44. *The Racemisation of Carboxylic Esters by Sodium Ethoxide and its Bearing on Claisen's Condensation.*

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Esters of optically active disubstituted acetic acids readily racemise in presence of sodium ethoxide; this is considered to afford strong support for the view that ionised sodio-derivatives of the esters are formed under these conditions as has been suggested in several postulated mechanisms for Claisen's condensation.

The various mechanisms which have been proposed for the condensation of esters by means of sodium ethoxide (Claisen's condensation) postulate the initial formation of a sodium derivative of the ester. The earliest (Claisen, *Ber.*, 1887, **20**, 646) postulates the addition compound $CH_2R\cdot C(ONa)(OEt)_2$, but later ones (*e.g.*, Nef, *Annalen*, 1897, **298**, 218) involve a sodio-derivative of the ester of the type $[\overset{-}{C}HR\cdot CO_2Et]\overset{+}{N}a$, which is believed by some investigators to react in the form $CHR{:}C(ONa)(OEt)$ (cf. Michael, *Ber.*, 1900, **33**, 3731) or in a mesomeric modification thereof (Hauser, *J. Amer. Chem. Soc.*, 1938, **60**, 1957; Arndt and Eistert, *Ber.*, 1936, **69**, 2381).

The use of esters of optically active disubstituted acetic acids should afford additional means of deciding which of these two views more closely represents the structure of the sodio-derivative of the ester, for Claisen's addition compound on decomposition should yield the original ester with unchanged rotatory power, whereas the sodio-derivative postulated by the alternative views should yield the original ester in its racemised form.

Accordingly, we have examined the action of potassium methoxide and sodium ethoxide on the esters of three optically active disubstituted acetic acids; the results are in the table. The action of metallic potassium on one of these esters was also investigated: as might be anticipated from the results of Scheibler and Voss (*Ber.*, 1920, **53**, 388), the recovered ester was completely racemised.

Racemisation undergone by esters in presence of alkali alkoxide at room temperature.

Ester.	$\alpha_{5461}^{20°}$.	*l*.	Alkoxide.	Time.	Ratio, ester : alkoxide.	$\alpha_{5461}^{20°}$ of recovered ester (*l*, 0·5).	Extent of racemisation, %.
(−)CHPhMe·CO$_2$Me	−20·34°	0·5	MeOK	20 hrs.	1 : 1	± 0°	100
,,	−20·34	0·5	MeOK	48 hrs.	1 : 0·042	−19·32	5
,,	−20·34	0·5	EtONa	10 secs.	1 : 0·5	− 8·80	56·8
,,	−20·34	0·5	EtONa	24 hrs.	1 : 0·5	− 0·26	98·7
(−)CHEtBu·CO$_2$Et	− 2·92	2·0	EtONa	5 mins.	1 : 1	− 0·76	0
,,	− 2·92	2·0	EtONa	20 hrs.	1 : 1	− 0·66	10
,,	− 2·92	2·0	EtONa	20 mins.*	1 : 1	± 0	100
(+)CHMeEt·CO$_2$Et	+ 1·92	0·5	K	15 mins.	1 : 1	± 0	100
,,	+ 1·92	0·5	EtONa	1 hr.	1 : 1	+ 1·62	15
,,	+ 1·92	0·5	EtONa	40 hrs.	1 : 1	+ 0·62	68
,,	+ 1·92	0·5	EtONa	70 hrs.	1 : 1	± 0	100
,,	+ 1·92	0·5	EtONa	45 mins.*	1 : 1	± 0	100

* At 80°.

The tabulated results show that these esters undergo racemisation very readily when mixed with a molecular proportion of sodium ethoxide in concentrated alcoholic solution, the most marked example being methyl phenylmethylacetate, which might be expected to show a greater tendency towards proton release than the two purely aliphatic esters.

There is a considerable body of evidence (contributed largely by McKenzie and his co-workers) showing that extensive and often complete racemisation occurs during the alkaline hydrolysis of α-substituted carboxylic esters, and it appears that racemisation of the ester precedes its saponification. This conclusion receives additional support from Bickel's recent findings (*J. Amer. Chem. Soc.*, 1938, **60**, 927) that, whereas methyl *l*-β-benzoyl-α-phenylpropionate readily undergoes racemisation at 26° when dissolved in an excess of a methyl-alcoholic solution of sodium hydroxide, yet the free acid remains unaffected.

Finally, it may be recalled that esters of trisubstituted acetic acids and of acids containing an asymmetric centre other than in the α-position undergo alkaline hydrolysis without suffering any loss of optical activity.

There can be little doubt, therefore, that the action of sodium ethoxide on an ester does in fact result in the formation of a sodio-derivative in appreciable quantity, and that its formation involves the release of a proton from the α-carbon atom.

EXPERIMENTAL.

Materials.—(i) *dl*-Methylethylacetic acid was partially resolved by means of brucine (Marckwald, *Ber.*, 1896, **29**, 53) and esterified. The resulting (+)ethyl methylethylacetate had b. p. 35°/16 mm., $\alpha_{5893}^{20°}$ + 1·72°, $\alpha_{5461}^{20°}$ + 1·92° (*l*, 0·5); $n_D^{15°}$ 1·4002.

(ii) *dl*-Ethyl-*n*-butylacetic acid was partially resolved by means of cinchonidine (unpublished observation) and esterified. The resulting (−)ethyl ethyl-*n*-butylacetate had b. p. 90—91°/25 mm., $\alpha_{5893}^{20°}$ − 2·47°, $\alpha_{5461}^{20°}$ − 2·92° (*l*, 2); $n_D^{15°}$ 1·4179.

(iii) *dl*-Phenylmethylacetic (hydratropic) acid was partially resolved by means of strychnine (Raper, J., 1923, **123**, 2557) and esterified. The resulting (−)methyl phenylmethylacetate had b. p. 109—110°/20 mm.; $\alpha_{5461}^{20°}$ − 20·34° (*l*, 0·5); $n_D^{16°}$ 1·4997.

General Procedure.—In each experiment the optically active ester (4—5 g.) was added to 1 mol. (or less, see table) of an approximately saturated solution of the alkoxide in the corresponding alcohol. After the appropriate interval a slight excess of cold dilute hydrochloric acid was added, and the liberated ester extracted with ether. In all cases the recovered ester was characterised by its b. p. and refractive index. The amount of distilled ester recovered was of the order of 80—90%; the rest of the reaction product was generally insufficient for anything but a determination of its b. p., which was much higher than that of the ester from which it was derived. In the one experiment, where metallic potassium was used, the procedure adopted was to add the ester to an atomic proportion of the " powdered " metal suspended in pure benzene.

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