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A NEW SYNTHESIS OF DIETHYL β-KETOADIPATE[1]

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Abstract—A new and reliable synthesis of diethyl β-ketoadipate (Ia) is described, in which the ethoxymagnesio derivative of ethyl t-butyl malonate is condensed with β-carbethoxypropionyl chloride to the triester (VI, R = Et), which is decomposed by refluxing under vacuum in the presence of added acid. Distillation gives pure diethyl β-ketoadipate (Ia). Previously described procedures for the preparation of Ia are shown to give impure products.

DIETHYL β-ketoadipate (Ia) and the related dimethyl (Ib) and ethyl methyl (Ic) esters, have been widely and fairly successfully used as polyfunctional intermediates in the synthesis of polycyclic systems and natural products,[2] while β-ketoadipic acid itself (Id) has been the subject of over forty papers dealing with its biochemical importance.[3] Surprisingly, there have been few applications of these attractive intermediates to the synthesis of heterocyclic compounds.[4]

To date, all of the procedures developed for the preparation of the esters (Ia,b,c) have been based on classical β-keto ester syntheses. Thus, acylation of an acetoacetic ester with a β-carbalkoxypropionyl chloride followed by alkaline hydrolysis of the intermediate II is reported to give moderate yields of I(a,b,c).[5] Similarly, acylation of diethyl malonate under a variety of conditions gave the intermediate III which could then be transformed in a number of ways to the esters (Ia,b,c).[6] Unfortunately, these deceptively simple syntheses, and especially the various modifications introduced to effect the decomposition of the intermediates II and III, have led to considerable

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[1] This work was supported by a grant to Princeton University from the Smith Kline and French Laboratories, Philadelphia, Pa.

[2] W. E. Bachmann and R. E. Holmen, *J. Amer. Chem. Soc.* 73, 3660 (1951); T. Asao, G. Büchi, M. M. Abdel-Kader, S. B. Chang, E. L. Wick and G. N. Wogan, *Ibid.* 87, 882 (1965); Ref. 5*a*.

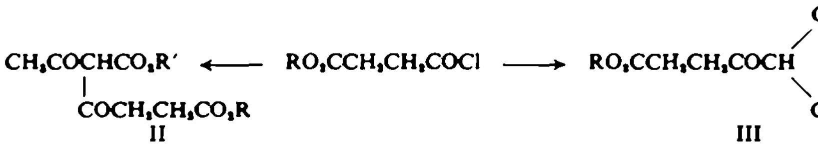
[3] P. D. Shaw, J. R. Beckwith and L. P. Hager, *J. Biol. Chem.* 234, 2560 (1959); P. D. Shaw and L. P. Hager, *J. Amer. Chem. Soc.* 81, 6527 (1959); W. Flaig and K. Haider, *Arch. Mikrobiol.* 40, 212 (1961).

[4a] P. Ruggli and A. Maeder, *Helv. Chim. Acta* 26, 936 (1942); [b] S. F. MacDonald and R. J. Stedman, *Canad. J. Chem.* 33, 458 (1955); [c] Y. H. Wu, J. R. Corrigan and R. F. Feldkamp, *J. Org. Chem.* 26, 1531 (1961).

[5a] J. C. Bardhan, *J. Chem. Soc.* 1848 (1936); [b] R. Robinson and J. S. Watt, *Ibid.* 1536 (1934); [c] D. K. Banerjee and K. M. Sivanandaiah, *J. Org. Chem.* 26, 1634 (1961); [d] J. A. Korman, *Ibid.* 22, 848 (1957); [e] B. R. Baker, R. E. Schaub and J. H. Williams, *Ibid.* 17, 116 (1952); [f] M. Viscontini and N. Merckling, *Helv. Chim. Acta* 35, 2280 (1952) and M. Viscontini and H. Köhler, *Ibid.* 37, 41 (1954); [g] P. Ruggli and A. Maeder, *Ibid.* 25, 936 (1942); [h] J. R. Stevens and R. H. Beutel, *J. Amer. Chem. Soc.* 65, 449 (1943); Ref. 4*b*.

