

309. *Alkaline Hydrolysis of O-Acylglycollic Esters.* *Part I.*

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The products of reaction of ethyl *O*-acylglycollates (I) with potassium hydroxide in 4:1 ethanol-water have been examined. Two competing reactions occur when the ester:base molar ratio is 1:1; hydrolysis at C-1 of the glycollate to give the *O*-acylglycollic acid (II), and alcoholysis at C-1' to give the ethyl carboxylate. The yields of the *O*-acylglycollic acids obtained in the series have been related to the rate of alkaline hydrolysis of the corresponding ethyl carboxylate ($R\cdot CO_2\cdot Et$). A base-catalysed alcoholysis of the initially formed *O*-acylglycollic acid occurs when the ester:base molar ratio in the reaction is 1:1.25.

ETHYL *O*-ACYLGLYCOLLATES were prepared by refluxing the carboxylic acid with ethyl bromoacetate and potassium carbonate in dry acetone. This is more convenient than the established methods.^{1,2} High yields were obtained, except in a few instances where the potassium salt of the acid formed during reaction had a low solubility in the reaction mixture. We examined the products of reaction of a series of ethyl *O*-alkanoyl-, and ethyl *O*-aroyl-glycollates with potassium hydroxide in 4:1 ethanol-water when the molar ratio of ester to base is either 1:1 or in a few cases 1:1.25.

Results of reaction between ethyl *O*-acylglycollates (1 mole) and potassium hydroxide (1 mole) in 4:1 ethanol-water at 25° for 0.25 hour are summarised in the Table. Reaction was complete with ethyl *O*-benzoylglycollate within this time. The *O*-acylglycollic acids (II) were obtained in yields ranging from 36 to 94% with two exceptions. Ethyl *O*-*p*-nitrobenzoylglycollate gave ethyl *p*-nitrobenzoate with some *p*-nitrobenzoic acid and similarly ethyl *O*-*p*-bromobenzoylglycollate gave mainly ethyl *p*-bromobenzoate and a mixture of acids including *p*-bromobenzoic acid. The *O*-acylglycollic acids obtained in low yield were accompanied by appreciable quantities of the ethyl carboxylates ($R\cdot CO_2\cdot Et$),

¹ Burton and Fife, *J. Amer. Chem. Soc.*, 1952, **74**, 3935.

² Haynes and Stanners, *J.*, 1956, 4103.

Hydrolysis of ethyl *O*-acylglycollates ($R\cdot CO_2\cdot CH_2\cdot CO_2\cdot Et$).

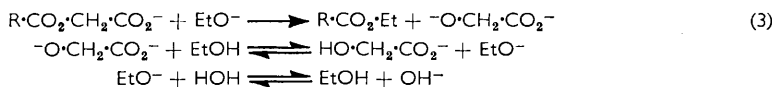
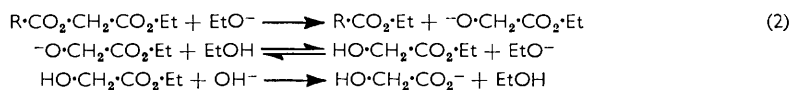
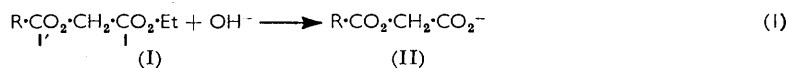
R	Products	Crude yield (%)	$10^3 k_{OH}$ (l. mole ⁻¹ sec. ⁻¹) for $R\cdot CO_2\cdot Et$ *
Bu ^t	$R\cdot CO_2\cdot CH_2\cdot CO_2H$	94	0.0254 ^a
<i>p</i> -MeO·C ₆ H ₄	"	79 †	0.115 ^b
<i>p</i> -Me·C ₆ H ₄	"	86	0.251 ^b
Ph	"	72	0.550 ^b
Pr	"	51	1.72 ^a
Ph·CH ₂	$R\cdot CO_2\cdot Et$ (+ $R\cdot CO_2\cdot CH_2\cdot CO_2H$)	(36)	10.1 ^c
<i>p</i> -Br·C ₆ H ₄	$R\cdot CO_2\cdot Et + R\cdot CO_2H$	—	2.89 ^b
<i>p</i> -NO ₂ ·C ₆ H ₄	$R\cdot CO_2\cdot Et + R\cdot CO_2H$	99 total	56.70 ^b

* 85% ethanol, 25°. † After recrystallisation.

