Competitive Reaction with IIA and IIB.—This experiment produced an 80% yield of the known 1,5-diphenyl-3-*p*-tolyl-4-benzylaminopyrazoline,[1] m.p. 121–123°. About 30% of the unreacted IIA was recovered.

Competitive Reaction with IIIA and IIIB.—This experiment gave an 80% yield of the pale yellow 1,3,5-triphenyl-4-cyclohexylaminopyrazoline (XIV), m.p. 143–145°. Seventy per cent. of the unreacted IIIA was recovered.

Anal. Calcd. for $C_{27}H_{29}N_3$: C, 82.03; H, 7.34. Found for XIV: C, 82.24; H, 7.39.

1,5-Diphenyl-3-*p*-tolyl-4-methylaminopyrazoline (XV).—This compound was obtained as pale yellow crystals in a 75% yield from the reaction of V in absolute ethanol, m.p. 157–158°.

Anal. Calcd. for $C_{23}H_{23}N_3$: C, 80.94; H, 6.45. Found for XV: C, 81.25; H, 6.65.

Reaction with 1-Cyclohexyl-2-benzoylethylenimine (VII).—In absolute ethanol this ethylene imine ketone gave a 54% yield of a colorless compound, m.p. 84–85°, identical with an authentic sample of 1,3-diphenylpyrazole[19] which was prepared in the usual way[20] from α,β-dibromopropiophenone.

1,5-Diphenyl-3-*p*-tolyl-4-aminopyrazoline (XVI).—This compound was obtained in 25% yield from the reaction of VI in absolute ethanol solution, m.p. 134–136° (recrystallized from methanol). This aminopyrazoline was rather unstable in warm acid solutions. If the preparation reaction mixture was heated for only 15 minutes no aminopyrazoline could be isolated but instead 1,5-diphenyl-3-*p*-tolylpyrazole resulted.

Anal. Calcd. for $C_{22}H_{21}N_3$: C, 80.73; H, 6.42. Found for XVI: C, 81.08; H, 6.73.

Absorption Spectra Studies

Ultraviolet Absorption Spectra.—These measurements were made using a Beckman model DU photoelectric quartz spectrophotometer. Unless otherwise indicated in the tables all determinations were made in pure[21] heptane-from-petroleum using silica cells over the range of 220 to 600 mμ. The maxima and their extinction coefficients are given in Table I and the curves are shown in Figs. 1–6.

Infrared Absorption Spectra.—Most of these measurements were made by Samuel P. Sadtler and Son, Inc., Philadelphia 3, Pa., using a Baird recording infrared spectrophotometer. Samples were in the form of Nujol mulls and measurements were made over the range of 5000 cm.$^{-1}$ (2 μ) to 625 cm.$^{-1}$ (16 μ). A few of the compounds were also studied by Dr. H. S. Gutowsky and Miss E. M. Petersen of the Department of Chemistry, University of Illinois, Urbana, Ill. These latter studies were done with a Perkin-Elmer model 12B infrared spectrophotometer and the samples were in the form of Nujol mulls, and as 0.05 mm. chloroform solutions. The curves from 2000 cm.$^{-1}$ (5 μ) to 1000 cm.$^{-1}$ (10 μ) are shown in Figs. 7–12 while the important carbonyl frequencies are given in Table II.

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(19) Knorr and Duden, *Ber.*, **26**, 115 (1893).

(20) Barnes and Dodson, THIS JOURNAL, **65**, 1585 (1943).

(21) Weissberger, "Physical Methods of Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1946, p. 767.

