125. *The Separation of Diastereoisomerides by Selective Adsorption on Optically Inactive Material.*

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Diastereoisomerides should have different coefficients of adsorption on adsorbents devoid of stereo-orientation. It is shown that *l*-menthyl *d*- and *l*-mandelates are adsorbed selectively on alumina.

There are two ways in which the technique of the adsorption column could be used to separate the active forms of a racemic substance. The first (Karagunis and Coumoulos, *Praktika*, 1938, **13**, 414; *Nature*, 1938, **142**, 162; Henderson and Rule, J., 1939, 1568) consists in running a solution of the racemic mixture down a column of optically active adsorbent (quartz; lactose). In the second, which corresponds more closely to classical methods of resolution, the racemic substance would be converted into diastereoisomerides by combination with a second purely *d*- or *l*-compound, whereupon selective adsorption might be expected to take place on *non*-asymmetrical material, since the diastereoisomerides should have different coefficients of adsorption. Stoll and Hofmann (*Z. physiol. Chem.*, 1938, **251**, 155), apparently without theoretical justification, attempted to separate the two forms of *dl*-*iso*lyserg-*d*-β′-hydroxy*iso*propylamide, but the facts that they crystallised and inoculated their chromatographically separated fractions (opening up the possibility of resolution) and that their observed rotations were very small make this an unsatisfactory example for the demonstration of the important fundamental principle, apart from the fact that the constitution of lysergic acid is unknown.

In order to investigate the question we have taken the *l*-menthyl esters of *dl*-mandelic acid, which McKenzie (J., 1904, **85**, 378, 1249) was unable to separate by fractional crystallisation during a thorough search using a large variety of solvents. Alumina (Birlec) was used as adsorption material, and all solvents were purified finally by running them down a column of this material.

The following specific rotations of optically pure compounds were determined in ethyl alcohol for reference :

l-Menthyl *l*-mandelate, m. p. 81—82°, $[\alpha]_{5461}^{19\cdot0^\circ}$ $-163\cdot5^\circ$ ($c = 2\cdot3072$; $l = 2$)
l-Menthyl *dl*-mandelate, m. p. 85—86°, $[\alpha]_{5461}^{19\cdot7^\circ}$ $-87\cdot3^\circ$ ($c = 1\cdot2485$; $l = 2$)
l-Mandelic acid, m. p. 133°, $[\alpha]_{5461}^{19\cdot5^\circ}$ $-184\cdot6^\circ$ ($c = 1\cdot6780$; $l = 2$)

The *l*-mandelic acid was obtained from amygdalin; the esters were prepared according to McKenzie (*loc. cit.*), who also gives the m. p. of *l*-menthyl *d*-mandelate as 99—100°.

Experimental.

In the present work three types of experiment have been carried out, all of which demonstrate that preferential adsorption does occur; an example of each follows.

(1) A solution of 5 g. of *l*-menthyl *dl*-mandelate in 500 c.c. of light petroleum (b. p. 80—100°) was run down a column of alumina (4 ft. × ½ in. diam.), followed by 250 c.c. of the pure solvent. The top 6-in. portion of the column was then completely extracted by a mixture of alcohol and benzene, and the solvent evaporated. The resulting solid residue in

ethyl-alcoholic solution had $\alpha^{19\cdot7^{\circ}}_{5461}$ −1·10° (c = 0·5492; l = 2), whence $[\alpha]^{19\cdot7^{\circ}}_{5461}$ = − 100·2°, representing 58·5% of *l*-menthyl *l*-mandelate and 41·5% of *l*-menthyl *d*-mandelate. Total saponification of the product by heating for a short time with aqueous-alcoholic potash gave an acid having $\alpha^{19\cdot7^{\circ}}_{5461}$ = −0·64°, $[\alpha]^{19\cdot7^{\circ}}_{5461}$ = −18·2° (c = 1·6660; l = 2). This and all other saponification experiments were carried out using an excess of potash, in order to avoid the possibility of partial saponification giving preferential release of one form of the acid: considerable racemisation is inevitable (see McKenzie, *loc. cit.*). Elution of the fourth 6-in. portion of the column gave an ester having $\alpha^{19\cdot7^{\circ}}_{5461}$ −0·93° in alcohol (c = 1·4820; l = 2), $[\alpha]^{19\cdot7^{\circ}}_{5461}$ −31·9° (86·5% of *d*-ester). Saponification gave an acid having $\alpha^{19\cdot7^{\circ}}_{5461}$ +0·57° (c = 0·4450; l = 2), $[\alpha]^{19\cdot7^{\circ}}_{5461}$ = + 64·0°.

