[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SAN JOSE STATE COLLEGE]

THE DIRECTION OF EPOXIDE RING OPENING IN THE REACTION OF STYRENE OXIDE WITH AMMONIA[1]

A. J. CASTRO, D. K. BRAIN, H. D. FISHER, AND R. K. FULLER

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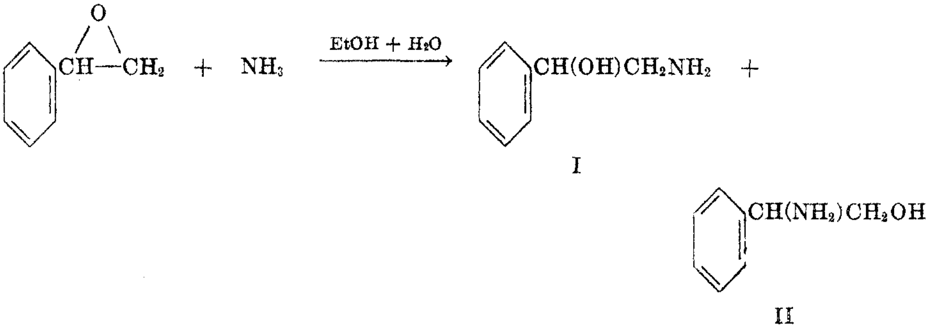
The reaction of styrene oxide with ammonia has been assumed (1) to yield α-phenyl-β-aminoethanol (I). This was based on the fact that α-phenyl-β-dimethylaminoethanol is produced in a quantitative yield from reaction of the epoxide with dimethylamine in benzene (2). We have established that α-phenyl-β-aminoethanol is indeed the major product when the reaction is carried out in aqueous alcohol. However, β-amino-β-phenylethanol (II) is also formed.



The two amino alcohols were isolated as their hydrochlorides and benzoyl derivatives. These were identified by comparison with the same derivatives of the two isomers synthesized through paths that leave no doubt regarding their constitutions. α-Phenyl-β-aminoethanol was synthesized through the route: acetophenone → isonitrosoacetophenone → ω-aminoacetophenone hydrochloride → α-phenyl-β-aminoethanol hydrochloride → α-phenyl-β-aminoethanol. In another series ω-aminoacetophenone hydrochloride was prepared by the hydrochloric acid hydrolysis of the ω-bromoacetophenone-hexamethylenetetramine adduct. β-Amino-β-phenylethanol was synthesized through the sequence: phenylglycine → ethyl phenylglycinate hydrochloride → ethyl phenylglycinate → β-amino-β-phenylethanol.

Benzoylation of α-phenyl-β-aminoethanol by the method of Schotten-Baumann gave the N-benzoyl derivative (3) as the main product accompanied by a small quantity of what is apparently the dibenzoyl derivative. The only product isolated in the case of β-amino-β-phenylethanol was the dibenzoyl derivative.

An estimate of the relative amounts of the isomeric amino alcohols produced in the reaction of the epoxide with ammonia was obtained through separation of the mixture of their benzoyl derivatives. This was made remarkably easy by the observation that the N-benzoyl derivative of α-phenyl-β-aminoethanol crystal-

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[1] Taken in part from the thesis of D. K. Brain for the degree of Master of Science in the Graduate School of the University of Arizona.

lized from a benzene solution of the mixture and the dibenzoyl derivative of β-amino-β-phenylethanol was obtained when the product remaining in solution was crystallized from 95% ethyl alcohol. The ratio of I to II as indicated by the quantities of benzoyl derivatives recovered is 3.6:1 (64% recovery); in a second experiment, 3.3:1 (74% recovery).

These results establish conclusively that although the principal point of attack by ammonia is at the primary carbon atom (4) of styrene oxide, the epoxide ring is opened in both theoretically possible directions under the experimental conditions employed. The recent report of Browne and Lutz (5) wherein it is recorded that benzylamine also opens the ring in both directions is especially interesting in this connection.

