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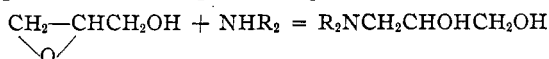
STUDIES OF GLYCIDOL. III. REACTIONS WITH ACID CHLORIDES¹

BY T. H. RIDER

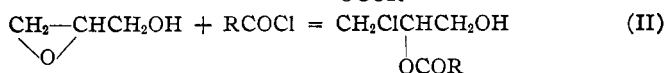
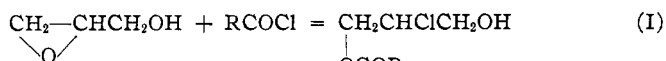
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Earlier papers in this series have described the preparation of glycidol² and its reactions with secondary amines.³ The reaction with these amines was found to proceed according to the equation



the amino group always assuming the alpha position. In the reaction of glycidol with acid chlorides two modes of addition are possible, and both are found to occur.



It is obvious that in the presence of an excess of acid chloride, monochlorohydrin di-esters will be formed. Thus, glycidol when treated with a slight excess over two moles of acetyl chloride gave a mixture of α - and β -monochlorohydrin diacetate. Alcoholysis of this mixture yielded a mixture of α - and β -monochlorohydrins in which both isomers were detected by the preparation and separation of their phenylurethans according to the method given in the first paper of this series. It would be of interest to determine the percentage of the two isomeric products resulting from the reactions of glycidol with a series of acid chlorides. This might be accomplished by alcoholysis of the resulting esters and a study of the resulting monochlorohydrin mixture by the physical chemical method described by Smith.⁴ This is not entirely feasible, however, since the alcoholysis and subsequent distillation of the monochlorohydrin mixture entail about a 15% loss of material, and it is impossible to assume that the ratio of α - and β -isomers is comparable to that in the original esters.

The reactions of glycidol with *p*-nitrobenzoyl chloride have been accorded somewhat more attention due to the interest attached to the resulting esters as intermediates for the production of local anesthetics. A

¹ A portion of the material in this paper is taken from the thesis presented by T. H. Rider to the Faculty of the Graduate School of Yale University in candidacy for the Degree of Doctor of Philosophy, June, 1928.

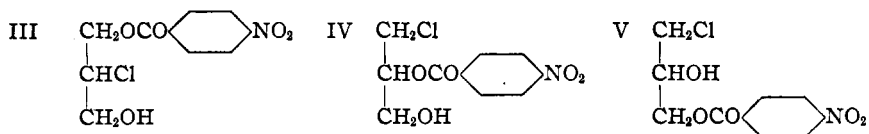
² Rider and Hill, *THIS JOURNAL*, **52**, 1521 (1930).

³ Rider with Hill, *ibid.*, **52**, 1528 (1930).

⁴ Smith, *Z. physik. Chem.*, **92**, 717 (1918); *ibid.*, **93**, 59 (1919); *ibid.*, **94**, 723 (1920).

nitrobenzoate chlorohydrin ester, by reaction with a suitable amine and subsequent reduction of the nitro group, would yield an aminobenzoic acid ester of an amino alcohol whose structure would be analogous to that of novocaine.

The reaction between glycidol and *p*-nitrobenzoyl chloride according to reactions I and II would yield the two products III and IV.



A third ester (V) isomeric with these two can be obtained by the action of *p*-nitrobenzoyl chloride on monochlorohydrin. In the latter reaction it is to be assumed that only the one product will result since the alpha hydroxyl will react preferentially, while it is obviously impossible that the direct addition of *p*-nitrobenzoyl chloride to glycidol could yield this same product. The mononitrobenzoates of monochlorohydrin resulting from these two reactions appear, however, to be identical at least in so far as boiling point is concerned. Therefore the chances for separating these isomers by fractional distillation is nil.

