

55. *Optical Activity dependent on Restricted Rotation in a Benzene Derivative.*

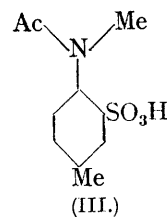
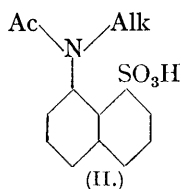
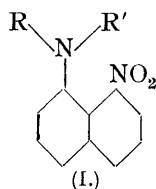
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AFTER the molecular dissymmetry of substitution derivatives of diphenyl, discovered by Kenner and Christie (J., 1922, 121, 614), had been interpreted as a consequence of the restrictive effect of the substituent groups on the relative rotation of the two benzene nuclei in the diphenyl molecule, it was shown by one of us and Elliott (J., 1928, 1292) that *peri*-disubstituted derivatives of naphthalene could exhibit an analogous phenomenon.

Proof of this was given by obtaining a compound of the type (I) in optically active forms. In this compound the optical activity arose from the restriction of the rotation of a disubstituted α -amino-group, R-N-R', about the nitrogen-naphthyl valency bond, the restriction being effected by the nitro-group in the adjacent *peri*-position.

It is shown in the present communication that optical activity can be produced in a similar way in the benzene series. The rotation of a disubstituted amino-group attached to

a benzene nucleus can be restricted by a substituent in the ortho-position so as to give rise to molecular dissymmetry of considerable persistence.



An investigation carried out in this laboratory by one of us with P. J. Garner and S. Marriage, the results of which will shortly be communicated, has shown that substitution derivatives of 1-naphthylamine-8-sulphonic acid of the type (II) (in which Alk represents an alkyl group and Ac an acyl group) can be obtained, like the nitro-compound (I), in optically active forms.

The rates of racemisation of a number of these *peri*-compounds were measured, and found to vary greatly with the nature of the acyl substituent Ac. The acetylmethyl derivative, in particular, possessed so high a degree of optical stability that we were led to make a similar investigation of an analogously constituted ortho-compound of the benzene series.

We accordingly prepared and studied *N*-acetyl-*N*-methyl-*p*-toluidine-3-sulphonic acid (III) and found that the salts of this compound could, in fact, be obtained in an optically active form. The dextrorotatory modification was obtained by means of brucine. The *brucine* salt showed mutarotation when dissolved in chloroform, the repeatedly recrystallised compound giving in chloroform solution an initial specific rotation $[\alpha]_{5461} + 2.4^\circ$, which gradually fell, according to the unimolecular law, to an equilibrium value of -5.8° with a half-change period, at 16.7° , of 2.8 hours.

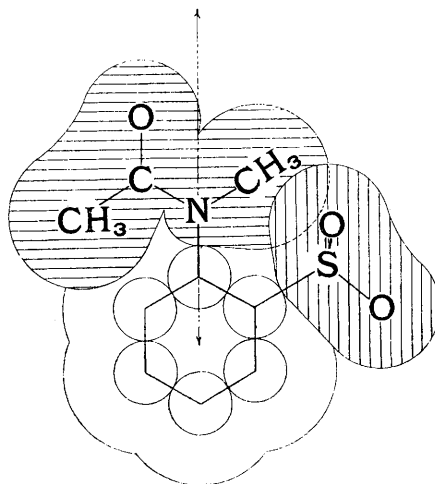
The disappearance of dextrorotation shown in the mutarotation indicated that in this salt the brucine was combined with an optically labile dextrorotatory form of the acid. This was confirmed by converting the brucine salt into the *sodium* salt by treatment in chloroform solution with an alcoholic solution of sodium ethoxide. The sodium salt precipitated had the composition $C_8H_7Me(NMeAc) \cdot SO_3Na \cdot 2H_2O$ and was dextrorotatory. It showed an initial specific rotation $[\alpha]_{5461}$ of $+6.06^\circ$, which gradually fell to zero, the half-change period at 16.6° being 5.25 hours.

