98. *Optical Activation by Asymmetric Solvent Action.*

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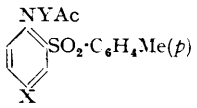
Both first- and second-order asymmetric transformations have been observed to occur when potentially optically active, but optically unstable, compounds are dissolved in an optically active solvent. The compounds so obtained have a sufficiently high rotation to allow observations to be made of their rates of racemisation in an inactive solvent and to compare the effect of substituents on the optical stability of closely related compounds.

The existence of a differential solvent effect of an optically active solvent on the two enantiomorphic forms of another active substance was established by Patterson and Buchanan (*J.*, 1940, 290 : cf. also Patterson and Lamberton, *J.*, 1937, 1453) who showed that, while the molecular solution volumes of a pair of enantiomorphs were identical when measured in a symmetrical solvent, they differed by a small, but definite, amount when measured in an asymmetric solvent. Several workers have examined the possibility of resolving racemates by means of an asymmetric solvent, *e.g.*, by determining the solubility of the two enantiomorphs separately in an active solvent or by crystallising or extracting the racemate by means of an active solvent. No differentiation of the kind sought was found (Turner and Harris, *Quart. Reviews*, 1948, 327). Turner and Harris (*loc. cit.*) state that " Generally speaking, racemates cannot be even partially resolved by crystallisation from an optically active solvent. This is what might be expected, unless one antipode crystallised with solvent of crystallisation. An example remains to be discovered in which association with an optically active solvent, by hydrogen bonding for example, is responsible for solubility differences in a pair of optical isomerides . . . Some such loose association, with preference for one isomeride, must be responsible for cases of partial resolution by adsorption on optically active adsorbents." The very slight solvent effect observed by Patterson and Buchanan also supports the view that resolution of an optically stable compound is unlikely. We thought, however, that this effect might be made more manifest by examining optically unstable compounds of the type used in asymmetric trans-

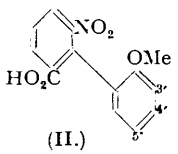
formations, *i.e.*, that the asymmetric solvent might influence the relative stabilities and solubilities of these compounds in such a manner as to lead to products showing a measurable rotation. To test this possibility a representative series of optically active but optically unstable compounds was examined in an optically stable solvent.

The asymmetric solvent employed most generally was ethyl (+)-tartrate, which, apart from its ready availability, possessed several advantages. It is a most powerful solvent, a large variety of compounds of most diverse type dissolving in it, including the sodium salts of sulphonic acids. Owing to the fact that it is water-soluble its removal from solid materials after recrystallisation is a matter of extreme ease, while water-soluble compounds can be freed from it by extraction with ether.

The first compound to be examined extensively was 2-acetomethylamido-5 : 4′-dimethyldiphenyl sulphone (I, X = Y = Me), which owes its asymmetry to restricted rotation about



(I.)



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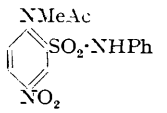

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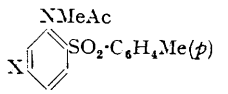


(IV.)

the bond joining nitrogen to the benzene ring. Experiments with this compound are typical of the procedure employed. A supersaturated solution, prepared by warming (I) with ethyl (+)-tartrate, was kept at room temperature till crystallisation appeared to be complete. The resulting crystals were separated as far as possible from the mother-liquor by filtration at the pump, washed with a little alcohol and copiously with water, and dried *in vacuo*. In chloroform solution these crystals gave a dextrorotation ($\alpha \sim +0{\cdot}2°$). The material remaining in the ethyl (+)-tartrate mother-liquors was precipitated by addition of water, washed, and dried : this gave a lævorotation ($\alpha \sim -0{\cdot}15°$) in chloroform solution. Both samples mutarotated to zero rotation, the half-life period at room temperature being 19 minutes.

When a sufficiently dilute solution of the sulphone in ethyl (+)-tartrate was kept at room temperature for a few hours so that no crystallisation occurred, the material in solution was found to be lævorotatory. As this was the whole amount of the originally optically inactive sulphone, a first-order transformation must have occurred, while the activity of the sample obtained by crystallisation was almost certainly due to a second-order transformation. It is of interest that this compound obeys the van't Hoff–Dimroth relationship, which states that the less soluble form of the compound should also be the less stable.

