[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF WAYNE UNIVERSITY]

Epoxyethers. X. The Preparation and Some Chemical Reactions of an Amino Epoxyether[1]

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The amino epoxyether I and the corresponding methiodide II were prepared and shown to be relatively stable to ring-opening reactions. The hydrochloride of I decomposed at the melting point to form 2-chloroisobutyrophenone and dimethylaminoethanol.

For some time it has been known that the chemical properties associated with the formation and cleavage of an acetal group are changed profoundly by the presence of an amino group within the same molecule. Thus glycosides of 2-amino sugars are particularly stable to acid-catalyzed cleavage reactions, and methanolic hydrogen chloride is unable to convert a 2-amino sugar into the glycoside derivative.[3] Moggridge and Neuberger[4] suggested that the unusual stability of these amino glycosides could be explained satisfactorily by the positive charge developed on the nitrogen atom in acidic media, the positive charge effectively hindering further approach of a proton to catalyze the glycoside cleavage.

Epoxyethers may be considered to be glycosides of two carbon sugars or analogs of 1,2-anhydrosugars. The most characteristic reactions of epoxyethers[5] are the rapid, exothermic, acid-catalyzed ring-opening reactions corresponding to the hydrolytic cleavage of sugar glycosides. The purpose of the present study was to determine whether the chemical principles involved in hindering the cleavage of amino sugar glycosides could be used to moderate the ring-opening reactions of epoxyethers. An epoxyether containing a *t*-amino group was prepared and this ketal, as well as certain derivatives, proved to be markedly more resistant to acid-catalyzed cleavage than were similar epoxyethers without an amino group.

The amino epoxyether I, 1-phenyl-1-(2-dimethylamino)-ethoxy-2-methyl-1,2-epoxypropane, was prepared in 65–80% yield from α-bromoisobutyrophenone and the sodium salt of dimethylaminoethanol. As predicted from the properties of 2-amino sugar glycosides, compound I was difficult to hydrolyze but acid-catalyzed hydrolysis could be accomplished in aqueous solution when maintained at the reflux temperature for 66 hours. α-Hydroxyisobutyrophenone was isolated in 73% yield and dimethylaminoethanol was isolated as the methiodide salt in 76% yield. The isolation of these expected degradation products of I along with the fact that the infrared spectrum of I contained no carbonyl or hydroxyl band provided good evidence for the structure of this epoxyether.

The amino epoxyether I reacted rapidly with methyl iodide in dry ether to give 96% of the quaternary ammonium salt II. This crystalline derivative of the epoxyether I was immediately soluble in water from which it could be recovered unchanged after three hours by evaporation of the water at room temperature. These results are significant since II represents the first epoxyether that has been prepared which is soluble in water without being destroyed rapidly by hydrolysis.

The hydrolysis of II could be accomplished by heating a water solution to the reflux temperature for five hours, from which reaction 82% of α-hydroxyisobutyrophenone and 88% of the methiodide of dimethylaminoethanol could be isolated.

Every epoxyether that had been isolated previously in this Laboratory[5] reacted rapidly with the alcohol corresponding to the ether group of the epoxyether to give a hydroxy ketal. However, when the amino epoxyether I was dissolved in excess dimethylaminoethanol and the reaction mixture heated at the reflux temperature for 36 hours, only starting materials could be recovered. Also, the amino epoxyether methodide II could not be made to react with dimethylaminoethanol methiodide even though a solution of the two salts in nitromethane was heated to the reflux temperature for 66 hours. That these results represent only an inhibition of alcoholysis and not a chemical property fundamentally different from other epoxyethers was shown by the fact that II could be alcoholyzed by heating a methyl alcohol solution to the reflux temperature for four days. The hydroxy mixed ketal III could be isolated in 70% yield and the structure confirmed by hydrolysis to the hydroxy ketone and dimethylaminoethanol methiodide.

