[CONTRIBUTION FROM COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

ISOMERIC AMINO ALCOHOLS FROM THE REACTION OF STYRENE OXIDE WITH BENZYLAMINE[1]

COLIN L. BROWNE[2] AND ROBERT E. LUTZ

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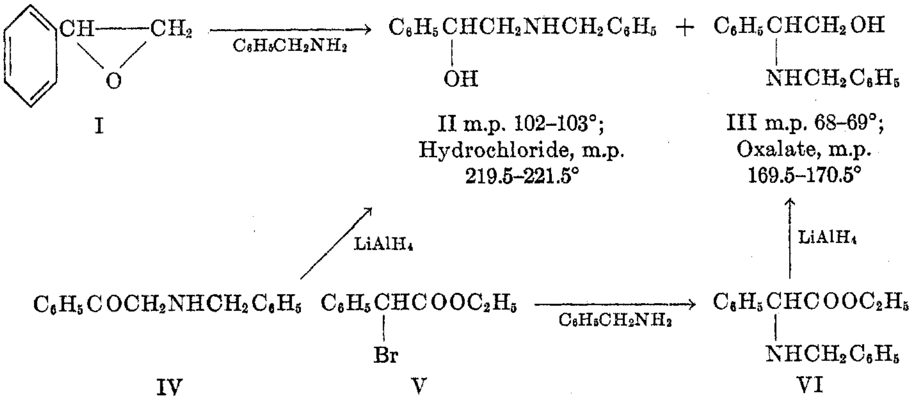
The reaction between styrene oxide (I) and benzylamine was carried out in connection with preparation of 1,2-amino alcohols of possible interest as tumor-necrotizing agents. The usual procedure involving addition of the oxide to an excess of refluxing amine over a period of several hours (1), was not satisfactory in the present case. However when the oxide was allowed to react with a 10% excess of benzylamine at room temperature over seven days the crystalline amino alcohol (II) separated from the mixture in 60% yield. Its properties agree with those reported for this compound as prepared by the reduction of 2,5-diphenyloxazole hydrochloride (2).



I

II m.p. 102–103°; Hydrochloride, m.p. 219.5–221.5°

III m.p. 68–69°; Oxalate, m.p. 169.5–170.5°

IV

V

VI

Because the yield of the compound (II) was low the residual oil from the reaction mixture was distilled; the principal fraction crystallized and proved to consist largely of the structural isomer (III). The hydrochloride of this new compound, in contrast with the hydrochloride of II, was hygroscopic and readily soluble in water, and a separation procedure for the two isomers was subsequently developed based upon these properties.

The assignments of the structures II and III were made on the basis of independent syntheses of these two compound as follows: The first compound (II) was obtained by lithium-aluminum hydride reduction of phenacylbenzylamine hydrobromide (IV) (3). The second (III) was obtained by lithium-aluminum

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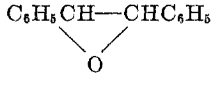
hydride reduction of ethyl α-benzylaminophenylacetate (VI) hydrochloride which had been made through condensation of ethyl α-bromophenylacetate (V) with benzylamine. The latter reactions provide a very convenient path to amino alcohols of this type.

Careful repetitions of the reaction between styrene oxide and benzylamine showed that the primary and secondary alcohols (II and III) were produced consistently in a constant ratio of 15–16 to 1, in a total yield of 65–67%. Since it has been observed that in the reactions of oxides with alcohols the proportion of the primary alcohol isomer is increased by acid catalysis (4–8, *cf.* also 9), it was decided to study the effect in the present reaction. Acid catalysis was achieved by saturating the reaction mixture with benzylamine hydrochloride (5–6%). It was found, as expected by analogy, that the ratio of II to III was now markedly lower, namely 6–7 to 1, as compared with 15–16 to 1 in the absence of an acid catalyst, but the β-reaction was still dominant. It was noted that the main reaction in the presence of the acid was at least three times faster than the uncatalyzed reaction.

