[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

The Reaction of Sodium Azide with Some Representative Epoxides

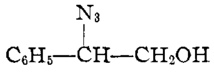
BY CALVIN A. VANDERWERF, ROBERT Y. HEISLER AND WILLIAM E. MCEWEN

RECEIVED JULY 7, 1953

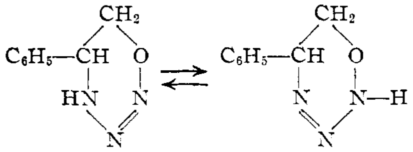
The SN2 type of reaction of the azide ion with a variety of epoxides has been studied. In all cases the products were azidoalcohols whose structures were proved by reduction to known aminoalcohols. Inversion was demonstrated in the reaction of the azide ion with cyclopentene oxide and with cyclohexene oxide. Predominant attack at the primary carbon atom of the epoxide ring was indicated in the reactions with propylene oxide and isobutylene oxide. A diazidoalcohol was obtained from epichlorohydrin. Butadiene monoxide afforded a mixture of 2-azido-3-butene-1-ol and 4-azido-2-butene-1-ol.

Introduction

Manifestly lacking from the large group of nucleophilic agents whose reactions with epoxides have been studied extensively is the azide ion. Quite recently it has been shown[1] that sodium azide reacts facilely with styrene oxide in aqueous dioxane to produce a single organic product, $C_8H_9N_3O$ (A) whose catalytic hydrogenation to 2-amino-2-phenylethanol indicates exclusive attack of the azide ion at the secondary carbon. Evidence to distinguish between the azidoalcohol structure, 2-azido-2-phenylethanol (I), and the cyclic structure, 5,6-dihydro-5-phenyl-1,2,3,4-oxatriazine (II), for A was, however, not conclusive.


$C_6H_5\text{—}\overset{N_3}{\overset{|}{C}}H\text{—}CH_2OH$

I



II

Catalytic hydrogenation of the crude monobenzoylated derivative of A gave 2-benzamido-2-phenylethanol,[2] but the possibility of O → N acyl migration[3] vitiates this fact as evidence for the cyclic structure. The infrared absorption spectrum of A[2] showed peaks at 4.8 and 8.0 mμ, characteristic of azides.[4] This was not regarded as conclusive evidence for the azidoalcohol structure, however, since infrared absorption data on the hypothetical oxatriazine structure are lacking. Examination of the infrared absorption spectrum of the monobenzoylated derivative of A, particularly the carbonyl region, would very likely have provided evidence for the structure of A; unfortunately, however, an analytically pure sample of the monobenzoylated derivative was never obtained.

The present work was undertaken in an attempt to prove the structure of A, to determine the general applicability of the reaction of azides with epoxides, to determine the direction of ring opening for a number of representative unsymmetrical epoxides, and to provide some evidence for the mechanism of the reaction. Of the various epoxides studied, 2,3-epoxybutane was selected in order to extend the generality of the reaction, propylene oxide, isobutylene oxide, epichlorohydrin and butadiene monoxide to determine the direction of ring opening, and cyclohexene oxide and cyclopentene oxide to determine the stereochemistry of the reaction and the effect of configuration and of ring size on possible formation of a fused ring system.

Results

Subjected to the hydrogenation procedure by which Conrad[2] obtained 2-benzamido-2-phenylethanol from the crude monobenzoylated derivative of A, 2-amino-2-phenylethyl benzoate underwent rearrangement to 2-benzamido-2-phenylethanol.

Reaction of cyclohexene oxide with sodium azide gave a product which, on the basis of its characteristic azide infrared absorption peaks, its catalytic hydrogenation to *trans*-2-aminocyclohexanol, and reduction of its monobenzoyl derivative to *trans*-2-benzamidocyclohexanol under conditions favorable to O → N benzoyl migration, was assigned the structure *trans*-2-azidocyclohexanol. *trans*-2-Aminocyclohexyl benzoate was found to rearrange to *trans*-2-benzamidocyclohexanol during the typical hydrogenation procedure.

Reaction of cyclopentene oxide with sodium azide gave *trans*-2-azidocyclopentanol, which was catalytically hydrogenated to *trans*-2-aminocyclopentanol. Hydrogenation of the monobenzoyl derivative gave, in this case, *trans*-2-aminocyclopentyl benzoate.

Reaction of 2,3-epoxybutane with sodium azide yielded 3-azido-2-butanol, which was catalytically hydrogenated to 3-amino-2-butanol.

Propylene oxide, with sodium azide, gave 1-azido-2-propanol, with perhaps a trace of the isomeric 2-azido-1-propanol. Catalytic hydrogenation of the monobenzoylated derivative of 1-azido-2-propanol produced 1-benzamido-2-propanol.

Isobutylene oxide reacted with sodium azide to form 1-azido-2-methyl-2-propanol, which upon catalytic hydrogenation afforded 1-amino-2-methyl-2-propanol. Perhaps a trace of the isomeric 2-azido-2-methyl-1-propanol was also formed.

