309. *Molecular Dissymmetry dependent on Restriction of Rotation about a Single Bond. Part II. Optically Active 8-Benzenesulphonylethylamino-1-ethylquinolinium Salts.*

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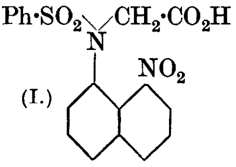
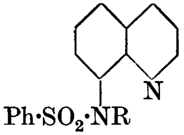
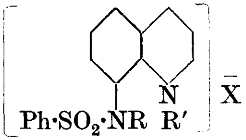
It was shown by one of us and Elliott (J., 1928, 1291) that benzenesulphonyl-8-nitro-1-naphthylglycine (I) could be obtained in optically active forms, and the molecular dissymmetry of this compound thus demonstrated was referred to the restriction, by the 8-nitro-group, of the rotation of the $Ph{\cdot}SO_2{\cdot}N{\cdot}CH_2{\cdot}CO_2H$ complex about the bond linking it to the naphthalene nucleus. At the same time it was pointed out that similar spatial relationships should exist in the quaternary salts of appropriate 8-substitution derivatives of quinoline.



(I.)



(II.)



(III.)

An account is now given of the preparation and stereochemical investigation of some quinoline derivatives of the type contemplated. These were quaternary salts of the general formula (III), in which R and R′ represent alkyl groups and X is the acid radical of the salt.

Whilst a fundamental change in chemical character is brought about through the replacement of the $\geqslant C(NO_2)$ complex in the naphthalene compound by the $\geqq\overset{+}{N}(Alk)\}\overset{-}{X}$ of the quinolinium salt, a close stereochemical relationship persists between the two types. The nitro-group and the alkyl radical are similarly placed with respect to a disubstituted amino-group in the 8-position. If, therefore, the optical activity of the naphthalene derivative was correctly attributed to the restricted rotation of the latter group, corresponding effects should be observed in the quinolinium salts, since in them the 1-alkyl group should similarly restrict the rotation of the adjacent $Ph{\cdot}SO_2{\cdot}NR$ complex.

The compounds investigated were obtained from 8-*benzenesulphonylaminoquinoline*. The mobile hydrogen atom in the $Ph{\cdot}SO_2{\cdot}NH$ group in this substance could be readily replaced by a series of different alkyl radicals—methyl, ethyl, *n*-propyl, and benzyl—to give bases of the general formula (II). The conversion of these bases into quaternary salts (III) was, however, difficult, except when the radical R′ was methyl, evidently on account of steric hindrance.

When the radical R′ in these compounds was a methyl group, no evidence of ability to exist in optically active forms was obtained. Thus, the crystalline 8-*benzenesulphonyl*-n-*propylamino*-1-*methylquinolinium* d-*bromocamphorsulphonate* showed no mutarotation in solution. It would appear, therefore (though we do not wish to stress this negative evidence), that the methyl group does not offer sufficient obstruction to the rotation of the $SO_2Ph{\cdot}NR$ complex to allow of optical activation being detected under the conditions of our experiments.

But when the radical R′ on the nitrogen atom of the quinoline nucleus is an ethyl group, its effect in restricting the rotation of the neighbouring disubstituted amino-group becomes apparent, for we were able to show that 8-*benzenesulphonylethylamino*-1-*ethylquinolinium iodide* (III; R = R′ = Et) can exist in optically active modifications. Like the naphthalene derivative (I), the substituted quinolinium ion shows only a limited optical stability, and its rotatory power in solutions of its salts diminishes more or less rapidly according to the temperature, the solvent, and the anion of the salt.

The activation was carried out with *d*-α-bromocamphor-π-sulphonic acid. When an acetone–ethyl acetate solution of the *d*-bromocamphorsulphonate was allowed to evaporate slowly, the *d*-8-benzenesulphonylethylamino-1-ethylquinolinium *d*-bromocamphorsulphonate was deposited as a *dihydrate* in large crystals. A solution of this salt in chloroform, kept at 19·5°, showed in the mercury green light an initial rotation α_{5461} of + 3·03°, which gradually sank during 12 days to a final value of + 1·08°. The mutarotation proceeded according to the law for a first-order reaction with a half-change period of 42 hours.

