The Optical Resolution and Racemisation of Some Diisoquinolyls.

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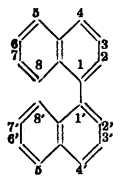
[Reprint Order No. 5377.]

Two new (5 : 5′- and 8 : 8′-) and a known (4 : 4′-) di*iso*quinolyl have been resolved optically. 1 : 1′-Di*iso*quinolyl (+)-tartrate mutarotates in solution. The active di*iso*quinolyls racemise rapidly in acid solution. Evidence is presented indicating that racemisation takes place by electrophilic hydrogen attack at one of the carbon atoms of the interannular bond, causing this atom to become tetrahedral. This mechanism is considered to operate generally during the racemisation of optically active diaryls.

FREE rotation about the interannular bond in 1 : 1′-dinaphthyl (I) is hindered, for although two of the four blocking positions (2 and 2′) remain filled with hydrogen atoms 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid has been resolved into optical isomers (Bell and Morgan, *J.*, 1954, 1716). The mechanical obstruction to free rotation must be very slight. In one planar position it amounts only to the overlap of the van der Waals envelopes of the pairs of hydrogen atoms 2 : 8′ and 2′ : 8. The failure to resolve naphthidine [4 : 4′-diamino-derivative of (I)] (Bell and Morgan, *J.*, 1950, 1963), a finding now confirmed, is therefore not very surprising. Unexpectedly, however, the very similar compounds, 4 : 4′- and 5 : 5′-diquinolyl (I, with N in positions 4 : 4′ and 5 : 5′ respectively) were recently resolved by us (*J.*, 1952, 4133). Further resolutions of this type of compound have now been achieved with 1 : 1′-, 4 : 4′-, 5 : 5′-, and 8 : 8′-di*iso*quinolyl (I, with N in positions 2 : 2′, 3 : 3′, 6 : 6′ and 7 : 7′ respectively), with the reservation that active forms of the first were not isolated. Mutarotation of its (+)-tartrate occurred in solution. The half-lives of the active forms



(I)

TABLE 1.

Di*iso*quinolyl	Resolving acid	$[\alpha]_D$ maximum observed		Approx. half-life * Racemisation of base in N-HCl (min.)	Approx. half-life * Mutarotation of salt (min.)
1 : 1′	Tartaric	0°	0°	—	1·3 ± 0·3 (N-HCl)
4 : 4′	Tartaric	+1·65	−1·32	26 ± 11	5 ± 2 ($H\cdot CO\cdot NMe_2$)
5 : 5′	Tartaric	+0·97	−1·50	16 ± 5	20 ± 7 (EtOH)
8 : 8′	Malic	+0·69	−7·30	12 ± 1	—

* The limits for the half-life values have been computed on the basis of a ±0·02° error in polarimeter readings, which is generous.

of 4 : 4′- and 5 : 5′-diquinolyl in acid solution are 2·5 and 1·3 hr. respectively (Crawford and Smyth, *loc. cit.*). Table 1 shows that the active di*iso*quinolyls are much shorter-lived.

The di*iso*quinolyls resemble the parent substance, *iso*quinoline, in ultra-violet absorption (see Table 2) except that the bands are moved to slightly longer wave-lengths. This resemblance indicates that as in the diquinolyls there is a resistance to assumption of uniplanar form.

In 1 : 1′-di*iso*quinolyl (I, with N in positions 2 and 2′) there are no hydrogen atoms in the blocking positions 2 and 2′, but these are present during the attempted resolution as the substance is in the salt form. Even then there is a high rate of mutarotation. The same considerations apply to a smaller degree in the case of 8 : 8′-di*iso*quinolyl (I, with N

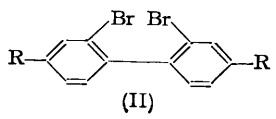
in positions 7 and 7'). The 7- and the 7'-hydrogen atom, present in the salt form, are absent in the free base. This absence of a substituent next to a blocking position may account for the rather high rate of racemisation even in acid solution in which a certain

