85. *The Stereochemistry of 2 : 2'-Disubstituted Diphenyls. Part IV. The Diphenates of the Cinchona Alkaloids.*

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It was observed by Kuhn (*Annalen,* 1927, **455**, 272; see also Bell and Robinson, J., 1927, 2234) that the quinine salt of 4 : 4'-dinitrodiphenic acid was strongly *dextro*rotatory, and he referred to this change as an " asymmetric transformation of the first kind." Assuming (1) that the salt groups in positions 2 and 2' are sufficiently large to collide with the 6'- and 6-positions (C or H), (2) that in the solvent used there is only partial ionic or thermal dissociation, and (3) that the free acid and the once or twice ionised acid are capable of unrestricted rotation, it is clear that asymmetric transformation could, and should, occur, even without separation of any solid salt, since the quinine *d*- and *l*-salts will almost certainly have different stabilities from the point of view of their ionic or thermal dissociation (see Mills and Elliott, J., 1928, 1297).

In order to obtain more evidence as to the nature of the effect noticed by Kuhn, we have made a number of observations with diphenic acid itself, since it cannot be supposed that the nitro-groups in Kuhn's acid were responsible for the result described. We find that in alcohol–chloroform solution the diphenates of the lævorotatory alkaloids quinine, dihydroquinine, and cinchonidine are strongly dextrorotatory, whilst those of the dextrorotatory alkaloids quinidine and cinchonine are strongly lævorotatory; *i.e.*, Kuhn's effect is shown in all five cases. An additional fact was also noticed, *viz.*, that slight mutarotation always occurred, the rotation increasing with time.

Quinine diphenate crystallises from alcohol and from acetone with 1 mol. of solvent of crystallisation; *cinchonine* and *cinchonidine diphenates* crystallise with 1EtOH; *quinidine diphenate* crystallises with 2EtOH, and *dihydroquinine diphenate* with 3EtOH. All the salts are well defined.

Some typical results are shown in Table I. Rotations were measured at 20° in a mixture of 99·5% alcohol (2 vols.) and chloroform (1 vol.) in 4-dcm. tubes,* the λ 5791 line being used. The concentration at which the parent (anhydrous) alkaloids were examined is approximately that at which the alkaloids were present in the solutions of the corresponding salts. The initial readings were made five minutes after wetting of

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* The same conditions were used in all the experiments described in this paper, except where otherwise stated.

the solids with solvent. The figures in parentheses are the specific rotations calculated on alkaloid present.

TABLE I.

Substance.	*c.*	α. 5 min.	α. 15 hr.	[α]. 5 min.	[α]. 15 hr.
Quinine	1·0092	−6·63°		−164·2°	
Quinine diphenate (+EtOH)	1·4602	+1·89°	+2·07°	+32·4°	+35·4° (+51·1)
Quinine diphenate (+COMe$_2$)	1·4124	+1·79	+1·97	+31·7	+34·9 (+51·1)
Dihydroquinine	1·0340	−6·15		−148·7	
Dihydroquinine diphenate (+3EtOH)	1·4236	+3·98	+4·06	+69·9	+71·3 (+112·5)
Cinchonidine	1·0340	−4·61		−111·5	
Cinchonidine diphenate (+1EtOH)	1·4012	+1·93	+1·99	+34·4	+36·8 (+53·2)
Quinidine	1·0084	+10·72		+265·8	
Quinidine diphenate (+2EtOH)	1·5004	−1·26	−1·31	−20·9	−21·8 (−33·0)
Cinchonine	0·9950	+9·47		+238·0	
Cinchonine diphenate (+1EtOH)	1·4410	−1·72	−1·79	−34·0	−35·2 (−50·8)

During the course of this work, more than 30 solutions of quinine diphenate in alcohol–chloroform have been observed to undergo mutarotation, so the effect cannot be doubted. The extent of the change depends on the concentration, as is shown in Table II, which relates to quinine diphenate alcoholate.

TABLE II.

c.	α. 5 min.	α. 15 hr.	[α]. 5 min.	[α]. 15 hr.	% Change in [α].
1·2147	+ 1·62°	+ 1·77°	+33·3°	+36·4°	9·3
2·2776	+ 3·62	+ 3·80	+39·7	+41·7	5·0
4·4108	+ 8·49	+ 9·00	+48·1	+51·0	4·0
6·0736	+12·38	+12·54	+50·1	+51·6	3·0
9·0215	+19·58	+19·65	+54·3	+54·4	0·2

In 99·5% alcohol (c = 1·3976) the $[\alpha]^{20°}_{5791}$ for quinine diphenate (+ EtOH) changed in 15 hours from − 0·54° to + 3·94°, that of the quinine diphenate (+ COMe$_2$) changing in the same time from + 0·36° to + 3·93°. In chloroform solution, neither salt showed mutarotation, the specific rotations being + 118·5° and + 119·0°, respectively.

In another set of experiments, the actual salts were not prepared beforehand, but polarimetric observations were made on solutions containing equivalent quantities of the anhydrous alkaloid and diphenic acid. With quinine and diphenic acid (l = 4; c for salt 1·3964) the observed angle changed from + 1·82° to + 1·96° in 15 hours, corresponding with a change in $[\alpha]^{20°}_{5791}$ of + 32·6° to + 35·1°.

