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Dimethyl β-Ketoadipate

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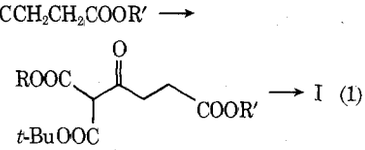
Several years ago there was reported a new and improved synthesis of several esters of the important biomolecule β-ketoadipic acid (I).[1] The starting materials employed were alkyl *tert*-butyl malonate and β-carboalkoxypropionyl chloride (eq 1). We report here an improvement

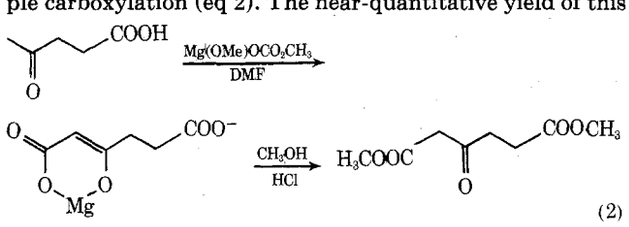
$$ROOCCH_2COO\text{-}t\text{-}Bu + ClOCCH_2CH_2COOR' \longrightarrow$$



$$\longrightarrow I \quad (1)$$

in the preparation that (a) avoids the problem of synthesis of the starting materials above and (b) employs cheap levulinic acid as starting material.

Carboxylation of levulinic acid by the procedure of Finkbeiner and Wagner[2] followed by Fischer esterification of the crude product affords a 92% isolated yield of dimethyl β-ketoadipate. There was no evidence for formation of the isomeric dimethyl acetylsuccinate or products from multiple carboxylation (eq 2). The near-quantitative yield of this



(2)

preparation requires use of a large (tenfold) excess of the carboxylating agent methylmagnesium carbonate. The regioselective nature of this reaction is consistent with the findings of Crombie, *et al.*, in an analogous case.[3]

Dimethyl β-Ketoadipate. A solution of 10.6 g (91.4 mmol) of levulinic acid (Eastman Technical) in 360 ml (920 mmol) of 2.56 *M* methylmagnesium carbonate in dimethylformamide (DMF)[2] was heated at 135° for 24 hr. The DMF was removed by distillation under vacuum at 60°. Trituration of the residue with ether gave after filtration and air drying of 136 g of yellow solid. The solid was suspended in 820 ml of methanol in a 3-l., three-necked, round-bottom flask equipped with a mechanical stirrer, a condenser, and a gas inlet tube. After cooling to −10°, hydrogen chloride was passed over the mixture until saturation had occurred. After standing overnight and warming to 25°, the mixture was concentrated at 40° under reduced pressure. The syrupy residue was poured on ice and the aqueous solution was extracted four times with chloroform. The organic extracts were washed with saturated bicarbonate solution and water and dried over anhydrous sodium sulfate. Distillation through an 1-in. Vigreux column gave 15.8 g (92% yield) of dimethyl β-ketoadipate as a colorless liquid: bp 94–96° (0.35 mm) [lit.[1] bp 110–111° (0.25 mm)]; nmr ($CDCl_3$) δ 2.70 (4 H, A_2B_2 multiplet), 3.49 (2 H, singlet), 3.62 (3 H, singlet), and 3.67 (3 H, singlet).

Registry No.—Dimethyl β-ketoadipate, 5457-44-3; levulinic acid, 123-76-2.

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Phenacyl Kojate Compared with Crown Ethers

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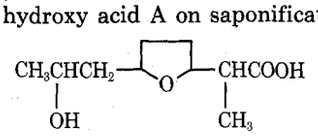
Crown ethers are of interest because of their ability to form complexes with sodium chloride and related salts. Following Pedersen's papers[1] there has been considerable development of this area. A comprehensive summary[2] has appeared recently. It lists 107 references, most of which are selected from the past decade. The area is diverse, and includes carbohydrates, for example. One obtains $C_{12}H_{22}O_{11} \cdot 2CH_3COOK$ when ether is added to a 0.02 *M* solution of sucrose[3] in ethanol that contains 0.4 *M* potassium acetate. Again, Sidgwick and Brewer[4] reported that the dihydrate of sodio-1-phenyl-1,3-butanedione was soluble in toluene whereas the anhydrous sodio derivative was insoluble. This observation was confirmed and extended by Bright, Milburn, and Truter.[4]

Nonactin is a neutral antibiotic, $C_{40}H_{64}O_{12}$, obtainable from *actinomyces*. It is a macrocyclic ester that yields four molecules of hydroxy acid A on saponification. Nonactin[5]



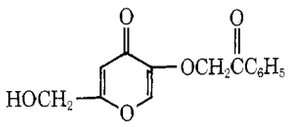
A

binds KCNS to form a complex wherein K^+ is surrounded by eight oxygens, four coming from the four ether oxygens and four from the four ester carbonyls. Also there are acidic

antibiotics[2] that complex with Na^+ or K^+, as monensin, nigericin, or dianemycin, which are open-chain rather than macrocyclic. Although the structures of these compounds show linear arrays of O-heterocyclic rings, the oxygens are so positioned as to surround the Na^+, thus resembling the macrocyclic esters and the crown ethers. There are but a few of the examples which have stimulated present interest.