TABLE 2. *Ultra-violet absorption of diisoquinolyls in ethanol.*

		Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
1 : 1'	λ (mμ)	218	250	274	282	284	300	312	—	323·5
	ε	77,900	5660	7370	6800	6920	4450	6480	—	9430
4 : 4'	λ (mμ)	217	252	275	—	285	301	311	314	323·5
	ε	96,200	5760	8280	—	7800	5540	8120	7940	12,300
5 : 5'	λ (mμ)	217·3	249	276·5	279	285	303	310·5	316	323·5
	ε	96,200	6040	9290	9120	9600	6140	7350	6780	8880
8 : 8'	λ (mμ)	216·5	251	276	282·5	285	301	311	313	324
	ε	91,900	5220	8270	7830	7930	5030	7350	7280	11,400

concentration of free base will always be present. In 4 : 4'- and 5 : 5'-di*iso*quinolyl and diquinolyl the nitrogen atoms are not in blocking positions. These compounds are therefore comparable with the dinaphthyl derivatives already mentioned. Possible causes of optical stability and instability in such compounds will now be examined.

Interannular Conjugation.—The interannular bond in diphenyl has a length of 1·48 Å in the crystal, the two rings being coplanar (Dhar, *Indian J. Physics*, 1932, **7**, 43). The electron-diffraction method gives the value 1·54 Å for the vapour state (Karle and Brockway, *J. Amer. Chem. Soc.*, 1944, **66**, 1974), indicating non-coplanarity, which presumably obtains also in solution. In a dinaphthyl or diquinolyl the length of the interannular bond will likewise vary as the two halves of the molecule rotate. In either of the positions of coplanarity interannular conjugation will reach maximum and bond length minimum values. When substituents in non-blocking positions can assist this conjugation rotation might be correspondingly impeded by the bond shortening. Calvin (*J. Org. Chem.*, 1939, **4**, 256) has attempted to account for relative rates of racemisation of diphenyls along such lines. Recognising that amino-groups facilitate racemisation, *e.g.*, (II; R = NH_2) is unresolvable whereas (II; R = CO_2H) has a half-life of 5—10 min. at 0° (Searle and Adams, *J. Amer. Chem. Soc.*, 1934, **56**, 2112), he points out that in acid solution these groups are in the form NH_3^+ and therefore cannot participate in resonance and interannular bond shortening. This, however, does not account for the positive racemising effect of the introduction of the group. It is true that the heterocyclic nitrogen in 4 : 4'- and 5 : 5'-diquinolyl would be better able to conjugate with the interannular bond than in 4 : 4'- and 5 : 5'-di*iso*quinolyl, in agreement with the greater optical stability of the former, but this can be explained more satisfactorily by the electron-displacement hypothesis referred to below.

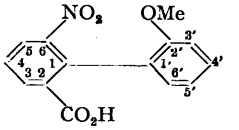


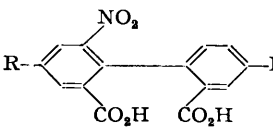
(II)

Buttressing Effect.—In 4 : 4'-di*iso*quinolyl (I, with N in positions 3 and 3') there are no hydrogen atoms attached in positions 3 and 3' next to the blocking positions. Any buttressing effect normally exerted by these hydrogens would be absent, thus permitting the hydrogens in the blocking positions to move apart more readily, so facilitating racemisation. Buttressing effects, however, are usually only observed in the case of large groups. Since 5 : 5'-di*iso*quinolyl, in which there can be little if any such effect, racemises more quickly than the 4 : 4'-isomer, this effect can be discounted.

Electron Displacement.—It is very significant that the resolvable compounds of the types being considered contain groups which are deactivating towards aromatic electrophilic substitution, namely, carboxyl or heterocyclic nitrogen of the pyridine type. When an activating group, namely, amino, is present resolution does not succeed. To be certain of such an effect a large number of compounds would have to be examined. Fortunately very extensive series of easily racemisable diphenyls containing three groups other than hydrogen in the blocking positions have been studied by Adams and others (for summaries, see Maitland, *Ann. Reports*, 1939, **36**, 257; Gilman, "Organic Chemistry," 2nd Edn., Wiley, New York, 1943, p. 362; Remick, "Electronic Interpretations of Organic Chemistry," 2nd Edn., Wiley, New York, 1949, p. 296). In 2'-methoxy-6-nitrodiphenyl-2-carboxylic acid (III) substituted by various groups in positions 3', 4', or 5', Adams

measured the half-lives of the optically active isomers dissolved in acetone or ethanol. His relevant results are given in Table 3. No satisfactory, complete explanation has hitherto been given. The introduction of a substituent into the 3'-position in (III), *i.e.*, next to the blocking group, clearly retards racemisation either by a buttressing action or by forcing the methyl of the methoxyl group to swing round to the blocking side of the