^a Evans, Gordon, and Watson, *J.*, 1938, 1439. ^b Ingold and Nathan, *J.*, 1936, 222. ^c Levenson and Smith, *J. Amer. Chem. Soc.*, 1940, 62, 2324.

and even *O*-benzoylglycollic acid, obtained in 72% yield, was accompanied by some ethyl benzoate.

The *O*-acylglycollic acids are presumably formed by nucleophilic attack at carbon atom C-1 by hydroxyl ion (scheme 1), in accord with the generally accepted mechanism of ester hydrolysis ($B_{AC}2$),³ whereas, the ethyl esters ($R\cdot CO_2\cdot Et$) and corresponding acids ($R\cdot CO_2H$), are formed by ethoxide and hydroxyl ion attack, respectively, at C-1' (scheme 2); these reactions occur simultaneously.



There is a correlation between the yield of the *O*-acylglycollic acid formed from an ethyl *O*-acylglycollate and the rate of alkaline hydrolysis of the corresponding ethyl carboxylate ($R\cdot CO_2\cdot Et$) (see the Table). This relationship suggests that the effect of (R) on the adjacent reactive centres (carbon atom in italic type) in the systems $R\cdot CO_2\cdot CH_2\cdot CO_2\cdot Et$ and $R\cdot CO_2\cdot Et$ is qualitatively the same throughout the two series, and, furthermore, that the electrophilic character of C-1 compared with that of C-1' varies over a much narrower range; this is to be expected since the electron density at C-1' can exert only a weak inductive effect at C-1 by relay through the adjoining two-atom chain.

Ethyl *O*-acylglycollates which give a high yield of the *O*-acylglycollic acid clearly have C-1 more electrophilic than C-1'. The results obtained with the ethyl *O*-acylglycollates that give a low yield of the *O*-acylglycollic acid or with ethyl *O*-*p*-bromo-, and ethyl *O*-*p*-nitro-benzoylglycollates, where the main reaction is ethoxide ion attack at C-1', cannot be so readily interpreted, since in 4 : 1 ethanol-water, 41% of the base exists as ethoxide ion, and the nucleophilic activity of this ion is nearly three-fold that of the hydroxyl ion.⁴ When reaction was conducted in 1 : 1 dioxan-water a 68% yield of *p*-nitrobenzoic acid was obtained showing that C-1' is more electrophilic than C-1 in ethyl *O*-*p*-nitrobenzoylglycollate.

Reaction conditions for preparation of *O*-benzoylglycollic acid from ethyl *O*-benzoylglycollate were very specific. Reaction of the ester and base in the molar ratio 1 : 1.25

³ Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons, Ltd., London, 1953, p. 754.⁴ Bender and Glasson, *J. Amer. Chem. Soc.*, 1959, 81, 1590.

at 25° for 0.25 hour gave a mixture of ethyl benzoate and a low yield of acidic material from which was isolated benzoic acid and *O*-benzoylglycollic acid. However, when the reaction time was increased to 4 hours the acidic fraction was nearly all benzoic acid. Similar results were obtained after a 4-hour reaction period with ethyl *O*-*p*-methylbenzoylglycolate (I; R = *p*-C₆H₄·CH₃). *O*-Benzoylglycollic acid gave the same products as ethyl *O*-benzoylglycolate after 0.25 and 4 hours.

These results are consistent with a mechanism of base-catalysed ester interchange between ethoxide ion and the *O*-acylglycolate ion, either initially present or formed *in situ*. Although ethoxide ion is not consumed during the alcoholysis reaction it is eventually depleted as the hydroxyl-ion concentration decreases since the relative concentrations of these two ions remains constant by rapid equilibration between the two species [see scheme (3)].⁵ The hydroxyl-ion concentration is depleted by reaction with the *O*-acylglycollic acid at C-1' and with the ethyl carboxylate formed by the alcoholysis.