During the preparation of the hydrochloride of I a very interesting sequence of changes was discovered. When an ether solution of dry hydrogen chloride was added to an ether solution of the amino epoxyether I a gelatinous precipitate formed immediately. The salt was formulated as the amine hydrochloride IV and proved to be very hygroscopic. In attempting to determine a melting point of the salt a further chemical change was noted at 150°. From the pyrolysis of a larger sample of the hydrochloride at 150° for 15 minutes a 73% yield of α-methylacrylophenone could be isolated. The most reasonable mechanism for the formation of α-methylacrylophenone would involve attack of the chloride ion at the carbon atom (C_2 in formula IV) of the epoxide which contains the two methyl groups to give α-chloroisobutyrophenone and dimethylaminoethanol, with subse-

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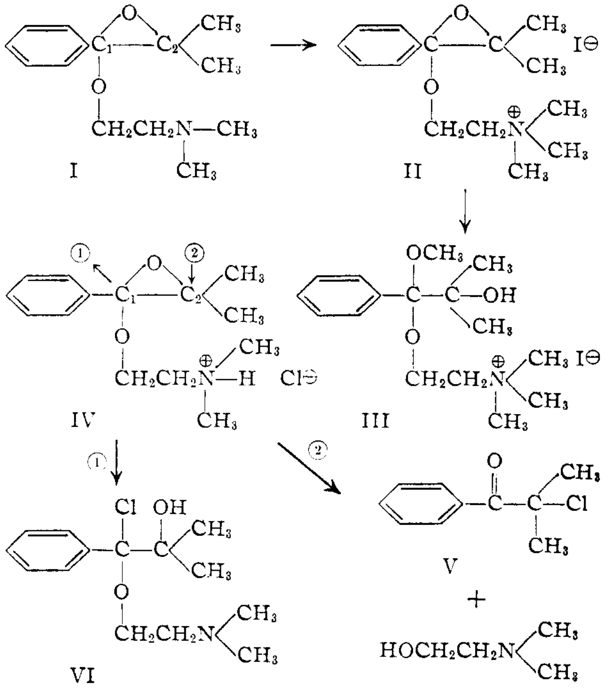
[2] Abstracted from the thesis submitted by Bruce V. Ettling in August, 1954, to the Graduate School at Wayne University in partial fulfillment of the requirements for the degree of Master of Science.

[3] For a discussion of the glycoside derivatives of 2-amino sugars, see A. B. Foster and M. Stacey, *Adv. in Carbohydrate Chem.*, **7**, 271 (1952).

[4] R. C. G. Moggridge and A. Neuberger, *J. Chem. Soc.*, 745 (1938).

[5] C. L. Stevens and S. J. Dykstra, THIS JOURNAL, **76**, 4402 (1954). Also see the preceding articles in this series.



quent dehydrohalogenation of the α-haloketone by the t-amine. This mechanism was supported by the independent preparation of α-methylacrylophenone from α-haloisobutyrophenone and a t-amine. More important evidence for this mechanism was the actual isolation of α-chloroisobutyrophenone (V) from a pyrolysis mixture in 33% yield.

