55. *The Stability of Racemates. Mandelic Acid and Some of its Derivatives.*

By W. Rogie Angus and R. P. Owen.

M. p. or f. p. curves for mixtures of the active and racemic forms of mandelic, acetyl- and propionyl-mandelic acids, and of methyl, ethyl, and *iso*butyl mandelates have been determined. Racemate stability is increased by acylation and by esterification.

In order to obtain some information regarding the stability of racemates of mandelic acid derivatives, the melting or freezing point curves of six compounds have been investigated.

Experimental.

Preparation of Materials.—*r*-Mandelic acid was recrystallised from acetone–benzene. Its resolution was effected by *l*-ephedrine, Roger's modification (J., 1935, 1544) of Skita, Keil, and Meiner's method (*Ber.*, 1933, **66**, 979) being used.

In this way both *d*- and *l*-mandelic acid were obtained. The *l*-acid had m. p. 133·5°, $[\alpha]_{5461}^{20^\circ}$ − 189·5° (*c*, 14·3 in acetone) {Skita *et al.* record m. p. 132·5—133·5°; $[\alpha]_{D}^{19^\circ}$ − 155·3°; Roger (*loc. cit.*) gives $[\alpha]_{5461}$ in acetone − 189·8°, and (in J., 1932, 2168) $[\alpha]_{5461}^{20^\circ}$ − 189·9° for pure *l*-acid.}

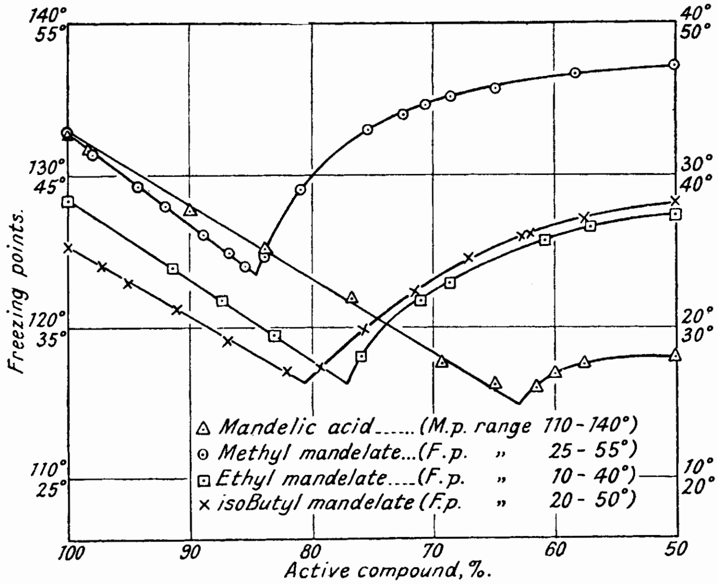
(a) O-*Acetyl*-r-*mandelic acid.* This was prepared by the method of Anschütz and Böcker (*Annalen*, 1909, **368**, 57). The needle crystals, obtained from water, are a dihydrate, m. p. 52°. Exhaustive desiccation gave the anhydrous form, m. p. 79°. [Anschütz and Böcker give m. p. 80°; Kaufler and Hertzog (*Ber.*, 1909, **42**, 3872) 76°; Savarian (*Compt. rend.*, 1908, **146**, 297) 79°; Dupont (*ibid.*, 1910, **150**, 1525) 74—75°].