Base-catalysed alcoholysis of the *O*-acylglycolate ion is not considered to occur when the molar ratio of ester to base is 1 : 1, since the base is more likely to react with the *O*-acylglycolate ester at C-1' before its depletion. This view is supported by evidence from the rate of alkaline hydrolysis of esters R·CO₂Me, for when R = ·CH₂·CO₂Me the rate is seventy-two times faster than when R = ·CH₂·CO₂⁻; ⁶ the carboxylate ion in the latter presumably behaves as a repulsive centre towards the nucleophilic reagent. The mechanism for the formation of the ethyl carboxylates when the molar ratio of ester to base is 1 : 1 is then best expressed by scheme (2) where the base is eventually removed by reaction with the ethyl glycolate formed (k_{OH} at 25° = 60.5 l. mole⁻¹ min.⁻¹; cf. ref. 7).

EXPERIMENTAL

Melting points are corrected. The light petroleum had b. p. 60—80°.

Preparation of Ethyl O-acylglycolates: General Method.—The acid (0.25 mole), ethyl bromoacetate (46 g., 0.275 mole), anhydrous potassium carbonate (30 g.), and acetone (300—500 c.c.), were refluxed for 5 hr. The acetone was removed, water (400 c.c.) was added to the residue, and the mixture was extracted with ether. Evaporation of the dried (Na₂SO₄) ethereal extract gave the ethyl *O*-acylglycolate. The following ethyl *O*-acylglycolates (I), were prepared by this method. (I; R = *p*-Me·C₆H₄) (52%), m. p. 49—50.5° (Found: C, 65.0; H, 6.4. C₁₂H₁₄O₄ requires C, 64.8; H, 6.35%); (I; *p*-MeO·C₆H₄) (42%), b. p. 141—143°/0.4 mm. (Found: C, 59.95; H, 6.0. C₁₂H₁₄O₅ requires C, 60.5; H, 5.9%); (I; R = *p*-Br·C₆H₄) (46%), b. p. 119—121°/0.3 mm., m. p. 48.5—50° (Found: C, 45.9; H, 3.9; Br, 28.1. C₁₁H₁₁O₄Br requires C, 46.0; H, 3.9; Br, 27.8%); (I; R = Ph·CH₂) (91%), b. p. 105—107°/0.3 mm.²; (I; R = Ph) (82%), b. p. 118—119°/1.5 mm.⁸; (I; R = *p*-NO₂·C₆H₄) (83%), b. p. 128°/0.1 mm., m. p. 39—39.5°⁹; (I; R = *p*-HO·C₆H₄) (21%), m. p. 94.5—95.5°¹⁰; (I; R = Me) (76%), b. p. 71—72°/11 mm.¹; (I; R = Pr) (94%), b. p. 87—88°/8 mm.¹; (I; R = Pr^l) (89%), b. p. 85—88°/11 mm.¹; (I; R = Bu^l) (85%), b. p. 87—88°/10.5 mm.¹.

Ethyl O-Acylglycolates and Potassium Hydroxide in 4 : 1 Ethanol-Water.—(a) *Molar ratio 1 : 1.* Ethyl *O*-benzoylglycolate (5 g., 0.025 mole), was dissolved in 4 : 1 ethanol-water (41 c.c.), containing potassium hydroxide (0.025 mole), and the solution was maintained at 25° for 15 min. The solution was then poured into water and extracted with ether (neutral fraction). The mother-liquors were acidified with hydrochloric acid (10N; 10 c.c.) and extracted with ether (acidic fraction). Evaporation of the dried (Na₂SO₄) ethereal extract (acidic fraction) gave *O*-benzoylglycollic acid (3.10 g., 71.5%), m. p. 112—114° (lit.,¹¹ m. p.

⁵ Burns and England, *Tetrahedron Letters*, 1960, **24**, 1.

⁶ Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons, Ltd., London, 1953, p. 758.

⁷ Salmi and Leino, *Suomen Kem.*, 1944, **17**, B, 19.

⁸ Elkik, *J. Recherches Centr  Nat. Recherche Sci. Lab.*, 1958, **40**, 176.

⁹ Kharasch, Rudy, Nudenberg, and B chi, *J. Org. Chem.*, 1953, **18**, 1030.

¹⁰ Sakai, Minoda, Saito, and Sato, *J. Sci. Research Inst., Tokyo*, 1956, **50**, 93.

¹¹ Hurd and Filachione, *J. Amer. Chem. Soc.*, 1939, **61**, 1156.

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111—112°). (Found: Equiv., 178·8. Calc. for $C_9H_8O_4$; Equiv., 180·2). The neutral fraction gave ethyl benzoate (0·54 g.), b. p. 204—208°.