In analogy with the observation that the proportion of the already large α-reaction of styrene oxide with sodium phenoxide is increased by hydrogen-bonding solvents such as alcohol and is diminished by hydrogen acceptors such as dioxane (9), we find in two experiments that in methanol using two widely different concentrations and in both cases using half of the amine in the form of the hydrobromide (under heating), an actual reversal in the ratio of yields of the two amino alcohols occurs and the primary alcohol isomer of the type III becomes dominant (II:III = 1:1.5–2.0). However the total yields of the mixture of isomers in the two experiments (41 and 24% respectively) are low as a result of production of large amounts of non-basic materials.

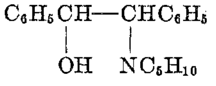
In connection with the above reactions of styrene oxide, a study was made of the effect of acid catalysis on the analogous reactions between piperidine and the *cis*- and *trans*-stilbene oxides (VII) (cf. 4) where the stereochemistry can be followed and where the different structural reactivities inherent in an unsymmetrically substituted oxide would be absent. It was found that the rates of conversion of both the *cis*- and *trans*-isomers respectively to the *threo*- and *erythro*-amino alcohols (VIII) were approximately doubled when piperidine hydrochloride was present; furthermore the rates of both the catalyzed and uncatalyzed reactions of the *trans*-oxide were greater than those of the *cis* (also approximately doubled). It can therefore be said that in both the catalyzed and uncatalyzed reactions there is obtained consistently in each case only one amino alcohol which results from an inversion type mechanism.



VII

$$\text{A}(cis) \longrightarrow (threo)\text{A}$$

$$\text{B}(trans) \longrightarrow (erythro)\text{B}$$



$$C_6H_5CH(OH)—CH(NC_5H_{10})C_6H_5$$

VIII

Discussion of results. Both electronic and steric factors influence the direction and facility of opening of unsymmetrically substituted ethylene oxide rings, and steric factors appear to be particularly important in such compounds as the styrene oxides (5–18). Reactions with nucleophilic reagents have been regarded generally as *trans*-bimolecular nucleophilic displacements (S_N2) accompanied by Walden inversion (11–18). On the other hand in a recent investigation involving styrene oxide and phenol it has been argued that attack at the α-carbon is S_N1 because of the decrease in the α-reaction brought about by the substitution of a *para*-nitro group, which is similar to the effect of a *para*-nitro group on the S_N1 reactivity of benzyl chloride (10).[3] However the assumption of simple analogy in the structurally more complicated oxides may be open to question because any effect of the *para*-nitro group on the α-reaction, which still involves a drastic steric effect at this point, should be accompanied by simultaneous (transmitted) effects, on the β-carbon where steric interferences are far less, and on the oxygen with respect to protonation and hydrogen bonding.

The kinetically demonstrated S_N2 reaction at the 2-carbon (*alpha* to the phenyl) of 1-benzoyl-2-phenyl ethylene oxide (19, 20) is of interest in this connection.

The consistent inversion occurring in the acid-catalyzed reactions between piperidine and the *cis*- and *trans*-stilbene oxides constitutes an argument for the S_N2 mechanism, as also does the greater facility of the reaction in the case of the *trans*-isomer [it is here assumed that in the *cis*-oxide the greater steric strains would relatively facilitate the rate-determining ionization step of an S_N1 reaction (*cf.* 21), and that neighboring group participation by the second (and β) phenyl would be negligible (*cf.* 22)]. If analogies are to be trusted here, it would appear that the acid-catalyzed styrene oxide aminations are S_N2 reactions.[4]

The relatively sharp increase in attack at the α-carbon as compared with attack at the β-carbon in the reaction between styrene oxide and benzylamine under acid catalysis (*cf.* 23) and in a hydrogen-bonding solvent such as methanol, may be explained in terms of protonation of the oxide-oxygen and the ability of the protonated molecule to accommodate its formal charge in the nucleus, with consequent weakening of the α-carbon-oxygen bond by resonance stabilization of the transition state.

