

The Effect of Temperature upon the Equilibrium between Partially Labile Diastereoisomers. Part I. Quinidine Salts in Chloroform Solution.

By MARGARET M. HARRIS.

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When quinidine and one molecular proportion of an optically labile acid, *N*-benzoyl-6-methyldiphenylamine-2-carboxylic acid (III; R = Me; R' = R'' = R''' = H) are dissolved together in chloroform the solution shows a wide variation of optical rotation with temperature. This has been proved to be due to variation in the position of the equilibrium (+)-Acid, Quinidine \rightleftharpoons (-)-Acid, Quinidine with temperature. Several other acids show similar behaviour, in some cases with, and in some without, detectable mutarotation.

THE salts formed between an optically labile acid (\pm)-R·CO₂H and one form of an optically stable base (+)-B are diastereoisomeric and in suitable circumstances will be in equilibrium, (+)-R·CO₂H, (+)-B \rightleftharpoons (-)-R·CO₂H, (+)-B. The composition of the equilibrium mixture would be expected to be dependent upon temperature, a dependence which would show itself in a change of optical rotation when the equilibrated solution is viewed successively at different temperatures [Ingram (*J.*, 1950, 2318) reports such a case for the optically stable (+)-camphor-10-sulphonic acid with the optically stable base 10-*m*-aminobenzylideneanthrone].

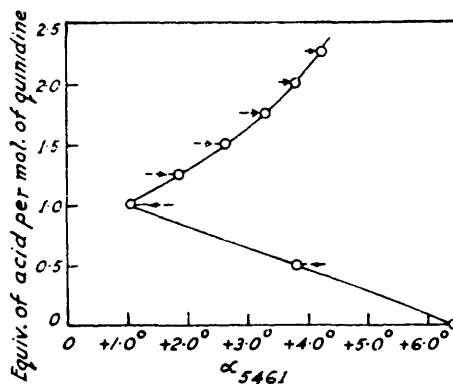
In the series of substituted *N*-benzoyldiphenylaminecarboxylic acids, suitable members of which are known to be optically active and optically labile (Jamison and Turner, *J.*, 1938, 1646; 1940, 264; Harris, Potter, and Turner, *J.*, 1955, 145), it seems reasonable to assume that salt formation between one molecular proportion of quinidine and one of acid is virtually complete because (*a*) addition of further acid causes a *sharp backward* turn of the curve in which equivalents of acid per equivalent of base are plotted against rotation (*e.g.*, Fig. 1) and (*b*) the freezing-point depression for one mol. of acid and one mol. of base (in this case cinchonidine) dissolved together in the comparable solvent bromoform is equal to that for one mol. of naphthalene (Harris, Potter, and Turner, *loc. cit.*).

The optical rotation of certain single substances, alone or in solution, having only one centre of asymmetry is known to vary with temperature (see, for example, Kauzmann, Walter, and Eyring, *Chem. Rev.*, 1940, 26, 373) and it would be necessary to be aware of any changes of rotation of this nature before attributing an observed change to shifting of

equilibrium between members of a diastereoisomeric pair. This can be done in three ways. First, the base and an acid which is incapable of optical activity or is optically stable can be taken as a standard of comparison; it should resemble chemically the acid to be investigated as closely as possible: Ingram (*loc. cit.*) used a similar test in an examination of the large change in rotation with temperature of 10-*m*-[(-)-menthoxyacetamido]benzylideneanthrone in chloroform solution; 9-*m*-[(-)-menthoxyacetamido]benzylidene-fluorene and (-)-menthoxyacetanilide showed rotations with a much smaller dependence on temperature. Ingram suggested that the large change in rotation was due to the variation in equilibrium composition of the two diastereoisomeric (-)-menthoxyacetyl derivatives of the 10-*m*-aminobenzylideneanthrone: no other manifestation of optical activity could be found, although the structure of the molecule is such that optical activity should be observable if the degree of restriction of rotation is sufficient. 10-*m*-[(-)-Menthoxyacetamido]benzylideneanthrone is particularly interesting in this connection, because the two optically active centres of the diastereoisomers are in chemical combination and not subject to the uncertainties of salt formation. Secondly, if the optical stability permits, the rotation of the partially racemic salt, (\pm)-R \cdot CO₂H, (+)-B, can be found at various temperatures and compared with the rotations of the equilibrium mixtures. Thirdly, removal of the base

FIG. 1. Addition of *N*-benzoyl-6-methyldiphenylamine-2-carboxylic acid to quinidine in chloroform at 20°.