Epichlorohydrin, in its reaction with 2 moles of sodium azide, yielded 1,3-diazido-2-propanol, which was catalytically hydrogenated to 1,3-diamino-2-propanol.

Reaction of butadiene monoxide with sodium azide yielded two products: (1) 2-azido-3-butene-1-

---

(1) W. E. McEwen, W. E. Conrad and C. A. VanderWerf, THIS JOURNAL, **74**, 1168 (1952).

(2) W. E. Conrad, Ph.D. Dissertation, University of Kansas, 1951.

(3) (a) G. Fodor and J. Kiss, *Nature*, **163**, 287 (1949); (b) **164**, 917 (1949); (c) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, THIS JOURNAL, **71**, 637 (1949); (d) L. H. Nelson, *ibid.*, 3500 (1949); (e) W. S. Johnson and E. N. Schubert, *ibid.*, **72**, 2187 (1950); (f) G. E. McCasland and D. A. Smith, *ibid.*, 2190 (1950); (g) G. Fodor and J. Kiss, *ibid.*, 3495 (1950); (h) G. E. McCasland, *ibid.*, **73**, 2295 (1951); (i) A. P. Phillips and A. Baltzly, *ibid.*, **69**, 200 (1947).

(4) (a) J. H. Boyer, *ibid.*, **73**, 5248 (1951); (b) E. Lieber, D. R. Levering and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

ol, which was reduced by means of lithium aluminum hydride to 2-amino-3-butene-1-ol and the latter then hydrogenated catalytically to 2-amino-1-butanol, and (2) 4-azido-2-butene-1-ol, which was similarly reduced to 4-amino-2-butene-1-ol and that product hydrogenated to 4-amino-2-butanol.

Experimental[5]

Rearrangement of 2-Amino-2-phenylethyl Benzoate.—An authentic sample of 2-amino-2-phenylethyl benzoate[6] was subjected to the typical hydrogenation procedure employed by Conrad[2] for the monobenzoylated derivative of A. To a solution of 1.00 g. (0.00362 mole) of 2-amino-2-phenylethyl benzoate hydrochloride in 50 ml. of ethanol, 0.206 g. (0.00362 mole) of 95% sodium methoxide was added. The mixture was shaken for 24 hr. on a Parr hydrogenator at 3 atmospheres pressure in the presence of 0.1 g. of Adams catalyst. Removal of the catalyst by filtration and of the alcohol by distillation left a colorless solid which, upon recrystallization from a mixture of benzene and ligroin, afforded 0.9 g. (90% of the theoretical) of colorless 2-benzamido-2-phenylethanol, m.p. 152.2–154.0°,[7] which was insoluble in hydrochloric acid and did not depress the melting point of the product reported by Conrad.[2]

General Procedure for Reaction of Epoxides with Sodium Azide.—A solution of the epoxide in dioxane was heated to reflux in an appropriately sized round bottomed flask equipped with a reflux condenser and an addition funnel. Then a saturated aqueous solution of sodium azide, containing a slight theoretical excess of the azide, was added dropwise. During a 16–40 hr. refluxing period, the solution formed two layers. These were separated, the lower aqueous layer was washed with several 50-ml. portions of dioxane, the dioxane layers were combined, and the dioxane was removed by distillation. The product was then obtained by distillation of the residue under reduced pressure.

General Procedure for Reduction of Reaction Products of Epoxides with Sodium Azide to Aminoalcohols.—An ethanol solution of the material was shaken on the Parr hydrogenator for 24- to 48-hr. periods at a hydrogen pressure of 3 atmospheres in the presence of 0.1 g. of Adams catalyst. The catalyst was removed by filtration and the alcohol by distillation. The aminoalcohol(s) was then isolated by distillation of the residue under reduced pressure.

Reaction of Cyclohexene Oxide with Sodium Azide.—Refluxing for 20 hr. of the solution obtained by addition of a solution of 68.0 g. (1.15 moles) of sodium azide in 175 ml. of water to a refluxing solution of 81.3 g. (0.83 mole) of cyclohexene oxide in 1300 ml. of dioxane gave 71.4 g. (61.4%) of colorless liquid, b.p. 70–71° at 1.5 mm., $n^{21}\text{D}$ 1.4950, which crystallized upon standing. On the basis of its analysis, its characteristic azide infrared absorption peaks at 4.7 and 7.9 mμ, its catalytic hydrogenation to *trans*-2-aminocyclohexanol, reduction of its monobenzoyl derivative to *trans*-2-benzamidocyclohexanol under conditions favorable to $O \rightarrow N$ benzoyl migration, and its close resemblance to the corresponding product from cyclopentene oxide, it was assigned the structure *trans*-2-azidocyclohexanol.

Anal. Calcd. for $C_6H_{11}N_3O$: C, 51.0; H, 7.9; N, 29.8. Found: C, 50.8; H, 7.8; N, 29.5.

Hydrogenation of *trans*-2-Azidocyclohexanol.—Catalytic hydrogenation of 14.1 g. (0.10 mole) of *trans*-2-azidocyclohexanol yielded 9.3 g. (81%) of *trans*-2-aminocyclohexanol, b.p. 70° at 2 mm., a colorless, highly hygroscopic solid.