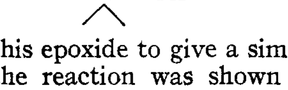
[CONTRIBUTION FROM THE AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Reactions of Epoxy Ketones and Alcohols with Amines. Mechanism Studies

BY NORVAL G. BARKER[1] AND NORMAN H. CROMWELL

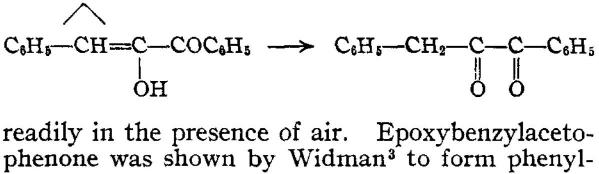
Epoxybenzylacetophenone has been found to react with secondary heterocyclic amines to yield α-hydroxy-β-*t*-aminoketones, but none of the desired product was obtained with dialkyl amines. The reaction of morpholine with this epoxy ketone was shown to follow second order kinetics within experimental error, confirming the mechanism previously postulated[2] for such reactions. Both secondary heterocyclic amines and some dialkyl amines undergo reaction with the epoxy alcohol, 1,1,3-triphenyl-2,3-epoxypropanol-1, forming 1,1,3-triphenyl-3-*t*-aminopropan-1,2-diols.

The following report describes a continuation of studies designed to obtain more information about reactions of epoxides with amines. Our preliminary investigations[2] had shown that the major products resulting from the reaction of epoxybenzylacetophenone with morpholine and piperidine were the α-hydroxy-β-*t*-aminoketones (I) and (II), respectively. It has now been found that tetrahydroisoquinoline also undergoes reaction with this epoxide to give a similar product (III). Thus the reaction was shown to be quite general for secondary heterocyclic amines. On the other hand, diethylamine, dimethylamine and N-methylbenzylamine gave no reaction with this epoxy ketone under identical reaction conditions although these amines have basic strengths similar to those which did react. This apparent anomaly indicated that steric factors must greatly influence the rate of reaction. When the time and temperature were increased in order to speed the reaction with these latter amines, a change occurred but no solid products could be isolated. The α-hydroxy-β-*t*-aminoketones (I), (II) and (III) were shown to be unstable in basic media especially at higher temperatures. Even in the solid state (II) slowly decomposes to a brown tarry substance, traces of which give the red-brown coloration with ferric chloride in alcohol which is characteristic of phenylbenzyldiketone. This ketone is known to oxidize readily in the presence of air. Epoxybenzylacetophenone was shown by Widman[3] to form phenyldiketone readily upon warming with sodium methoxide solution. Thus neither the epoxy ketone nor the α-hydroxy-β-aminoketones are stable at higher temperatures in basic media so none of the desired products can really be expected under these conditions.



$$C_6H_5-\underset{\underset{\wedge}{N}}{CH}-\underset{OH}{CH}-COC_6H_5$$

I, >N—, NC_4H_8O
II, >N—, NC_5H_{10}
III, >N—, NC_9H_{10}



$$C_6H_5-\underset{\underset{\wedge}{N}}{CH}-\underset{OH}{CH}-COC_6H_5 \longrightarrow$$

$$C_6H_5-CH=\underset{OH}{C}-COC_6H_5 \longrightarrow C_6H_5-CH_2-\underset{O}{\overset{}{C}}-\underset{O}{C}-C_6H_5$$

Acetylation of the α-hydroxy-β-aminoketone (III) gave α-acetoxy-β-tetrahydroisoquinolino-

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(1) Abstracted from the Ph.D. thesis of Norval G. Barker, U. S. Public Health Project Research Assistant, 1949–1950, University of Nebraska.

(2) Cromwell and Barker, THIS JOURNAL, **72**, 4110 (1950).

(3) Widman, *Ber.*, **49**, 484 (1916).

benzylacetophenone. This product was shown to be identical with that later obtained from the reaction of α-bromo-β-tetrahydroisoquinolinobenzylacetophenone and triethylammonium acetate.[4] Lithium aluminum hydride reduction of (III) produced the corresponding aminopropyleneglycol.