In aqueous solution the mutarotation was very much more rapid, the half-change period being 0·9 min. at 0°. The final molecular rotation in aqueous solution was exactly that of the *d*-bromocamphorsulphonate of an optically inactive kation. It was to be inferred, therefore, that the mutarotation was due to the autoracemisation of a dextrorotatory form of the substituted quinolinium ion, and it was possible to prove this by showing that the corresponding *iodide* was dextrorotatory.

The replacement of the bromocamphorsulphonate ion by the iodide ion was effected by shaking the colourless chloroform solution of the bromocamphorsulphonate with an aqueous solution of potassium iodide. The resulting quinolinium iodide, being sparingly soluble in water, is kept practically entirely in the chloroform layer, which accordingly becomes yellow, and the potassium bromocamphorsulphonate formed passes wholly into the aqueous layer. The change

$$\mathrm{Qu{\cdot}C_{10}H_{14}BrSO_3 + KI \longrightarrow QuI + K{\cdot}C_{10}H_{14}BrSO_3}$$

thus proceeds practically to completion.

On account of the yellow colour of the iodide, it was necessary to employ the yellow mercury light and to use very dilute solutions for the polarimetric observations. In spite of the low concentrations employed the solutions showed dextrorotations of just over 1°. These dextrorotations diminished in accordance with the law for a first-order reaction and finally sank to zero, showing that the bromocamphorsulphonate had been completely converted into the corresponding iodide. Since the salts were losing optical activity from the moment of contact with a solvent, and the operations of dissolving the bromocamphorsulphonate and its conversion into iodide required some minutes to carry out, accurate values for the specific and molecular rotations evidently could not be obtained. Thus, in a series of different experiments the earliest readings obtainable gave values for the specific rotations of the iodide (in moist chloroform solution) of $[\alpha]_{5780}$ + 410°, 424°, and 368°. The highest of these numbers corresponds with a molecular rotation $[M]_{5780}$ + 1982°, and even this must necessarily be considerably below the true value. The optically pure iodide is therefore a compound of very high rotatory power.

The extent to which variations in the environment of the quinolinium complex modify the effectiveness of the obstruction which the 1-ethyl group opposes to the rotation of the adjacent disubstituted amino-group is noteworthy. Thus, at 18° the inactivation of the complex, when present as bromocamphorsulphonate in chloroform solution, proceeds with a half-change period of over 43 hours, but as iodide in moist chloroform its half-change period is about 14 minutes. Moreover, whilst the half-change period of the bromocamphorsulphonate in chloroform is 43 hours, in alcohol it is less than 4 minutes, and in water it is much shorter still.

Also, the more readily the racemisation occurs, the less is the heat of activation as calculated from the effect of temperature on the change. Thus, whilst the heat of activation in the racemisation of the complex as iodide in chloroform is 37·4 kg.-cals., that as bromocamphorsulphonate in alcohol is 14·6 kg.-cals.

In the case of the 8-nitro-1-naphthylglycine it was possible, with the aid of a single alkaloid, to obtain either the *d*- or the *l*-form according to the solvent employed for the crystallisation of the salt. A similar phenomenon was observed with 8-benzenesulphonylethylamino-1-ethylquinolinium bromocamphorsulphonate, and provided a method for obtaining the lævorotatory iodide.