When two proportions of the acid chloride are used, and the di-esters formed, it is obvious that mono esters IV and V will yield identical di-esters, while III will yield an isomeric di-ester. These two di-esters have been described previously by Fairbourne and Foster,⁵ and suggested by them as the basis of a method of detecting α - and β -monochlorohydrins in a mixture. They treated the chlorohydrin with two molecular proportions of *p*-nitrobenzoyl chloride in chloroform solution using quinoline as an acceptor for the hydrogen chloride formed. The reaction mixture was taken up in ether, washed with water, dilute sulfuric acid, sodium bicarbonate solution, again with water and dried over sodium sulfate. After drying they removed the solvents and reported that a quantitative yield of monochlorohydrin di-*p*-nitrobenzoate was obtained in this manner.

This work was not overlooked, as suggested by Fairbourne,⁶ at the time the writer published as co-author the method for the detection of the isomeric chlorohydrins by means of their phenylurethans, but the method could not be duplicated. In the progress of this later work the difficulty was discovered. The isomeric monochlorohydrin di-*p*-nitrobenzoates are insoluble in ether, although their crystallization from ether is retarded by traces of chloroform. When Fairbourne and Foster's method was again repeated, the desired product was found not in the dried ether solution, but as a solid precipitate mixed with the drying agent,

⁵ Fairbourne and Foster, *J. Chem. Soc.*, 3148 (1926).

⁶ Fairbourne, Gibson and Stephens, *ibid.*, 445 (1931).

from which it could be isolated by digestion with water. No doubt if the drying period were curtailed, a fairly large percentage of the ester still would be retained in solution. The writer has prepared glycerol α -monochlorohydrin di-*p*-nitrobenzoate by an alternative method with success, and has found that one method of purification consists in dissolving the product in chloroform, treating with norite, filtering, diluting with ether and allowing it to crystallize out slowly. The product purified in this way melted at 108–109° uncorr. (Fairbourne and Foster reported m. p. 107–108°).

The writer, in agreement with the earlier work of Fairbourne and Foster, finds that the mixed di-*p*-nitrobenzoates of the α - and β -chlorohydrins melt at decidedly lower temperatures, although he has not, as yet, isolated sufficient of the pure β -isomer (m. p. 121–122°) for accurate analysis. Such a mixture of the isomeric di-esters results from the action of two molecular proportions of *p*-nitrobenzoyl chloride on glycidol.

Experimental

The Action of Acetyl Chloride on Glycidol (Monochlorohydrin Diacetate).—Three hundred grams of acetyl chloride is placed in a three-necked round-bottomed flask equipped with a mechanical stirrer, an efficient reflux condenser and a dropping funnel. The acetyl chloride is brought to the boiling point, the heating stopped and 100 g. of glycidol allowed to drop slowly into the reaction mixture during stirring. After the addition is complete, the solution is heated for several hours to insure completion of the reaction and the excess acetyl chloride removed. The residue is now transferred to a Claisen bulb and distilled. Under a pressure of 0.4–0.6 mm., monochlorohydrin diacetate distils at 96.5–97° (102–105° at 6 mm.). The yield is 69%.

Anal. Calcd. for $C_7H_{11}O_4Cl$: Cl, 18.25. Found: Cl, 18.58, 18.66.

The Alcoholysis of Monochlorohydrin Diacetate.—The diacetate is refluxed with five times its weight of absolute methyl alcohol containing dry hydrogen chloride. After heating for six hours, the excess alcohol and methyl acetate are removed and the residue of glycerol monochlorohydrin is distilled (b. p. 81° at 0.5 mm.). The yield is 81–85%.

Anal. Calcd. for $C_3H_7O_2Cl$: Cl, 32.09. Found: Cl, 32.07, 31.91.

The presence of both α - and β -isomers was detected by the preparation and separation of their phenylurethans as described in the first paper of this series.

The Action of *p*-Nitrobenzoyl Chloride on Glycidol (Ratio 1:1).—92.8 g. of *p*-nitrobenzoyl chloride and 37 g. of glycidol are mixed in ether solution and refluxed for ten hours. The ether must be strictly anhydrous or two by-products will be formed in large quantities, namely, *p*-nitrobenzoic acid anhydride (m. p. 188°), and monochlorohydrin. The ether is removed and the residue distilled, collecting the fraction from 197–217° at 1 mm. This material redistills from 205–207° at 0.8 mm. The yield is 70–75%.

