded the eneynol V on reaction with sodium acetylide in liquid ammonia.[1] The formation of IX from VIII by inversion at C_2 leads to the *threo* structure for the epoxide, a conclusion independently reached by Waters and van der Werf.[4] Treatment of IX with sodium-potassium alloy led to a mixture of *cis* and *trans* crotyl alcohols VI and VII.



The reaction of 3-bromo-1,2-epoxybutane (IX) with 2 moles of sodium acetylide in liquid ammonia produced hex-3-en-4-yn-2-ol (V) identified by its absorption at 222 mμ (log ε 3.99) and its nonidentity with either the *cis* or *trans* isomers of 3-methylpent-3-en-4-yn-1-ol (XVII).[8] Compound V formed a crystalline α-naphthyl urethan, m.p. 83–84.5°, corresponding to the reported value.[1] This substance was further characterized by hydrogenation to hexanol-2 identified by comparison of its α-naphthyl urethan derivative (m.p. 59.5–61°) with an authentic sample.

In contrast to the observations of Petrov,[7] treatment of the dibromobutanol (VIII) in ether solution with solid potassium hydroxide gave little or no 3-bromo-1,2-epoxybutane (IX) but instead yielded an unsaturated bromo alcohol. The latter was shown to be 2-bromobut-2-en-1-ol (XII) by chromic acid oxidation to *trans*-α-bromocrotonic acid (XV), identical with material prepared from successive oxidation and dehydrobromination of VIII as well as from the bromination-dehydrobromination of crotonic acid (XIV) itself.[9] The latter sequence con-

---

[7] A. A. Petrov, *J. Gen. Chem. U.S.S.R.*, **11**, 713 (1941); *Chem. Abstr.*, **36**, 404 (1942); *Chem. Z.*, **I**, 2865 (1942) flash-distilled dibrombutanol of unknown stereochemical purity from potassium hydroxide and obtained 3-bromo-1,2-epoxybutane.

[8] The authors are indebted to Dr. P. I. Pollak of these Laboratories for making available authentic specimens of cis- and *trans*-3-methylpent-3-en-4-yn-1-ol for comparison purposes.

[9] T. C. James, *J. Chem. Soc.*, 1565 (1910); A. Michael, *J. prakt. Chem.*, **46**, 260, 273, 403, (1892); A. Michael and O. Schulthess, *J. prakt. Chem.*, **43**, 587 (1891).

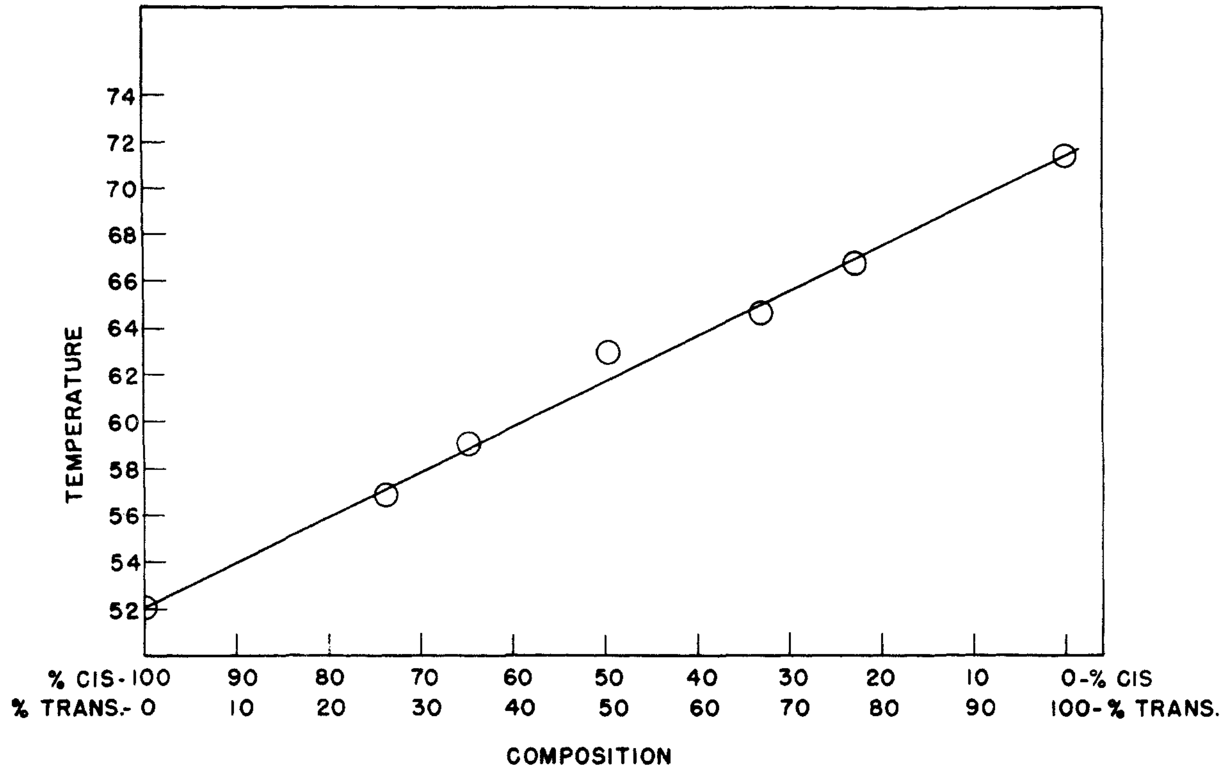
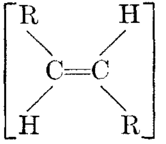