Ethyl *O-p*-nitrobenzoylglycollate (6·3 g.), gave *p*-nitrobenzoic acid (1·1 g.), m. p. 239—240° (from benzene) and ethyl *p*-nitrobenzoate (2·2 g.), m. p. 57·5—58°.

Ethyl *O-p*-bromobenzoylglycollate (5·5 g.) gave *p*-bromobenzoic acid (0·3 g.), m. p. 253—254·5° (from benzene) and ethyl *p*-bromobenzoate (1·87 g.), b. p. 255°.

Ethyl *O-p*-methylbenzoylglycollate (5·5 g.) gave *O-p*-methylbenzoylglycollic acid (3·68 g.), m. p. 125·5—127° (from benzene—light petroleum) (Found: C, 61·9; H, 5·7. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·2%).

Ethyl *O-p*-methoxybenzoylglycollate (6·0 g.) gave *O-p*-methoxybenzoylglycollic acid (4·18 g.), m. p. 108·5—109·5° (from benzene—light petroleum) (Found: C, 57·05; H, 5·0. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%).

Ethyl *O*-phenylacetyl glycollate (5·55 g.) gave *O*-phenylacetyl glycollic acid (0·55 g.), m. p. 76—77·5° (from benzene—light petroleum) (Found: C, 62·2; H, 5·0. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·2%), and ethyl phenylacetate (2·0 g.), b. p. 224°.

Ethyl *O*-butyrylglycollate (17·4 g.) gave *O*-butyrylglycollic acid (7·21 g.), b. p. 137—138°/9 mm. (Found: Equiv., 147·5. $C_6H_{10}O_4$ requires Equiv., 146·1) [*p*-bromophenacyl ester, m. p. 80° (Found: C, 49·2; H, 4·5; Br, 23·5. $C_{14}H_{15}BrO_5$ requires C, 49·0; H, 4·4; Br, 23·3%)], and ethyl butyrate (1·78 g.), b. p. 120—122°.

Ethyl *O*-pivaloylglycollate (7·05 g.) gave *O*-pivaloylglycollic acid (3·10 g.), m. p. 42·5—44° (Found: C, 52·5; H, 7·5. $C_7H_{12}O_4$ requires C, 52·5; H, 7·6%).

(b) *Molar ratio* 1 : 1·25. The previous experiments were repeated with the reactants at a molar ratio 1 : 1·25, the period of reaction being 0·25 hr. and, in some cases 4 hr. Results were as follows.

Ethyl *O*-benzoylglycollate (5 g.) gave *O*-benzoylglycollic acid (0·42 g.), m. p. 111—113°, benzoic acid (0·35 g.), m. p. 121·5—122·5°, and ethyl benzoate (1·92 g.), b. p. 206—208°. When the reaction time was 4 hr. the products were benzoic acid (0·54 g.), m. p. 122—123° and ethyl benzoate (1·83 g.), b. p. 206—208°.

Reaction of ethyl *p*-methylbenzoylglycollate (5·55 g.) for 0·25 hr. gave *O-p*-methylbenzoylglycollic acid (1·92 g.), m. p. 125·5—127·5°, and ethyl *p*-methylbenzoate (1·25 g.), b. p. 227—230°. Reaction for 4 hr. gave *p*-toluic acid, m. p. 177·5—179° (from light petroleum) and ethyl *p*-methylbenzoate (2·33 g.), b. p. 227—230°.

Reaction of *O*-benzoylglycollic acid (4·5 g.) for 0·25 hr. gave *O*-benzoylglycollic acid (1·26 g.), m. p. 111—112°, benzoic acid (0·22 g.), m. p. 120—121·5° and ethyl benzoate (1·57 g.), b. p. 208°. Reaction for 4 hr. gave benzoic acid (0·39 g.), m. p. 122—123° and ethyl benzoate (1·95 g.), b. p. 204—206°.

Ethyl O-p-Nitrobenzoylglycollate and Potassium Hydroxide in 1 : 1 Dioxan-Water; Molar Ratio 1 : 1.—The ester (6·32 g., 0·025 mole), was dissolved in 1 : 1 dioxan-water (40 c.c.), containing potassium hydroxide (0·025 mole) and maintained at 25° for 0·25 hr. The acidic fraction gave *p*-nitrobenzoic acid (1·68 g.), m. p. 236—238° (from benzene).