[6a] B. Riegel and W. M. Lilienfeld, *J. Amer. Chem. Soc.* 67, 1273 (1945); [b] G. S. Grinenko and V. I. Maksimov, *Zh. Obsh. Khim.* 28, 528 (1958); [c] V. Eisner, J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.* 2223 (1950).

discord and disagreement in the literature as to the yield and purity of the esters (Ia,b,c) so obtained.[7]



$$CH_3COCH(COCH_2CH_2CO_2R)CO_2R' \text{ (II)} \longleftarrow RO_2CCH_2CH_2COCl \longrightarrow RO_2CCH_2CH_2COCH(CO_2C_2H_5)_2 \text{ (III)}$$

II III

$RO_2CCH_2CH_2COCH_2CO_2R'$

I

a, $R = R' = C_2H_5$ b, $R = R' = CH_3$

c, $R = C_2H_5$, $R' = CH_3$ d, $R = R' = H$

Attempted repetition of the best of the literature procedures[8] has led, in our hands, to disappointing results. The intermediates II(a,b,c) and III proved extremely difficult to purify because of thermal decomposition during distillation, and both the crude and distilled products were shown by GLC to be mixtures of not less than four compounds. Repeated fractional distillation failed to give any pure products, and as yet we have been unsuccessful in preparing any of the pure intermediates (IIa,b,c or III). Decomposition of the crude intermediates (IIa,b,c and III) according to the various literature procedures served only to complicate matters further, since GLC demonstrated that an average of eight to ten compounds were present in the distilled products.[9]

An alternative approach to the esters (Ia,b) involves hydrolysis and decarboxylation of the intermediate III to give β-ketoadipic acid (Id), followed by esterification, even though the latter step has been shown to proceed in only 38% yield.[4b] However, treatment of crude III according to the prescribed directions[6c] gave *succinic*, not β-ketoadipic acid.

The above results thus not only confirm previous observations[7,9] but show clearly that these procedures are quite unsuitable for the preparation of the pure esters (Ia,b,c).[10] Failure to obtain the esters II and III in a pure state would seem to imply

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[7] See Ref. 5*b, c, d, g*; Ref. 6*a, c*.

[8] Ref. 4*b*; Ref. 5*c, d, h*; Ref. 6*a, c*.

[9] For some time Aldrich Chemical Company, Inc., 2371 N. 30th St., Milwaukee, Wisc., 53210, offered dimethyl β-ketoadipate for sale. On attempting to purchase this chemical, we were informed by Dr. Alfred Bader, Chief Chemist, that 'despite the recently published procedure for the preparation of dimethyl β-ketoadipate, we have found that pure material is very hard to make, and batch after batch has been rejected by our Analytical Department'. This item was subsequently withdrawn from their catalog.

[10] Numerous other procedures were examined in attempts to prepare the desired diethyl β-ketoadipate. For example, rearrangement of the epoxide (i) under a variety of conditions and acidic catalysts (BF_3/Et_2O, $MgBr_2$, $HClO_4$, HBF_4) gave either unchanged starting material or complex mixtures. This failure of a disubstituted epoxide to rearrange is supported by recent studies (F. J. McQuillin, W. O. Ord. and P. L. Simpson, *J. Chem. Soc.* 5526 (1964)). Addition of picryl azide (cf. P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey and G. P. Nowack. *J. Amer. Chem. Soc.* **87**, 306 (1965); P. Scheiner, *J. Org. Chem.* **30**, 7 (1965)) to the olefin (ii) either gave no reaction or black tars; however, the preparation of ketones by this procedure has recently been shown to require a strained double bond (A. S. Bailey, J. J. Merer, and J. E. White, *Chem. Comm.* **1**, 4 (1965). A Reformatsky condensation between β-carbethoxypropionyl chloride and ethyl bromoacetate failed, as did an attempted hydroboration-oxidation sequence with ii or the corresponding diacid chloride.

$C_2H_5OOC{-}CH_2CH{-}CHCH_2{-}COOC_2H_5$ (epoxide O bridging CH–CH)

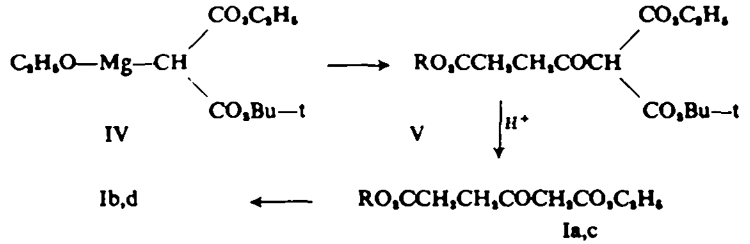
i

$C_2H_5OOC{-}CH_2CH{=}CHCH_2{-}COOC_2H_5$

ii

that diacylation and, especially in the case of acetoacetic esters, that O-acylation may contribute to the observed mixture of products. Decomposition of intermediates of the type II and III, on the other hand, in known to be a complex reaction which may lead to a variety of products.[11]