FIG. 1.—MELTING POINT-COMPOSITION DIAGRAM FOR *cis*- AND *trans*-CROTYL ALCOHOL 3,5-DINITROBENZOATES.

firms the *erythro* configuration for the dibromobutanol (VIII) as independently reported by Waters and van der Werf[4] and also establishes the position of the halogen in the unsaturated bromo alcohol XII. The latter was adjudged to be of a high degree of stereochemical homogeneity in as much as it formed a sharp-melting 3,5-dinitrobenzoate derivative in high yield, under conditions whereby both *cis* and *trans*-crotyl alcohol formed their respective 3,5-dinitrobenzoate derivatives without attending isomerization.

If it be assumed that the conversion of *erythro*-VIII → XII proceeds by normal *trans*-elimination then it follows that XII should possess the structure of *cis*-2-bromobut-2-en-1-ol as formulated. The fact that oxidation of XII gives rise to *trans*-α-bromocrotonic acid (XV) is not surprising in view of the fact that *cis*-α-bromocrotonic acid (XVI) is itself converted quantitatively to the *trans* isomer (XV) under the oxidizing conditions.

In order to secure chemical support for the geometry of XII, this substance was reductively dehalogenated with sodium in liquid ammonia by the method of Hoff, Greenlee, and Boord.[9] These authors have shown that vinylic halo-alkenes are reductively dehalogenated with sodium in liquid ammonia to give olefins possessing a high degree of retention of configuration. The product obtained from XII under these conditions, however, consisted of a 2:1 mixture of *trans*- and *cis*- crotyl alcohols. The product composition was determined from the melting point of the 3,5-dinitrobenzoate derivative relative to the melting point diagram (Fig. 1) prepared from pure *cis*-crotyl alcohol 3,5-dinitrobenzoate (m.p. 50–51°) and *trans*-crotyl alcohol 3,5-dinitrobenzoate (m.p. 70–71°). *cis*-Crotyl alcohol[10] as well as *trans*-crotyl alcohol were both recovered essentially unchanged on treatment with sodium in liquid ammonia under the conditions of the dehalogenation. Further, the x-ray powder diagram of the 3,5-dinitrobenzoate derivative of the sodium-liquid ammonia debromination product was identical with that of a 2:1 synthetic mixture of the 3,5-dinitrobenzoate derivatives of *cis* and *trans*-crotyl alcohol respectively. Although it was not possible to secure chemical corroboration for the *cis*-character of XII, in view of the apparent homogeneity of XII (see above) the formation of a mixed butenol product by the action of sodium in liquid ammonia attests to the absence of stereochemical retention of configuration in the reductive dehalogenation of this substance.

It was of interest to observe that the infrared spectra of both *cis* and *trans* crotyl alcohol exhibit an intense band at *ca.* 10.3 μ (Figs. 2 and 3). This band position has been associated with the C—H bending of a *trans*-disubstituted olefin linkage  and has been employed as such

---

(9) M. C. Hoff, K. W. Greenlee, and C. E. Boord, *J. Am. Chem. Soc.*, **73**, 3329 (1951).

(10) Prepared according to the method of L. F. Hatch and S. S. Nesbitt, ref. 5b.