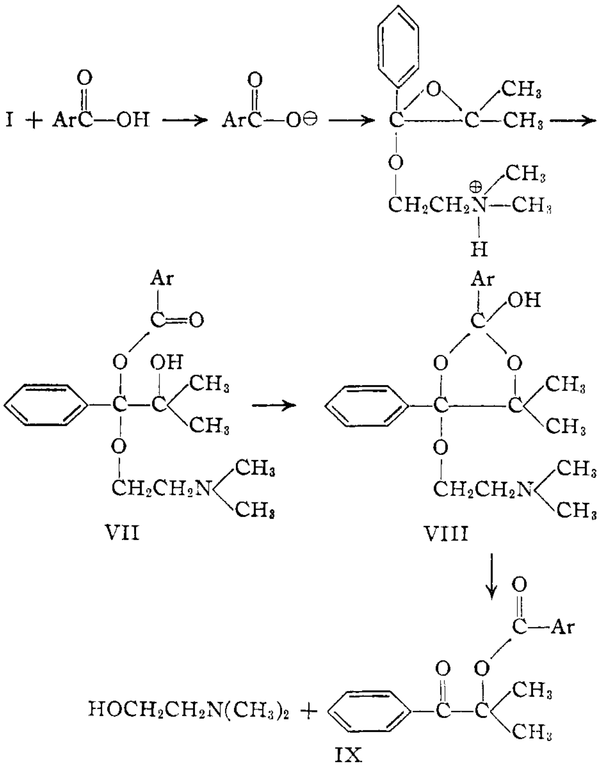
Although reasonable precautions were taken to exclude water from the preparation and pyrolysis of the salt, in view of the hygroscopic nature of the salt one further experiment was performed to exclude the possibility that the reaction proceeded *via* hydrolysis of this salt. The hydrolysis products, α-hydroxyisobutyrophenone and dimethylaminoethanol hydrochloride, were mixed and subjected to the pyrolysis conditions from which the α-hydroxyketone could be recovered unchanged.

The isolation of α-chloroisobutyrophenone (V) is especially significant because all previously recorded ring-opening reactions of epoxyethers can be interpreted on the basis of attack of the nucleophilic reagent initially upon the epoxide carbon (C_1 in formula IV) which is in the ketal state of oxidation.

In this particular instance attack at C_2 is understandable since attack at C_1 might be expected to be fruitless. Attack at C_1 would give an α-chloro-β-hydroxy ether VI, but it is specifically known that an α-chloro-β-hydroxy ether in the presence of ammonia yields an epoxyether.[6] Thus, in VI, the base is incorporated within the same molecule and elimination of hydrogen chloride would merely convert VI back to the epoxyether hydrochloride.

Another characteristic reaction of epoxyethers is that with carboxylic acids. The amino epoxyether I was dissolved in ether and 3,5-dinitrobenzoic acid added. After 30 minutes at 35° α-hydroxyisobutyrophenone 3,5-dinitrobenzoate (IX) could be isolated in 89% yield. In view of the previous work done in this Laboratory[5] on the mechanism of the reactions of epoxyethers with carboxylic acids, this reaction is formulated as proceeding by means of an irreversible ester interchange *via* the pseudoester VII and orthoester VIII.

The fact that the amino epoxyether I does not differ markedly from other epoxyethers in the rate of reaction with dinitrobenzoic acid indicates that the rate-determining step of this reaction may be the attack of 3,5-dinitrobenzoate ion on I after the amino group of I has accepted a proton to form the substituted ammonium salt.



Experimental

1-Phenyl-1-(2-dimethylamino)-ethoxy-2-methyl-1,2-epoxypropane (I).—To 10.1 g. (0.44 g. atom) of sodium was added 78 g. (0.88 mole) of dimethylaminoethanol in a flask with a stirrer and reflux condenser. After the sodium had reacted, the flask was heated to 100° *in vacuo* with stirring to remove the excess alcohol. The alkoxide, which appeared as a very viscous fluid, was cooled to room temperature and 95 g. (0.47 mole) of α-bromoisobutyrophenone was added. Within 30 minutes the alkoxide dissolved, after which time the mixture was refluxed for two hours. The sodium bromide was filtered and the oil was distilled rapidly at 1 mm. pressure. The liquid was then fractionated to give 39 g. (63%) of the amino epoxyether I, b.p. 91–93° (0.6 mm.), $n^{25}D$ 1.4885, d^{25}_4 0.9896. The highest yield in a similar experiment was 81%.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; *M*D, 68.97. Found: C, 71.51; H, 8.80; *M*D, 68.57.