There was found to be an appreciable difference in the light absorption of epoxybenzylacetophenone and α-hydroxy-β-morpholinobenzylacetophenone (see Fig. 1) in the range from 252 to 260 mμ. Based on this difference, a method was devised for following the course of the reaction of the epoxide with morpholine. Second order kinetics were found to be followed within experimental error. These results are in entire accord with the mechanism postulated previously[2] for the reaction of epoxybenzylacetophenone with amines. This mechanism would seem to involve a bimolecular nucleophilic attack (S_N2) on the β-carbon of the epoxy ketone by the amine.

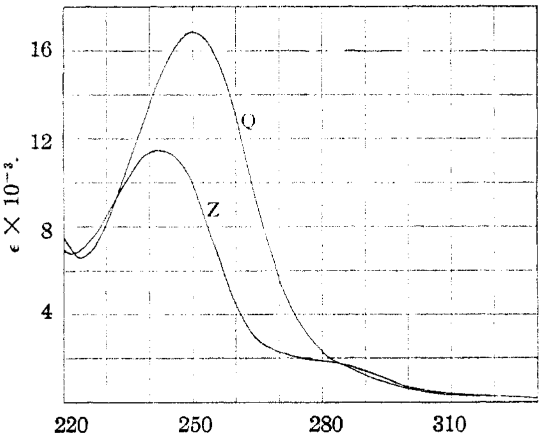
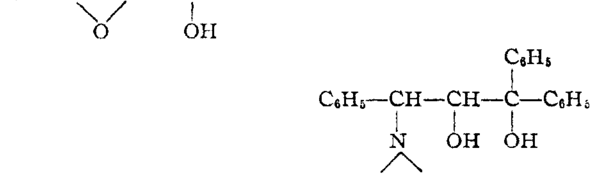


Fig. 1.—Ultraviolet absorption spectra of Q, epoxybenzylacetophenone, and Z, α-hydroxy-β-morpholinobenzyl acetophenone.

It was of interest to determine if the benzoyl group was the major directive influence for the attack by amines at the β-position of this epoxide. In order to do this the reactions of 1,1,3-triphenyl-2,3-epoxypropanol-1 with various secondary amines were studied. This epoxy alcohol readily undergoes reaction with piperidine or morpholine to form 1,1,3-triphenyl-3-*t*-aminopropan-1,2-diols (IV) and (V). Compound (IV) has been reported previously.[2,5] These aminopropyleneglycols and the epoxy alcohol from which they were derived are much more stable than the epoxy ketone or α-hydroxy-β-*t*-aminoketones. By increasing the reaction time and temperature, N-methylbenzylamine and dimethylamine reacted with the above epoxy alcohol to give good yields of (VI) and (VII), respectively. It was found that a compound identical with (VI) could be obtained by reaction of α - acetoxy - β - N - methylbenzylaminobenzylacetophenone with phenyl lithium. Thus it seems probable that all of these glycols have the structures which have been assigned to them.



$$C_6N_5-\underset{\diagdown O \diagup}{CH-CH}-\overset{C_6H_5}{\underset{OH}{C}}-C_6H_5 \xrightarrow{>N-} C_6H_5-\underset{\underset{\wedge}{N}}{CH}-\underset{OH}{CH}-\overset{C_6H_5}{\underset{OH}{C}}-C_6H_5$$

IV, >N—, NC_5H_{10}
V, >N—, NC_4H_8O
VI, >N—, $CH_3—N—CH_2—C_6H_5$
VII, >N—, $CH_3—N—CH_3$

It was found that diethylamine could not be made to react with either the epoxy alcohol or epoxy ketone, indicating that steric factors must influence the rate of both reactions.

Acknowledgment.—This investigation was supported in part by a research grant to one of us from the National Cancer Institute, U. S. Public Health Service.

Experimental[6]

α-Hydroxy-β-*t*-aminobenzylacetophenone (III).—A mixture of 20 g. (0.089 mole) of epoxybenzylacetophenone and 30 g. (0.226 mole) of tetrahydroisoquinoline in 30 ml. of methanol was warmed slightly to obtain solution and allowed to stand at room temperature. After one day the solution was filtered to give 30 g. (94% yield) of (III), m.p. 134–135° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.90; H, 6.48; N, 3.92.

