The Direct Synthesis of β-Hydroxy-acids by a Modified Reformatskii Reaction

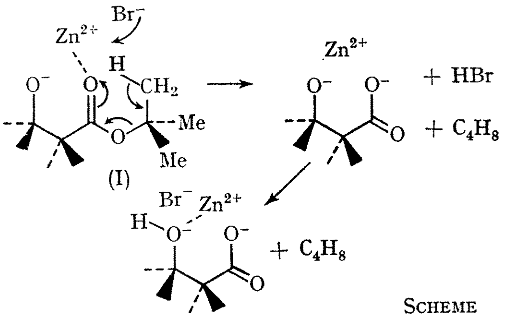
By A. E. OPARA and G. READ*

(*Department of Chemistry, University of Exeter, Exeter*)

Summary β-Hydroxy-acids are obtained in good yields when suspensions of the zinc complexes, formed in Reformatskii reactions involving t-butyl esters, are heated in benzene.

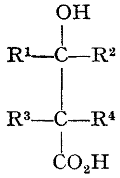
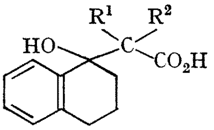
THE Reformatskii reaction[1] has long been recognised as a convenient method for preparing β-hydroxy-esters, which in turn can be converted to αβ-unsaturated esters and acids in excellent yields. However, good yields of β-hydroxy-acids generally cannot be obtained from the corresponding esters, for β-elimination competes with hydrolysis. In an attempt to circumvent this limitation and also to avoid one of the side reactions commonly associated with the Reformatskii reaction, namely Claisen-type condensations,[2] we have examined the scope of the reaction using t-butyl esters. We report a modified Reformatskii procedure using t-butyl esters which leads directly to β-hydroxy-acids.

The adducts formed from a variety of carbonyl compounds and the Reformatskii reagents derived from t-butyl α-bromoacetate, t-butyl α-bromopropionate and t-butyl α-bromoisobutyrate in refluxing tetrahydrofuran† were stable in this solvent and the corresponding β-hydroxy-esters could be isolated on working up the solutions with dilute acid in the normal manner. However, when the adducts were transferred to anhydrous benzene, and the resulting suspension heated under reflux, virtually pure β-hydroxy-acids could be obtained by working-up with dilute acid and isolating the acidic fraction by extraction with aqueous $NaHCO_3$ of the benzene layer. The Table lists the acids formed and the average yields obtained in duplicate runs on a 0·02—0·03 M scale. The hydroxy-acids were identified by direct comparison with authentic samples. No attempt was made to determine the conditions for the maximum yield of each reaction; a standard procedure was adopted which allowed 1 hr. for the adduct formation and 2 hr. for the dealkylation of the ester. In several cases, notably those involving acetone [(i), (ii), and (iii)] and isobutyrate [(iii), (vi), (ix), and (xiii)], the time allowed for the dealkylation was insufficient and the hydroxy-ester was isolated in the neutral fraction. More prolonged treatment with benzene improved the yields.



SCHEME

TABLE

	Hydroxy-acid	Yield (%)
	(i) $R^1=R^2=Me; R^3=R^4=H$	33
	(ii) $R^1=R^2=R^3=Me; R^4=H$	51
	(iii) $R^1=R^2=R^3=R^4=Me$	74
	(iv) $R^1=Pr^n; R^2=R^3=R^4=H$	80
	(v) $R^1=Pr^n; R^2=R^3=H; R^4=Me$	94[a]
	(vi) $R^1=Pr^n; R^2=H; R^3=R^4=Me$	36
	(vii) $R^1=Ph; R^2=R^3=R^4=H$	90
	(viii) $R^1=Ph; R^2=R^3=H; R^4=Me$	91[a]
	(ix) $R^1=Ph; R^2=H; R^3=R^4=Me$	75
	(x) $R^1=R^2=Pr^i; R^3=R^4=H$	85
	(xi) $R^1=R^2=H$	76
	(xii) $R^1=H; R^2=Me$	72[a]
	(xiii) $R^1=R^2=Me$	60

[a] Diastereoisomeric mixture.

The formation of the hydroxy-acid salts in the benzene suspension appears to be catalysed by the zinc ions of the adduct, in a process analogous to the acid catalysed dealkylation of t-butyl esters.[3] In the absence of a solvent with strong donor properties such as tetrahydrofuran, the metal ion will co-ordinate with the carbonyl oxygens (or alkoxyl oxygens) of the esters to give complexes of the type (I) which can decompose to the corresponding salts. The Scheme depicts this decomposition as an intramolecular process but, since the bulk of the complex is in the form of a suspension, an intermolecular process is a distinct alternative possibility.

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† The Reformatskii reagents from the α-bromo t-butyl esters could not be obtained in ether or benzene.

[1] S. Reformatskii, *Ber.*, 1887, **20**, 1210.
[2] R. L. Schriner, *Org. Reactions*, 1942, **1**, 1; K. A. Kocheshkov and L. V. Abramova, "Methods of Elemento-Organic Chemistry," Vol. 3, 1967, p. 121.
[3] R. W. Roeske, *Chem. and Ind.*, 1959, 1211; G. W. Anderson and F. M. Callahan, *J. Amer. Chem. Soc.*, 1960, **82**, 3359.