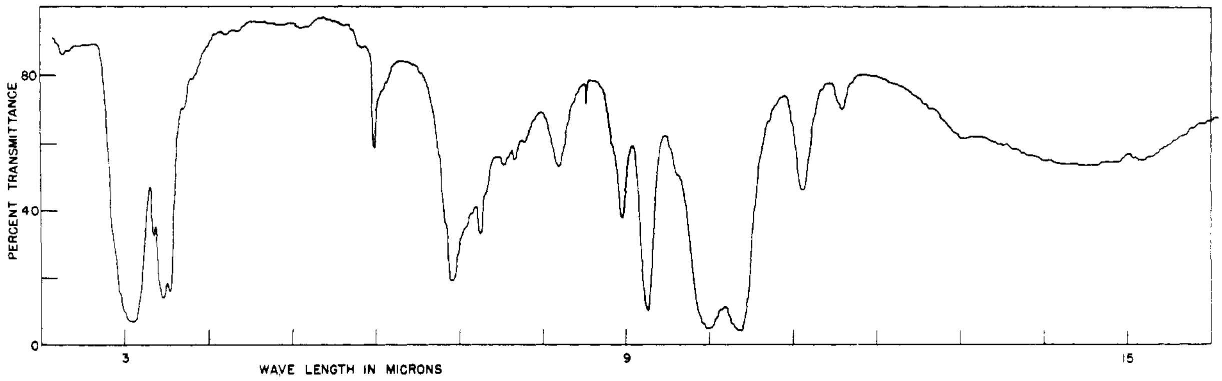


FIG. 2.—INFRARED SPECTRUM OF *trans*-CROTYL ALCOHOL.

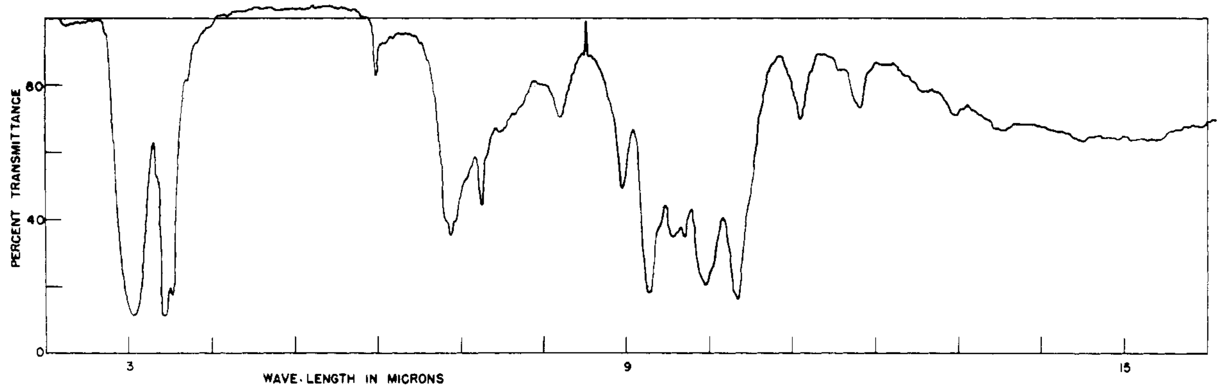


FIG. 3.—INFRARED SPECTRUM OF *cis*-CROTYL ALCOHOL.

for configurational assignment.[11] The occurrence of this band in both *cis* and *trans* crotyl alcohols suggests an interesting structure limitation on the use of this band position as a configurational diagnostic.

Acknowledgment. The authors are indebted to Mr. Fred Bacher for the X-ray powder diagram and melting point diagram determinations. We are also grateful to Messrs. Walker and Trenner for infrared data and R. N. Boos for analyses.

EXPERIMENTAL

trans-Crotyl alcohol (VI) was prepared by the reduction of crotonaldehyde (Eastman, b.p. 100–102°) with lithium aluminum hydride.[5a,5b] The alcohol gave the following constants: b.p. 120–121°; n_D^{24} 1.4270; *3,5-dinitrobenzoate,* m.p. 71°; (Reported: b.p. 121.2°; n_D^{25} 1.4262; m.p. 70°). Infrared spectrum, Fig. 2.

cis-Crotyl alcohol (VII) was prepared according to Hatch,[5b] b.p. 60–61° at 60 mm.; n_D^{24} 1.4343; *3,5-dinitrobenzoate,* m.p. 50.5–51.5°. Infrared spectrum, Fig. 3.

2,3-Dibromobutan-1-ol (VIII). Bromination of *trans*-crotyl alcohol in chloroform[6] gave an 85% yield of 2,3-dibromobutan-1-ol, b.p. 70° at 3 mm.; n_D^{24} 1.5434 and m.p. 32–33° after recrystallization from petroleum ether.

3-Bromo-1,2-epoxybutane (IX). A solution of 116 g. (0.5 mole) of 2,3-dibromobutanol-1 in 250 ml. of ether was shaken at room temperature for 2 hours with 300 ml. of 1.707 *N* potassium hydroxide. The ether layer was separated, washed to neutrality with water, and dried over magnesium sulfate. Distillation afforded 62.2 g. (82.5%) of 3-bromo-1,2-epoxybutane, b.p. 81–82° at 70 mm.; n_D^{25} 1.4731.

