409. *The Preparation and Resolution of an Externally Compensated Formyl Acid.*

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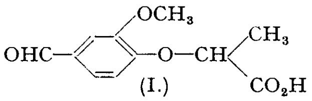
α-(2-Methoxy-4-formylphenoxy)propionic acid has been prepared and resolved into its (+)- and (−)-forms by fractional crystallisation of its cinchonine salt.

In general, the resolution of racemic aldehydes into their optically active forms involves combination with a reagent such as (+)- or (−)-menthylhydrazine (compare Galloway and Read, *J.*, 1936, 1222). Few such reagents are readily available and there are even fewer accounts in the literature of the use of optically active aldehydes in the resolution of substances with which they combine. Erlenmeyer (*Ber.*, 1903, **36**, 976) resolved 2-hydroxy-1 : 2-diphenylethylamine by combination with helicin, but a readily available optically active aldehyde which could be used to resolve neutral externally compensated compounds containing reactive methylene groups has obvious potential uses, and we have directed our attention to the preparation of such a compound.

Sodium vanilloxide (Meldrum and Patel, *J. Indian Chem. Soc.*, 1928, **5**, 191) was condensed with ethyl α-bromopropionate in dry alcoholic solution to give *ethyl α-(2-methoxy-4-formylphenoxy)propionate*, which was hydrolysed by hydrochloric acid to give the free *acid* (I). The (−)-*acid* was obtained by crystallisation of the cinchonine salt, and had $[\alpha]_{\mathrm{D}}^{25}$ $-32{\cdot}5^\circ$. An optically impure (+)-acid having $[\alpha]_{\mathrm{D}}$ $-7{\cdot}9^\circ$ was obtained from the quinine salt, and repeated attempts to prepare the optically pure acid by varying the conditions of crystallisation of this salt were unsuccessful. If, however, the aqueous mother-liquors from the crystallisation of the cinchonine salt of the (−)-acid were concentrated to small volume and this salt separated as completely as possible, the much more soluble salt of the (+)-acid remained in solution, and the (+)-acid, $[\alpha]_{\mathrm{D}}^{15}$ $+33{\cdot}0^\circ$,


(I.)

was obtained on removal of the alkaloid. A mixture of equal amounts of the (+)- and the (−)-acid regenerated the externally compensated acid. When the pure (+)-*acid* was combined with quinine, a *salt* was obtained which did not crystallise satisfactorily, and prolonged boiling of its solution did not bring about racemisation. It is probable, therefore, that the failure to resolve the (±)-acid by means of quinine is due to the formation of a partly racemic salt contaminated with varying amounts of the salt of the (+)-acid. The (±)-acid did not form salts with brucine or strychnine.

EXPERIMENTAL.

Ethyl α-(2-Methoxy-4-formylphenoxy)propionate.—Sodium vanilloxide (50 g.) and ethyl α-bromopropionate (42·0 g.) in absolute alcohol (400 ml.) were heated under reflux in an oil-bath at 120—125° for 45 hours. The solution was cooled and filtered, the alcohol distilled off, and sodium bromide, which crystallised, removed. The residual yellow oil was distilled, giving *ethyl α-(2-methoxy-4-formylphenoxy)-propionate* as a colourless viscous oil (35·4 g.), b. p. 166—167°/3 mm. When kept it set to a waxy white solid (Found : C, 61·9; H, 6·5. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·35%). The 2 : 4-*dinitrophenylhydrazone* crystallises in very small prisms from alcohol; m. p. 164—165° (Found : C, 52·6; H, 4·45. $C_{19}H_{20}O_8N_4$ requires C, 52·7; H, 4·6%).

α-(2-Methoxy-4-formylphenoxy)propionic Acid.—The above ester (13·7 g.) in absolute alcohol (41 ml.) and concentrated aqueous hydrochloric acid (41 ml.) were kept at room temperature for 3 days. The mixture was diluted with water (100 ml.), and the alcohol evaporated; on cooling and scratching, a white crystalline solid was deposited which was purified by dissolving it in dilute sodium carbonate solution, filtering from unchanged ester, and reprecipitating it with concentrated aqueous hydrochloric acid. The free *acid* (10·6 g.) crystallised from benzene–light petroleum (b. p. 60—80°) as fine hygroscopic needles, m. p. 79—80° (Found : C, 59·1; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%).