We wish to report at this time a simple, rapid synthesis of the esters (Ia,b,c) which not only proceeds in excellent yield (85–95%) but gives products which are homogeneous to GLC. Based on the β-keto ester synthesis introduced by Breslow, *et al.*,[12] the procedure consists of acylation of the ethoxymagnesio derivative of ethyl *t*-butyl malonate (IV) with a carbalkoxypropionyl chloride to give the intermediate triester V. This intermediate is not isolated, but refluxed under vacuum in the presence of added acid catalyst, when decomposition proceeds rapidly. Distillation then gives the esters I(a,c) in >95% purity (GLC), and re-fractionation yields the pure esters. Conversion of Ic to Ib proceeds in high yield by simple ester exchange with sodium methoxide.[6c] β-Ketoadipic acid (Id) can be obtained from the esters (Ia,b,c) by acid hydrolysis.



$$C_2H_5O{-}Mg{-}CH\begin{matrix}CO_2C_2H_5\\CO_2Bu{-}t\end{matrix}\ (IV) \longrightarrow RO_2CCH_2CH_2COCH\begin{matrix}CO_2C_2H_5\\CO_2Bu{-}t\end{matrix}\ (V) \xrightarrow{H^+} RO_2CCH_2CH_2COCH_2CO_2C_2H_5\ (Ia,c) \longrightarrow Ib,d$$

The NMR spectrum of diethyl β-ketoadipate can serve as a striking and very convenient criterion for its purity. The spectrum of pure Ia is reproduced in Fig. I. The presence of as little as 1% of diethyl malonate, diethyl succinate, unchanged triester III (R=Et) or ethyl t-butylmalonate (known to be present in small amounts in the crude product resulting from acid-catalyzed decomposition of III (R = Et)) can readily be detected. The same criterion can be used to determine the purity of Ib and Ic.

EXPERIMENTAL[13]

Diethyl β-ketoadipate (Ia). To a 250-ml three-necked flask fitted with a Hg sealed stirrer, dropping funnel and reflux condenser were added 11·4 g (0·10 mole) finely powdered, freshly prepared magnesium ethoxide and 75 ml Na dried ether. The mixture was stirred, 18·8 g (0·10 mole) ethyl t-butyl malonate[14] added all at once, and the resulting mixture stirred and refluxed for 15 min. To the cooled, cloudy soln was then added as rapidly as possible a soln of 18·1 g (0·11 mole) β-carbethoxypropionyl chloride[15] in 75 ml anhydrous ether. After the vigorous, exothermic reaction had subsided, the soln was stirred and refluxed for a further 3 hr. The cooled soln was then acidified with 4N H_2SO_4, the ether layer separated, the aqueous layer extracted with ether (3 × 25 ml) and the combined extracts dried ($MgSO_4$). Removal of the solvent left a colorless oil which decomposed upon attempted distillation and which was converted to Ia without purification as follows.

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[11] R. N. Isbell, B. Wojcik and H. Adkins, *J. Amer. Chem. Soc.* **54**, 3678 (1932).

[12] D. S. Breslow, E. Baumgarten and C. R. Hauser, *J. Amer. Chem. Soc.* **66**, 1286 (1944).

[13] M.ps: Thomas-Hoover silicon-bath apparatus, are uncorrected. Microanalyses: Robertson Microanalytical Laboratory, Florham Park, N.J. IR spectra: liquid films on a Perkin-Elmer Model 237B Grating Infracord; NMR spectra: CCl_4 internal TMS standard on Varian A60 and Varian A60-A.

[14] *Organic Syntheses* Coll. Vol. IV, p. 417.

[15] *Organic Syntheses* Coll. Vol. III, p. 169.