(b) O-*Acetyl*-l-*mandelic acid.* Similarly prepared, this acid recrystallised from water as a monohydrate and on exhaustive desiccation gave the anhydrous acid, m. p. 96·8°, $[\alpha]_{5461}^{20^\circ}$ − 194·1°, $[\alpha]_{D}^{20^\circ}$ − 157° (*c*, 2·4 in acetone). {McKenzie and Humphries (J., 1909, **95**, 1106) also obtained a monohydrate and gave the m. p. of the anhydrous acid as 96·5—98°, $[\alpha]_{D}^{20^\circ}$ − 157·7° (*c*, 2·2 in alcohol), $[\alpha]_{D}^{20^\circ}$ − 153·7° (*c*, 2·058 in acetone); Walden (*Z. physikal. Chem.*, 1895, **17**, 706) gives $[\alpha]_{D}^{20^\circ}$ − 156·4°.}

(c) O-*Propionyl*-r-*mandelic acid.* *r*-Mandelic acid (20 g.) and propionyl chloride (14 g.) were heated on a water-bath for 3 hours, excess propionyl chloride distilled off, and the resulting oil taken up in a little chloroform and precipitated as a solid by ligroin. On recrystallisation from water, the acid formed a dihydrate (m. p. indefinite, but about 50°); on recrystallisation from ligroin (b. p. 40—60°), 18 g. of anhydrous *propionyl*-r-*mandelic acid*, m. p. 51·2°, were obtained (Found : C, 63·35; H, 5·8. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·75%).

(d) O-*Propionyl*-l-*mandelic acid.* This *acid*, similarly prepared, had m. p. 70—71°, $[\alpha]_{5461}^{15^\circ}$ − 172·4°, $[\alpha]_{D}^{15^\circ}$ − 139·1° (*c*, 0·855 in carbon disulphide); $[\alpha]_{5461}^{15^\circ}$ − 134·2°, $[\alpha]_{D}^{15^\circ}$ − 124·5° (*c*, 0·466 in alcohol); $[\alpha]_{5461}^{15^\circ}$ − 133·2°, $[\alpha]_{D}^{15^\circ}$ − 107·5° (*c*, 0·327 in acetone) (Found : C, 63·3; H, 5·8%).

FIG. 1.



(e) O-*Benzoyl*-r-*mandelic acid.* *r*-Mandelic acid (20 g.) and benzoyl chloride (20 g.) were heated under reflux for 3 hours and subsequently treated as in (c). On recrystallisation from ligroin, 10 g. of anhydrous *benzoyl*-r-*mandelic acid*, m. p. 114—115°, were obtained (Found : C, 70·1; H, 4·7. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

Esters. These were prepared by the general method of Fischer and Speier (*Ber.*, 1895, **28**, 3254) and gave the following values for physical constants : Methyl *r*-mandelate, m. p. 58° [Zincke and Breuer (*Ber.*, 1880, **13**, 636) give 47—49°; Rupe (*Ber.*, 1895, **28**, 259) 52°; Acree (*Ber.*, 1904, **37**, 2767) 58°; Findlay and Turner (J., 1905, **87**, 752) 57°]. Methyl *d*-mandelate, m. p. 54—55° [Walden (*loc. cit.*) gives 55°; McKenzie and Wren (J., 1908, **93**, 312) 54·3°; Freudenberg and Markert (*Ber.*, 1925, **58**, 1753) 58°]; $[\alpha]_{5461}^{20^\circ}$ + 272·6°, $[\alpha]_{D}^{20^\circ}$ + 219·6° (*c*, 1·6 in carbon disulphide) (McKenzie and Wren give $[\alpha]_{D}^{20^\circ}$ + 214° in carbon disulphide). Ethyl *r*-mandelate, m. p. 29° [Michael and Jeanpetre (*Ber.*, 1892, **25**, 1682) give 34°; McKenzie (J., 1899, **75**, 755) 37°; Findlay and Turner (*loc. cit.*) 29°]. Ethyl *l*-mandelate, m. p. 31° [Walden (*loc. cit.*) gives 35°; Walker (*Chem. Zentr.*, 1909, ii ,2113) 30°; Freudenberg and Markert (*loc. cit.*) 34°]. *iso*Butyl *r*-mandelate, m. p. 39° [Walden (*loc. cit.*) gives 35°]. *iso*Butyl *l*-mandelate, m. p. 35·8° [Wood, Chrisman, and Nicholas (J., 1928, 2186) give 35·5°]; $[\alpha]_{5461}^{20^\circ}$ − 185·6°, $[\alpha]_{D}^{20^\circ}$ − 149·7° (*c*, 1·27 in carbon disulphide) (Walden gives $[\alpha]_D$ − 144° in carbon disulphide; Wood *et al.* give − 124·58° for the molten ester).