The hydrochloride, prepared by addition of gaseous hydrogen chloride to an alcohol–ether solution of the free base, melted at 175.6–176.4° after recrystallization from alcohol-ether.

Anal. Calcd. for $C_6H_{14}ClNO$: C, 47.5; H, 9.4; Cl, 23.4. Found: C, 47.3; H, 9.2; Cl, 23.2.

The α-naphthylurea of *trans*-2-aminocyclohexanol, prepared from the free base and α-naphthyl isocyanate, melted at 258.7–259.0°.

Anal. Calcd. for $C_{28}H_{27}N_3O_3$: C, 74.2; H, 6.0; N, 9.3. Found: C, 74.3; H, 5.7; N, 9.2.

The dibenzoate, after repeated recrystallization from ligroin, melted at 207.4–207.8°, considerably lower than the reported[3c] 215–216°, but did not depress the melting point of an authentic sample of *trans*-2-benzamidocyclohexyl benzoate.[8]

Hydrogenation of *trans*-2-Azidocyclohexyl Benzoate.—A solution of 3.0 g. (0.021 mole) of *trans*-2-azidocyclohexanol and 3.0 g. (0.021 mole) of benzoyl chloride in 50 ml. of benzene was refluxed for 3 days. The solution was cooled, extracted first with 10 ml. of 2% sodium carbonate solution, then with 10 ml. of 2% hydrochloric acid, and finally with water. The liquid residue, after removal of the benzene, resisted attempts at both crystallization and distillation, and was finally hydrogenated directly to *trans*-2-benzamidocyclohexanol, m.p. after recrystallization from ligroin 172.0–172.8° (reported[3c] m.p. 175–176°). The m.p. was not depressed upon admixture with an authentic sample.[8]

Anal. Calcd. for $C_{13}H_{17}NO$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.0; H, 7.8; N, 6.3.

***trans*-2-Aminocyclohexyl Benzoate Hydrochloride.**—A mixture of 4.7 g. (0.022 mole) of *trans*-2-benzamidocyclohexanol, 15.5 ml. of ethanol and 9.3 ml. of 5 *N* ethanolic hydrogen chloride was heated to 100° for 4 hr. in a sealed tube. The mixture was cooled and the precipitated solid was collected by suction filtration and recrystallized from ethanol. The pure, colorless product melted at 265.0–267.0° (reported[3g] for *trans*-2-aminocyclohexyl benzoate hydrochloride, 258.5–260.5°) and did not depress the melting point of an authentic sample[8] of *trans*-2-aminocyclohexyl benzoate hydrochloride.

Rearrangement of *trans*-2-Aminocyclohexyl Benzoate During Typical Hydrogenation Procedure.—A solution of 0.633 g. (0.00270 mole) of *trans*-2-aminocyclohexyl benzoate hydrochloride in 100 ml. of ethanol was treated with 0.141 g. (0.00270 mole) of 95% sodium methoxide, and the resulting solution was shaken on the Parr apparatus for 36 hr. with 0.1 g. of Adams catalyst, under a hydrogen pressure of 3 atmospheres. After removal of the catalyst and of the solvent, the residue was recrystallized from benzene–ligroin, yielding 0.4 g. of *trans*-2-benzamidocyclohexanol, m.p. 171.6–172.8°, whose m.p. was not depressed upon admixture with an authentic sample.[8]

Reaction of Cyclopentene Oxide with Sodium Azide.—A solution of 27.2 g. (0.42 mole) of sodium azide in 70 ml. of water was added to a refluxing solution of 27.8 g. (0.33 mole) of cyclopentene oxide in 650 ml. of dioxane. The resulting solution was refluxed for 40 hr. Isolation of the product gave 26.3 g. (64.0%) of a colorless liquid, b.p. 72.5–74.0° at 3 mm., $n^{24}\text{D}$ 1.4878, which, on the basis of its analysis, its infrared absorption peaks at 4.7 and 8.0 mμ characteristic of azides, its catalytic hydrogenation to *trans*-2-aminocyclopentanol, hydrogenation of its monobenzoyl derivative to *trans*-2-aminocyclopentyl benzoate, and the established fact that fusion of a five-membered ring to a six-membered ring in the *trans*-configuration is accompanied by strain, was assigned the structure *trans*-2-azidocyclopentanol.

Anal. Calcd. for $C_5H_9N_3O$: C, 47.2; H, 7.1; N, 33.1. Found: C, 47.1; H, 7.3; N, 33.3.

Hydrogenation of *trans*-2-Azidocyclopentanol—Catalytic hydrogenation of 5.00 g. (0.0394 mole) of *trans*-2-azidocyclopentanol afforded 2.0 g. (48.5%) of *trans*-2-aminocyclopentanol, b.p. 107–108° at 17 mm., n^{24}_{D} 1.5010.

Anal. Calcd. for $C_5H_{11}NO$: C, 59.2; H, 10.9; N, 13.8. Found: C, 59.3; H, 10.8; N, 13.8.