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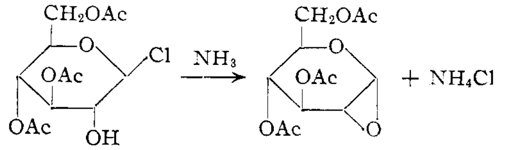
(6) Brigl's anhydride is prepared from an α-chloro-β-hydroxy ether



and ammonia. P. Brigl, *Z. physiol. Chem.*, **122**, 245 (1922); W. J. Hickenbottom, *J. Chem. Soc.*, 3140 (1928).

A mixture of 6.04 g. (0.026 mole) of I and 25 ml. of water containing 5 drops of 5% hydrochloric acid was heated to the reflux temperature for 66 hours and then made acidic with concentrated hydrochloric acid. The resulting oil was extracted with ether and distilled to give 3.08 g. (73%) of α-hydroxyisobutyrophenone[7] b.p. 71° (0.5 mm.). A semicarbazone derivative melted at 181–183°. A mixture melting point with an authentic sample, made by hydrolysis of the bromoketone followed by conversion to the derivative, was not depressed. The aqueous solution was concentrated, made alkaline and distilled. Methyl iodide was added to the distillate and the water evaporated overnight. Dimethylaminoethanol methiodide (4.50 g., 0.019 mole) remained and melted at 256–258°. The yield was 76% and a mixture melting point with an authentic sample was not depressed.

A mixture of 5 g. of I and 3 g. of dimethylaminoethanol was heated to the reflux temperature for 36 hours, after which time the reaction mixture was fractionated. Only starting materials were recovered

Preparation of 1-Phenyl-1-(2-dimethylamino)-ethoxy-2-methyl-1,2-epoxypropane Methiodide (II).—To 9.40 g. (0.040 mole) of I dissolved in 100 ml. of dry ether was added 7.2 g. (0.051 mole) of methyl iodide. The mixture was refluxed for two hours and the white salt was filtered and recrystallized from benzene–acetone solution. The yield was 14.5 g. (96%) and melted at 143–144°.

Anal. Calcd. for $C_{15}H_{24}INO_2$: C, 47.75; H, 6.41. Found: C, 47.94; H, 6.21.

To 1.5 g. (0.004 mole) of II was added 10 ml. of water and the solution refluxed for five hours. The mixture was extracted with ether and after the solvent was removed, 0.54 g. (82%) of α-hydroxyisobutyrophenone (III) remained. The ketone was identified by comparison of its infrared spectrum with that of a known sample.

The water was evaporated from the aqueous layer to give 0.81 g. (88%) of the methiodide of dimethylaminoethanol, m.p. 263–264°. A mixture melting point with an authentic sample was not depressed.

Reaction of I with 3,5-Dinitrobenzoic Acid.—To a solution of 1.50 g. (0.0064 mole) of I in 10 ml. of ether was added 1.34 g. (0.0064 mole) of solid 3,5-dinitrobenzoic acid. The mixture warmed to 35° as the acid reacted. After thirty minutes the precipitate was filtered. After drying, the solid was washed with dilute sodium carbonate solution. The residue after recrystallization from benzene–petroleum ether amounted to 2.45 g. (89%), m.p. 150–152°. A mixture melting point with a previously prepared[8] sample of α-hydroxyisobutyrophenone 3,5-dinitrobenzoate was not depressed.

Preparation of α-Methylacrylophenone.—To 7.95 g. (0.035 mole) of bromoisobutyrophenone was added 25 ml. of triethylamine, 3 ml. of pyridine and 25 ml. of benzene. The mixture was refluxed for 48 hours after which 5.0 g. (77%) of triethylamine hydrobromide was separated by filtration. After the solvent was removed, the oil was distilled at 42–44° (0.2 mm.) to give 3.7 g. (73%) of the α-methylacrylophenone,[9] $n^{25}D$ 1.5373.

