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STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XXIII. ALDEHYDES AND KETONES FROM GLYCIDATES[1]

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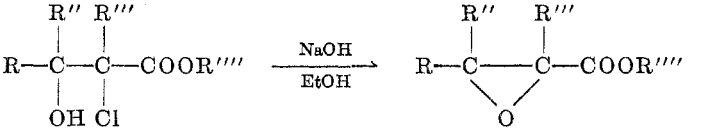
One of the important reactions of glycidic esters or their corresponding acids, is their ability to undergo enzymatic (1) or chemical decarboxylation to give rise to aldehydes or ketones.

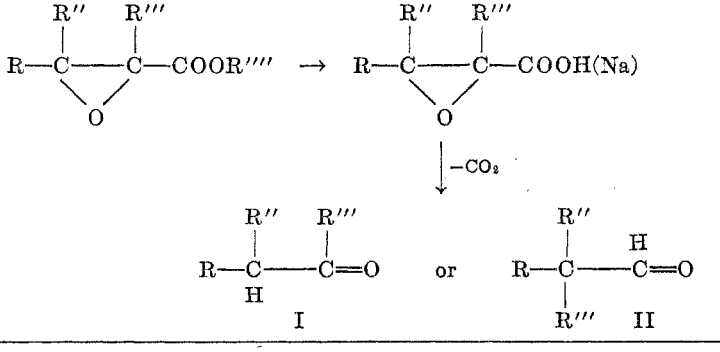
This offers a convenient way of lengthening the chains of aldehydes or ketones. When both the original starting compound and the final product are aldehydes, the chain has been increased by one carbon atom. On the other hand, when the carbonyl compound is an aldehyde and the final product is a ketone the carbon skeleton has been enlarged by two or more carbon atoms.

Generally, the ester is prepared as has been reported in an earlier paper in this series (2). However, it is also possible to prepare glycidic esters by reacting α-chloro-β-hydroxy esters with alcoholic sodium hydroxide to form the necessary epoxy compound:



This ester is then saponified with either alcoholic sodium or potassium hydroxide to give the alkali salt which can be easily converted to the acid or can be used directly. In some cases the acid is so unstable that one is forced to use the alkali salt.

The over-all reaction can be pictured as follows:



[1] This investigation was carried out under the aegis of the Office of Naval Research. Presented at the Fourth Meeting-in-Miniature, New York Section, American Chemical Society, February 8, 1952. For Paper XXII of this series see Vaitiekunas and Nord, *J. Am. Chem. Soc.*, **75**, 1764 (1953).

[2] The data recorded were taken from a part of the thesis of M. E. D. submitted to the Graduate School of Fordham University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

When R''' represents hydrogen, an aldehyde is always formed (I). When R''' is either alkyl or aryl, the product is a ketone (I). An aldehyde (II) can be formed only after a rearrangement.

There are numerous reports in the literature in which advantage is taken of the glycidic ester condensation followed by decarboxylation for the production of an aldehyde which is either not available or obtainable only with difficulty *via* another synthetic route. However, many of these reports convey the impression that the procedure was chosen either at random or to fit the particular ester or acid to be decarboxylated. For this reason we have chosen four representative glycidic esters and have subjected them to five methods of decarboxylation in order to ascertain their efficacy in causing decarboxylation with the yield of carbonyl compound as the criterion. Furthermore, we have also compared them, from the standpoint of the time required for the completion of the reaction as well as from the view of the indispensable time needed for carrying out the procedure and its simplicity.

The four esters chosen were: methyl β-phenylglycidate, ethyl α-methyl-β-phenylglycidate, methyl β-(2-thienyl)glycidate, and ethyl α-methyl-β-(2-thienyl)-glycidate. These esters would give phenylacetaldehyde, phenylacetone, 2-thienylacetaldehyde, and 2-thienylacetone respectively.

The procedures for decarboxylation were: (a) Pyrolysis of the sodium salt; (b) Use of superheated steam; (c) Acidification with 4 *N* phosphoric acid; (d) Acidification with dilute hydrochloric acid; and (e) Acidification with dilute acetic acid.

All of these procedures are those which use the sodium salt of the above acids. This was because some of the acids were unstable under the conditions of isolation. Then too, all of the esters were liquids at room temperature whereas the sodium salts were solids and consequently were more convenient for weighing. The first method had been used with success (3) upon cyclohexene glycidate. Procedure (b) had been applied (4) generally for the preparation of aldehydes from glycidates. Method (c) was chosen since this reagent had been used for the isolation of the free glycidic acid. Method (d) was applied because of the sensitivity of the epoxy linkage to hydrogen chloride, and procedure (e) because while it had never been used as had been phosphoric acid, acetic acid is also a weak acid and has not been reported as exerting the same effect upon the ethylene oxide as had the hydrogen halides.