The hydrochloride, prepared from the free base in alcohol–ether, melted at 191.6–192.8°[9] and did not depress the m.p. of an authentic sample of *trans*-2-aminocyclopentanol hydrochloride.[8]

***trans*-2-Azidocyclopentyl Benzoate.**—A mixture of 25.4 g. (0.200 mole) of *trans*-2-azidocyclopentanol, 15.8 g. (0.200 mole) of pyridine, 100 ml. of benzene and 30.0 g. (0.210 mole) of benzoyl chloride was refluxed for 30 minutes. The precipitate of pyridinium chloride which formed was removed by filtration and the benzene by distillation. Vacuum distillation of the residue yielded 29.1 g. (63.0%) of *trans*-2-azidocyclopentyl benzoate, b.p. 128–130° at 0.1 mm.

---

(5) All melting points are corrected, boiling points uncorrected.

(6) S. Gabriel and J. Colman, *Ber.*, **47**, 1866 (1914).

(7) H. Reihlen, L. Knopfle and W. Sapper, *Ann.*, **534**, 247 (1938), reported 153°.

(8) Kindly supplied by G. E. McCasland, University of Toronto, Toronto, Canada.

(9) G. E. McCasland and D. A. Smith, ref. 3f, reported the m.p. of *trans*-2-aminocyclopentanol hydrochloride as 193–194°.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.7; N, 18.2. Found: C, 62.5; H, 5.6; N, 18.3.

Hydrogenation of *trans*-2-Azidocyclopentyl Benzoate.—Catalytic hydrogenation of 10.00 g. of *trans*-2-azidocyclopentyl benzoate afforded eventually 5.00 g. (47.7%) of pure *trans*-2-aminocyclopentyl benzoate, b.p. 106° at 0.06 mm., soluble in dilute hydrochloric acid.

The hydrochloride, prepared from the free base in alcohol-ether, melted at 193.0–194.0°.

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C, 59.6; H, 6.7. Found: C, 59.6; H, 6.5.

Reaction of 2,3-Epoxybutane with Sodium Azide.—Reaction of 59.7 g. (0.83 mole) of 2,3-epoxybutane, of undetermined stereochemical configuration, with 68.0 g. (1.15 moles) of sodium azide yielded, together with 4.5 g. of an unidentified higher boiling material, 50.1 g. (52.5%) of a colorless liquid, b.p. 83-84° at 31 mm., $n^{17.5}_{D}$ 1.4562, which, on the basis of analysis and infrared spectrum, was assigned the structure 3-azido-2-butanol.

Anal. Calcd. for $C_4H_9N_3O$: C, 41.7; H, 7.9. Found: C, 42.0; H, 7.7.

Hydrogenation of 3-Azido-2-butanol.—Catalytic hydrogenation of 8.00 g. of 3-azido-2-butanol over Adams catalyst gave 5.00 g. of colorless liquid, b.p. 78–79° at 33 mm., $n^{17.5}_{D}$ 1.4466, which was assigned the structure 3-amino-2-butanol. No attempt was made to determine the stereochemical identity of the product.

Anal. Calcd. for $C_4H_{11}NO$: C, 53.9; H, 12.4; N, 15.7. Found: C, 54.0; H, 12.2; N, 15.2.

Reaction of Propylene Oxide with Sodium Azide.—From the reaction of 48.2 g. (0.83 mole) of propylene oxide with 68.0 g. (1.15 moles) of sodium azide, there was obtained 47.8 g. of a colorless liquid A, b.p. 80–82° at 32 mm., $n^{17.5}_{D}$ 1.4552, and 13.4 g. of a second colorless fraction B, which distilled over the range 83–109° at 32 mm. and from which no individual compound could be isolated. Each of the fractions decomposed upon standing even in a sealed ampule, and analyses gave erratic results.

Catalytic hydrogenation of a mixture of 30.0 g. of A and 12.0 g. of B gave, in addition to a tarry, non-distillable residue from which no amine derivative could be prepared, 18.8 g. (*ca.* 60%) of 1-amino-2-propanol, b.p. 157.0–159.0°, n^{16}_{D} 1.4515. The melting points of the phenylthiourea (106.5–107.5°),[10] of the picrate (142.1–143.2°),[11] and of the chloroplatinate (194.5–197.0°)[12] agreed with the respective literature values for 1-amino-2-propanol and were, in every case, not depressed by samples of the corresponding derivatives of an authentic sample of 1-amino-2-propanol.[13]

Catalytic hydrogenation of A, alone, gave 1-amino-2-propanol in over 80% yield, with no appreciable tarry residue. 1-Amino-2-propanol was also found to be stable under the conditions used for the hydrogenation and subsequent isolation of product. On the basis of these results, and of its infrared spectrum, A was assigned the structure 1-azido-2-propanol. Catalytic hydrogenation of the monobenzoylated derivative of A yielded 1-benzamido-2-propanol, m.p. 92.2–92.8°,[14] which apparently arose as the result of a typical O → N benzoyl migration.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8. Found: C, 67.0; H, 7.5; N, 7.9.