Freezing-point Curves.—Although it was impossible to determine transition points, the f.-p. curves give an indication of the effect of substitution on the stability of the racemic forms; those for various mixtures of active and inactive compounds were obtained by the cooling curve method, and for all mixtures (except those of mandelic acid) the f. p.'s were taken instead of the m. p.'s. Only half of the full temperature–composition curve was determined, since the curves are symmetrical around the 50% co-ordinate.

(a) *Mandelic acid.* The f.-p. curve of this acid could not be determined because, on heating, it undergoes some form of internal condensation (see Note, this vol., p. 249). Instead, the m.-p. curve was determined by making artificial mixtures of the active and the racemic form and determining their m. p.'s by heating *once* only. The results are given in Table I and Figs. 1 and 2; the data from previous determinations [Adriani (*Z. physikal. Chem.*, 1900, **33**, 468) and Centnerszwer (*ibid.*, 1899, **29**, 715)] are included. The present results differ from those of the earlier workers in respect of the racemic portion. Each value now recorded has been confirmed several times and no reason can be given for the divergence. The eutectic point occurs at 114·8° and 63% of *l*-acid; Adriani gives 113° and 60% of *l*-acid.

Acetylmandelic acid (Table II and Fig. 1). The eutectic point is at 65° and the eutectic mixture contains 68·2% of *l*-acid.

Propionylmandelic acid (Table III; Fig. 1). Eutectic point, 37·8°; *l*-acid in eutectic mixture, 69·5%.

TABLE I.

l-Acid, %.	Adriani.	Melting points. Centnerszwer.	Authors.	*l*-Acid, %.	Adriani.	Melting points. Centnerszwer.	Authors.
100·0	133·0°	132·7°	133·0°	70·0	118·2°	—	—
98·2	—	—	131·8	69·2	—	—	117·5°
95·0	—	129·9	—	65·0	115·8	—	116·1
90·0	128·1	—	127·7	62·5	—	117·9°	—
87·5	—	126·7	—	61·7	—	—	116·0
83·8	—	—	125·1	60·0	113·0	—	117·0
80·0	123·2	—	—	57·6	—	—	117·5
76·9	—	—	121·8	55·0	—	119·2	—
75·0	120·6	120·6	—	50·0	118·0	121·0	118·0

FIG. 2.

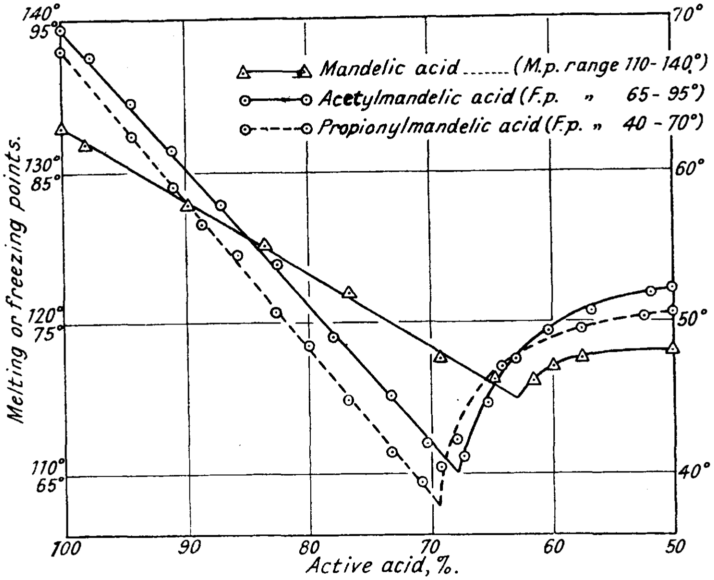


TABLE II.