The rates of racemisation of the sodium salt in aqueous solution were measured at four different temperatures ranging from 16.6° to 35° , and the corresponding values of the unimolecular reaction velocity constant k (time in minutes) are given in the following table :

<i>t.</i>	16.6° .	24° .	28° .	35° .
k (found)	0.0022	0.0055	0.0097	0.022
k (calc.)	0.0021	0.0057	0.0095	0.022

The critical energy increment for the racemisation, calculated from the slope of the $\log_e k - 1/T$ curve, is 22.6 kg.-cals. The values given for k (calc.) are those calculated from the Arrhenius equation $k = \chi e^{-E/RT}$, the values 2.797×10^{14} and 22,613 being used for the constants χ and E . These values give the best straight line through the points representing the values found for k at the four temperatures on the $\log_e k - 1/T$ diagram, and the differences between k (found) and k (calc.) serve to indicate the order of magnitude of the experimental errors of the determinations.

The figure, which is a scale drawing of the essential parts of the molecule of the acid, gives



an approximate idea of the probable amount of overlap of the *N*-methyl- and the *N*-acetyl-group with the SO_3 -group. It is based on the following values (in Å.) of the dimensions concerned : internuclear distances, $C_{\text{Ar.}}-C_{\text{Al.}}$ 1.39, $C_{\text{Ar.}}-\text{S}$ 1.82, $\text{S}-\text{O}$ 1.50, $C_{\text{Ar.}}-\text{N}$ 1.44, $C_{\text{Al.}}-\text{N}$ 1.48 ; external radii (based on the distances of closest approach observed in crystals), CH_3 1.6, O 1.33.

The overlap of the groups must evidently be smaller when they occupy two *o*-positions in benzene than when they are in two *peri*-positions in naphthalene, and the critical increment of energy for racemisation is, in fact, less for the benzene derivative (22.6 kg.-cals.) than had been found for the corresponding naphthalene derivative (26.9 kg.-cals.).

The brucine salt of *N*-acetyl-*N*-methylantranilic acid was also examined. This acid contains a carboxyl in place of the sulphonic group of the compound (III), but since no permanent overlap of the Me-*N*-Ac grouping and a carboxyl in the *o*-position is to be anticipated, it should not be capable of showing optical activity, and, in fact, its brucine salt gave no sign of mutarotation.

EXPERIMENTAL.

N-Acetyl-*N*-methyl-*p*-toluidine (compare Thielepape, *Ber.*, 1935, 68, 751).—Finely granulated sodium (12 g.) is added to a solution of perfectly dry aceto-*p*-toluidide (80 g.) in benzene (600 c.c.), and the mixture heated on a water-bath with frequent shaking. The sodium dissolves slowly (2—2½ hrs.) to give a white semi-solid mass of sodioacet-*p*-toluidide. Methyl sulphate (68 g.) is then slowly added, and after the initial vigorous reaction has subsided, the heating on the water-bath is continued for a further 1½ hours. Water (300 c.c.) is added to dissolve sodium sulphate present as a gel, and the benzene layer separated, dried over calcium chloride, and concentrated to about 100 c.c. *N*-Acetyl-*N*-methyl-*p*-toluidine crystallises (m. p. 80°), and is sufficiently pure for the following stage.

Sodium N-Methyl-*p*-toluidine-3-sulphonate.—*N*-Acetyl-*N*-methyl-*p*-toluidine (16 g.) is treated with concentrated sulphuric acid (13 g.) with the addition of ammonium vanadate (0.2 g.) as catalyst. The mixture is mechanically stirred under reduced pressure (20 mm.), the reaction vessel being maintained at 170—180° in an oil-bath. Sulphonation and elimination of the *N*-acetyl radical take place together, and the process is complete when acetic acid ceases to distil from the reaction vessel (about 2 hrs.). The hot liquid mass of crude *N*-methyl-*p*-toluidine-3-sulphonic acid is poured into water (300 c.c.), the liquid made alkaline with sodium hydroxide, and steam-distilled to remove unsulphonated *N*-methyl-*p*-toluidine. The resulting solution of sodium *N*-methyl-*p*-toluidine-3-sulphonate, after decolorisation with animal charcoal and concentration, deposits the pure salt (16.5 g.) on cooling.