No distillable product could be isolated following catalytic hydrogenation of B.

Reaction of Isobutylene Oxide with Sodium Azide.—From reaction of 60.6 g. (0.830 mole) of isobutylene oxide and 68.0 g. (1.15 moles) of sodium azide, there was obtained 38.4 g. (40.6%) of a colorless liquid, b.p. 75.8–77.9° at 32 mm., together with a small amount of higher boiling material which distilled over a considerable range. On the basis of its analysis and catalytic hydrogenation to 1-amino-2-methyl-2-propanol, the main product was assigned the structure 1-azido-2-methyl-2-propanol.

Anal. Calcd. for $C_4H_9N_3O$: C, 41.7; H, 7.9; N, 36.5. Found: C, 41.6; H, 8.0; N, 36.3.

Catalytic Hydrogenation of 1-Azido-2-methyl-2-propanol.—Catalytic hydrogenation of 8.00 g. (0.0695 mole) of 1-azido-2-methyl-2-propanol afforded 3.4 g. (57%) of 1-amino-2-methyl-2-propanol, b.p. 148.5–151.2°,[15] together with 2.6 g. of unreduced starting material.

Anal. Calcd. for $C_4H_{11}NO$: C, 53.9; H, 12.4; N, 15.7. Found: C, 53.8; H, 12.4; N, 15.8.

The hydrochloride, prepared from the free base in alcohol-ether, was a colorless hygroscopic solid, m.p. 74.1–75.3°.[16] A picrate, prepared from the free base in ether, melted at 133.0–134.5°, considerably lower than the reported value of 165–175°.[16]

Anal. Calcd. for $C_{10}H_{14}N_4O_8$: C, 37.7; H, 4.3; N, 17.6. Found: C, 37.7; H, 4.3; N, 17.3.

The thiourea melted at 135.0–136.1°, in agreement with the reported[16] 136–137°.

Each of the various derivatives showed no depression in melting point upon admixture with the corresponding derivative of an authentic sample of 1-amino-2-methyl-2-propanol obtained by reaction of isobutylene oxide with ammonia. 2-Amino-2-methyl-1-propanol[17] gave a thiourea, m.p. 127.0–128.5°, which sharply depressed the m.p. of each of the other thioureas. Attempted preparation of a solid picrate from the 1-propanol was unsuccessful.

Reaction of Epichlorohydrin with Sodium Azide.—From the reaction of 76.8 g. (0.830 mole) of epichlorohydrin with 136.0 g. (2.80 moles) of sodium azide, there was obtained, along with 2.0 g. of an unidentified higher boiling material which distilled over a wide range and 10.2 g. of a residue which decomposed upon attempted distillation, 64.9 g. (55%) of 1,3-diazido-2-propanol, b.p. 85–87° at 3 mm., $n^{17.5}_{D}$ 1.5060.

Anal. Calcd. for $C_3H_6N_6O$: C, 25.4; H, 4.3; N, 59.1. Found: C, 25.5; H, 4.3; N, 59.0.

Hydrogenation of 1,3-Diazido-2-propanol.—Catalytic hydrogenation of 10.0 g. (0.070 mole) of 1,3-diazido-2-propanol afforded 5.0 g. (76%) of 1,3-diamino-2-propanol, b.p. 93–95° at 3 mm.

Anal. Calcd. for $C_3H_{10}N_2O$: C, 40.0; H, 11.2. Found: C, 40.2; H, 11.2.

The dihydrochloride melted at 183.2–184.6° dec., undepressed by the dihydrochloride of an Eastman Kodak Co. sample of 1,3-diamino-2-propanol. The picrate melted at 236.0–237.2° dec.[18]

Reaction of Butadiene Monoxide with Sodium Azide.—Attempts at the isolation of the products by distillation under reduced pressure resulted in violent explosions, even before all of the dioxane solvent had been removed. Therefore, from the mixture resulting from the reaction of butadiene monoxide (58.1 g., 0.830 mole) with sodium azide (55.3 g., 0.850 mole), the water–dioxane azeotrope was removed by distillation up to 98°, and the residue was added dropwise to a solution of 31.6 g. (0.830 mole) of lithium aluminum hydride in 250 ml. of anhydrous ether under reflux. After a 1-hr. period of refluxing and stirring, moist ether was added to destroy excess lithium aluminum hydride, and then 50 ml. of water to hydrolyze the salt complex. The mixture was cooled, the salts were removed by filtration and the ether, water and dioxane by distillation. Fractional distillation under reduced pressure afforded 14.7 g. (22.8%) of 2-amino-3-butene-1-ol, b.p. 81–82° at 14 mm., $n^{12.5}_{D}$ 1.4470, and 10.3 g. (15.7%) of 4-amino-2-butene-1-ol, b.p. 110–112° at 14 mm.