Anal. Calc'd for C_4H_7BrO: C, 31.81; H, 4.67; Br, 52.92. Found: C, 31.81; H, 4.70; Br, 52.89.

The infrared spectrum showed no hydroxyl absorption.

Hex-3-en-5-yn-2-ol (V). To a stirred suspension of sodium acetylide, prepared from 21.6 g. (0.94 mole) of sodium, in 550 ml. of ammonia cooled in a Dry Ice-ethanol bath (nitrogen atmosphere) was added dropwise over a period of 0.5 hour 67.9 g. (0.45 mole) of 3-bromo-1,2-epoxybutane. The reaction mixture was stirred for 22 hours. During the last half of this period the ammonia was allowed to reflux. Ammonium chloride (51 g.) was added and the ammonia was allowed to evaporate. The residue was slurried with ether, and the ether was decanted. The residue was dissolved in water and extracted three times with ether. The combined ether solutions were washed with 2 *N* sulfuric acid, water, and dried over magnesium sulfate. Distillation gave 9.61 g. (22.2%) of hex-3-en-5-yn-2-ol as a colorless liquid, b.p. 38–40° at 3–4 mm., n_D^{25} 1.4770, λ_{max} 222 mμ, log ϵ 3.99.

α-Naphthyl urethan. Crystallization from ligroin gave prisms of m.p. 83–84.5° (Reported[1] m.p. 83–84°).

Anal. Calc'd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.66; H, 5.94; N, 5.02.

Hydrogenation of hex-3-en-5-yn-2-ol. On reduction over platinum in ethanol hex-3-en-5-yn-2-ol (1.0 g.) absorbed 2.7 equivalents of hydrogen and afforded after distillation 0.45 g. of hexanol-2, identified as its α-naphthyl urethan, m.p. 59.5–61°, undepressed on admixture with an authentic sample.

Oxidation of 2,3-dibromobutan-1-ol (VIII). Solutions of 2,3-dibromobutan-1-ol (2.32 g., 0.01 mole) in 20 ml. of acetic acid and chromic acid (1.36 g., 0.013 mole) in 10 ml. of 90% acetic acid were combined with external cooling and

---

[11] See for example S. J. Rhoads, R. Raulins, and R. Reynolds, *J. Am. Chem. Soc.*, **76**, 3456 (1954); W. Oroshink, G. Karmas, and R. A. Mallory, *J. Am. Chem. Soc.*, **76**, 2375 (1954).

allowed to stand at room temperature for 20 hours. Methanol (1 ml.) was added and the solvents were removed *in vacuo* below 45°. The residue was dissolved in ether, washed with water, dried, and the solvent was evaporated. The residue was an oil which slowly crystallized on cooling. Two crystallizations from petroleum ether gave 2,3-dibromobutyric acid, m.p. 87–88°, no depression on admixture with an authentic sample prepared by bromination of crotonic acid (XIV).

2-Bromobut-2-en-1-ol (XII). To a vigorously stirred suspension of 95 g. (1.7 moles) of powdered potassium hydroxide in 100 ml. of ether in an atmosphere of nitrogen there was added at a rate to maintain gentle refluxing 131 g. (0.57 mole) of 2,3-dibromobutan-1-ol diluted to 250 ml. with ether. The orange reaction mixture then was refluxed for 2 hours. The salts were filtered off and washed with ether. The combined ether solutions were washed to neutrality with water, dried, and distilled through a 7-inch Widmer column. There was obtained 15.9 g. of 3-bromo-1,2-epoxybutane, b.p. 80–82° at 55 mm., and 38.6 g. of the desired 2-bromobut-2-en-1-ol, b.p. 102–103° at 53 mm. Redistillation gave material, b.p. 98° at 47 mm.; n^{25}_{D} 1.5803.

Anal. Calc'd for C_4H_7BrO: C, 31.81; H, 4.67; Br, 52.92. Found: C, 31.90; H, 4.55; Br, 53.09.

The compound gave a yellow color with tetranitromethane and did not give a precipitate with alcoholic silver nitrate; its infrared spectrum showed hydroxyl absorption at 3.40 μ and double bond absorption at 6.06 μ.

The 3,5-dinitrobenzoate, prepared from 0.25 g. of XII, was obtained in quantitative yield, m.p. 95–97°. Recrystallization from aqueous acetone afforded 0.37 g. (91%), m.p. 96–98°. Further crystallization did not alter the melting point.