(The broken lines represent the observed range of mutarotation.)



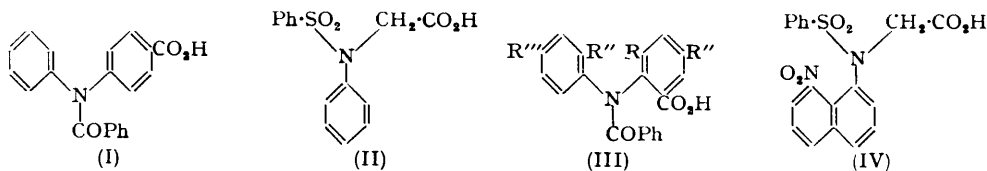
from the mixtures equilibrated at different temperatures should leave specimens of acid which are in varying degrees optically active. All of these methods are exemplified in the present work.

The *N*-benzoyldiphenylaminecarboxylic acids provide excellent material for this investigation because the series includes examples of a large variation in optical stability, from *N*-benzoyldiphenylamine-2-carboxylic acid itself, which is so unstable optically as to show no mutarotation in chloroform in presence of alkaloids even at -33°, to *N*-benzoyl-4'-bromo-2'-chloro-6-methyldiphenylamine-2-carboxylic acid which is sufficiently stable to be isolated in an active form (Harris, Potter, and Turner, *loc. cit.*).

Throughout the present work quinidine has been used as the optically stable, salt-forming base in chloroform solution and the effect of change of temperature upon the equilibrium rotation of its salts with a variety of acids has been ascertained. The concentration of quinidine was constant in all the determinations and equimolecular proportions of the acids were used; the results, which are directly comparable with each other, are plotted in Fig. 2. It will be seen that the acids fall into two main categories, those in which the rotation alters only slightly with temperature and those in which it changes to a substantial degree. The former are the optically inactive acids, benzoic acid, *N*-benzoyldiphenylamine-4-carboxylic acid (I), and *N*-benzenesulphonyl-*N*-phenylglycine (II); the latter are the *N*-benzoyldiphenylamine-2-carboxylic acids (III) and *N*-benzenesulphonyl-8-nitro-1-naphthylglycine (IV) (Mills and Elliott, *J.*, 1928, 1291), all of known low optical stability. *N*-Benzoyldiphenylamine-2-carboxylic acid has never been demonstrated to be optically active by "classical" methods, but its activity is inferred from the effect of excess of the (\pm)-acid on its cinchonidine and (+)-nor- ψ -ephedrine salts (Jamison and Turner, *loc. cit.*, 1938).

The values of the rotations shown in Fig. 2 are in many cases (*h, i, j, k, l*) the final values of observed mutarotations (first-order asymmetric transformations); there is little doubt that the same is true of curves *e, f*, and *g* but that the mutarotations are too fast for observation at the temperatures employed. *N*-Benzoyl-6-methyldiphenylamine-2-carboxylic acid (III; R = Me, R' = R'' = R''' = H) was selected for more detailed study in this connection.

To a solution of 0.4143 g. of this acid dissolved in 16 c.c. of chloroform at temperature T° was added 0.4050 g. (1 mol.) of quinidine. The resulting solution was quickly poured



into a polarimeter tube thermostatically controlled at T° and readings of α_{5461} were made at recorded intervals of time while first-order asymmetric transformation took place. Extrapolation of a logarithmic plot to zero time (the time of adding the quinidine) gave a value for the rotation of the (\pm)-acid,quinidine salt. The procedure was repeated at several temperatures (Fig. 3). This method is obviously subject to errors, but as the initial polarimetric readings were made very quickly (within 1—2 minutes of adding the quinidine) the extrapolated values are sufficiently accurate to show that the *initial* temperature-rotation curve is of the same type as the curves for optically inactive acids. In other words, the greater part of the temperature-rotation effect shown in a graph such as the bottom line in Fig. 3 is due to the change in the (+)-acid,quinidine \rightleftharpoons (-)-acid,quinidine equilibrium.

First-order asymmetric transformation of quinidine N-benzoyl-6-methyldiphenylamine-2-carboxylate in chloroform (Fig. 3).