l-Acid, %	100·0	97·86	94·70	91·30	87·40	82·40	78·25	73·60
F. p.	94·6°	92·6°	89·6°	86·4°	83·8°	78·8°	74·0°	70·0°
l-Acid, %	70·60	67·70	65·40	63·14	60·50	56·85	52·0	50·0
F. p.	67·0°	66·0°	69·6°	72·4°	74·3°	75·6°	76·8°	77·0°

TABLE III.

l-Acid, %	100·00	98·21	94·56	92·10	88·80	86·00	82·83	80·10	77·00
F. p.	68·0°	65·0°	62·4°	60·0°	56·5°	54·4°	50·6°	48·4°	44·6°
l-Acid, %	73·50	71·20	69·30	68·05	64·30	57·70	52·50	50·0	
F. p.	41·4°	39·4°	40·4°	42·2°	47·0°	49·4°	50·2°	50·5°	

Methyl mandelate (Table IV; Fig. 2). Eutectic point 38·4°; eutectic composition, 84·5% of *l*-acid. The m. p. curve had been determined by Centnerszwer (*loc. cit.*) by taking the m. p.'s of artificial mixtures in capillary tubes, and his results are given for comparison. There is a great lack of agreement: Centnerszwer's values do not lie on a smooth curve; further, his m. p. for the racemic ester is 8° lower than ours, and the composition of his eutectic mixture considerably different. Although his m. p. curve should not coincide with our f.-p. curve there should be similarity in shape. Confirmation of each of our points several times, and comparison with the values for other esters, suggest that our curve is the more trustworthy.

TABLE IV.

d-Ester,	F. p.		*d*-Ester,	F. p.		*d*-Ester,	F. p.	
%.	Centnerszwer.	Authors.	%.	Centnerszwer.	Authors.	%.	Centnerszwer.	Authors.
100·0	54·6°	47·8°	86·69	—	39·8°	70·46	—	49·6°
98·42	—	46·8	85·32	—	39·0	68·60	—	50·2
95·1	52·3	—	83·84	—	41·6	64·80	—	50·7
94·42	—	44·4	80·82	—	44·0	62·4	48·3°	—
92·15	—	43·0	75·5	47·5°	—	58·10	—	51·7
88·87	—	41·2	75·25	—	48·0	54·8	49·2	—
87·5	50·0	—	72·50	—	49·0	50·0	50·0	52·2

Ethyl mandelate (Table V; Fig. 2). Eutectic point 16·2°; eutectic composition, 76% of *l*-ester.

TABLE V.

l-Ester, %	100·00	91·40	87·40	83·18	76·10	71·03	68·48	60·80	57·10	50·00
F. p.	28·4°	24·0°	21·8°	19·4°	18·0°	21·8°	23·0°	25·8°	26·6°	27·4°

iso*Butyl mandelate* (Table VI; Fig. 2). Eutectic point, 26·2°; eutectic composition, 80·5% of *l*-acid. Centnerszwer's m. p. data (*loc. cit.*) are given for comparison: they do not agree with ours.

TABLE VI.

l-Ester, %.	F. p. Centnerszwer.	F. p. Authors.	*l*-Ester, %.	F. p. Centnerszwer.	F. p. Authors.	*l*-Ester, %.	F. p. Centnerszwer.	F. p. Authors.
100·0	35·3°	35·2°	82·1	—	27·0°	62·7	—	35·8°
97·6	—	34·1	79·4	—	27·3	62·6	37·8°	—
95·2	—	32·8	75·6	—	29·8	62·0	—	36·0
95·0	33·3	—	75·0	37·0°	—	57·4	—	37·1
91·3	—	31·2	71·4	—	32·2	54·7	38·2	—
87·3	32·9	29·0	67·0	—	34·6	50·0	38·7	38·2

All thermometers were checked against N.P.L. certified instruments.