The same sample can be repeatedly activated in this manner and allowed to racemise in chloroform solution, each activation giving substantially the same rotation value, while the sample at the end remains unchanged in melting point. Thus the observed rotations cannot be due to any interaction between the solute and solvent with formation of an optically active impurity derived from the optically active solvent. Moreover, in several of the examples described below the observed rate of racemisation agrees well with that recorded by other workers who activated the substances by formation of diastereoisomeric salts in the normal manner.

With increase in temperature of the solution the activation effect decreases, and, in the case of this sulphone, is negligible at 84°. This temperature effect was observed to apply both to first- and to second-order transformations.

Compound (I) was also examined in other optically active solvents. Ethyl (−)-tartrate, as expected, gave the same results as ethyl (+)-tartrate except for the reversal of the direction of rotation, *i.e.*, the crystals were lævorotatory and the material precipitated from the mother-liquors dextrorotatory. (−)-Menthyl acetate gave a second-order transformation. No transformation was observed, however, when (+)- or (−)-*sec.*-octyl alcohol was used as asymmetric solvent. The solubility of the sulphone in cold *sec.*-octyl alcohol is low and crystallisation took place rapidly; crystallisation of the sulphone from ethyl tartrate took several days. However, crystallisation of the sulphone from menthyl acetate was also rapid, so it is difficult to say whether rate of crystallisation is an important factor.

The related *N*-ethyl compound (I; X = Me, Y = Et) has also been found to undergo both first- and second-order transformations in ethyl (+)-tartrate. As expected, it was found to be optically much more stable than the *N*-methyl compound, having a half-life period of about 6 hours as against 19 minutes. This is of interest as showing that a compound of such relatively

high optical stability is capable of undergoing asymmetric transformations in an asymmetric solvent.

Another closely related compound, sodium *N*-acetyl-*N*-methyl-*p*-toluidine-3-sulphonate, was found to undergo a first-order transformation in ethyl (+)-tartrate and a second-order transformation in (+)-*sec.*-butyl alcohol. The half-life period of racemisation was 150 minutes at 18° ; Mills and Kelham (*J.*, 1937, 274) give 175 minutes at 16·6° and 70 minutes at 25°.

These results show that optical activation can be achieved by asymmetric solvent action. Moreover, this method can be applied to compounds which lack a salt-forming group and so cannot be resolved by the normal means. The compounds obtained, although not optically pure, have a sufficiently high rotatory power to allow observations to be made of their rates of racemisation and thus to compare the optical stabilities of related compounds. It was decided to study a series of related sulphones and similar compounds in this way, in the hope that an example exhibiting a more complete activation effect might be obtained.

It has been shown by Adams and his school that, in the case of optically active diphenyl derivatives, substituents other than those actually involved in the steric interference can influence the optical stability of the compound (Adams *et al.*, *J. Amer. Chem. Soc.*, 1932, **54**, 2966, 4434; 1934, **56**, 1787; 1935, **57**, 1592). Adams investigated the series of compounds obtained when a substituent X is introduced into positions 3′, 4′, or 5′ of the diphenyl molecule (II). He found that for each of the three series of compounds the optical stability increases in the order $H < OCH_3 < CH_3 < Cl < Br < NO_2$. A similar investigation was carried out on the sulphone type of molecule. The substituents Cl, Br, OCH_3 were successively introduced in place of the *p*-methyl group (I; X = Cl, Br, OCH_3; Y = Me or Et); the *N*-methyl-*p*-bromo-compound, however, was not prepared in sufficient quantity for experiments with ethyl (+)-tartrate. Of these compounds, all underwent first-order transformations in ethyl (+)-tartrate and, with the single exception of the *N*-ethyl-*p*-chloro-compound, all underwent second-order transformations also. The relative optical stabilities are shown in Table I. Since the observed rotations are small, these values are only approximate, but they allow the various compounds to be arranged in order of optical stability, which decreases in the order $OCH_3 > CH_3 > Cl > Br$. It will be observed that the substituents fall into the same sequence as that observed by Adams but that the order is reversed.

TABLE I.

Half-life periods of racemisation of sulphones (I).

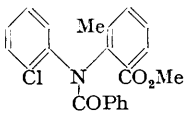
X =	Y = CH_3.	Y = C_2H_5.	X =	Y = CH_3.	Y = C_2H_5.
p-Br	—	30 mins.	*p*-CH_3	19 mins.	720 mins.
p-Cl	3 mins.	120 mins.	*p*-OCH_3	41 mins.	many hours

It was desired also to investigate the nitro-substituted sulphone (I; X = NO_2), but no route leading conveniently to its synthesis could be found. The closely related sulphonanilide (III) was not activated by ethyl (+)-tartrate, nor did 5-nitro-2-acetomethylamidobenzenesulphonic acid give any evidence of asymmetric transformation with brucine or quinidine. In so far as conclusions may be drawn from such negative results, it seems that a nitro-group *para* to the methylamido-group destroys the asymmetry of the molecule, possibly because of resonance involving both the nitro- and the amido-group.