The 2-amino-3-butene-1-ol was identified by means of its neutral oxalate, m.p. 155.8–157.8° (undepressed by an authentic sample of 2-amino-3-butene-1-ol neutral oxalate[19]), and by its catalytic hydrogenation in 85% yield to 2-amino-1-butanol, b.p. 51–53° at 3 mm. The m.p. of the picrate

---

[10] P. A. Levene and A. Walti, *J. Biol. Chem.*, **71**, 461 (1927), reported 107–108°.

[11] K. Krasuskii, *J. Gen. Chem.* (*U.S.S.R.*), **6**, 460 (1936), reported 143–144°.

[12] Reported, ref. 11, 195–200°, ref. 10, 205–210°.

[13] Kindly supplied by the Dow Chemical Company, Midland, Michigan.

[14] P. Hirsch, *Ber.*, **23**, 964 (1890), reported 92–93°.

[15] K. Krasuskii, *J. Russ. Phys. Chem. Soc.*, **40**, 155 (1908), reported 150.5–151.5°.

[16] H. Dersin, *Ber.*, **54**, 3158 (1921), reported 70–72°.

[17] Kindly supplied by the Commercial Solvents Corporation, Terre Haute, Indiana.

[18] M. Bergmann, F. Radt and E. Brand, *Ber.*, **54**, 1645 (1921), reported 240–241°.

[19] Kindly supplied by Dr. M. G. Ettlinger, The Rice Institute, Houston, Texas. See M. G. Ettlinger, THIS JOURNAL, **72**, 4792 (1950).

of the 2-amino-1-butanol, 128.4–129.2°, was not depressed by the picrate prepared from an authentic sample of 2-amino-1-butanol.[19]

The 4-amino-2-butene-1-ol was identified by its catalytic hydrogenation to 4-amino-1-butanol, b.p. 95° at 10 mm. (reported[20] 100° at 15 mm.), n^{20}_D 1.4578 (reported[21] n^{20}_D 1.4581). The structure of the latter was proved by identification of its picrate, m.p. 86.6–88.6°, with the picrate of an authentic sample of 4-amino-1-butanol, b.p. 104° at 15 mm., which was obtained from tetrahydrofuran by the following steps: (a) treatment with acetyl chloride to give 4-chlorobutyl acetate; (b) reaction of 4-chlorobutyl acetate with potassium phthalimide to yield 4-phthalimidobutyl acetate; (c) hydrolysis of the latter with 50% sulfuric acid. Mixed melting points of the oxalate, m.p. 174.6–175.6°, of the presumed 4-amino-2-butene-1-ol with authentic samples[19] of 1-amino-3-butene-2-ol neutral and acid oxalates and of 2-amino-3-butene-1-ol neutral and acid oxalates all showed large depressions. Similarly, the m.p. of the picrate of the 4-amino-1-butanol was sharply depressed upon admixture with the picrate, m.p. 124.5–125.6°, of 1-amino-2-butanol, b.p. 70° at 12 mm., prepared by reaction of 1,2-epoxybutane with ammonia.

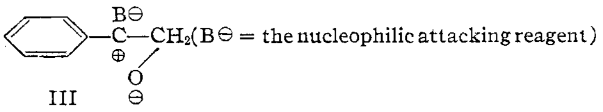
Discussion of Results

The reaction of sodium azide with epoxides has been shown to be general; azide ion attacks epoxide ring carbons with facility, in a typical bimolecular nucleophilic displacement reaction which proceeds with inversion, to produce azidoalcohols. Inversion was clearly demonstrated in the reaction with cyclohexene and cyclopentene oxides, and it appears eminently probable for all cases. In saturated unsymmetrical epoxides of the type $\underset{\diagdown O \diagup}{\text{R–CH–CH}_2}$, the attack appears to be largely, if not entirely, at the primary carbon atom. The direction of ring opening is that characteristically observed for reactions of monoalkyl-substituted epoxides under S$_N$2 conditions and is probably dictated by both steric and electronic factors.

The azidoalcohol, in preference to the cyclic oxatriazine structure appears to be definitely established. The only line of evidence which might be construed as suggesting the cyclic structure, *i.e.*, the catalytic hydrogenation of the monobenzoyl derivative of the usual azide–epoxide reaction product to the corresponding benzamido–alcohol, can be rationalized in terms of the ease of O → N benzoyl migration under conditions employed in the hydrogenation.

When this work was first undertaken, it was thought that the oxatriazines might be the normal products of the reaction. If this were the case, the product in the reaction with cyclopentene oxide, where the strain arising from fusion of a five-membered ring to a six-membered ring in the *trans* configuration would perhaps preclude the formation of the cyclic structure and force the formation of the azidoalcohol, might be expected to differ quite markedly from the products obtained in all other cases.[22] Actually, it was similar in every respect, including infrared absorption behavior, to the products of all the other reactions, and this is strong confirmatory evidence for the azidoalcohol structure in all cases. Particularly interesting, however, is the fact that only for the *trans*-2-azidocyclopentanol did catalytic hydrogenation of the monobenzoyl derivative lead to isolation of the unrearranged amino-substituted benzoate ester. Formation of the cyclic intermediate, proposed by Fodor and Kiss[3a] and Welsch[3d] as the key step in the mechanism for O→N rearrangement of 1,2-aminobenzoates, would for *trans*-2-aminocyclopentyl benzoate involve the *trans* fusion of two five-membered rings. Although such a fusion has been reported,[23] it is likely only rarely achieved, because of the almost prohibitive strain involved. Failure of *trans*-2-aminocyclopentyl benzoate to undergo rearrangement is therefore confirmatory evidence for the proposed mechanism.[24]

