[Contribution from the Research Laboratories of The Quaker Oats Company and Northwestern University]

BASE-CATALYZED CONDENSATION OF α-HALOGENATED KETONES WITH β-KETO ESTERS

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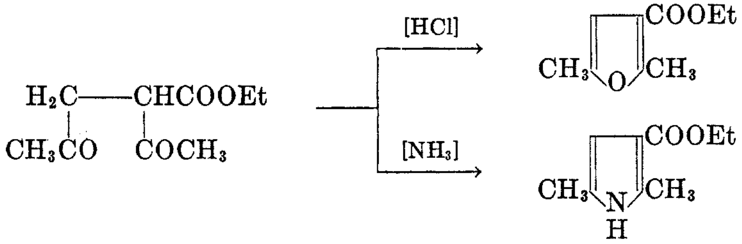
In the reaction of chloroacetone and other α-halo ketones with β-keto esters the mode of condensation is influenced by the nature of the condensing agent. Thus, C-alkylation of the ester is a well-established result under certain conditions, whereas the nature of the products in other instances has led to the postulation of O-alkylation as an intermediate step. It is the object of this paper to subject the existing evidence to critical examination and, for the reactions now regarded as O-alkylations, to present an alternative explanation particularly as it applies to the mechanism of formation of certain furan types.

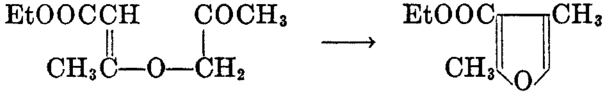
Paal (1) placed chloroacetone in reaction with ethyl sodioacetoacetate and obtained ethyl acetonylacetoacetate (I) from which a dimethylfuroic acid of m.p. 136° was obtained on treatment with hydrochloric acid. The structure claimed was 2,5-dimethyl-3-furoic acid, but no conclusive evidence to support it appeared until 1948 when Hurd and Wilkinson (2) obtained the same acid through an unequivocal synthesis starting with 2,5-dimethylfuran. The latter was converted into 2,5-dimethyl-3-furyl methyl ketone (by acetic anhydride, stannic chloride) which was then subjected to the haloform reaction, yielding 2,5-dimethyl-3-furoic acid, m.p. 135.4°.

It is certain from this evidence that C-alkylation of the acetoacetic ester occurred in Paal's work.



I

A similar C-alkylation explains the formation of 2,5-dimethyl-3-pyrrolecarboxylic acid by condensation of chloroacetone with acetoacetic ester in the presence of an excess of aqueous ammonia (3), but according to Feist (4) there is also formed a furan acid, melting at 122°. Feist believed this to be 2,4-dimethyl-3-furoic acid formed by way of the O-alkylation intermediate, ethyl 3-acetonyloxycrotonate (II), since he wrote "Es entsteht hierbei ein *O*-Acetonderivat des Ketonsäuresters." This step was in mind.

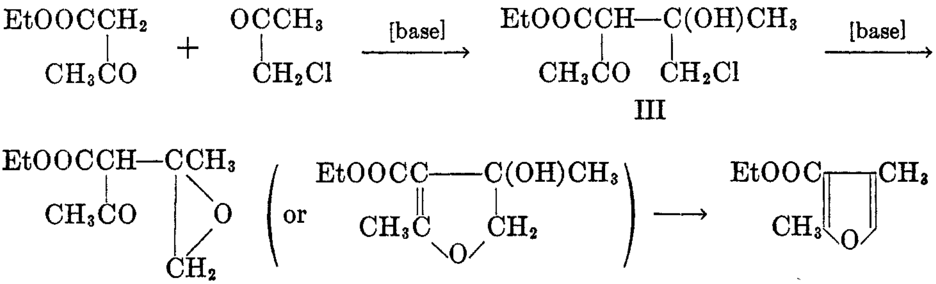


II

Feist's work proved neither the mechanism nor the 2,4-dimethyl structure, although the latter now seems unquestioned in view of the recent (2) proof of structure of the 2,5-isomer.

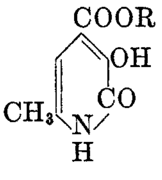
Chloroacetone, then, appears to condense with acetoacetic ester in two different ways depending upon the nature of the basic condensing medium. The published information can be summarized as follows. Sodium ethoxide (1, 2) produces, for the most part, the C-alkylation product, I, which on exposure to concentrated mineral acids is cyclized to 2,5-dimethyl-3-furoic acid. Aqueous ammonia (3, 4) also effects C-alkylation but, in addition, promotes condensation to a different intermediate, which is convertible to the 2,4-dimethyl isomer. Dry ammonia (2, 4) has been shown to bring about the latter result, as has aqueous sodium hydroxide (5). Actually, it is not improbable that reaction proceeds in both directions in each instance; that the ratio of the two intermediate products is influenced by the nature of the base and other experimental conditions. The published information, however, does not permit clarification of this point.