In much of the previous work on the direct reactions between amines and styrene oxide and other aryl ethylene oxides, and on the indirect reactions through the action of amines on the corresponding halohydrins (1, 24–27), the only products reported have been the result of attack at the β-carbon. However, according to the early work of Mannich, 3,4-dimethoxy- and 3,4-methylenedioxy-styrene bromohydrins in ethanol react (presumably through their oxides) with amines to give mixtures of the two isomeric amino alcohols, and these reactions are consistent and comparable with the acid-catalyzed reaction here reported between benzylamine and styrene oxide.

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[3] Since this paper was submitted another has appeared (29) which reports dominance of the α-reaction upon substitution of a *para*-methoxyl.

[4] It is of course quite possible that α-reactions of α,α-diarylethylene oxides would proceed *via* the S_N1 mechanism because of the extra α-aryl group and the quaternary nature of the α-carbon (cf. ref. 29).

It is of interest to note that relative to styrene oxide as a standard of reference, the reactivities of the many 4-quinolineethylene bromohydrins would be expected to give predominantly the β-reaction products, as they seem to do, because of the combination of the electrophilic nature and the greater steric effect of the quinoline nucleus. On the other hand in the case of the 3,4-dimethoxy- and 3,4-methylenedioxy-styrene oxides (presumably formed in the reactions of the bromohydrins) the steric effect should not be far different from that in styrene oxide itself, but the electron-donation effect of the *para*-oxygen facilitating the accommodation of the positive charge on polarization, protonation or hydrogen bonding of the oxide-oxygen should be much greater and might well favor the α-reaction. When the steric effect of the α-aryl group is counterbalanced by the similar effect of a β-methyl the reaction *alpha* with respect to the phenyl should and actually appears to be dominant under comparable reaction conditions (28).

TABLE I

SUMMARY OF REACTION DATA[a]

Styrene oxide[a]	0.5	0.25	0.25	0.25	0.5
Benzylamine[a]	0.55	0.28	0.28	0.28	0.6
Benzylamine hydrochloride	—	—	0.014[b]	0.014[b]	0.026[c]
Days reacted	7	7	1	2	7
Yield of II[a]	0.310	0.137	0.0872	0.132	0.262
Yield of II·HCl[a]	0.004	0.016	0.0145	0.008	0.005
Yield of III[a]	0.0198[d]	0.010[e]	0.0146[e]	0.022[e]	0.04[d]
Yield of II, %	62.8	61.2	40.7	56.0	53.4
Yield of III, %	4.0	4.0	5.8	8.8	8.0
Total yield, II–III, %	66.8	65.2	46.5	64.8	61.4
Ratio of II to III	15.9:1	15.31:1	6.97:1	6.36:1	6.68:1

[a] All quantities of material are expressed in moles. [b] Added in the form of solid benzylamine hydrochloride. [c] Added as benzylamine followed by standardized ethereal hydrogen chloride. [d] Liberated with 10% sodium hydroxide. [e] Liberated with solid sodium carbonate.

EXPERIMENTAL

The following is a *general procedure* which was developed and used without significant changes in all of the tabulated experiments (Table I). Commercially available materials were used. The reaction mixtures consisted of 30 g. (0.25 mole) of styrene oxide and 30 g. (0.28 mole) of benzylamine. In the experiments where the presence of some acid was desired the saturation amount (1.9 g.) of benzylamine hydrochloride was added either directly or as the equivalent amount of additional amine followed by an equivalent amount of standardized ethereal hydrogen chloride.

After the desired reaction period, the resulting mush was suction filtered and as much oil was pressed out as possible. The solid was then triturated thoroughly on the filter funnel with two 50-ml. portions of ligroin.[5] This procedure gave products (II) with melting points between 98° and 100°.

2-Benzylamino-1-phenylethanol (II). Samples obtained as above were repeatedly crystallized from isoöctane[5] or ligroin;[5] m.p. 102–103°.

Anal. Calc'd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16.
Found: C, 79.35; H, 7.22; N, 6.36.