When the *d*-bromocamphorsulphonate was dissolved in ethyl acetate–methyl alcohol and the solution was allowed to evaporate slowly, crystals similar to those obtained from ethyl acetate–acetone solutions, but much smaller, were formed. On polarimetric examination they were found to be the d-*bromocamphorsulphonate* of the *l*-quinolinium base. Observed in chloroform solution at 18·5° in the green mercury light, they showed an initial lævorotation which gradually diminished to zero in 37 hours and then passed into a dextrorotation which increased towards a steady value which was practically attained after 15 days. The specific rotation corresponding with this equilibrium value was identical with that found for the *d*-bromocamphorsulphonate of the *d*-base in chloroform, and the velocity constants for the partial racemisation of the two salts were practically the same.

From this bromocamphorsulphonate of the *l*-base, the *l*-iodide was obtained in the same way as the *d*-iodide from the bromocamphorsulphonate of the *d*-base. It showed an initial specific rotation $[\alpha]_{5780}^{18 \cdot 5°}$ — 398° in moist chloroform, which gradually sank to zero in over 70 mins. with a half-change period at 18·5° of 13·7 mins.

There is thus very definite evidence that 8-benzenesulphonylethylamino-1-ethylquinolinium iodide can exist in optically active forms. This compound, therefore, shows the behaviour to be expected on the theory of the mechanical restriction of rotation about a single bond. And the fact that the procedure by which the ethiodide was activated failed to activate either the corresponding methiodide or the *propyl* methiodide would appear to confirm this theory.

EXPERIMENTAL.

8-*Benzenesulphonylaminoquinoline* was prep. by adding a pyridine solution of benzenesulphonyl chloride gradually to a solution of the equiv. quantity of 8-aminoquinoline in the same solvent and leaving the mixture over-night. The *product*, obtained by pptn. with H_2O and recrystn. from alcohol, formed colourless crystals, m. p. 133·5° (Found: S, 11·3. $C_{15}H_{12}O_2N_2S$ requires S, 11·3%).

8-*Benzenesulphonylethylaminoquinoline*.—To a solution of 8-benzenesulphonylaminoquinoline in abs. EtOH, the equiv. quantity of an alc. solution of KOEt was added. The K derivative, pptd. as fine greenish-yellow crystals, was dried at 150° and heated in quantities of 10 g. in sealed tubes with a slight excess of EtI (3 c.c.) for 6 hrs. at 115°. The product was extracted with hot EtOH, and, on cooling, colourless crystals, m. p. 136·5°, were deposited in 67% yield (Found: C, 65·6; H, 5·2; S, 10·3. $C_{17}H_{16}O_2N_2S$ requires C, 65·4; H, 5·1; S, 10·3%).

8-*Benzenesulphonylethylamino*-1-*methylquinolinium Iodide*.—The foregoing compound was heated on the water-bath with 1 equiv. of Me_2SO_4 until the resulting oil solidified (½ hr.). The product, cryst. from Me_2CO, gave minute colourless crystals of the methosulphate, m. p. 192°. This, treated with excess of KI aq., yielded the methiodide as an orange oil which crystallised on standing. Recryst. from EtOH or Me_2CO, the pure *methiodide* was obtained as orange crystals, m. p. 169·5° (Found: I, 27·9. $C_8H_{19}O_2N_2SI$ requires I, 28·0%).

8-*Benzenesulphonylethylamino*-1-*methylquinolinium* d-α-*Bromocamphor*-π-*sulphonate*.—The above methiodide was treated in abs. EtOH with the equiv. quantity of silver α-bromo-π-camphorsulphonate. The filtrate from the AgI, evaporated in a vac. desiccator, left a gum which crystallised after some weeks (Found: Br, 12·1; S, 9·7. $C_{28}H_{33}O_6N_2S_2Br$ requires Br, 12·5; S, 10·0%). Attempts to recrystallise the *salt* were unsuccessful, and it gave no evidence that the original crystn. had been accompanied by activation since it showed no mutarotation in $CHCl_3$ solution at 17·5°. The polarimetric data were : $l = 2$; $c = 0{\cdot}9432$; $\alpha_{5461} = + 1{\cdot}12°$; $[\alpha]_{5461} = + 59{\cdot}4°$.