Cinchonine salt. Cinchonine (15·16 g.) and the (±)-acid (11·54 g.) were heated under reflux in water (1220 ml.) for 1 hour and filtered. The crystals deposited on cooling were collected and fractionally crystallised from water. The mother-liquor (*M*) was set aside (see below). The final fraction after 5 crystallisations of the *salt* had $[\alpha]_D^{15}$ +77·35° (c = 1·049 in alcohol, l = 1) (Found : C, 63·5; H, 6·7; N, 5·1. $C_{30}H_{34}O_6N_2,3H_2O$ requires C, 62·9; H, 7·05; N, 4·9%).

(−)-*α-(2-Methoxy-4-formylphenoxy)propionic Acid.*—The final fraction of the cinchonine salt was shaken with excess of sodium carbonate solution (33%). The cinchonine was filtered off, and the aqueous solution extracted 15 times with chloroform to ensure complete removal of the cinchonine. The solution of the sodium salt was acidified with concentrated hydrochloric acid, and the precipitated (−)-*acid* collected, washed, and dried. The aqueous solution, when extracted with ether, gave a further quantity of (−)-acid, which crystallised from benzene–light petroleum in fine colourless needles, m. p. 89—90°; α_D^{15} −0·328° (l = 1, c = 1·008 in alcohol), $[\alpha]_D^{15}$ −32·5° (Found : C, 58·6; H, 5·4. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%).

(+)-*α-(2-Methoxy-4-formylphenoxy)propionic Acid.*—The mother-liquors (*M*) were concentrated to 100 ml., and the white solid crystallising out removed; when the filtrate was concentrated to 50 ml., no further solid separated. The solution was shaken with excess of sodium carbonate, and the (+)-*acid* recovered as described for the (−)-acid. It crystallised from benzene–light petroleum as fine colourless needles, m. p. 89—90°, α_D^{15} +0·301° (l = 1, c = 0·912 in alcohol), $[\alpha]_D^{15}$ 33·0° (Found : C, 58·9; H, 5·3%).

A mixture of 0·0715 g. each of the (+)- and the (−)-acid made up to 10 ml. in absolute alcohol was inactive. The (±)-acid recovered from this measurement had m. p. 78—79°, not depressed on admixture with authentic (±)-acid, m. p. 79—80°.

Quinine salt. (*a*) Quinine (12·94 g.) and (±)-acid (8·97 g.) were heated under reflux in water (600 ml.) for 2 hours and filtered. The crystals deposited on cooling were collected and dried. The *salt* was fractionally crystallised from water, the final fraction after 6 crystallisations having $[\alpha]_D^{18}$ −86·8° (c = 8·68 in alcohol, l = 1) (Found : C, 63·8; H, 6·4. $C_{31}H_{36}O_7N_2,2H_2O$ requires C, 63·7; H, 6·9%). The acid was recovered from the final fraction similarly to the (−)-acid; m. p. 84—85°; α_D^{16} +0·103° (l = 1, c = 0·76 in alcohol), $[\alpha]_D^{16}$ +13·2° (Found : C, 58·7; H, 5·6%).

(*b*) Quinine (7·088 g.), (±)-acid (11·1984 g.), and sodium carbonate (1·1595 g.) were heated under reflux in water (750 ml.) for 4 hours and concentrated to 500 ml.; the crystals which separated were collected and dried. The salt was fractionally crystallised from water, the final fraction after 6 crystallisations having $[\alpha]_D^{15}$ −80·9° (c = 8·18 in absolute alcohol, l = 1) (Found : C, 63·9; H, 6·8%). The acid, recovered from the final fraction similarly to the (−)-acid, had m. p. 81—82°; α_D^{15} +0·0825° (l = 1, c = 1·04 in alcohol), $[\alpha]_D^{15}$ +7·9° (Found : C, 59·3; H, 5·7%).

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