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EXPERIMENTAL[2]

Reaction of styrene oxide with ammonia. Styrene oxide (100 g.) was added over a period of 20 minutes to a stirred and cooled mixture of 834 ml. of concentrated ammonium hydroxide (28% NH_3) and 584 ml. of 95% ethyl alcohol. At the start the temperature was 9°. After all the epoxide was added stirring was continued for 1½ hours, when the temperature had fallen to −4°. The reaction mixture was transferred to an ice-bath and allowed to come to room temperature, as the ice melted upon standing overnight. Fractionation of the reaction mixture yielded 40.7 g. (36%) of a mixture of the isomeric amino alcohols, collected as a very pale yellow viscous oil, b.p. 135–144° (4–6 mm.)

Isolation of derivatives of isomeric amino alcohols from the reaction of styrene oxide with ammonia. (a) *Hydrochlorides.* The mixture of amino alcohols used in this work was prepared as described, b.p. 139–152° (6 mm.)

A saturated solution of dry hydrogen chloride in dry ethyl ether (150 ml.) was added to 10 g. of the amino alcohol mixture in 20 ml. of absolute alcohol. A white cloud appeared immediately and on the following day 10.7 g. of white crystalline solid, m.p. 125.0–171.0° (uncorr.) had precipitated. Repeated crystallization from a dry ether-ethanol mixture gave 1.27 g. of white crystalline hydrochloride, m.p. 210.3–212.7° (dec.). The properties exhibited by this compound when heated were otherwise like those described for the reduction product of ω-aminoacetophenone hydrochloride. A mixture of the two showed no depression of the melting point, and in other respects showed the same behavior when heated.

The mother liquor from the solid of m.p. 125.0–171.0° was allowed to stand a week when a second crop of white crystals was deposited. After two recrystallizations from an ether-alcohol solution 0.27 g. of white crystals were obtained. This compound exhibited the same two melting points described below for β-amino-β-phenylethanol hydrochloride and a mixture of the two gave the same results.

(b) *Benzoyl derivatives.* A 6.38-g. quantity of the mixture of amino alcohols, b.p. 135–144° (4–6 mm.) was rinsed into a flask with 25 ml. of ethyl ether and benzoylated by the method of Schotten-Baumann. The white granular solid that precipitated was filtered and washed with water. Nothing further was obtained from the filtrate. The solid was dissolved in boiling benzene and the water that had been entrained was removed. Upon standing, 5.60 g. of shiny white crystals, m.p. 148.6–149.1° separated from the benzene solution. No depression of the melting point was observed for a mixture of this substance with the N-benzoyl derivative of α-phenyl-β-aminoethanol.

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[2] Melting points are corrected, except where noted otherwise; boiling points are uncorrected.

The mother liquor from the above solid was evaporated and the residue was dissolved in hot 95% ethyl alcohol. A white solid, m.p. 145.4–146.7°, precipitated from the cooled solution. This was recrystallized from 95% ethyl alcohol and 2.23 g. of the dibenzoyl derivative of β-amino-β-phenylethanol was obtained, m.p. 152.9–153.4°. The identity of this product was established through a mixture melting point determination.

An additional 0.03 g. (total yield 50%) of the N-benzoyl derivative of α-phenyl-β-aminoethanol and 0.05 g. (total yield 14%) of the dibenzoyl derivative of β-amino-β-phenylethanol was recovered from the mother liquors.

In a second experiment 7.70 g. of the amino alcohol mixture yielded 7.96 g. (59%) of the N-benzoyl derivative of α-phenyl-β-aminoethanol and 3.52 g. (18%) of the dibenzoyl derivative of β-amino-β-phenylethanol.