8-*Benzenesulphonylethylamino*-1-*ethylquinolinium Iodide*.—8-Benzenesulphonylethylaminoquinoline was heated with 1 equiv. of Et_2SO_4 for 5 hrs. at 125°. The resulting hard gum was dissolved in H_2O, a small amount of unchanged material being filtered off, and an excess of KI was added, the *ethiodide* being then pptd. Recryst. from Me_2CO, it formed orange crystals, m. p. 173° (Found : I, 27·0. $C_{19}H_{21}O_2N_2SI$ requires I, 27·1%).

8-*Benzenesulphonylethylamino*-1-*ethylquinolinium* d-*α-Bromocamphor-π-sulphonate*.—A dil. solution of the foregoing ethiodide in abs. EtOH was added gradually to the equiv. quantity of silver bromocamphorsulphonate in the same solvent. The filtrate from the pptd. AgI was evaporated in a desiccator, the gummy residue dissolved in Me_2CO, EtOAc added, and the mixture allowed to evaporate slowly. During 5 days large colourless tabular crystals were deposited, some of them being 1·5 cm. long. These were a *dihydrate* of the bromocamphorsulphonate, m. p. 104—107° (Found : H_2O, 5·1 ; C, 50·9 ; H, 5·8. $C_{29}H_{35}O_6N_2S_2Br,2H_2O$ requires H_2O, 5·2 ; C, 50·7 ; H, 5·7%). The anhyd. salt can be obtained in cryst. form by slow pptn. of the abs. EtOH solution of the gummy salt with anhyd. Et_2O.

Mutarotation of d-8-*Benzenesulphonylethylamino*-1-*ethylquinolinium* d-*Bromocamphorsulphonate*.—(a) *In aqueous solution*. The following observations of the mutarotation of this compound were made on an aq. solution (16 c.c.) of the anhyd. salt (0·168 g.) in a 2-dm. tube at 1·8°. The first reading was taken 0·75 min. after wetting the salt. The first-order reaction velocity const. k in this table and throughout this paper is calculated with decadic logarithms.

t, mins.	α_{5461}.	k.	t, mins.	α_{5461}.	k.	t, mins.	α_{5461}.	k.
0	+2·09°	—	2·13	+1·29°	0·346	4·95	+1·13°	0·342
0·44	1·78	0·376	2·57	1·22	0·369	5·50	1·12	0·362
0·92	1·60	0·327	3·18	1·19	0·372	6·75	1·12	0·296
1·25	1·46	0·357	3·75	1·16	0·345	17·50	1·11	—
1·75	1·37	0·329	4·35	1·14	0·349	∞	1·11	—

In a second series of observations made at 1·5° an aq. solution (16 c.c.) of the anhyd. salt (0·2344 g.) showed in a 2-dm. tube an initial rotation $\alpha_{5461} + 2{\cdot}45°$ (1·47 mins. after wetting the salt), and this sank to a final value + 1·55° in 18 mins. in accordance with the law for a reaction of the first order ($k = 0{\cdot}314$).

(b) *Mutarotation in chloroform solution*. The remaining observations were carried out with the more readily obtainable dihydrate of the salt. The following readings were made on a $CHCl_3$ solution (25 c.c.) of the dihydrate (0·2285 g.) in a 2-dm. tube at 18·5° : Initial obs. rotations $\alpha_{5780} + 2{\cdot}67°$, $\alpha_{5461} + 3{\cdot}03°$, $\alpha_{4358} + 4{\cdot}57°$; final obs. rotations (after 12 days) $\alpha_{5780} + 0{\cdot}88°$, $\alpha_{5461} + 1{\cdot}08°$, $\alpha_{4358} + 2{\cdot}45°$; mean value of k (hr.) = 0·0072.