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[5] Isoöctane = 2,2,4-trimethylpentane. Ligroin, b.p. 90–110°.

The ligroin washings were evaporated and the resulting oil combined with that pressed from the solid (II). This oil was poured with mechanical stirring into 125 ml. of 2 *N* hydrochloric acid overlaid with 50 ml. of ethyl acetate. The mixture was stirred for a half-hour and the precipitated *II-hydrochloride* was filtered; m.p. 213–216°; recrystallized from absolute ethanol, m.p. 219.5–221.5°.

Anal. Calc'd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; N, 5.31.
Found: C, 68.30; H, 7.14; N, 5.36.

Evaporation of the ethyl acetate layer from the preparation of II-hydrochloride left a dark brown oil. No other pure product was isolated.

2-Benzylamino-2-phenylethanol (III). Following the isolation of II (above) the acid filtrate from the crystallization of II-hydrochloride was separated and neutralized with solid sodium carbonate or 10% sodium hydroxide. The isomer (III) separated as an oil. Cracked ice was added and the oil was then induced to crystallize; it was filtered off and recrystallized from isoöctane; m.p. 58–62°. Further purification brought the melting point to 68–69°.

Anal. Calc'd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16.
Found: C, 78.72; H, 7.36; N, 6.40.

III-Oxalate was prepared by treatment of III in ether solution with saturated ethereal oxalic acid; recrystallized from abs. ethanol; m.p. 169.5–170.5° with decomp.

Anal. Calc'd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41.
Found: C, 64.10; H, 6.32; N, 4.47.

The styrene oxide-benzylamine reaction in methanol. A mixture of 9.4 g. (0.05 mole) of benzylamine hydrobromide, 5 g. (0.05 mole) of benzylamine, 12.0 g. (0.10 mole) of styrene oxide, and 250 ml. of methanol was warmed on a steam-bath for 3 hours. Evaporation gave a heavy oil which was poured into 200 ml. of 2 *N* hydrochloric acid. After stirring for 1 hour the acid solution was decanted and treated with 10% sodium hydroxide, and III separated and solidified on chilling; 5 g. (26%), m.p. 52–65° (identified by recrystallization and mixture m.p.).

The residual yellow oil (II-hydrochloride) was converted to the base and crystallized from isoöctane containing a little benzene; 3.5 g. (15%), m.p. 92–96° (recrystallized and identified by mixture m.p.).

In a similar experiment using instead 75 ml. of methanol the reaction mixture was poured into 200 ml. of 2 *N* hydrochloric acid and stirred for 1 hour. The acid solution was decanted and treated with 10% sodium hydroxide; the product, which did not crystallize completely, was dissolved in isoöctane and precipitated as the salt of III with ethereal oxalic acid; 5 g. (16%), m.p. 165–167° (identified by further purification and mixture m.p.). The yellow oil remaining after treatment with acid was crystallized from ether containing a little ethanol; 2 g. (8%), m.p. 216–218° (identified as II-hydrochloride by mixture m.p.). The filtrate gave 9 g. of heavy non-basic oil (57% calculated as mono-methylglycol ether).

Synthesis of 2-benzylamino-1-phenyl-ethanol (II) *from phenacylamine* (IV). To a thoroughly stirred mixture of 300 ml. of absolute ether and 1.8 g. (0.02 mole) of lithium aluminum hydride was added 3 g. (0.01 mole) of phenacylbenzylamine (IV) hydrobromide (3) with stirring and gentle refluxing for one hour; 100 ml. of water was then added slowly followed by 10% sodium hydroxide. The ether layer was separated, washed, dried over sodium sulfate, and evaporated; this gave a white solid (II) and an orange oil. The solid was recrystallized from ligroin; 2.0 g. (88%), m.p. 100.5–101.5°. A mixture melting point with the sample above showed no depression.