Anal. Calc'd for $C_{11}H_9BrN_2O_6$: N, 8.12; Br, 23.16. Found: N, 8.01; Br, 23.30.

Oxidation of 2-bromobut-2-en-1-ol (XII). 2-Bromobut-2-en-1-ol (1.51 g., 0.01 mole), was oxidized with chromic acid in acetic acid as described above. The acid material was isolated by extraction of the ether solution with 5% sodium carbonate solution. Two crystallizations of the acidic fraction (0.30 g.) yielded α-bromocrotonic acid (XV) m.p. 106–107°, undepressed on admixture with an authentic sample.[8]

Isomerization of α-bromoisocrotonic acid (XVI). α-Bromoisocrotonic acid (m.p. 91–92°), 0.84 g., was treated with chromic acid (0.10 g.) in acetic acid as described in the above oxidation. There was obtained 0.42 g. of α-bromocrotonic acid (XV) as needles from water, m.p. and m.m.p. 106–107°.

Reaction of 2-bromobut-2-en-1-ol (XII) *with sodium in liquid ammonia.* To a stirred solution of 27.6 g. (1.2 moles) of sodium in 400 ml. of liquid ammonia cooled in a Dry Ice-acetone bath was added over a period of 10 minutes 30.2 g. (0.2 mole) of the unsaturated bromo alcohol (XII) in 25 ml. of ether. The mixture was stirred for 1 hour and the excess sodium was decomposed by addition of ammonium chloride. Ether (250 ml.) was added and the ammonia was evaporated with the addition of fresh ether to maintain a constant volume. Water then was added and the aqueous phase was separated and extracted twice with ether. The combined ether solutions were washed to neutrality with 2 *N* sulfuric acid, 5% sodium bicarbonate, and water. Distillation of the dried solution gave 4.37 g. of a crotyl alcohol mixture,[12] b.p. 118–120°, n^{25}_{D} 1.4250.

The 3,5-dinitrobenzoate was prepared and crystallized from ether-petroleum ether, m.p. 64–67°. This material corresponds to *ca.* a 33% *cis*- and 67% *trans*-crotyl alcohol 3,5-dinitrobenzoate mixture from the melting point data (Fig. 1).

Reaction of 3-bromo-1,2-epoxybutane with sodium-potassium alloy.[13] To a stirred mixture of the alloy, prepared from 4.6 g. of sodium and 3.9 g. of potassium, in 50 ml. of ether was added dropwise 22.6 g. (0.15 mole) of 3-bromo-1,2-epoxybutane in 50 ml. of ether over a period of 2 hours. The dark blue reaction mixture was stirred an additional 30 minutes at room temperature, then cooled to 0° prior to the cautious addition of water. The ether layer was separated, washed with water, 2 *N* sulfuric acid, 5% sodium bicarbonate, and a saturated sodium chloride solution. After drying and distillation there was obtained 6.3 g. of a crotyl alcohol fraction, b.p. 121–122°, n^{25}_{D} 1.4277.

The 3,5-dinitrobenzoate was prepared and was crystallized from ether-petroleum ether, m.p. 58–61°.

Anal. Calc'd for $C_{11}H_{10}N_2O_6$: C, 49.63; H, 3.79; N, 10.53. Found: C, 50.22; H, 3.86; N, 10.96.

From the m.p.-composition diagram (Fig. 1) this material corresponds to *ca.* 65% *cis*- and 35% *trans*-crotyl alcohol 3,5-dinitrobenzoate. X-ray diffraction patterns of the derivative m.p. 58–61°, and a synthetic mixture consisting of 65% *cis* and 35% *trans* derivative were essentially identical.[14]

Treatment of 3-bromo-1,2-epoxybutane (IX) *with powdered potassium hydroxide.* 3-Bromo-1,2-epoxybutane, 15.1 g. (0.10 mole), was treated with powdered potassium hydroxide (11.2 g., 0.20 mole) in ether exactly as described above in the preparation of XII. The reaction mixture became dark orange in color and some bromide ion was liberated. There was recovered, however, by distillation 11.6 g. (76.5%) of starting material, b.p. 81° at 71 mm., n^{23}_{D} 1.4737, as the only identified product.

RAHWAY, NEW JERSEY

---

[12] Pure *cis*- and pure *trans*-crotyl alcohols were recovered unchanged on treatment with sodium in liquid ammonia as described in this experiment.

[13] R. Paul and H. Normant, *Bull. soc. chim.*, 484 (1943).

[14] Solubility analysis data show that the 3,5-dinitrobenzoate derivatives of *cis*- and *trans*-crotyl alcohols form solid solutions, a fact further substantiated by x-ray diffraction.