(c) *Mutarotation in alcoholic solution*. An alc. solution (25 c.c.) of the dihydrate (0·0453 g.) in a 2-dm. tube at 17·4° showed the following rotations, the first reading having been taken 4·75 mins. after wetting the salt : Initial reading $\alpha_{5461} + 0{\cdot}47°$; final reading (25 mins.) $\alpha_{5461} + 0{\cdot}20°$; mean value of k 0·077.

A second series of readings was made on an alc. solution (25 c.c.) of the dihydrate (0·0461 g.) in a 2-dm. tube at a lower temp. (5·5°), the first observation having been made 5·50 mins. after wetting the salt : Initial reading $\alpha_{5461} + 0{\cdot}55°$; final reading (after 40 mins.) $\alpha_{5461} + 0{\cdot}21°$; mean value of k 0·026.

From the mean values of the velocity consts. in the two foregoing series of observations, *viz.*, $k_{17\cdot4^\circ} = 0\cdot077$ and $k_{5\cdot5^\circ} = 0\cdot026$, the calc. heat of activation is 14,610 cals.

Dextrorotatory 8-*Benzenesulphonylethylamino*-1-*ethylquinolinium Iodide.*—A $CHCl_3$ solution (25 c.c.) of the bromocamphorsulphonate dihydrate (0·0462 g.) was shaken with conc. KI aq. The yellow $CHCl_3$ solution of the *d*-iodide thus obtained was examined in a 2-dm. tube in the yellow mercury light at 19°. On account of the absorption of the light it was necessary to use dil. solutions. The initial reading was taken 4 mins. after adding the KI aq. The initial rotation obs. was $\alpha_{5780} + 1\cdot03^\circ$, and this sank, in accordance with the unimolecular law, to zero in over 70 mins. (mean value of k 0·022).

Another solution, prep. in the same way from 0·0436 g. of the bromocamphorsulphonate dihydrate, showed an initial rotation, α_{5780}, of 1·01°, which sank to zero in over 70 mins. at 19·5° with a first-order reaction velocity const. (time in mins.) of 0·0235.

A similar series of readings of the mutarotation of the *d*-iodide in moist $CHCl_3$ was taken at 4·7°, the iodide being prepared from a $CHCl_3$ solution (25 c.c.) of the bromocamphorsulphonate dihydrate (0·0275 g.) and KI aq. The initial rotation obs. was $\alpha_{5780} + 0\cdot55^\circ$, and this sank to zero in over 650 mins., the mean value of k being 0·00077.

The values of the velocity consts. in the three series of observations on the *d*-iodide being taken as $k_{19^\circ} = 0\cdot022$, $k_{19\cdot5^\circ} = 0\cdot0235$, and $k_{4\cdot7^\circ} = 0\cdot00077$, combination of the 1st and 3rd values gives a heat of activation of 37,650 cals. and of the 2nd and 3rd 37,140 cals.

Salts of the Lævorotatory Form of the 8-*Benzenesulphonylethylamino*-1-*ethylquinolinium Ion.*—(a) *The* d-*bromocamphorsulphonate.* The crystals obtained by allowing a solution of the gummy form of the bromocamphorsulphonate in EtOAc–MeOH to evaporate were found, on polarimetric examination, to consist of a salt of the lævorotatory base. The following readings were taken on a $CHCl_3$ solution (25 c.c.) of the salt (0·1765 g.) in a 2-dm. tube at 18·4°: Initial obs. rotations $\alpha_{5780} -0\cdot70^\circ$, $\alpha_{5461} -0\cdot68^\circ$, $\alpha_{4358} +0\cdot25^\circ$; final obs. rotations (after 12 days) $\alpha_{5780} + 0\cdot68^\circ$, $\alpha_{5461} + 0\cdot83^\circ$, $\alpha_{4358} + 1\cdot89^\circ$; mean value of k(hr.) = 0·0073.