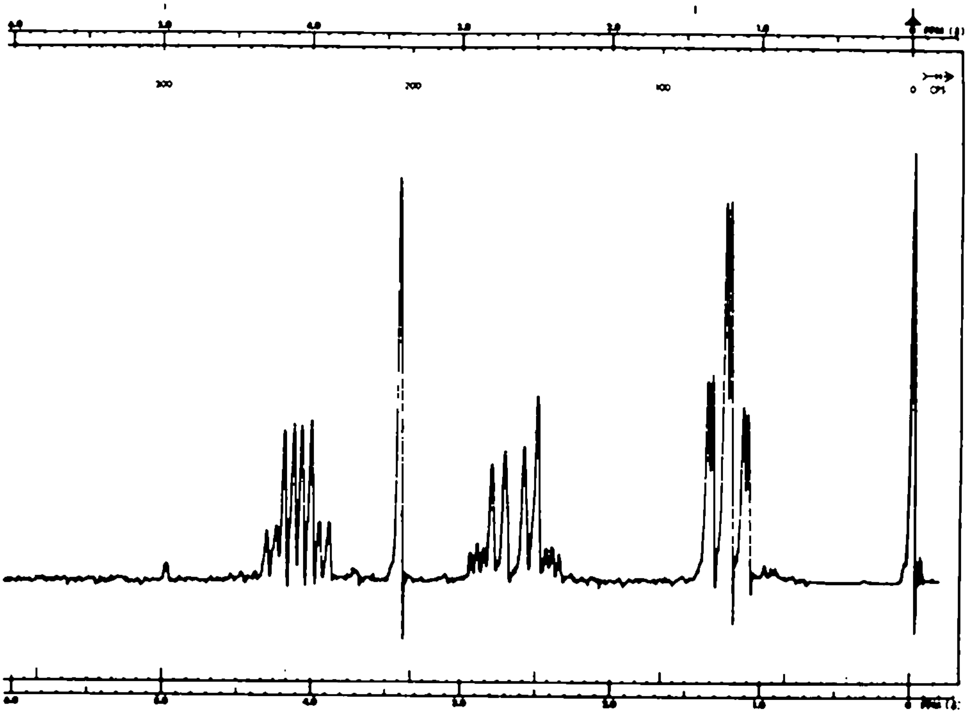

FIG. 1

The oil was transferred to a distillation apparatus and carefully heated under vacuum, whereupon 2–3 g of liquid distilled, b.p. 30–60°/0·1 mm. (This forerun consisted mainly of unchanged ethyl t-butyl malonate, contaminated by small amounts of diethyl malonate and diethyl succinate; the ethyl t-butyl malonate could be recovered by re-fractionation.) When no more forerun distilled, the residual oil was allowed to cool somewhat and about 0·1 g β-naphthalenesulfonic acid[16] added. The oil was then refluxed under high vacuum for 6–10 hr until the vigorous evolution of gas had subsided. Distillation of the residue then gave 18·6 g (86%) of Ia which was greater than 95% pure (GLC and NMR). Careful refractionation then gave pure Ia, b.p. 109–111°/0·35 mm.[17] (Found: C, 55·75; H, 7·54. Calc. for $C_{10}H_{16}O_5$: C, 55·54; H, 7·46.)

Ethyl methyl β-ketoadipate (Ic). Acylation of ethyl t-butyl malonate with β-carbomethoxypropionyl chloride[18] and decomposition of the intermediate triester as described for Ia gave Ic in 85–95% yield as a colorless oil, b.p. 104–105°/0·30 mm. (Found: C, 53·76; H, 6·98. Calc. for $C_9H_{14}O_5$: C, 53·76; H, 7·09.)

Dimethyl β-ketoadipate (Ib). Treatment of ethyl methyl β-ketoadipate with MeONa in MeOH gave 80–85% yields of Ib as a colorless oil, b.p. 110–111°/0·25 mm. (Found: C, 51·06; H, 6·47. Calc. for $C_8H_{12}O_5$: C, 51·06; H, 6·43.)

β-Ketoadipic acid (Id) was prepared by hydrolysis of the esters (Ia, b or c)[6c] and was obtained as a colorless solid m.p. 123–125° (dec) (lit.[6c], m.p. 115° (dec)).

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[16] *p*-Toluenesulfonic acid functions equally well as acid catalyst, but co-distils with the final product and is difficult to remove.

[17] The average yield, on a 0·1 molar scale, taken over more than 15 runs, was of the order of 90% of pure, redistilled material. The reaction can easily be run exactly as described above on a 0·5 or 1·0 molar scale, when the yield of pure isolated product is in the range 70–80%.