Temp.	5.2°	16.6°	24.9°	34.6°
α_{5461} : extrapolated to $t = 0$	+5.70°	+5.86°	+5.97°	+6.2° \pm 0.2°
observed, initial	+5.63	+5.63	+5.21	+5.43
„ final	+0.45	+1.80	+2.49	+3.41

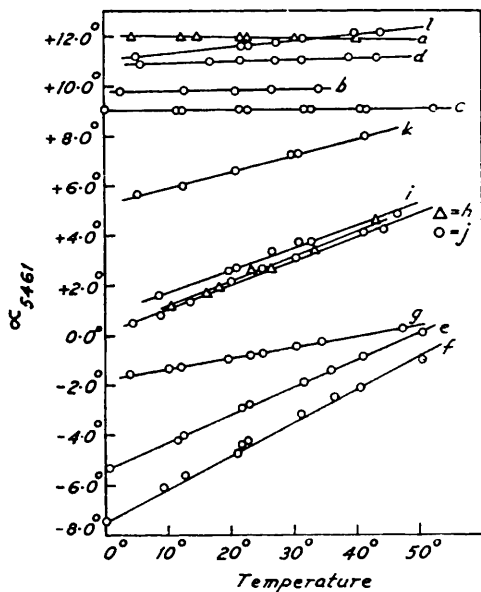
While a solution freshly prepared at 20.2° of the (\pm)-acid (0.4143 g.) and quinidine (0.4050 g.) in 16 c.c. of chloroform showed mutarotation from $\alpha_{5461} = +3.68^\circ$ after 13 minutes to +2.21° after 2 hours, one of the same composition which was left overnight at 3.5° and then quickly warmed to 21° changed in rotation from +0.56° to +2.23° in the same time (Fig. 4).

N-Benzoyl-6-methyldiphenylamine-2-carboxylic acid although previously described (Turner and his co-workers, *loc. cit.*, 1940, 1955) had not been obtained optically active. During the present work it was found possible to obtain it in the levorotatory form, in varying degrees of optical purity, in chloroform solution. When three of the equilibrated solutions represented by curve (*j*) (Fig. 2) were decomposed by ice-cold hydrochloric acid, specimens of active acid were obtained which racemized rapidly in chloroform at 21° (Fig. 5).

Lesslie, Turner, and Winton (*J.*, 1941, 257) observed a large variation with temperature in the rotation of quinine diphenate in ethanol-chloroform solution. It seems probable that they were observing a shifting equilibrium here, analogous to those recorded in Fig. 2.

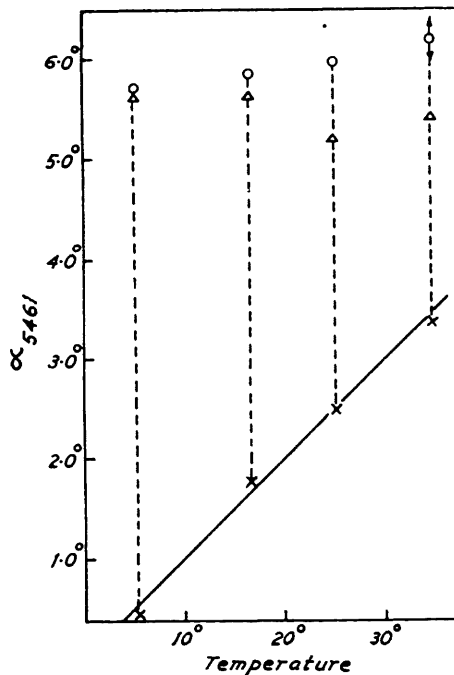
Although the temperature-rotation work now reported has all been carried out with quinidine as the optically active agent, preliminary experiments show that cinchonidine and cinchonine behave to a certain extent similarly and they are being investigated further. If the phenomenon is general and is capable of being distinguished from other temperature-dependent influences on rotation, it should be of value in the diagnosis of optical activity in highly labile compounds. It may also be noted that this temperature-dependent equilibrium could be an important factor in some asymmetric syntheses which proceed by way of optically labile diastereoisomeric transition states.

FIG. 2. Rotation of quinidine salts in chloroform.