ω-Aminoacetophenone hydrochloride. Acetophenone was converted to isonitrosoacetophenone, m.p. 130.0–131.7°, through reaction with isoamyl nitrite and sodium ethoxide according to the method of Claissen and Manasse (6). Isonitrosoacetophenone upon reaction with stannous chloride in the presence of hydrochloric acid and tin as described by Rupe (7) yielded ω-aminoacetophenone hydrochloride. It was observed that when this compound was recrystallized from 95% ethyl alcohol the solution became red. This was apparently due to loss of hydrogen chloride and subsequent conversion of the amino ketone to a colored product. If a little concentrated hydrochloric acid was added to the solution this change was markedly reduced and the product was obtained as cream-colored crystals, m.p. 190.1–191.2° (dec.). This compound was also synthesized from ω-bromoacetophenone by reaction with hexamethylenetetramine and hydrolysis of the adduct with hydrochloric acid as described by Mannich (8).

α-Phenyl-β-aminoethanol and derivatives. A solution of 7.6 g. of ω-aminoacetophenone hydrochloride and 0.1 g. of platinum oxide was heated to 45–55° and shaken in an atmosphere of hydrogen at an initial pressure of 50.2 lb. gauge. The uptake of hydrogen ceased before the reduction was complete. The mixture was filtered, an additional 0.1 g. of catalyst was added, and the hydrogenation was completed. Following removal of the catalyst the solution was evaporated yielding the crude crystalline hydrochloride. Recrystallization from a mixture of absolute ethanol and dry ether gave 3.8 g. (49%) of α-phenyl-β-aminoethanol hydrochloride. This compound sinters at about 132–133°, becomes a transluscent to almost clear mass at 178.6–180.9°, and melts with decomposition at 211.5–212.8°.

Anal.[3] Calc'd for $C_8H_{12}ClNO$: C, 55.33; H, 6.97; N, 8.07.

Found: C, 55.20, 55.31; H, 7.00, 7.04; N, 8.19, 8.26.

Bills and Noller (9) have prepared this compound in practically the same manner, except that the reduction was carried out at room temperature, and report a melting point of 176–177°. This corresponds to the intermediate change recorded herein.

To a solution of 3.48 g. of α-phenyl-β-aminoethanol hydrochloride in 25 ml. of absolute alcohol there was added a solution of sodium ethoxide prepared by dissolving 0.46 g. of sodium in 15 ml. of absolute alcohol. This was followed by 10 ml. of the alcohol used as a rinse. The solution was filtered from the precipitated sodium chloride and evaporated. The residue was distilled and 1.33 g. (48%) of α-phenyl-β-aminoethanol, b.p. 136–137° (5 mm.), was obtained. The product prepared in this manner was a colorless oil that crystallized to a white solid upon standing.

α-Phenyl-β-aminoethanol (1.038 g.) in a few milliliters of ethyl ether was benzoylated by the Schotten-Baumann procedure. Evaporation of the ether occurred during the reaction. The white product that precipitated was crystallized once from 95% ethyl alcohol, once from benzene, and 0.695 g. of the N-benzoyl derivative (3) was obtained as shiny white crystals, m.p. 148.2–148.7°.

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81.

Found: C, 74.70, 74.79; H, 6.33, 6.35; N, 5.81, 5.95.

An additional quantity of white crystals was obtained from the mother liquors of the solid, m.p. 148.2–148.7°. After recrystallization once from 95% ethyl alcohol, once from ben-

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[3] Analyses by Microchemical Specialties Co., Berkeley, California.

zene, and three times from 95% ethyl alcohol, 0.043 g. of the dibenzoyl derivative of α-phenyl-β-aminoethanol was obtained as white crystals, m.p. 142.3–142.8°.

Anal. Calc'd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.55.

Found: C, 76.78; H, 5.79.