Sodium N-Acetyl-*N*-methyl-*p*-toluidine-3-sulphonate.—Dry sodium *N*-methyl-*p*-toluidine-3-sulphonate (11 g.) is treated with twice the theoretical quantity of acetic anhydride (5 g.) and heated on a water-bath for 1 hour with occasional shaking. The cold product is powdered, and freed from unchanged acetic anhydride by extraction with ether in a Soxhlet apparatus. The crude material is finally crystallised twice from small quantities of ethyl alcohol. The pure *sodium N*-acetyl-*N*-methyl-*p*-toluidine-3-sulphonate dihydrate melts at 81—82°, and the *anhydrous* salt at 277—279° with darkening (Found : H_2O , 12.4. $\text{C}_{10}\text{H}_{12}\text{O}_4\text{NSNa}\cdot 2\text{H}_2\text{O}$ requires H_2O , 12.0%. Found, for anhydrous salt : N, 5.3 ; S, 12.1 ; Na, 8.8. $\text{C}_{10}\text{H}_{12}\text{O}_4\text{NSNa}$ requires N, 5.3 ; S, 12.1 ; Na, 8.7%).

Brucine N-Acetyl-*N*-methyl-*p*-toluidine-3-sulphonate.—A cold solution of brucine acetate (22.7 g.) in water (400 c.c.) was mixed with a cold solution of sodium *N*-acetyl-*N*-methyl-*p*-toluidine-3-sulphonate dihydrate (15.05 g.) in water (400 c.c.). After standing overnight, the brucine salt crystallised (16.5 g.), and concentration of the mother-liquor over concentrated sulphuric acid in a vacuum gave a further quantity (18 g.) (Found : C, 58.4 ; H, 6.5 ; N, 6.3 ; H_2O , 5.6. $\text{C}_{33}\text{H}_{39}\text{O}_8\text{N}_3\text{S}\cdot 2\text{H}_2\text{O}$ requires C, 58.8 ; H, 6.4 ; N, 6.3 ; H_2O , 5.4%). The brucine salt was recrystallised from warm water (60°), and a portion was dehydrated in a vacuum over phosphoric oxide and examined for mutarotation in chloroform solution : 0.44 g. of the salt in 30 c.c. ($l = 4$) gave $[\alpha]_{5461} - 0.56^\circ$, falling to $- 0.86^\circ$, the corresponding values of $[\alpha]_{5461}^{25}$ being $- 9.55^\circ$ and $- 14.67^\circ$, with mean value of $k = 0.0044$.

The brucine salt (75 g.) was then recrystallised from water eight times, each fraction being examined polarimetrically. A portion (0.3389 g.) of the eighth fraction (total 12 g.) in chloroform solution (25 c.c. ; $l = 4$; $t = 16.7^\circ$) gave the following results :

Time (mins.).	α_{5461} *	$[\alpha]_{5461}$	k .	Time (mins.).	α_{5461} *	$[\alpha]_{5461}$	k .
0	+0.131	+2.43	—	110	-0.156	-2.89	0.0041
5	+0.108	+2.0	0.0046	170	-0.202	-3.74	0.0035
10	+0.078	+1.45	0.0044	245	-0.247	-4.58	0.0034
25	+0.028	+0.52	0.0046	425	-0.300	-5.55	0.0035
65	-0.090	-1.66	0.0046	∞	-0.314	-5.81	—

Mean value of $k = 0.0041$, time of half-change = 169 mins.

* The values of α are each the mean of six readings, three taken before and three taken after the recorded times.

This purified brucine salt was used to prepare the optically active sodium salt, but we have no evidence that the resolution had been carried to completion.

d-Sodium N-Acetyl-N-methyl-p-toluidine-3-sulphonate.—To a solution of the purified brucine salt (4.244 g.) in chloroform (8 c.c.), a solution of sodium ethoxide in alcohol (0.1537 g. Na in 1.5 c.c. 90% ethyl alcohol) was added. The mixture was then strongly cooled in a freezing mixture, and after scratching (2 mins.), the optically active hydrated sodium salt of N-acetyl-N-methyl-p-toluidine-3-sulphonic acid crystallised (1.19 g.). It was collected and washed with chloroform (Found : Na, 8.7; S, 12.2. $C_{10}H_{12}O_4NSNa$ requires Na, 8.7; S, 12.1%).