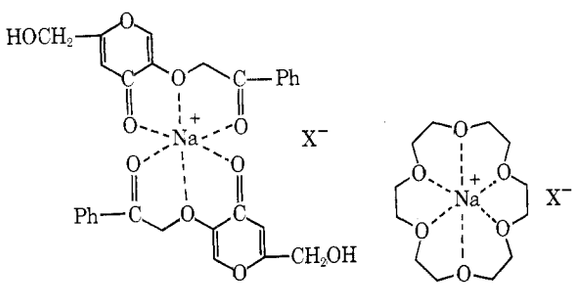
In view of this activity, therefore, it may be helpful to those working in this field to call attention to a related but obscure observation of ours[6] which was reported in a different context 25 years ago. We observed a beautifully crystalline complex from methanol that involved 2 mol of phenacyl kojate and 1 mol of sodium halide, $2C_{14}H_{12}O_5 \cdot NaX$. The NaX was removable by treating the complex with water.

In phenacyl kojate (I) all oxygen atoms are separated by two carbon atoms, a feature which also holds for the con-



I

ventional crown ethers. Structure II is proposed for the complex, by selecting OCCO sequences in phenacyl kojate that show cis relationships for the oxygens. This structure shows a striking similarity to III, the complex of a crown ether with NaX.



II III

There are two important differences, however, between II and III. In the first place, all oxygens in III classify as ether oxygens whereas in II four of the six participating oxygens are from carbonyl groups and the remaining two are more properly classified as ester oxygens than ether oxygens. This suggests that many other compounds that possess properly positioned nonether oxygens may also display complexing tendencies toward Na^+, K^+, or NH_4^+. Secondly, in III a single organic molecule holds all of the oxygens, whereas in II a pair of organic molecules are involved.

Registry No.—I, 49864-67-7.

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A Comparison between the Thermal and Photochemical 1,3-Cycloaddition Reactions of Ethyl 2-Methyl-3-phenylglycidate with Benzaldehyde. On the Thermal Fission of a Carbonyl Ylide

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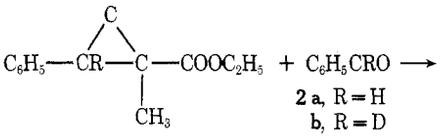
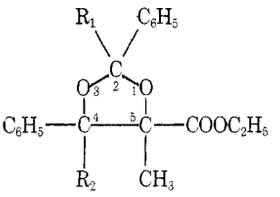
Compared to the wealth of information published on the photochemical behavior of oxiranes,[1] their thermochemistry has been particularly neglected. One puzzling question in this area concerns the requirements leading to the specific breaking of either the carbon–carbon or one of the carbon–oxygen bonds. In all the thermal 1,3-cycloaddition reactions of oxiranes published to date, there was cleavage of either the carbon–carbon bond[2] or one of the carbon–oxygen bonds,[3] but no competition between these two processes has been reported. This may have reflected either very different bond strengths in the oxirane or, in the case of comparable bond strengths, kinetic or thermodynamic factors in the product formation. In the cases of cycloaddition reactions with carbonyl dipolarophiles hitherto described, the products resulting from C–C or C–O bond breaking would have been chemically different and the effect of the latter factors could therefore have prevailed.

It was interesting to seek an example where *the same* structure would be obtained by either C–C or C–O bond breaking, and to use a label to determine the course of the cycloaddition reaction. We came across such a system, and recently described the photochemical cycloaddition reaction of ethyl 2-methyl-3-phenylglycidate (**1a**) with benzaldehyde (**2**) to give 2,5-diphenyl-4-methyl-4-carboethoxyl-1,3-dioxolane (**3**).[4] We proved by carbon-14 as well as by



1a, R = H
b, R = D

2a, R = H
b, R = D



3a, $R_1 = R_2 = H$
b, $R_1 = D$; $R_2 = H$
c, $R_1 = H$; $R_2 = D$

deuterium[5] labeling experiments that **2a** had added to an oxirane in which the C–C and at least one C–O bond had cleaved competitively.

The cycloaddition of **1a** with **2a** to produce **3a** proceeded smoothly in a sealed tube at 235–280°. The treatment of **1a** with deuterated benzaldehyde (**2b**) in this temperature range yielded **3c** exclusively, the product of C–C bond cleavage in the oxirane. This was determined by nmr analysis, where the signal corresponding to H-4 was absent, and where the integration of the signal for H-2 represented a full proton. No alternate cycloaddition to **3b** followed by exchange of the acetal deuterium had taken place, since the thermal condensation of the deuterated glycidic ester **1b** and **2a** yielded **3b**, in which the signal for H-2 was absent, and where H-4 integrated for one full proton.