Ethyl phenylglycinate. A mixture of 49.3 g. of phenylglycine (10) and 450 ml. of absolute ethanol was refluxed for two hours while dry hydrogen chloride was added. All of the acid had dissolved after about an hour and the addition of hydrogen chloride was terminated at the end of the second hour. The mixture was refluxed for an additional 2½ hours and was allowed to stand in a stoppered flask for two days. It was again heated to boiling, a small amount of insoluble material was removed by filtration, and the filtrate was concentrated at reduced pressure to about 180 ml. White crystals of the ester hydrochloride weighing 35.2 g. deposited upon standing. An additional 26.7 g. was recovered from the mother liquor. The two fractions were combined and recrystallized from absolute ethanol yielding 46.3 g. (66%) of ethyl phenylglycinate hydrochloride, m.p. 197.1–198.1° (dec.).

A solution of sodium ethoxide prepared from the reaction of 4.83 g. of sodium with 50 ml. of absolute alcohol was added to a refluxing solution of 45.3 g. of ethyl phenylglycinate hydrochloride in 150 ml. of dry ethanol. Following addition of the sodium ethoxide solution an additional 10 ml. of solvent was added as a rinse. All of the sodium ethoxide was added during nine minutes and the mixture then was refluxed for an additional ten minutes. The mixture was allowed to cool, and was filtered from the precipitated sodium chloride while still warm. The white residue was washed with dry alcohol and finally with a little dry ether. When the ether filtrate was combined with the rest of the filtered solution an additional small amount of white solid (presumably sodium chloride) precipitated and was removed. Upon concentrating the combined filtrates a golden-orange oily residue was obtained. Distillation of this material gave 28.7 g. (76%) of ethyl phenylglycinate that was collected as a colorless oil, b.p. 110.3–113° (1.3–1.7 mm.), n_D^{20} 1.5158.

β-Amino-β-phenylethanol and derivatives. A solution of 8.4 g. of ethyl phenylglycinate in 10 ml. of anhydrous ether followed by a 15-ml. ether rinse was added with stirring during a period of ten minutes to 2.3 g. of lithium aluminum hydride in 100 ml. of the same solvent. The mixture was stirred and refluxed for an hour. Water was added, the yellow ether layer was separated, and the aqueous layer was extracted three times with ethyl ether. Evaporation of the combined ether solution yielded 8.0 g. of a golden-brown oil. This was distilled and 3.9 g. (61%) of β-amino-β-phenylethanol was obtained, b.p. 135–140° (6 mm.). This compound distilled as a colorless oil that crystallized upon standing. The redistilled material boiled at 141–142° (6 mm.).

Anal. Calc'd for $C_8H_{11}NO$: C, 70.05; H, 8.08; N, 10.21.

Found: C, 69.36, 69.47; H, 8.12, 8.25; N, 9.99, 10.04.

The synthesis of β-amino-β-phenylethanol by this method has been reported (11), although the yield was not stated.

The *hydrochloride* was prepared by the addition of dry hydrogen chloride to an ether solution, and was purified by recrystallization from a dry ether-ethanol mixture. It appeared to melt and resolidify at 132.6° and upon further heating melted at 149.1–150.0°.

Anal. Calc'd for $C_8H_{12}ClNO$: C, 55.33; H, 6.97; N, 8.07.

Found: C, 55.49, 55.54; H, 6.83, 6.87; N, 7.96, 8.01.

The amino alcohol was benzoylated as in the case of α-phenyl-β-aminoethanol and the dibenzoyl derivative was the only product isolated. When crystallized from 95% ethyl alcohol this compound was obtained as a white solid m.p. 153.9–154.4°.

Anal. Calc'd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.55; N, 4.06.

Found: C, 76.80, 76.92; H, 5.87, 5.93; N, 4.11, 4.22.

SUMMARY

Styrene oxide reacts with ammonia in aqueous ethanol to yield a mixture of α-phenyl-β-aminoethanol and β-amino-β-phenylethanol, wherein the former predominates.

Under comparable conditions α-phenyl-β-aminoethanol is benzoylated by the procedure of Schotten-Baumann to yield the N-benzoyl derivative as the major product along with a small amount of a dibenzoyl derivative, while β-amino-β-phenylethanol is converted only to a dibenzoyl derivative.

SAN JOSE 14, CALIFORNIA

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