Anal. Calcd. for $C_{10}H_{10}O_5NCl$: N, 5.4; Cl, 13.7. Found: Cl, 13.6, 13.5; N, 5.2, 5.3.

The Action of *p*-Nitrobenzoyl Chloride on Glycerol α -Monochlorohydrin (Ratio 1:1).—Fifty-nine grams *p*-nitrobenzoyl chloride, 35 g. of glycerol α -monochlorohydrin and 50 g. (slight excess) of diethylaniline are mixed in ether solution and allowed to stand at room temperature. After two weeks a layer of light yellow oil has separated on the

bottom of the flask together with crystals of diethylaniline hydrochloride. The latter forms a complete layer between the ether and oil phases, so that the ether can be decanted. After washing out the hydrochloride crystals with water, the oil becomes ether soluble. If the reaction is run in hot benzene using pyridine instead of diethylaniline as the acceptor for hydrogen chloride the results are entirely similar, *i. e.*, an oil separates but redissolves in the benzene upon the addition of water. The ether or benzene solution is washed with dilute hydrochloric acid, sodium carbonate solution, water and dried over sodium sulfate. The solvent is removed and the residue distilled. A fraction collected from 225–260° at 1.5 mm. redistills from 202–205° at 0.2 mm. and at 207° under a pressure of 1.5 mm. The yields are 60–65%.

Anal. Calcd. for $C_{10}H_{10}O_3NCl$: N, 5.4; Cl, 13.7. Found: N, 5.2, 5.5; Cl, 13.5, 13.4.

The Action of *p*-Nitrobenzoyl Chloride on Glycidol (Ratio 2:1).—The first molecular proportion of *p*-nitrobenzoyl chloride is combined with glycidol as described above, and the resulting ethereal solution treated with a second molecular proportion of the acid chloride and slightly more than an equivalent amount of pyridine as acceptor for the hydrogen chloride. After refluxing for several hours to insure completion of the reaction, the ethereal solution is washed with dilute hydrochloric acid, sodium bicarbonate solution and water and dried over anhydrous sodium sulfate. The solution is filtered and the ether evaporated. Any solid material obtained from the ether solution⁷ is added to the drying agent and the combined solids extracted with a small amount of chloroform. The chloroform is filtered and mixed with five volumes of anhydrous ether. On standing the mixed di-*p*-nitrobenzoates of α - and β -monochlorohydrin are precipitated. This mixture melts at 97–98°. The yield is 85% of the theoretical.

Anal. Calcd. for $C_{17}H_{13}O_5N_2Cl$: N, 6.86; Cl, 8.7. Found: N, 6.6; Cl, 8.5, 8.8.

The Action of *p*-Nitrobenzoyl Chloride on Glycerol α -Monochlorohydrin (Ratio 2:1).—6.86 g. of *p*-nitrobenzoyl chloride is dissolved in enough pyridine to give a clear solution at room temperature; 2.7 g. of α -monochlorohydrin is added and the mixture allowed to stand for several days. The pyridine solution is then thrown into an excess of cold dilute hydrochloric acid and the solid di-*p*-nitrobenzoate is thrown out in 93–96% yield. The melting point of this crude solid is 105°. This product is dried, dissolved in a small amount of chloroform, treated with norite, filtered and a large volume of anhydrous ether added. After standing for two days the di-*p*-nitrobenzoate of α -monochlorohydrin has completely precipitated. This product melts at 108–109°. The yield is 96%.

Anal. Calcd. for $C_{17}H_{13}O_5N_2Cl$: N, 6.86; Cl, 8.7. Found: N, 6.48, 6.52; Cl, 8.6, 8.7.

Summary

The actions of *p*-nitrobenzoyl chloride on glycidol and on glycerol α -monochlorohydrin and the products resulting therefrom are described. The di-*p*-nitrobenzoate of glycerol α -monochlorohydrin is insoluble in ether, contrary to previous indications in the literature.

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⁷ Although the products are ether insoluble, they do not tend to precipitate from the ether solution until the last traces of pyridine have been washed out. Crystallization is then slow enough so that no material is lost before the ether solution is placed over the drying agent.