Mechanism of *O*-Acylation of β-Keto Esters

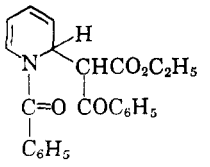
Sir:

It is well known that the *O*-acyl derivative of a β-keto ester is obtained by treatment of the β-keto ester with an acid chloride in pyridine solution.[1-6] For example, the reaction of benzoyl chloride with ethyl benzoylacetate in pyridine gives ethyl β-benzoxycinnamate (Ia) in 83% yield.[4] On the basis of analogy with closely related reactions, the suggestion has been made[5] that an intermediate condensation product, ethyl benzoyl(1-benzoyl-1,2-dihydro-2-pyridyl)acetate (II), is formed first, and this compound gives Ia and pyridine by way of a quasi six membered ring transition species, III. Kinetic evidence in support of this hypothesis has also been reported.[7]

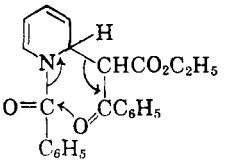
$RC(OCOC_6H_5) = CHCO_2C_2H_5$

Ia. R = C_6H_5

Ib. R = CH_3

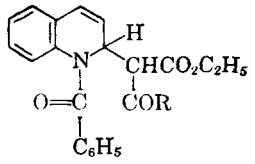


II



III

Direct evidence in support of this mechanism of reaction has now been obtained. Both ethyl benzoyl(1 - benzoyl - 1,2-dihydro - 2 - quinolyl)acetate (IVa) and ethyl aceto(1 - benzoyl - 1,2 - dihydro - 2 - quinolyl)acetate (IVb) have been prepared by the condensation of ethyl benzoylacetate and ethyl acetoacetate, respectively, with quinoline and benzoyl chloride. When IVa was refluxed in benzene solution for ten days, ethyl β-benzoxycinnamate (Ia) and quinoline were obtained in quantitative yield. Although IVb was unreactive under these conditions, this compound gave ethyl *O*-benzoylacetoacetate (Ib)[8] and quinoline when refluxed in xylene solution for three days. Owing to the conjugation of the phenyl group with the double bond and ester group in Ia, it is reasonable that the transition state derived from IVa leading to the formation of I, and having the same structural features in an incipient state, should be of lower energy content and thus more readily formed than the analogous transition state derived from IVb.



IV a. (R = C_6H_5)
IV b. (R = CH_3)

The structure of IVa was established in the following manner: Catalytic hydrogenation of IVa gave ethyl benzoyl(1-benzoyl-1,2,3,4-tetrahydro-2-quinolyl)acetate (V). Hydrolysis of this compound with a dilute solution of potassium hydroxide in ethanol afforded 1-benzoyl-2-phenacyl-1,2,3,4-tetrahydroquinoline, a known compound.[6]

The structure of IVb was established by a similar, but not identical, sequence of reactions. Ethyl aceto(1-benzoyl-1,2,3,4-tetrahydro-2-quinolyl)acetate (VI) was obtained by catalytic hydrogenation of IVb. Both V and VI gave the same product, *viz.*, 1-benzoyl-1,2,3,4-tetrahydro-2-quinolylacetic acid, by the action of a concentrated solution of potassium hydroxide in ethanol solution.

There is abundant evidence that pyridine and quinoline undergo many of the same types of condensation reactions with acid chlorides and bases[5,6,9-11] and that quinoline is better able than pyridine to form stable and isolable dihydro condensation products. Thus, the demonstration of the formation of products such as IVa and IVb and their conversion to the *O*-acyl derivatives of the β-keto esters upon application of heat may may be taken as powerful evidence for the formation of intermediates such as II when β-keto esters are treated with acid chlorides in pyridine solution. It is also worthy of mention that spectral evidence has been presented which indicates that phenols and aromatic amines undergo acylation in pyridine solution by a similar mechanism.[12,13]

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