Although O-alkylation was postulated to explain the formation of 2,4-dimethyl-3-furoic acid, another explanation suggests itself, namely, an aldol-like condensation according to the steps:

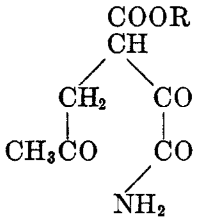


III

It is of interest to point out that Feist (4) suggested a related aldol-like process to explain products formed by interaction of chloroacetone, oxaloacetic ester, and aqueous ammonia. 5-Methyl-2,3-pyrroledicarboxylic ester was explained by C-alkylation, as was another product, IV, with V as the suggested intermediate.

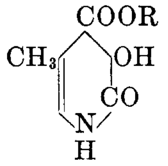


IV

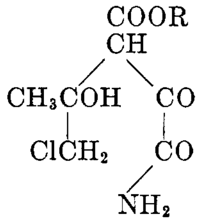


V

In view of his uncertainty regarding structure IV, however, he also proposed structure VI with VII as the intermediate. It is not clear why Feist did not suggest this type of intermediate (III) instead of O-alkylation (II) to account for his formation of 2,4-dimethyl-3-furoic acid.



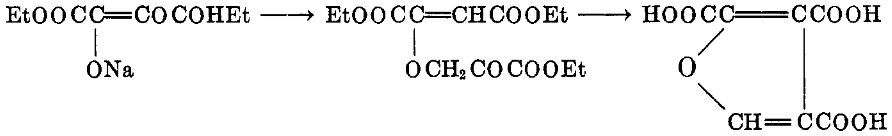
VI



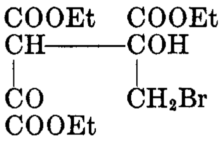
VII

Bromopyruvic ester, $BrCH_2COCOOR$, and chloroacetone, $ClCH_2COCH_3$, are closely related structurally, but apparently the two compounds respond differently towards the sodium salts of β-keto esters. If ethyl sodioöxaloacetate was C-alkylated by bromopyruvic ester (analogous to ethyl sodioacetoacetate and chloroacetone), then ring closure by hot hydrochloric acid should yield 2,3,5-furantricarboxylic acid. Sutter (6) believed he had effected this transformation. In any event, he obtained in 70% yield a compound of m.p. 79° which analyzed satisfactorily (C and H) for $C_{13}H_{18}O_8$ and changed into a furantricarboxylic acid by the action of mineral acids. This acid, said to be the 2,3,5-acid, melted at 273°.

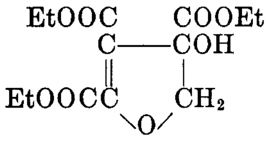
Reichstein and coworkers (7) showed that this was the 2,3,4-acid, not 2,3,5,- since it was also obtainable by decarboxylation of furantetracarboxylic acid. They postulated O-alkylation instead of C-alkylation:



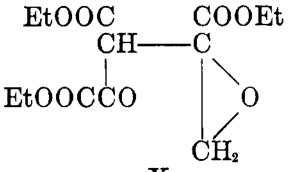
Let us assume instead that the aldol process is operative in the reaction with bromopyruvic ester. The initial adduct (VIII) would lose the elements of hydrogen bromide to form either IX or X, both of the empirical formula $C_{13}H_{18}O_8$ found by Sutter. Mineral acids would cause either of these structures to change into 2,3,4-furantricarboxylic ester (or acid), which was observed. Either structure (IX or X) explains the fact that ferric chloride gave a red color reaction. Of the two, we prefer IX, on the basis of the comparative ease of formation of a five-membered *versus* a three-membered ring.



VIII

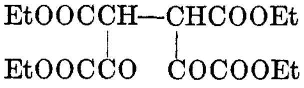


IX



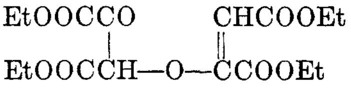
X

There is another reaction which must be considered, namely, Sutter's treatment of ethyl sodioöxaloacetate with bromine to form a tetracarboxylic ester. Analysis (C, H) of the latter was satisfactory for $C_{16}H_{22}O_{10}$. The compound melted at 83° and gave no color reaction with ferric chloride. Sutter assigned structure XI and showed that on refluxing the ester with hydrochloric acid cyclization, hydrolysis, and decarboxylation resulted to form the furantricarboxylic acid of m.p. 273°. Reichstein adopted structure XII, since he proved



$$\begin{array}{ccc} \text{EtOOCCH} & - & \text{CHCOOEt} \\ | & & | \\ \text{EtOOCCO} & & \text{COCOOEt} \end{array}$$

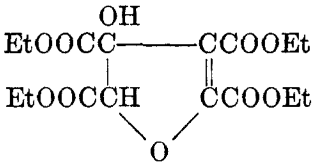
XI



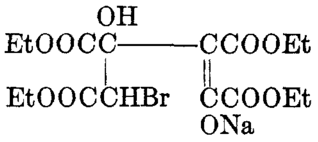
$$\begin{array}{lcl} \text{EtOOCCO} & & \text{CHCOOEt} \\ | & & \| \\ \text{EtOOCCH} & -\text{O}- & \text{CCOOEt} \end{array}$$