(III) 

 (IV)

oxygen atom. The effect of groups in the 4'- or the 5'-position is more difficult to explain. Hanford and Adams (*J. Amer. Chem. Soc.*, 1935, **57**, 1592) noted a parallelism with dipole moment. Kuhn and Albrecht (*Annalen*, 1927, **458**, 221) attributed the slower racemisation of 4 : 6 : 4'-trinitrodiphenic acid (IV; R = NO_2) compared with 6 : 4'-dinitrodiphenic acid (IV; R = H) to an increased moment of inertia. In addition to other suggestions (Gilman, *op. cit.*) and that of Calvin (*loc. cit.*) Baddeley (*Nature*, 1946, **157**, 694) has discussed the effect of groups in increasing electron density in the ring containing them and the possibility of the 1'-carbon atom's becoming tetrahedral. This is a valuable suggestion and is closely related to the explanation advanced by us in a preliminary note (Crawford and Smyth, *Chem. and Ind.*, 1954, 346).

TABLE 3. *Half-lives (in minutes) of optically active derivatives of* (II) *(in the temperature range* 23—26° *in ethanol except where specified).*

	NO_2	Br	Cl	Me	OMe
3'	1905	827	711	331	98
4'	115 *	18	8	3·2	3·6 *
5'	35	32	31	11·5	10·8

No substituent: 9·4 minutes.

* In acetone, in which values were found to be of the same order as in ethanol (see Hanford and Adams, *loc. cit.*; Chien and Adams, *J. Amer. Chem. Soc.*, 1934, **56**, 1787; Yuan and Adams, *ibid.*, 1932, **54**, 4434; Stoughton and Adams, *ibid.*, p. 4426).

Table 3 lists the groups in the order in which Adams found them to confer optical stability, which is roughly the order of their size. The reverse order, OMe > Me > Cl > Br > NO_2, namely, that of their relative promotion of racemisation, is significantly also the order of their effectiveness in activating aromatic rings to electrophilic substitution. That they indeed act in this way is supported by relating their orientation and their influence on racemisation. The nitro-group, known to deactivate *ortho*- and *para*-substitution, retards racemisation more when in the 4'-position (*para*) than when in the 5'-position (*meta*), whereas all the others, especially methyl and methoxyl, which are highly activating to *ortho*- and *para*-substitution, cause speedier racemisation when in the 4'- than in the 5'-position. The conclusion can hardly be escaped that the racemisation is the result of electrophilic attack.

As discussed in the preliminary note such electrophilic attack by protium cation from the solvent will give rise to a transition state in which one of the carbon atoms of the interannular bond becomes tetrahedral so facilitating rotation about this bond.

Among 1 : 1'-dinaphthyls the non-resolvability of naphthidine is now seen to be due to the two amino-groups, which are suitably placed to activate the 1- and the 1'-position to electrophilic attack. The optical stability of 1 : 1'-dinaphthyl-5 : 5'-dicarboxylic acid on the other hand is due to the deactivating effect of the two carboxyl groups. The same considerations account for the resolvability of (II; R = CO_2H) in contrast to the non-resolvable (II; R = NH_2). Similarly in 4 : 4'- and 5 : 5'-diquinolyl the strong deactivating effect of heterocylic nitrogen of the pyridine type is felt in the 4 : 4'- and the 5 : 5'-positions respectively, thus accounting for the unexpected resolvability of these compounds. In 4 : 4'- and 5 : 5'-di*iso*quinolyl, however, the heterocyclic nitrogen atom cannot conjugate directly with the interannular bond and so the deactivation is much reduced. This is

reflected in the faster racemisation of the latter compounds. The greater optical stability of (IV; R = NO_2) than of (IV; R = H) is also adequately explained by the presence of an additional deactivating nitro-group in the *para*-position to the interannular bond.