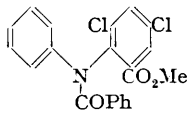
The unsubstituted and *m*-substituted compounds (IV; X = H, Br, Cl, CH_3, OCH_3) could not be activated by solution in ethyl (+)-tartrate. These observations were most surprising, having regard to the very consistent results obtained with the *p*-substituted sulphones. The explanation possibly lies in the difference in physical properties. The unsubstituted and *m*-substituted sulphones are much more soluble in common solvents than the *p*-compounds and display a greater tendency to form supersaturated solutions, the most extreme case being that of the *m*-chloro-compound, solutions of which in acetic acid remained supersaturated for up to two days, crystallising rapidly on the addition of a crystal of the sulphone. With one exception they did not crystallise from ethyl (+)-tartrate and had to be precipitated by water, the solute separating first as an oil which solidified on more or less prolonged standing. The *m*-nitro-compound (IV; X = NO_2), which did not display this tendency to form supersaturated solutions, was crystallised from ethyl (+)-tartrate but it gave no evidence of activation.

Derivatives of Benzodiphenylamide.—Three *o*-substituted benzodiphenylamides (V, VI, VII), compounds of low optical stability similar to compounds investigated by Turner and his school, have been examined. The acids corresponding to the first two of these esters have been resolved by Jamison and Turner (*J.*, 1940, 264), who measured their rates of racemisation;

both esters were observed to undergo both first- and second-order transformations in ethyl (+)-tartrate. The rotation of the product of the first-order transformation of (V) was the



(V.)



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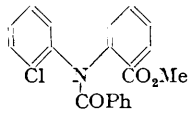

(VII.)

largest observed in the course of this work ($[\alpha]_{5461} = -4{\cdot}4°$). In this case the enantiomorph which is present in excess in solution also predominates in the crystals which separate out, which have $[\alpha]_{5461} = -0{\cdot}75°$. Crystallisation from ethyl (−)-tartrate gave a product having $[\alpha]_{5461} = +0{\cdot}79°$. The observed rates of racemisation (Table II) of these esters corresponded fairly satisfactorily with those recorded by Turner for the acids.

TABLE II.

	Half-life period, mins.		Half-life period, mins.
Acid (V)	10·5	Ester (V)	8
Acid (VI)	4·6	Ester (VI)	5

The third ester (VII) was observed to undergo a first- but not a second-order transformation. The crystals which separated from ethyl (+)-tartrate were optically inactive, but the material precipitated from the mother-liquors was lævorotatory. It is difficult to say why this compound should not have undergone a second-order transformation. It had been observed that, in the case of 2-acetomethylamido-5 : 4′-dimethyldiphenyl sulphone, any vigorous agitation of the ethyl (+)-tartrate solution while filtering the crystals, or any scratching or the walls of the containing vessel, caused precipitation of lævorotatory material from the mother-liquors along with the dextrorotatory crystals, thus obscuring the rotation of the material actually produced by crystallisation. It is possible that in this case also some form of coprecipitation obscures the effect of a possible second-order transformation. The half-life period of this compound was large compared with that of (VI) (15 mins. as against 5 mins.). This is not very surprising having regard to the observations made on the effect of substituents on the optical stability of the sulphones, and to similar observations in the diphenyl series recorded by Kuhn and Albrecht (*Annalen*, 1927, **458**, 221).

Prototropic Compounds.—A compound which exists in solution as an equilibrium mixture of two tautomers, one of which is asymmetric and the other symmetric, should be capable of undergoing asymmetric transformations. Only a few instances of this are recorded in the literature, and most of the compounds in question were unsuitable for the purposes of the present work. Leuchs and Wutke (*Ber.*, 1913, **46**, 2420; 1921, **54**, 1830) investigated two compounds of this type, 2-*o*-carboxybenzylindan-1-one and hydrocarbostyril-3-carboxylic acid. Of these, the first is difficult to prepare and the second sparingly soluble, so that only dilute solutions of the compound would be available for polarimetric examination and the slight activation to be expected by the use of an asymmetric solvent might be overlooked. More recently, Davidson and Turner (*J.*, 1945, 843) have shown that compounds of the malonoanilic acid type undergo asymmetric transformations with optically active bases.