Ethyl α-benzylaminophenylacetate (VI) *hydrochloride.* A solution of 12.1 g. (0.05 mole) of ethyl α-bromo-α-phenylacetate in 150 ml. of absolute ether was added dropwise under stirring to 10.7 g. of benzylamine in 150 ml. of absolute ether. After stirring and gently refluxing for four hours the precipitated benzylamine hydrobromide was filtered. The ether solution was then extracted twice with 2 *N* hydrochloric acid to separate the basic material from unreacted halide; the acid layer was neutralized with solid sodium carbonate and extracted with 100 ml. of ether. The ether layer was washed with water to remove unreacted benzylamine and was dried over sodium sulfate. Evaporation gave an oil which would not crystallize. This oil was taken up in ether and addition of ethereal hydrogen chloride precipitated 3.7 g. (24%) of the VI-hydrochloride which melted at 176–178°; recrystallized from abs. ethanol, m.p. 181.5–182.5°. The samples dried *in vacuo* at 55° contained approximately one molecule of water.

Anal. (sample dried at 100° *in vacuo*) Calc'd for $C_{17}H_{19}NO_2 \cdot HCl$: Cl, 11.60; N, 4.58.
Found: Cl, 11.56, 11.64; N, 4.91.

VI-Hydrochloride (1.5 g., 0.005 mole) was added slowly to 0.3 g. (0.008 mole) of lithium aluminum hydride in 150 ml. of abs. ether, and the resulting mixture was refluxed gently under stirring for four hours, after which 50 ml. of water was added slowly. The mixture was treated in a separatory-funnel with 10% sodium hydroxide and the ether layer was washed, dried over sodium sulfate, and evaporated. The residual oil upon chilling and rubbing crystallized slowly; 7 g. (60%), m.p. 66–67°. A mixture melting point with the sample obtained above showed no depression.

The acid-catalyzed reaction between piperidine and cis- and trans-stilbene oxides (VII). A mixture of 1 g. of the oxide (0.005 mole) and 0.75 g. of piperdine (0.009 mole) with or without 0.25 g. (0.0002 mole) of piperidine hydrobromide (which did not all dissolve in the reaction mixture) was immersed in a hot-water bath. After a specified time the products were taken up in absolute ether and acidified with ethereal hydrochloric acid (to Congo Red). The hydrochlorides were filtered and dissolved in water. The bases were precipitated by rendering alkaline (*p*H 8) and were purified and identified by mixture melting points. Non-basic material (crude unreacted oxide) was recovered by evaporation of the ether solution. The *trans*-oxide after 18 hours at 93–95°, with catalyst present, gave 86% of VIIIB (and 12% of VIIB); without catalyst the yield was 46% (and 45% of VIIB). At 88–90° the yields in the catalyzed and uncatalyzed reactions were 71 and 23% respectively. In the case of the *cis*-oxide (VIIA), in the catalyzed and uncatalyzed reactions, at 93–95° for 18 hours, the yields of VIIIA were 36 and 18% respectively (recoveries of VIIA, 50 and 75%); and at 93–95° for 48 hours at the same temperature, the yields were 61 and 29%, respectively (with recoveries of VIIA of 35 and 70%). The samples of VIIIA melted at 100–101° and of VIIIB at 110–111°. Had there been formed any significant quantities of the epimer in either case, sharp melting points such as these would not have been realized (the mixture melting point depression of the epimeric pair is around 30°).

SUMMARY

The two possible structurally isomeric 1,2-amino-alcohols produced from two different modes of ring opening have been isolated from the reaction of styrene oxide with benzylamine. Their structures have been proven by independent syntheses, the one through reduction of the phenacylamine and the other through condensation of α-bromophenylacetic ester with benzylamine and reduction. The rate of reaction and proportion of attack at the α-carbon are increased by acid catalysis.

trans-Stilbene oxide reacts more rapidly than the *cis*-isomer with piperidine, with or without an acid catalyst. Acid catalysis increases the rates significantly, with consistent formation in each case of the stereoisomeric aminoalcohol resulting from an inversion mechanism.

The results to date in this field seem to be consistent with the postulate that aminolysis of styrene oxide rings takes place by the S_N2 mechanism, and is controlled by both steric and electronic factors.

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