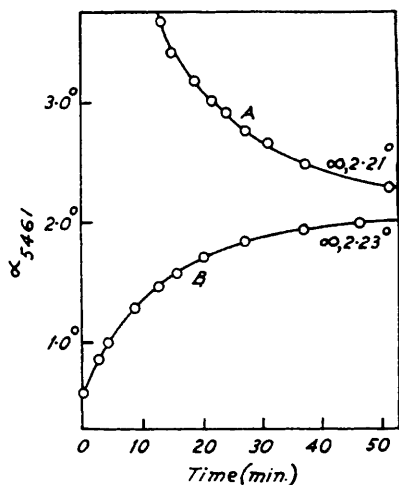
- (a) Quinidine alone.
- (b) Benzoic acid.
- (c) (I).
- (d) (II).
- (e) (III; R = R' = R'' = R''' = H).
- (f) (III; R = R' = H, R'' = R''' = Cl).
- (g) (III; R = R' = H, R'' = R''' = Me).
- (h) (III; R = R' = Cl, R'' = R''' = H).
- (i) (III; R = R' = Br, R'' = R''' = H).
- (j) (III; R = Me, R' = R'' = R''' = H).
- (k) (III; R = Me, R' = H, R'' = R''' = Cl).
- (l) (IV).

FIG. 3. First-order asymmetric transformation of N-benzoyl-6-methyldiphenylamine-2-carboxylic acid with quinidine in chloroform at various temperatures.



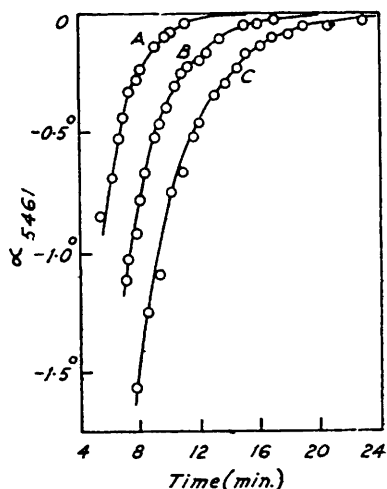
- \circ Extrapolated to $t = 0$.
- \times Observed final point.
- Δ Observed first point.

FIG. 4. N-Benzoyl-6-methyldiphenylamine-2-carboxylic acid with quinidine in chloroform.



- A, First-order asymmetric transformation at 20.2°.
- B, Equilibration at 21° of a solution which had been allowed to stand at 3.5°.

FIG. 5. Racemisation of (-)-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid in chloroform at 21°.



- From asymmetric transformation at (A) 45°, (B) 21°, (C) 0.8°.

EXPERIMENTAL

The diphenylaminocarboxylic acids were prepared as described by Jamison and Turner, and by Harris, Potter, and Turner (*loc. cit.*).

Chloroform for rotation experiments was washed repeatedly with water to remove ethanol and dried.

Quinidine.—A chloroform solution of quinidine (Harringtons) was dried (Na_2SO_4) and filtered, and dry light petroleum (b. p. 40—60°) added until crystallisation began: the first crop, which was oily, was filtered off quickly and the second crop kept. Repetition of this procedure gave a finely divided specimen which after vacuum-drying had m. p. 171°, $[\alpha]_{\text{D}}^{21.5} + 236^\circ$ (*c.* 2.531 in freshly washed and dried chloroform).

The measurement of variation of rotation with temperature was carried out in a well-lagged 2-dm. tube round which water was pumped at the required temperature. Polarimetric readings were made at steady temperatures, mounting from point to point up the range shown in the graphs; then the solution was cooled, readings being taken at descending intervals of temperature down to the lowest point recorded, and finally returning to the original temperature: this procedure guards against any irreversible change which might be mistaken for a shift of equilibrium.

Preparation of (-)-N-Benzoyl-6-methyldiphenylamine-2-carboxylic Acid in Chloroform Solution.—The (\pm)-acid (0.4143 g.) and quinidine (0.4050 g.) were dissolved together in chloroform (16 c.c.) and left for 2 days at 0.8°; at $t = 0$ min. the solution was washed with concentrated hydrochloric acid to which ice was added, with the same mixture twice again, then with ice-water; it was then run into a cooled flask containing anhydrous sodium sulphate, shaken, and filtered into a polarimeter tube (temp. 21°) at $t = 5.5$ min. The first polarimetric reading was made at 7.8 min. (curve *C*, Fig. 5). Curves *A* and *B* were obtained similarly, with the difference that the solutions before decomposition were left at 45° and 21° respectively.

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BEDFORD COLLEGE, UNIVERSITY OF LONDON.

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