It is doubtful whether racemisation of hindered diaryls by a mutual slipping-past of the interfering groups plays as important a rôle as believed. The fact that the diquinolyls and other related compounds can be obtained in optically active forms indicates that the overlap of van der Waals envelopes must offer appreciable resistance to slip-past. Overlap of atoms, as distinct from van der Waals envelopes, as in the case of most resolvable diaryls must constitute an almost insuperable barrier to slip-past. In such a process, bending of bonds or interpenetration of atoms or both is involved. For either of these to occur to any extent would require considerable activation energy, certainly much more than racemisation by conversion of the carbon atoms concerned into tetrahedral forms.

Racemisation of the type postulated represents a bimolecular reaction whereas passage through a uniplanar transition state must be unimolecular. The first-order kinetics found by Kuhn and Albrecht (*loc. cit.*; *Annalen*, 1927, **455**, 272) for the recemisation of some substituted diphenic acids would, however, be expected in either case, for their measurements were carried out in aqueous solution. Participation of solvent in the electrophilic attack would result in a *pseudo*-first-order reaction.

Experimental

Absorption Spectra.—These were determined with a Unicam SP500 Spectrophotometer.

Attempted Resolution of 1 : 1′-*Di*isoquinolyl.—(+)-Tartaric acid (0·375 g.) was added to a solution of 1 : 1′-di*iso*quinolyl (0·512 g.) in hot ethanol (3·0 ml.); the base was prepared according to Case (*J. Org. Chem.*, 1952, **17**, 471). After all had dissolved the cooled solution deposited a basic *tartrate* (0·31 g.), m. p. 164—165°, containing three mols. of base to one of acid (Found: C, 76·1; H, 4·7; N, 9·1. $C_{58}H_{42}O_6N_6$ requires C, 75·7; H, 4·6; N, 9·1%). Treatment of the filtrate with cold ammonia solution precipitated the base (0·21 g.), whose solution in N-hydrochloric acid, examined 5 min. later, was optically inactive.

Mutarotation of 1 : 1′-*Di*isoquinolyl *Basic Tartrate.*—A filtered solution of the basic tartrate (0·3 g. in 2·5 ml. of N-HCl) gave the following polarimeter readings in a 1-dm. tube: 5 min. after dissolution, α_D^{24} −0·30°; 5½ min. −0·22°; 6½ min. −0·09; 8½ min. −0·02°; 12½ min. +0·03°; 65 min. +0·05°; several hours +0·07°.

Resolution of 4 : 4′-*Di*isoquinolyl.—To (+)-tartaric acid (3 g. in 20 ml. of hot ethanol) was added 4 : 4′-di*iso*quinolyl, m. p. 149—150° (2·56 g. in 20 ml. of hot ethanol) (Ueda, *J. Pharm. Soc. Japan*, 1940, **60**, 536, through *Chem. Abs.*, 1941, **35**, 1791; *J. Pharm. Soc. Japan*, 1940, **60**, 210, through *Chem. Zentr.*, 1941, II, 480, and *Brit. Abs.*, 1941, *A* II, 337). After filtration and cooling, a *hydrogen tartrate* (2·64 g.) separated, having m. p. 197° (decomp.) (Found: C, 64·5; H, 4·3; N, 6·9. $C_{26}H_{22}O_{12}N_2$ requires C, 65·0; H, 4·5; N, 6·9%). In dimethylformamide solution (1 g. in 15 ml.) the following polarimeter readings were obtained in a 2-dm. tube: 3 min. after dissolution, α_D^{25} +0·03°; 8 min. +0·10°; 13 min. +0·14°; 73 min. +0·17° (final value). A portion (1·5 g.), suspended in ethanol, was decomposed with cold ammonia solution, thus liberating the active *base* (0·96 g.) (Found: C, 83·6; H, 4·8; N, 10·9. $C_{18}H_{12}N_2$ requires C, 84·4; H, 4·7; N, 10·9%). Its solution (0·90 g. in 17 ml. of N-HCl) in a 2-dm. polarimeter tube gave the following readings: 15 min. after dissolution, α_D^{25} −0·14°; 75 min. −0·03°; 120 min. 0°.

The mother-liquor from which the tartrate had crystallised was decomposed at once with cold ammonia solution, giving the active *base* (0·50 g.), m. p. 149°. Its solution (0·5 g. in 15 ml. N-HCl) in a 2-dm. tube gave the following readings: 8 min. after dissolution α_D^{25} +0·11°; 68 min. +0·01°; 128 min. 0°.