Pyrolysis of the Hydrochloride of I.—A solution of dry hydrogen chloride in ether was added dropwise to a solution of 8.07 g. (0.34 mole) of I in dry ether. A gelatinous precipitate formed immediately. As much ether as possible was decanted and the remainder was removed under reduced pressure. The resultant white powder (m.p. 147–150° dec.) amounted to 8.94 g. (96%). The hydrochloride contained 13.6% ionic chloride (calcd. 13.1%). A 3.49-g. (0.013 mole) sample of the hydrochloride was heated at 150° for 15 minutes. After this time the melt was cooled and neutralized with solid sodium carbonate. The liquid was decanted from the solids into a distilling flask and distilled under reduced pressure. After the volatile materials evaporated, 1.38 g. (73%) of α-methylacrylophenone was isolated, b.p. 41–43° (0.2 mm.), $n^{25}D$ 1.5324, and proved to be identical to the authentic sample prepared above by comparison of the infrared spectra.

In another experiment 18.8 g. (0.069 mole) of the epoxyether hydrochloride was heated in dibutyl ether at the reflux temperature for ten minutes. After this time all the solid had dissolved. The mixture was cooled and washed with dilute hydrochloric acid. The ether was removed by distillation at reduced pressure and the remaining oil distilled rapidly. Bromine was added to the distillate until the bromine color persisted to convert the α-methylacrylophenone to the higher boiling dibromide. Redistillation gave 3.35 g. (33%) of α-chloroisobutyrophenone, b.p. 76–79° (2 mm.).

The α-chloroisobutyrophenone was prepared independently. Chlorine was bubbled into a solution of 5.1 g. of isobutyrophenone in 15 ml. of chloroform at room temperature until the yellow color of chlorine persisted. The chloroform and hydrogen chloride were removed under reduced pressure, after which the α-chloroketone was distilled to give 5.5 g. (88%), b.p. 72–73° (0.7 mm.). The infrared spectra of the authentic sample and the material from the pyrolysis were virtually superimposable.

In a further experiment, 1.78 g. (0.02 mole) of dimethylaminoethanol was converted to the hydrochloride and 3.28 g. (0.02 mole) of α-hydroxyisobutyrophenone was added. The mixture was heated to 150° for 15 minutes and then cooled. Dilute hydrochloric acid was added and the mixture extracted with ether. The ether was evaporated and the resulting oil distilled to give 2.5 g. of the starting α-hydroxyketone, identified as the semicarbazone derivative.

Reaction of 1-Phenyl-1(2-dimethylamino)-ethoxy-2-methyl-1,2-epoxypropane Methiodide (II) with Methyl Alcohol.—A solution of 10 g. of II in 25 ml. of dry methanol containing a catalytic amount of phosphorus pentoxide was heated to the reflux temperature for four days. The methanol was removed under reduced pressure and to the remaining oil was added dry ether which caused the oil to crystallize. The solid III amounted to 7.6 g. (70%) and melted at 160–165°. Two recrystallizations from a mixture of acetone and chloroform raised the melting point to 176–177°.

Anal. Calcd. for $C_{16}H_{28}INO_3$: C, 46.95; H, 6.90; I, 31.2. Found: C, 46.79; H, 6.88; I, 31.4.

A solution of 0.5 g. of the mixed ketal in 7 ml. of water containing one drop of concentrated hydrochloric acid was heated to reflux for 2 hours. The oil that separated was extracted with ether. Evaporation of the aqueous layer gave 0.26 g. of dimethylaminoethanol methiodide, m.p. 256–258°. A mixture melting point with authentic material was not depressed.

Evaporation of the ether solution gave an oil, the semicarbazone derivative, m.p. 183–185°, of which was identical with α-hydroxyisobutyrophenone semicarbazone.

DETROIT 1, MICHIGAN

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[7] E. Blaise and E. Herzog, *Compt. rend.*, **184**, 1332 (1927).

[8] C. L. Stevens and J. Tazuma, THIS JOURNAL, **76**, 715 (1954).

[9] R. C. Fuson and J. Burckhalter, *ibid.*, **70**, 4184 (1948).