Discussion.—The f.-p. curves of mandelic acid and its derivatives can be divided into two classes, *viz.*, those of acids and of esters, which are essentially different in shape. In the three acid curves the f. p.'s of the active acids are considerably higher than those of their racemic isomerides. The straight-line portion of these curves occupies the greater portion of the curve, and the area under the racemic curve is comparatively small. With the esters, the f. p.'s of the racemates are a few degrees higher than those of the active forms, the racemate portions occupy the greater part of the curves, and the areas under the racemic curves are comparatively large.

The three factors which are considered in examining the influence of substituents on the stability of the racemate are collected in Table VII. They are (i) the percentage of active isomeride in the eutectic mixture, (ii) the difference between the f. p. or m. p. of the active and the racemic form, $\theta_a - \theta_r$, and (iii) the difference between the f. p. or m. p. of the racemate and the eutectic temperature, $\theta_r - \theta_e$.

TABLE VII.

	Active isomeride in eutectic, %.	$\theta_a - \theta_r$.	$\theta_r - \theta_e$.		Active isomeride in eutectic, %.	$\theta_a - \theta_r$.	$\theta_r - \theta_e$.
Acids:				*Esters*:			
Mandelic	63	15°	3·2°	Methyl	84·5	−4·4°	11·8°
Acetylmandelic	68·2	17·6	12·0	Ethyl	76·0	−1·0	11·2
Propionylmandelic	69·5	17·5	12·7	*iso*Butyl	80·5	−3·0	12·0

There is a slight difference, about 2·5°, in $\theta_a - \theta_r$, on acylation of mandelic acid. The values for $\theta_r - \theta_e$, however, increase from 3·2° for mandelic acid to 12·0° for the acetyl and 12·7° for the propionyl derivative. The comparatively small value of $\theta_r - \theta_e$ and the fairly large value for $\theta_a - \theta_r$ in mandelic acid indicate that the transition temperature of the racemic compound into the *dl*-mixture is not far removed from the f. p. of the racemic acid. With the substituted acids, however, although the values of $\theta_a - \theta_r$ are practically the same as for mandelic acid, there is a considerable increase in the values of $\theta_r - \theta_e$ and also in the areas beneath the racemic curves, thus indicating that the transition temperatures of these racemates are not very near their f. p.'s.

The composition of the eutectic mixtures becomes progressively richer in the optically active component in passing from mandelic through acetyl- to propionyl-mandelic acid; this indicates that the stability of the racemic forms has been progressively increased. This fact is also borne out by the progressive increase in the areas occupied by the racemic portions. Further, the value of $\theta_r - \theta_e$ is greater for the propionyl than for the acetyl derivative. The view that this difference has a significant relation to the stability of the racemate and increases with increasing stability finds substantiation in the results for the esters.

From the data in Table VII it is clear that esterification greatly reduces the values of $\theta_a - \theta_r$ and that, for the three esters examined, the f. p.'s of the racemates are slightly higher than those of the active forms. Examination of Table VII and Fig. 2 shows immediately that esterification leads to an increased racemate area and to a eutectic mixture considerably richer in active component. Further, the comparatively large difference between θ_r and θ_e for the esters would appear to indicate that the transition points are far removed from the f. p.'s of the racemates. From all these considerations it is concluded that esterification increases racemate stability.

Possibly because one of the esters has a branched chain, the progressive variation, on ascending the homologous series, in the stability of the racemate and in factors related to the stability is not encountered. In passing from the methyl to the ethyl ester, however, there is a diminution in stability.

The results of Findlay and Campbell (J., 1928, 1768) on derivatives of tartaric acid are in general agreement with those now reported for mandelic acid.

The investigation reported in this paper was commenced many years ago by one of us (W. R. A.) at the suggestion of Professor A. Findlay, to whom our thanks are due for allowing us to continue the work and for much helpful advice in its early stages.

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR.

[*Received, January 5th*, 1943.]