The fact that in reaction with styrene oxide, azide ion attacks exclusively at the secondary carbon atom of the epoxide ring is now reasonably well established. To the extent that attack of azide ion occurs at the epoxide ring in butadiene monoxide, it appears likewise to be exclusively at the secondary carbon. The role played by unsaturated groups, such as phenyl and vinyl, in promoting secondary attack on epoxides, in the face of opposing steric factors, even under typical S$_N$2 conditions, has by now been well established for a wide variety of nucleophilic reagents.[25,19] It may be explained in the case of styrene oxide, for example, on the basis of the high degree of resonance stabilization afforded the transition state due to the contributions of a number of structures of type III



III

involving interaction between the benzene ring and the somewhat positively charged secondary carbon atom. The effect of such resonance is, of course, to diffuse the positive charge on carbon in the transition state; otherwise, because of its high degree of charge separation and consequent instability, a structure like III makes only a minor contribution to the transition state resonance hybrid. It is noteworthy, moreover, that the effect of the phenyl and vinyl groups in promoting secondary attack reaches its peak, among all the nucleophilic reagents studied, for azide ion. This may be attributed in part to the fact that the linear azide ion has only relatively low steric requirements and also in part to the high polarizability of azide ion, which contributes to the further stabilization of the transition state through diffusion of the negative charge on B$^\ominus$ (in this case, the azide ion).

Isolation of 4-amino-1-butanol after successive lithium aluminum hydride reduction and catalytic hydrogenation of the higher-boiling product from the butadiene monoxide–sodium azide reaction strongly suggests that the product was 4-azido-2-

---

[20] J. von Braun and W. Sobscki, *Ber.*, **44**, 2529 (1911).

[21] Y. K. Yur'ev, G. P. Mikhailovsky and S. Z. Shapiro, *J. Gen. Chem.* (*U.S.S.R.*), **91**, 2219 (1951).

[22] See W. E. Grigsby, J. Hind, J. Chanley and F. H. Westheimer, This Journal, **64**, 2606 (1942), and M. S. Newman and C. A. VanderWerf, *ibid.*, **67**, 233 (1945), for a comparison between ease of *trans* fusion of two five-membered rings and of a five- to a six-membered ring in the *trans*-cyclopentanol- and cyclohexanol-2 acetic acids.

[23] R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934).

[24] *Cf.* E. E. van Tamelen, This Journal, **74**, 2074 (1952).

[25] (a) C. Mannich, P. Neumann and W. Jacobsohn, *Arch. Pharm.*, **248**, 127 (1910); (b) W. Reeve and I. Cristoffel, This Journal, **72**, 1480 (1950); (c) P. D. Bartlett and S. D. Ross, *ibid.*, **70**, 926 (1948); (d) D. Swern, G. N. Billen and H. B. Knight, *ibid.*, **71**, 1152 (1949); (e) L. W. Trevoy and W. G. Brown, *ibid.*, 1675 (1949); (f) R. M. Adams and C. A. VanderWerf, *ibid.*, **72**, 4368 (1950).

butene-1-ol resulting from SN2′[26] attack of azide ion on the oxide. 4-Azido-2-butene-1-ol might also, although less probably, have arisen through an allylic rearrangement of either 1-azido-2-butene-2-ol or 2-azido-3-butene-1-ol.

Most of the azidoalcohols studied were at least moderately stable. However, 1,3-diazido-2-propanol, which was the only product isolated from the reaction of epichlorohydrin with sodium azide even at a 1:1 molar ratio, decomposed violently when heated to over 150°. The explosive nature of the mixture of products from the butadiene monoxide–sodium azide reaction prevented an absolute proof of structure of these products.

Acknowledgment.—The authors are grateful to the University of Kansas for a University fellowship awarded to R.Y.H. for the completion of this investigation.

LAWRENCE, KANSAS

(26) (a) R. E. Kepner, S. Winstein and W. G. Young, THIS JOURNAL, **71**, 115 (1949); (b) W. G. Young, I. D. Webb and H. L. Goering, *ibid.*, **73**, 1076 (1951).

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

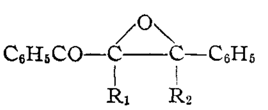
The Rearrangement of α,β-Epoxy Ketones. I. Chalcone Oxides

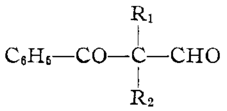
BY HERBERT O. HOUSE

RECEIVED OCTOBER 7, 1953

Four α,β-epoxy ketones have been found to isomerize in the presence of boron trifluoride. In each case the structure of the dicarbonyl compound produced is consistent with the hypothesis that the group which migrates is the one originally bonded to the carbon atom *alpha* to the carbonyl group of the epoxy ketone.

trans-Chalcone oxide (I) has been isomerized to formyldesoxybenzoin (II) by treatment either with aqueous sulfuric acid[1] or with a solution of sulfuric acid in acetic acid.[2] An ethereal solution of boron trifluoride has been found to be a superior agent for effecting this transformation.