(2) A solution of 5 g. of *l*-menthyl *dl*-mandelate in 1 l. of light petroleum (b. p. 60—80°) was put through a column of alumina (85 g.) (2 ft. × ½ in. diam.). The column was divided into six equal portions, each eluted with alcohol–light petroleum (b. p. 60—80°) (1 : 1), and the solvent removed by evaporation. The properties of the esters obtained and of the acids they yielded on saponification are tabulated below. The rotations are all measured in ethyl-alcoholic solution.

Esters.

	Weight, g.	M. p.	$\alpha^{19\cdot7^{\circ}}_{5461}$.	$[\alpha]^{19\cdot7^{\circ}}_{5461}$.	c, %.	Percentage of *l*-*l*-ester.
1	0·80	82—83°	−0·99°	−99·0°	0·5000	57·5
2	1·00	85—86	−0·95	−95·0	0·5000	55·0
3	0·975	85—86	−0·94	−94·0	0·5000	54·5
4	0·90	85—86	−0·94	−94·0	0·5000	54·5
5	0·70	80—87	−0·54	−54·0	0·5000	28·0
6	0·03	88—92	−0·12	−60·0	0·1000	32·0

Acids.

Sample of ester giving acid.	M. p.	$\alpha^{19\cdot7^{\circ}}_{5461}$.	$[\alpha]^{19\cdot7^{\circ}}_{5461}$.	c, %.
1 (above)	115—120°	−0·13°	−13·0°	0·5000
3 + 4	110—117	−0·09	− 9·0	0·5000
5 + 6	105—107	+0·14	+14·0	0·5000

(3) A solution of 5 g. of *l*-menthyl *dl*-mandelate in 250 c.c. of light petroleum (b. p. 60—80°) was run through 68 g. of alumina in a column 2 ft. × 0·45 in. diam. The column was then washed with pure solvent, the filtrate taken off in successive volumes of 250 c.c., each evaporated to dryness, and the residue of ester examined.

Ester from	Weight, g.	M. p.	$\alpha^{19\cdot7^{\circ}}_{5461}$.	$[\alpha]^{19\cdot7^{\circ}}_{5461}$.	c.	Percentage of *l*-*l*-ester.
1st portion 2nd ,,	0·52	90—95°	−0·32°	−32·0°	0·5000	14·0
3rd ,,	0·33	85—88	−0·57	−57·0	0·5000	30·0
4th ,,	0·1	81—82	−0·815	−81·5	0·5000	46·0

Elution of the first 4 in. of the column after this washing gave 0·35 g. of ester having m. p. 81—85°, $\alpha^{19\cdot7^{\circ}}_{5461}$ − 1·10° (c = 0·5000; l = 2), $[\alpha]^{19\cdot7^{\circ}}_{5641}$ = − 110·0° (65% of *l*-*l*-ester).

The actual observed angles of rotation are much larger than those of any previously recorded work on the use of adsorption in stereochemistry. Examination of the above results leaves no doubt that the coefficient of adsorption on inactive material can be added to the list of physical properties in which diastereoisomerides can be expected to differ. It is probable that, given a suitable adsorbent, diastereoisomeric *salts* could be separated in this way, and experiments in this direction will be undertaken when circumstances permit.

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