5 : 5′-*Di*isoquinolyl.—To a refluxing mixture of 5-bromo*iso*quinoline (10 g.), 1% palladium–calcium carbonate (10 g.), and 5% methanolic potassium hydroxide (500 ml.), there was added 90% hydrazine hydrate (10 ml.) slowly during 30 min. with stirring. A similar amount of hydrazine hydrate was added after another 30 min. The stirring and refluxing was continued for 8 hr. The hot liquid was then filtered, the residue was washed with boiling methanol, and the filtrate and washings were evaporated to small bulk with additions of water. A dark oil separated which solidified on cooling. This solid, dissolved in dilute hydrochloric acid (100 ml.), was decolorised by shaking with carbon for an hour and then reprecipitated with ammonia solution. Two recrystallisations from benzene–ligroin gave 5 : 5′-*di*isoquinolyl (2·2 g.) as colourless prisms, m. p. 159—160° (Found: C, 84·3; H, 4·9; N, 10·7%).

Resolution of 5 : 5′-*Di*iso*quinolyl*.—Solutions of 5 : 5′-di*iso*quinolyl (2·56 g.) and (+)-tartaric acid (3 g.) in hot ethanol (total vol. 50 ml.) were mixed, filtered hot, and cooled to 5°. A tartrate (3·42 g.) crystallised. This became gummy at room temperature, probably owing to loss of alcohol of crystallisation. It also separated from solution as a gum at room temperature. A portion was dried at room temperature and decomposed with cold ammonia solution. The active base (1 g. in 15 ml. of N-HCl) in a 2-dm. tube gave the following readings : 6 min. after dissolution α_D^{24} −0·20°; 21 min. −0·09°; 51 min. −0·03°; overnight 0°.

A portion of the mother-liquor left after the separation of the tartrate gave the following readings in a 2-dm. tube : α_D^{24} +0·79° ($[\alpha]_D^{24}$ +9·23°), after 15 min. +0·74°; 45 min. +0·67°; 75 min. +0·64° (final value). The remainder was decomposed to the active base (0·75 g.), a solution of which (0·7 g. in 15 ml. of N-HCl) gave the following readings in a 2-dm. tube : 6 min. after dissolution α_D^{24} +0·09°; 36 min. +0·02°; 66 min. +0·01°.

8 : 8′-*Di*iso*quinolyl*.—Reduction of 8-bromo*iso*quinoline (3·87 g.) with hydrazine hydrate similarly to the 5-isomer gave 8 : 8′-*di*iso*quinolyl* (0·51 g.) as prisms (from benzene–ligroin or leaflets from ethanol), m. p. 153—154° (Found : C, 83·9; H, 4·8; N, 10·9%).

Resolution of 8 : 8′-*Di*iso*quinolyl*.—Solutions of 8 : 8′-di*iso*quinolyl (0·64 g.) and (−)-malic acid (0·67 g.) in hot ethanol (total vol. 10 ml.) were mixed, filtered, and cooled. A *malate* separated (0·50 g.), having m. p. 145° (Found : C, 66·7; H, 5·1; N, 6·9. $C_{22}H_{18}O_5N_2$ requires C, 67·7; H, 4·7; N, 7·2%). A portion (0·3 g.) was decomposed with cold ammonia solution, to give the active base (0·12 g.), which (2·5 ml. in N-HCl) gave the following readings in a 1-dm. tube : 5 min. after dissolution, α_D^{23} −0·35°; 25 min. −0·09°; 40 min. −0·06°; overnight, 0°.

The mother-liquor after separation of the malate was decomposed with cold ammonia solution, so freeing the active base of opposite sign (0·23 g.), m. p. 154°. Its solution (0·18 g. in 2·5 ml. of N-HCl) in a 1-dm. tube gave the following readings : 6 min. after dissolution, α_D^{23} +0·05°; 30 min. +0·02°; overnight, 0°.

Attempts to Resolve Naphthidine.—Naphthidine camphorsulphonate was prepared separately in ethanol, ethanolic chlorobenzene, and aqueous dimethylformamide. The tartrate was also prepared in ethanolic chlorobenzene. In no case was mutarotation observed in solutions of these salts nor was active base obtained.

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