Treatment of epoxybenzylacetophenone with diethylamine, dimethylamine or N-methylbenzylamine according to the above conditions yielded only starting materials. When stronger conditions were employed such as higher temperatures and pressures and increased reaction time, the solutions rapidly darkened. No solid products could be isolated from these solutions.

α-Acetoxy-β-tetrahydroisoquinolinobenzylacetophenone.—On warming slightly with a small amount of acetic anhydride 0.5 g. of (III) gave 0.30 g. (55% yield) of colorless crystals, m.p. 155–156°.

Anal. Calcd. for $C_{26}H_{25}NO_3$: C, 78.15; H, 6.31; N, 3.51. Found: C, 78.35; H, 6.39; H, 3.69.

This product was shown to be identical with that obtained from the reaction of α-bromo-β-tetrahydroisoquinolinobenzylacetophenone and triethylammonium acetate as described below.[4]

To a benzene suspension of 30.1 g. (0.0716 mole) of α-bromo - β - tetrahydroisoquinolinobenzylacetophenone was added 6.45 g. of glacial acetic acid and 10.9 g. of triethylamine (representing 1.5 molar equivalents of triethylammonium acetate). The suspension was stored at room temperature for 15 hours. At the end of this time 11.84 g. of triethylamine hydrobromide was recovered from the reaction mixture. Upon concentration of the filtrate and addition of petroleum ether, 6.5 g. (23% yield) of the acetoxy amino ketone was obtained.

1,3-Diphenyl-3-tetrahydroisoquinolinopropan-1,2-diol.—A 7-g. sample of (III) was placed in the cup of a Soxhlet extraction apparatus and refluxed for 4 hours with a dry ether solution of four molar equivalents of lithium aluminum hydride. The reaction mixture was decomposed with water and 6.05 g. (85% yield) of product isolated from the ether layer by evaporation of the solvent. In order to purify this product the hydrochloride was prepared, recrystallized from chloroform and then converted back to the free amine. After recrystallization from benzene–petroleum ether the amino glycol melted at 90–91°.

Anal. Calcd. for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.02; N, 3.90. Found: C, 79.96; H, 7.25; N, 3.70.

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[4] Reaction carried out by Dr. Fred W. Starks, Ph.D. thesis, University of Nebraska, 1950.

[5] Cromwell and Starks, THIS JOURNAL, **72**, 4108 (1950).

[6] Microanalyses for carbon, hydrogen and nitrogen were determined by Clark Microanalytical Laboratory, Urbana, Ill.

1,1,3-Triphenyl-3-*t*-aminopropan-1,2-diols, (IV) to (VII).—A mixture of 2.1 g. (0.007 mole) of 1,1,3-triphenyl-2,3-epoxypropanol-1 and 0.014 mole of the corresponding amine in 10 ml. of methanol was heated at reflux temperature for 1 to 8 hours. After cooling the solution was filtered and the precipitate recrystallized from absolute ethanol. The reaction mixture containing piperidine gave 73% yield of (IV), m.p. 173–174°. This product was identical with that obtained previously.[2,5]

Reaction with morpholine produced 94% of (V) melting at 193–194°, identical with the compound prepared by Tsou and Cromwell[7] from (I) and phenylmagnesium bromide.

The N-methylbenzylamine solution gave 82% of (VI), m.p. 167–168°.

Anal. Calcd. for $C_{29}H_{29}NO_2$: C, 82.24; H, 6.90; N, 3.31. Found: C, 82.54; H, 7.08; N, 3.30.

For the reaction of the epoxy alcohol and dimethylamine a sealed tube was necessary. A 95% yield of (VII) was obtained, m.p. 164–165°

Anal. Calcd. for $C_{23}H_{25}NO_2$: C, 79.50; H, 7.25; N, 4.03. Found: C, 79.71; H, 7.24; N, 3.96.