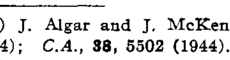
$C_6H_5—CO—\overset{R_1}{\underset{R_2}{C}}—CHO$

I, $R_1 = R_2 = H$
III, $R_1 = H$; $R_2 = CH_3$
VI, $R_1 = H$; $R_2 = C_6H_5$
IX, $R_1 = C_6H_5$; $R_2 = H$

II, $R_1 = H$; $R_2 = C_6H_5$
IV, $R_1 = CH_3$; $R_2 = C_6H_5$
VII, $R_1 = R_2 = C_6H_5$

In the presence of this catalyst each of the isomeric dypnone oxides III yielded 2-methyl-1,2-diphenyl-1,3-propanedione (IV), isolated as its mono-2,4-dinitrophenylhydrazone. A boiling, ethanolic solution of sodium acetate converted the crude product to α-methyldesoxybenzoin (V); this facile loss of formic acid is in accord with the previous experience of Wittig, Bangert and Kleiner.[3] Similarly, the oxide of β,β-diphenylacrylophenone (VI) afforded 1,2,2-triphenyl-1,3-propanedione (VII), isolated as the deformylated α-phenyldesoxybenzoin (VIII).

Only one of the two possible racemic modifications of α,β-diphenylacrylophenone oxide (IX) could be obtained from the reaction of α,β-diphenylacrylophenone with alkaline hydrogen peroxide. The action of boron trifluoride converted the epoxy ketone IX to phenyl benzhydryl diketone (X) which was isolated as its quinoxaline.

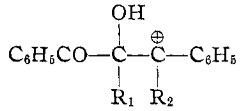


$C_6H_5CO—\underset{CH_3}{CH}—C_6H_5$ V

$C_6H_5COCH(C_6H_5)_2$ VIII

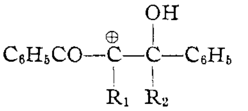
$C_6H_5COCOCH(C_6H_5)_2$ X

In each case the structure of the dicarbonyl compound produced is consistent with the hypothesis that the group which migrates is the one originally bonded to the carbon atom alpha to the carbonyl group of the epoxy ketone. This result would be predicted by a comparison of the possible ionic intermediates XI and XII.[4] The intermediate XII is especially unfavorable since this structure incorporates adjacent atoms, each bearing at least a partial positive charge.[5]



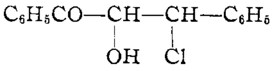
$C_6H_5CO—\overset{OH}{\underset{R_1}{C}}—\overset{\oplus}{\underset{R_2}{C}}—C_6H_5$

XI



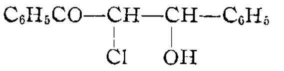
$C_6H_5CO—\overset{\oplus}{\underset{R_1}{C}}—\overset{OH}{\underset{R_2}{C}}—C_6H_5$

XII



$C_6H_5CO—\underset{OH}{CH}—\underset{Cl}{CH}—C_6H_5$

XIII



$C_6H_5CO—\underset{Cl}{CH}—\underset{OH}{CH}—C_6H_5$

XIV

The action of stannic chloride in benzene solution Cl on chalcone oxide (I) failed to give a rearranged product, the chlorohydrin XIII being isolated instead. The chlorohydrin XIII was converted to benzyl phenyl diketone, isolated as its quinoxaline, by the method of Baker and Robinson.[6] This transformation has been effected previously by Kohler and Barnes,[7] who did not isolate the intermediate XIII. The action of hydrogen chloride on the oxide I in alcoholic solution has been reported to give the isomeric chlorohydrin XIV.[8,9]

---

[1] J. Algar and J. McKenna, *Proc. Royal Irish Acad.*, **49**, 225 (1944); *C.A.*, **38**, 5502 (1944).

[2] E. Weitz and A. Scheffer, *Ber.*, **54**, 2344 (1921).

[3] G. Wittig, F. Bangert and H. Kleiner, *ibid.*, **61**, 1140 (1928).

[4] The same argument has been used by Winstein and Henderson [in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 49] to predict the products obtained when ethylene oxides bearing only alkyl and aryl substituents undergo acid-catalyzed rearrangement.

[5] L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1948, p. 199.

[6] W. Baker and R. Robinson, *J. Chem. Soc.*, 1798 (1932).

[7] E. P. Kohler and R. P. Barnes, THIS JOURNAL, **56**, 211 (1934).

[8] O. Widman, *Ber.*, **49**, 477, 2778 (1916).

[9] Analogous chlorohydrins have been prepared in a related series by H. Jorlander [*Ber.*, **49**, 2782 (1916)].