The following table gives the results of a series of observations of α_{5461} made at 16.6° on an aqueous solution of the sodium salt thus obtained ($c = 1.928$; $l = 4$).

Time, mins.	α_{5461} , obs.	α_{5461} , calc.	Time, mins.	α_{5461} , obs.	α_{5461} , calc.	Time, mins.	α_{5461} , obs.	α_{5461} , calc.	Time, mins.	α_{5461} , obs.	α_{5461} , calc.
0	0.47°	0.46°	50	0.41°	0.41°	175	0.315°	0.31°	360	0.21°	0.21°
5	0.46	0.45	80	0.38	0.38	210	0.29	0.29	450	0.18	0.17
15	0.45	0.44	115	0.36	0.36	270	0.25	0.25	475	0.16	0.16
30	0.43	0.43	135	0.345	0.34						

The mean value of the unimolecular reaction velocity constant k calculated from the natural logarithms of the observed rotations and the times of observation by Campbell's method (*Phil. Mag.*, 1924, **47**, 816) was 0.00220. The numbers given for α , calc., were calculated by using this value of k , and their close agreement with the experimental observations shows that the racemisation follows the unimolecular law. The specific rotation $[\alpha]_{5461}$ calculated from the first observation was + 6.06°.

The later stages of the racemisation are not recorded in the foregoing table, since the rotations became too small to be measured with sufficient accuracy for use in the determination of k . Examined on the following day, the solution was found to have become completely inactive.

Critical Energy Increment for the Racemisation.—Observations of the rate of racemisation of the dextrorotatory sodium salt, similar to those made at 16.6°, were made at 24°, 28°, and 35°, and the results are recorded in the following tables. The unimolecular reaction velocity constants

Time, mins.	α_{5461} , obs.	α_{5461} , calc.	Time, mins.	α_{5461} , obs.	α_{5461} , calc.	Time, mins.	α_{5461} , obs.	α_{5461} , calc.	Time, mins.	α_{5461} , obs.	α_{5461} , calc.
<i>Racemisation at 24° ($c = 1.820$; $l = 4$).</i>											
0	0.35°	0.35°	20	0.31°	0.31°	50	0.265°	0.26°	115	0.18°	0.18°
5	0.34	0.34	25	0.30	0.30	65	0.25	0.24	140	0.16	0.16
11	0.32	0.33	30	0.295	0.29	80	0.23	0.22	175	0.13	0.13
16	0.31	0.32	40	0.28	0.28	90	0.205	0.21	210	0.11	0.11
$[\alpha]_{5461}$ (initial) = 4.83°; k (found) = 0.00553.											
<i>Racemisation at 28° ($c = 1.768$; $l = 4$).</i>											
0	0.44	0.45	13	0.40	0.39	35.5	0.31	0.32	68	0.23	0.23
5	0.43	0.43	17	0.39	0.38	43	0.29	0.30	88	0.20	0.19
8	0.42	0.42	22	0.365	0.365	55	0.26	0.26	118	0.15	0.14
10	0.42	0.41	28	0.35	0.34						
$[\alpha]_{5461}$ (initial) = 6.03°; k (found) = 0.00969.											
<i>Racemisation at 35° ($c = 1.928$; $l = 4$).</i>											
0	0.50	0.50	16	0.37	0.36	30	0.26	0.26	70	0.11	0.11
5	0.45	0.46	19	0.33	0.34	35	0.235	0.24	90	0.07	0.07
8	0.42	0.43	22	0.31	0.31	45	0.20	0.19	120	0.03	0.04
12	0.40	0.39	26	0.29	0.29	55	0.15	0.15	160	0.015	0.015
$[\alpha]_{5461}$ (initial) = 7.49°; k (found) = 0.02198.											

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k were calculated as described for the observations made at 16.6° , and the values given for k (calc.) were obtained as there explained. In each case it was verified that the solutions finally became optically inactive. The solution kept at 35° ceased to show detectable activity after $8\frac{1}{2}$ hours.

The critical increment of energy for the racemisation at all four temperatures was calculated as described on p. 275.

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