44. *The Salts of Diphenic Acid with Optically Active Bases.*

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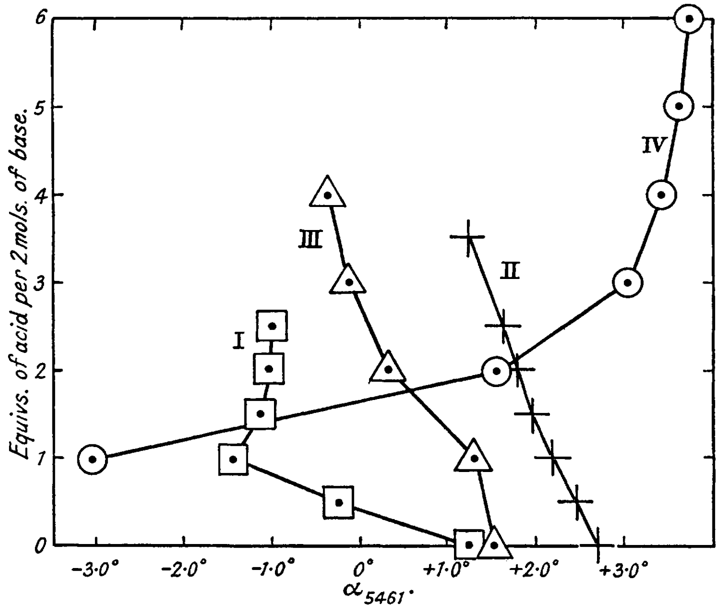
The specific rotation of quinine diphenate in alcohol–chloroform has an unusually high temperature coefficient. This was responsible for certain apparent mutarotations described previously. At −30°, diphenic acid undergoes rapid optical activation in chloroform or acetone–chloroform in presence of nor-*d*-ψ-ephedrine.

In a previous communication (Lesslie and Turner, J., 1934, 347) certain alkaloidal salts of diphenic acid were described as exhibiting slight mutarotation in alcoholic or alcohol–chloroform solution, and it was inferred that asymmetric induction was responsible for the effects observed, and was made possible by the low optical stability of diphenic acid. Further examination of the problem has now shown that the specific rotation of quinine diphenate has an unusually high temperature coefficient, and that the "mutarotation" described in 1934 was due to this. The following figures were obtained for a solution of quinine diphenate alcoholate in a mixture of ethyl alcohol (2 vols.) and chloroform (1 vol.) ($l = 4$; $c = 4{\cdot}472$):

Temp.	0·8°	20·1°	24·8°	29·5°	35·4°	39·5°	43·1°	45·5°
α_{5791}	+ 9·14°	+ 8·36°	+ 7·99°	+ 7·48°	+ 6·93°	+ 6·19°	+ 5·62°	+ 5·23°
α_{5461}	+10·54°	+ 9·75°	+ 9·31°	+ 8·70°	+ 8·03°	+ 7·18°	+ 6·55°	+ 6·07°

Corresponding figures were obtained several times, and on no occasion was mutarotation observed at any temperature within the above limits. Again, solutions of mixtures of equivalent proportions of quinine and diphenic acid also exhibited no motarotation when rigid temperature control was exercised. Our new results thus agree with those of Kharasch, Senior, Stanger, and Chenicek (*J. Amer. Chem. Soc.*, 1934, **56**, 1646). We are permitted to say that Dr. Breckenridge, in a private communication to Professor McKenzie (Jan. 16th, 1940), has stated that the mutarotation observed by Breckenridge and Smith (J., 1939, 1536) with alkaloidal salts of 2-phenylpyridine-2′ : 3-dicarboxylic acid is also due solely to a temperature effect, no mutarotation in the real sense of the word being involved (compare McKenzie and Wood, J., 1939, 1536).

Since the appearance of our 1934 paper, a method (Jamison and Turner, J., 1938, 1646; 1940, 264) has become available for the detection of the optical activity of optically unstable acids, and we have therefore applied it to the examination of diphenic acid. By adding diphenic acid in continually increasing quantities to a chloroform solution of nor-*d*-ψ-ephedrine, addition curve (I) was obtained, and for acetone and mixtures of acetone (1 vol.) and chloroform (4 vols.) addition curves (II) and (III), respectively, were constructed. From curve (I) it may be inferred that when diphenic acid is present in excess over the base, optical activation occurs, and results in the formation of a preponderance of the *d*-base *d*-acid salt. In acetone (curve II) and in acetone–chloroform (curve III), the *d*-base *l*-acid salt would appear to be formed in excess.



We then applied the test of rapidly mixing solutions of acid and base (*a*) in chloroform and (*b*) in acetone–chloroform at — 30° in the apparatus used previously (Jamison and Turner, *loc. cit.*). In a 2-dcm. tube, the following observations were made:

(*a*) Chloroform solution. 0·2 G. of nor-*d*-ψ-ephedrine in 5 c.c. of chloroform mixed with 0·5 g. of diphenic acid in 30 c.c. of chloroform:

Time after mixing (mins.)	0·17	0·45	0·75	1·25	1·55	4·5
Observed angle (λ 5461)	+0·15°	+0·30°	+0·35°	+0·40°	+0·42°	+0·42°

(*b*) Chloroform (4 vols.)–acetone (1 vol.) solution. 0·15 G. of nor-*d*-ψ-ephedrine in 3 c.c. of chloroform, mixed with 0·3 g. of diphenic acid in 20 c.c. of chloroform + 5 c.c. of acetone:

Time after mixing (mins.)	0·15	0·60	1·20	2·95	6·15
Observed angle (λ 5461)	−0·76°	−0·94°	−1·02°	−1·10°	−1·10°

In the apparatus used, it is quite impossible to make a polarimetric reading unless thermal homogeneity is complete, and the observed mutarotations are therefore unequivocal evidence of rapid optical activation. This observation must be taken as indicating that, at — 30°, diphenic acid, or at any rate the diphenate ion in electrostatic combination with the nor-*d*-ψ-ephedrinium ion, has a perceptible optical stability. From the extremely low optical stability of the nor-*d*-ψ-ephedrine salts of diphenic acid at — 30°, it must, however, be inferred that, although at room temperature optical activation of diphenic acid in presence of optically active bases might be detectable by the addition curve technique, yet it is equally clear that no mutarotation could be expected whatever the nature of the base used.

The addition curve (IV) for cinchonine and diphenic acid indicates that base *d*-acid is considerably more stable than base *l*-acid in acetone solution. Owing to the sparing solubility of cinchonine in this solvent, its rotation does not appear on the curve, and for a similar reason it was impracticable to carry out experiments at low temperatures.

When nor-*d*-ψ-ephedrine is dissolved in acetone, mutarotation occurs. Thus, in obtaining the data for curve (II), α_{5461} changed during an hour at room temperature from + 2·13° to + 2·69°, whilst in the case of curve (III) it changed from + 1·20° to + 1·55°. The final values are given on the curves. These mutarotations do not invalidate the above conclusions drawn from the addition curves, since the salt, nor-*d*-ψ-ephedrine diphenate, does not give rise, at the ordinary temperature, to mutarotation in either of the solvents concerned.

One of us (E. R. W.) thanks the Carnegie Trust for the Universities of Scotland for the award of a scholarship.

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