(b) *The lævorotatory iodide.* A $CHCl_3$ solution (25 c.c.) of *l*-8-benzenesulphonylethylamino-1-ethylquinolinium bromocamphorsulphonate (0·0384 g.) was shaken with conc. KI aq. and the resulting solution of the quinolinium iodide in moist $CHCl_3$ was polarimetrically examined in a 2-dm. tube at 18·5°. The readings were as follows, the first having been made 4—5 mins. after contact with the KI aq.: Initial reading, $\alpha_{5780} - 0\cdot83^\circ$; final reading (after >70 mins.) 0·00°; mean value of $k = 0\cdot023$.

8-*Benzenesulphonyl*-n-*propylaminoquinoline.* — 8-Benzenesulphonylaminoquinoline was converted into its K derivative as before (p. 2213), and this was heated in portions of 10 g. with the equiv. quantity of $Pr^{\alpha}I$ in sealed tubes at 120° for 3—4 hrs. The product was extracted with EtOH, and the solution, after filtration from unchanged K salt, was poured into H_2O, and the pptd. *propyl* derivative taken up in Et_2O. The Et_2O solution, dried (K_2CO_3) and concentrated, deposited the *substance* as colourless crystals, m. p. 66·5°, very sol. in EtOH, Et_2O, or C_6H_6 (Found: N, 8·8, 8·7. $C_{18}H_{18}O_2N_2S$ requires N, 8·6%).

8-*Benzenesulphonyl*-n-*propylamino*-1-*methylquinolinium Iodide.*—8-Benzenesulphonyl-*n*-propylaminoquinoline was heated with the equiv. quantity of Me_2SO_4 on the water-bath till solid (½ hr.). The product, recryst. from

Me_2CO, gave colourless crystals of the methosulphate, m. p. 168°, very sol. in H_2O or EtOH. The *methiodide* was obtained, by treating the aq. solution of the methosulphate with KI, as orange crystals, m. p. 162° (Found : I, 27·0. $C_{19}H_{21}O_2N_2SI$ requires I, 27·1%).

8-*Benzenesulphonyl*-n-*propylamino*-1-*methylquinolinium* d-*a*-*Bromocamphor*-*π*-*sulphonate*.—This was obtained in the usual way from silver bromocamphorsulphonate and the iodide in alc. solution as a gum which crystallised from H_2O as a *trihydrate*, m. p. 105° (Found : H_2O, 7·6. $C_{29}H_{35}O_6N_2S_2Br,3H_2O$ requires H_2O, 7·7%). The $3H_2O$ was lost in a vac. desiccator, giving the *anhydrous* salt, m. p. 170° (Found : Br, 12·3; S, 10·0. $C_{29}H_{35}O_6N_2S_2Br$ requires S, 9·8; Br, 12·3%). A $CHCl_3$ solution of the hydrated salt was examined polarimetrically : $l = 2$; $c = 0·9532$; $\alpha_{5461} = + 1·12°$; $[\alpha]_{5461}$ $+ 58·8°$. No mutarotation was observed.

8-*Benzenesulphonylbenzylaminoquinoline* was obtained by heating the K derivative of 8-benzenesulphonylaminoquinoline with slightly more than 1 equiv. of CH_2PhBr at 160° for 2 hrs. The product was dissolved in hot EtOH, and unchanged K derivative filtered off ; the *benzyl* compound crystallised on cooling. Recryst. from EtOH, it was obtained as yellowish crystals, m. p. 124° (Found : C, 70·4; H, 4·9. $C_{22}H_{18}O_2N_2S$ requires C, 70·6; H, 4·8%).

8-*Benzenesulphonylbenzylamino*-1-*methylquinolinium Iodide*.—8-Benzenesulphonylbenzylaminoquinoline was heated with the equiv. quantity of Me_2SO_4 for 3 hrs. on the water-bath. The resulting methosulphate was crystallised from Me_2CO, giving colourless crystals, m. p. 219°, and then converted by KI aq. in the usual way into *iodide*, which formed orange crystals, m. p. 176° (Found : I, 24·5. $C_{23}H_{21}O_2N_2SI$ requires I, 24·6%).

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