XII

that the latter was the 2,3,4-acid. His evidence was based on the isolation of furantetracarboxylic ester from XII (or XI) by treatment with concentrated sulfuric acid. Hydrolysis of this ester with boiling hydrochloric acid yielded furantetracarboxylic acid without any decarboxylation, but similar treatment of XII gave rise to Sutter's furantricarboxylic acid, m.p. 273°. Reichstein rationalized this decarboxylation as "ketonic hydrolysis" of the β-keto ester part of XII. Structure XI would have yielded the 2,3,5-isomer. XI and XII are both β-keto esters; hence both are unsatisfactory in explaining the non-reaction with ferric chloride. This observation would be explained if structure XIII was taken as the structure of Sutter's $C_{16}H_{22}O_{10}$ compound. Its formation is readily visualized by way of the intermediate aldol, XIV.



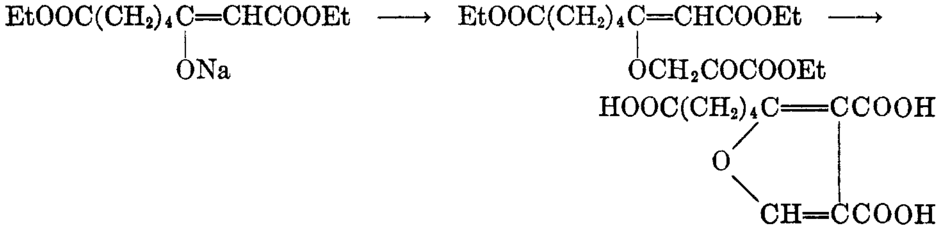
XIII



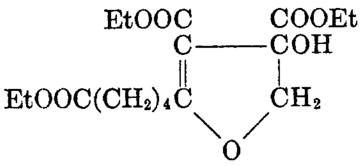
$$\begin{array}{lcl} \text{OH} & & \\ \text{EtOOCC} & - & \text{CCOOEt} \\ | & & \| \\ \text{EtOOCCHBr} & & \text{CCOOEt} \\ & & \text{ONa} \end{array}$$

XIV

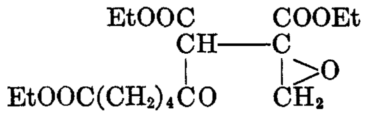
Archer and Pratt (8) also reported C-alkylation not to occur in the condensation of ethyl bromopyruvate and ethyl sodio-β-ketosuberate, since subsequent ring closure yielded 2-δ-carboxybutyl-3,4-furandicarboxylic acid. They accepted Reichstein's postulate of O-alkylation to explain their results:



With C-alkylation, Archer's compound would have been 5-δ-carboxybutyl-2,4-furandicarboxylic acid. Here again, no evidence precludes the possibility of an aldol type of intermediate (XV or XVI).



XV



XVI

There is other evidence also which strongly supports the aldol rather than the O-alkylation mechanism. Among other things, a suitable mechanism must account for facile cyclization of the intermediate, III or II, by a base to produce 2,4-dimethyl-3-furoic ester. That this is accomplished with great ease was demonstrated by Hurd and Wilkinson (2), who showed that mere passage of ammonia gas into an ether solution of chloroacetone and acetoacetic ester yielded a liquid reaction product boiling at 95–98° (14 mm.). This compound is ethyl 2,4-dimethyl-3-furoate—reported (9) to boil at 100–101° at 20 mm.—and not II, since it yields the furan acid on simple saponification. This result is readily explained if the aldol type of intermediate is assumed, but very difficult to reconcile with the O-alkylation intermediate. As a matter of fact it is unlikely that the latter, in basic medium, would cyclize to a furan under any conditions.

SUMMARY

Base-catalyzed reactions between α-halogenated ketones and β-keto esters which have been represented as O-alkylations are more probably aldol-type condensations. The existing evidence is examined critically.

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REFERENCES

(1) PAAL, *Ber.*, **17**, 2765 (1884).
(2) HURD AND WILKINSON, *J. Am. Chem. Soc.*, **70**, 739 (1948).
(3) HANTZSCH, *Ber.*, **23**, 1474 (1890).
(4) FEIST, *Ber.*, **35**, 1545 (1902).
(5) GILMAN AND BURTNER, *Iowa State Coll. J. Sci.*, **5**, 189 (1931).
(6) SUTTER, *Ann.*, **499**, 56 (1932).
(7) REICHSTEIN, *et al.*, *Helv. Chim. Acta*, **16**, 276 (1933).
(8) ARCHER AND PRATT, *J. Am. Chem. Soc.*, **66**, 1656 (1944).
(9) BLOMQUIST AND STEVENSON, *J. Am. Chem. Soc.*, **56**, 146 (1934).