The esters in which R''' was a methyl group and from which the product derived would be a methyl ketone (see Table I) appear to be more susceptible to decarboxylation, while those esters which are unsubstituted in this positon seem to be more difficult to decarboxylate. However, regardless of the ester, the acidification of the sodium salt with dilute acetic acid proved the most suitable both from the standpoint of yield from this reaction, and that of ease of manipulation.

Since all of the carbonyl products were known and the physical constants of their semicarbazones have been reported in the literature, the products of the above mentioned procedures, if any, were converted into this derivative, and the yield calculated upon this basis assuming the conversion to be quantitative. The semicarbazone of 2-thienyl acetone had been reported (5) to have m.p. 192°.

The semicarbazone prepared in this investigation had m.p. 179°. Admixture with an authentic sample (6) showed no depression of the melting point.

There are limitations to this reaction which must be kept in mind when one chooses it as a synthetic tool. The first and most important limitation is the availability of the starting carbonyl compound. This can be mitigated to some extent by using the corresponding α-chloro-β-hydroxy ester to prepare the epoxy ester if the original starting aldehyde or ketone cannot be prepared. Then too, it should not be assumed that the carbon chain can be extended *ad infinitum* since as the aliphatic portion of the molecule increases, its reactivity in this type of condensation decreases.

TABLE I

DECARBOXYLATION OF GLYCIDIC ESTERS

GLYCIDATE	METHOD									
	A		B		C		D		E	
	YIELD, %	TIME	YIELD, %	TIME	YIELD, %	TIME	YIELD, %	TIME	YIELD, %	TIME
Methyl β-phenyl-	Negligible	2 hrs.	Negligible	5 hrs.	12	1 hour	7	1 hour	25	1 hour
Methyl β-(2-thienyl)-	Negligible		Negligible		15		5		19	
Ethyl α-methyl-β-phenyl-	28		18		30		15		30	
Ethyl α-methyl-β-(2-thienyl)-	31		62		62		27		83	

EXPERIMENTAL

The glycidic esters used in this study were prepared according to our directions (2) from either benzaldehyde or 2-thenaldehyde and both methyl chloroacetate and ethyl α-chloropropionate.

Sodium salts of glycidic esters. The ester (20 g.) was dissolved in 20 ml. of ethanol in a 200 ml. round-bottom flask fitted with a reflux condenser and heated with the aid of a Glas-Col mantle. To this solution was added a 5% solution of sodium hydroxide in ethanol and the mixture was refluxed for four hours. After cooling, the alkali salt was filtered and dried in a vacuum desiccator over sulfuric acid.

Decarboxylation of glycidic esters. Since all five methods were used with the four salts in the same detail, only the general description will be given. The letters *A*, *B*, etc., refer to the procedures as listed in Table I.

A. Pyrolysis of the sodium salt. An intimate mixture of the salt (0.5 g.) and sodium hydroxide (0.1 g.) was prepared in a 5-ml. Claisen flask with the aid of 1 ml. of ethanol. Upon removal of the alcohol, the dried mixture was heated *in vacuo* until the decomposition was completed. Both the distillate (if any) and the residue in the flask were extracted with ether, the ether removed and the residual oil converted into its semicarbazone, filtered, dried, and weighed.

B. Use of superheated steam. The salt (0.5 g.) was dissolved in 20 ml. of water in a 200-ml. round-bottom flask, fitted for steam-distillation and acidified with 6 *N* hydrochloric acid until acid to Congo Red. The mixture was then distilled with superheated steam (180°) for five hours. The distillate was then extracted twice with ether, the ether removed, and the residue converted into its semicarbazone, filtered, dried, and weighed.

C. Acidification with 4 N phosphoric acid. The alkali salt (0.5 g.) was dissolved in the minimum amount of water (usually 5 to 10 ml.) and to it was added, dropwise, 4 *N* phosphoric acid until either effervescence had ceased or the solution was acid to Congo Red. The mixture was then extracted twice with 20-ml. portions of ether, the ether removed, and the residual oil converted to the semicarbazone and worked up as previously described.

D. Acidification with dilute hydrochloric acid. The sodium salt (0.5 g.) was dissolved in the minimum amount of water and to it was added, dropwise, dilute (1 part of acid to 2 parts of water) hydrochloric acid, until either effervescence had ceased or the solution was acid to Congo Red. The reaction mixture was worked up as described above.

E. Acidification with acetic acid. The sodium salt (0.5 g.) was dissolved in the minimum amount of water and to it was added, dropwise, dilute (1 part of acid to 3 parts of water) acetic acid. The reaction was the same as previously described.

The *semicarbazones* were prepared according to an earlier method (7).

SUMMARY

1. Five methods of decarboxylation were applied to four glycidic esters.

2. Epoxy esters in which the *alpha* position is substituted with a methyl group are more easily decarboxylated than are esters unsubstituted in the same position.

3. Acidification of a water solution of the sodium salt of the acid was shown to be the most convenient method of decarboxylation.

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