The N-methylbenzylamine derivative (VI) was also prepared by treatment of 0.2 g. (0.0005 mole) of α-acetoxy-β-N-methylbenzylaminobenzylacetophenone[5] with 0.001 mole of phenyllithium for 1 hour at reflux temperature. Decomposition of the addition product with water and concentration of the solution gave 0.14 g. (65%) of (VI), m.p. 167–168°.

Absorption Spectra.—Using a Beckman Model DU spectrophotometer and absolute ethanol as the solvent, the spectra of epoxybenzylacetophenone and α-hydroxy-β-morpholinobenzylacetophenone were determined (Fig. 1).

Kinetics for the Reaction of Epoxybenzylacetophenone with Morpholine.—For each experiment: (a) Weighed samples of the epoxide and morpholine were mixed in 50 ml. of methanol and placed in a constant temperature water-bath at 25.0 ± 0.1°. (b) Pipet samples were removed at intervals during the course of the reaction and diluted to suitable concentrations for use with the spectrophotometer (this dilution was shown to quench the reaction). (c) The optical density was determined at five wave lengths (252, 254, 256, 258 and 260 mμ) and the concentration of α-hydroxy-β-morpholinobenzylacetophenone calculated for each of these wave lengths. From an average of these values the concentration in the reaction solution was found. (d) For each experiment log $b(a - x)/a(b - x)$ was plotted against time in minutes, as shown in Fig. 2, in which a and b are initial concentrations of morpholine and epoxide (moles/l.), respectively. Zero time for the calculations was taken at 1 hour after reagents had been mixed. The second order constants (liters mole^{-1} min.$^{-1}$) were then determined from the slopes of the straight lines. These values, together with their maximum deviation from constants determined individually at each time interval, are recorded in Table I. For comparison, the average first order constants are included. Thus the reaction was shown to follow second order kinetics within experimental error.

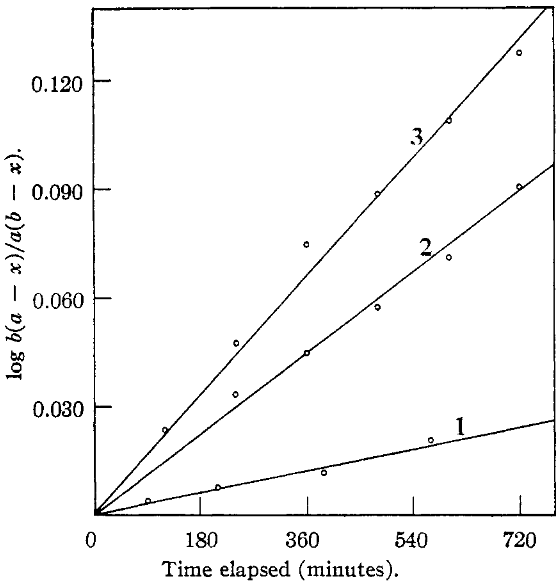

Fig. 2.—Second order curves for the reaction of epoxybenzylacetophenone with morpholine in methanol at 25°: curve (1), concn. morpholine 0.192 mole/l., concn. epoxide, 0.120 mole/l.; curve (2), concn. morpholine, 0.338 mole/l., concn. epoxide, 0.118 mole/l.; curve (3), concn. morpholine, 0.442 mole/l., concn. epoxide 0.112 mole/l.

TABLE I

In experiment (1) dry methanol was used as the reaction media and for the latter two runs a 0.2% solution of water in methanol was used.

Expt.	a	b	Second order 10^3k	First order 10^4k
1	0.192	0.120	1.1 ± 0.4	2.1
2	.338	.118	1.3 ± 0.2	4.3
3	.442	.112	1.3 ± 0.2	5.9

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[7] Tsou and Cromwell, *J. Org. Chem.*, **15**, 1293 (1950).