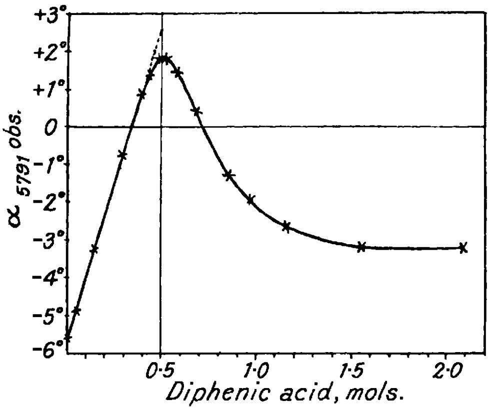
Table III shows the rotations obtained for (1) a mixture of anhydrous quinidine (2 mol.) and diphenic acid (1 mol.) (c = 1·4396 of anhydrous salt); (2) quinidine diphenate + 2EtOH (c = 1·4378 of this substance). The figures in parentheses are those obtained by correcting for the solvent of crystallisation, and excellent agreement is seen to exist between the two sets of readings. Certain irregularities were observed in our first experiments with quinidine, but they disappeared when the alkaloid was twice crystallised from alcohol and then dried in a vacuum at 60°.

TABLE III.

Expt.	α_{5791}. 10 min.	α_{5791}. 15 hr.	$[\alpha]_{5791}$. 10 min.	$[\alpha]_{5791}$. 15 hr.	α_{5461}. 10 min.	α_{5461}. 15 hr.	$[\alpha]_{5461}$. 10 min.	$[\alpha]_{5461}$. 15 hr.
1	−0·67°	−0·71°	−11·6°	−12·3°	−0·87°	−0·91°	−15·1°	−15·8°
2	−0·615	−0·65	−10·7 (−11·8)	−11·3 (−12·5)	−0·79	−0·827	−13·7 (−15·2)	−14·3 (−15·8)

When successive quantities of diphenic acid are added to an alcohol–chloroform solution of quinine, the lævorotation decreases as a linear function of the amount of acid added until 0·4 mol. of the latter is present. The rotation reaches a maximum when exactly 0·5 mol. of acid is in solution, and thereafter falls, until, at the point corresponding to 1·5 mol. of acid, it remains constant. One set of results is shown in the annexed diagram, in which the value of α ($l = 2$) observed 5 minutes after making the solution is plotted against mols. of acid. The concentration of quinine ($c = 1{\cdot}663$) was kept constant.

The maximum ($\alpha = 1{\cdot}83$; c for salt 2·284) corresponds with $[\alpha]^{20°}_{5791}$ + 40·1° for quinine diphenate. Extrapolation of the linear portion of the curve to meet the ordinate representing 0·5 mol. of acid gives $\alpha = + 2{\cdot}6°$. On the assumption that this value corresponds to completely undissociated quinine diphenate, the $[\alpha]^{20°}_{5791}$ for the latter is + 56·9° for this particular set of conditions. It will be observed (Table II) that this value is almost reached for $c = 9{\cdot}02$.



All of the above results are consistent with the idea that when the alkaloid diphenates (or the equivalent mixture of base and acid) are dissolved in certain solvents there occurs a very rapid process of asymmetric induction,* *only the last stages of this* being detectable with the polarimetric apparatus at our disposal. Many attempts have been made to measure the rotation of solutions of alkaloid diphenates within a minute or so of preparing them. In most cases limited and rapid mutarotation occurred within the first five minutes, but quantitative reproduction of the readings was impossible.

Asymmetric induction being assumed to be responsible for the results obtained, the specific rotation of a solution of quinine diphenate should be more positive the higher the percentage of undissociated salt present, *i.e.*, the higher the concentration. That this is so is shown by Table II. Similarly, by increasing the ionisation it should be possible to decrease the extent of the induction process. In aqueous alcohol, therefore, the rotation of quinine diphenate should be less positive the greater the amount of water present, and might even become strongly negative. Table IV gives the rotations of solutions of quinine diphenate (+ EtOH) in alcohol–water mixtures ($l = 4$) ; in the last column are given the dielectric constants for the mixtures used. The results provide further support for the foregoing explanation. It will be noticed that the mutarotation is inappreciable in 92·7% alcohol, but that in all the other cases it proceeds in the right direction.

TABLE IV.

EtOH, %		α_{5791}.		$[\alpha]^{20°}_{5791}$.		α_{5461}.		$[\alpha]^{20°}_{5461}$.		
(wt.).	c.	10 min.	15 hr.	10 min.	15 hr.	10 min.	15 hr.	10 min.	15 hr.	ϵ.
99·5	0·6486	−0·37°	−0·27°	− 14·3°	− 10·4°	−0·43°	−0·31°	− 16·6°	− 11·95°	26·5
92·7	0·6774	−1·21	−1·21	− 44·7	− 44·7	−1·41	−1·41	− 52·0	− 52·0	29·0
83·3	0·7226	−2·04	$-1{\cdot}98_5$	− 70·6	− 68·7	−2·38	$-2{\cdot}30_5$	− 82·35	− 79·75	32·8
67·6	0·6736	−2·60	−2·52	− 96·5	− 93·5	−3·02	−2·93	−112·0	−108·7	40·0
54·7	0·6598	−2·82	−2·79	−106·9	−105·7	−3·27	−3·24	−123·9	−122·7	47·2

We hoped to determine the specific rotation of quinine diphenate in mixtures of ethyl alcohol and acetonitrile in view of the relatively high dielectric constant of the latter,

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* When an actual salt is used, the induction process has naturally occurred in its preparation. Its optical composition will depend on the conditions of preparation, but, in general, further equilibration will occur on redissolving it.

but owing to solubility difficulties we only made one measurement (solvent, 60%MeCN, 40%EtOH by weight; $l = 4$; $c = 1{\cdot}471$):

α_{5791}.		$[\alpha]^{20°}_{5791}$.		α_{5461}.		$[\alpha]^{20°}_{5461}$.	
10 min.	15 hr.	10 min.	15 hr.	10 min.	15 hr.	10 min.	15 hr.
+3·06°	+3·21°	+52·0°	+54·6°	+3·58°	+3·74°	+60·8°	+63·6°

The specific rotation is surprisingly high, but mutarotation was again observed.

In view of the small mutarotational changes recorded, we examined solutions of *quinine phthalate*. This substance affords an excellent standard of comparison, as it is somewhat similar to quinine diphenate in type, and, moreover, also crystallises with 1 mol. of ethyl alcohol. The specific rotation did not alter with time, and corresponds approximately with that due to the quinine present:

c.	$\alpha^{20°}_{5791}$.	$[\alpha]^{20°}_{5791}$ for salt.	$[\alpha]^{20°}_{5791}$ for quinine present.
7·0440	−37·95°	−134·7°	−178·7°
4·9308	−27·00	−136·8	−181·5
1·0280	− 5·90	−142·9	−189·7

Although asymmetric induction affords an explanation of the results obtained with salts of diphenic acid, it is possible that when more evidence is obtained from a study of alkaloidal salts of other acids an alternative method of interpretation will be found, although the slight mutarotation effects observed would have to be accounted for. Were it not for these, the induction hypothesis would be untenable, since asymmetric induction can only occur with optically unstable acids, yet it has frequently been observed (Christie and Kenner, J., 1926, 470; Stanley, *J. Amer. Chem. Soc.*, 1931, **53**, 3104; Stoughton and Adams, *ibid.*, 1930, **52**, 5263) that the sign of rotation of an optically stable acid is reversed in some of its salts, and we find that the quinine salt of *dl*-4 : 6 : 4′ : 6′-tetranitrodiphenic acid (the most optically stable diphenic acid known) is *dextro*rotatory (0·2160 g. of quinine and 0·1406 g. of acid in 100 c.c. of a mixture of 1 vol. of alcohol and 2 vols. of chloroform; $l = 4$; $\alpha^{20°}_{5791} + 0{\cdot}36°$: whence $[\alpha]^{20°}_{5791}$ for quinine present = + 41·7°. No mutarotation).

EXPERIMENTAL.

Quinine diphenate alcoholate. Diphenic acid (1 mol.) was added to a boiling suspension of 2 mols. of quinine in absolute alcohol. On cooling, prisms separated, m. p. 217—218°. From the mother-liquor similar crops were obtained (Found: C, 71·7; H, 7·0; diphenic acid, 25·7. $C_{54}H_{58}O_8N_4,C_2H_6O$ requires C, 71·6; H, 6·9; diphenic acid, 25·85%).

Quinine diphenate acetonate. A warm solution of quinine dihydrate (3·6 g.) in 80 c.c. of acetone was added to a warm solution of 1·21 g. of diphenic acid in 20 c.c. of acetone. After a few minutes, rapid separation of crystals occurred; m. p. 217—218° (Found: C, 72·1; H, 6·75; diphenic acid, 25·8. $C_{54}H_{58}O_8N_4,C_3H_6O$ requires C, 72·1; H, 6·8; diphenic acid 25·5%).

Quinine phthalate alcoholate was obtained by mixing the components in hot alcohol, and allowing the solution to cool (Found: phthalic acid, 19·0. $C_{48}H_{54}O_8N_4,C_2H_6O$ requires phthalic acid, 19·3%). *Quinidine diphenate* (+ 2EtOH), *cinchonine diphenate* (+ EtOH), *cinchonidine diphenate* (+ EtOH), and *dihydroquinine diphenate* (+ 3EtOH) were prepared with alcohol as solvent (Found: diphenic acid, 24·6, 27·3, 27·9, 23·6. $C_{54}H_{58}O_8N_4,2C_2H_6O$, $C_{52}H_{54}O_6N_4,C_2H_6O$, $C_{52}H_{54}O_6N_4,C_2H_6O$, $C_{54}H_{62}O_8N_4,3C_2H_6O$ require diphenic acid, 24·6, 27·6, 27·6, 23·45% respectively).

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