One of these compounds, benzylmalono-*o*-toluidic acid, was prepared and recrystallised from ethyl (+)-tartrate. The material which crystallised was lævorotatory; no mutarotation occurred in alcoholic solution but the rotation disappeared on addition of alcoholic alkali. These observations are in accord with Turner's findings. No polarimetric measurements could be made on the material recovered from the ethyl tartrate mother-liquors owing to the presence of highly coloured impurities.

On the basis of Leuchs and Wutke's observations on the substituted indanone it seemed possible that the hydrogen atom attached to a carbon atom adjacent to a single carbonyl group might be sufficiently mobile to permit of asymmetric transformations. An α-alkyldeoxybenzoin was thought to be a suitable compound for experiment, and the α-benzyl compound was accordingly prepared. α-Benzyldeoxybenzoin, however, apparently reacted with ethyl (+)-tartrate to give a highly active product, which we were unable to isolate in a pure state and did not examine further. The related compound, *α-benzyldeoxybenzoin-2-carboxylic acid*, was resolved in the usual manner. This acid formed a brucine salt from which, after four crystallisations from ethyl acetate, the (−)-base, (+)-acid was isolated, $[\alpha]_{5461} = -12{\cdot}1°$. On treatment with hydrochloric acid, the (+)-acid was produced, $[\alpha]_{5461} = +27{\cdot}5°$. This

acid did not racemise in chloroform solution, as did that of Leuchs and Wutke. It racemised slowly, however, on crystallising from hot acetic acid; it also racemised in hot aqueous-alcoholic alkali. Esterification of the active acid with diazomethane produced the (+)-*methyl* ester, $[\alpha]_{5461} = +29{\cdot}3°$. This ester was heated under reflux in methanolic solution for 48 hours; the recovered ester had $[\alpha]_{5461} = +31{\cdot}8°$, showing that no racemisation had taken place in the process. The increase in rotation of the ester was presumed to be due to some purification that had taken place in the course of the attempted racemisation. This result is rather difficult to reconcile with Leuchs and Wutke's claims, but it indicates that α-benzyldeoxybenzoin itself would be unlikely to undergo an asymmetric transformation.

Optically inactive methyl α-benzyldeoxybenzoin-2-carboxylate was crystallised from ethyl (+)-tartrate solution. Almost all the ester separated from the solution : the crystals showed no rotation.

αα′-Dinitrodibenzyl, which contains the nitro–*aci*nitro-system, was also investigated. This substance has been shown to exist in two isomeric forms, one m. p. 235° and the other m. p. 152° (Schmidt, *Ber.*, 1901, **34**, 3540; Brown and Shriner, *J. Org. Chem.*, 1937—1938, **2**, 376). The compound contains two asymmetric carbon atoms; one of the isomers will be the racemic and the other the *meso*-form of the compound. No means of distinguishing them exists, since, as they lack any salt-forming group, no method of resolution, other than asymmetric solvent action, is applicable. It was hoped that the racemic form might undergo an asymmetric transformation in ethyl (+)-tartrate solution, and there was a possibility that the *meso*-form might undergo partial conversion into its isomer under the influence of the ethyl (+)-tartrate.

The higher-melting isomer crystallised rapidly from the ethyl tartrate. In the first experiment the crystals were found to be lævorotatory in nitrobenzene solution; mutarotation occurred at room temperature. A certain amount of decomposition of the dinitrodibenzyl had taken place, however, as indicated by the evolution of nitrous fumes; it had been necessary to heat the dinitrodibenzyl and the ethyl tartrate for rather a long time near the boiling point of the ethyl tartrate to bring the sparingly soluble nitro-compound into solution. The experiment was repeated, care being taken to avoid any decomposition of the nitro-compound; the crystals which separated were optically inactive. No rotation was detected in the crystals when the first crystals were allowed to separate at 86° (to permit of slow crystallisation). The rotation observed in the first instance was possibly due to chance preferential inoculation of the solution or to an asymetric decomposition. All these samples melted at 235°; there was no indication of any conversion into the lower-melting isomer. When the other isomer was crystallised from ethyl (+)-tartrate there was no indication of any asymmetric transformation or of any conversion into the higher-melting isomer.

Experimental.

(All polarimeter readings were made in a 2-dm. tube with mercury green light, $\lambda = 5461$ A.; all m. p.s are uncorrected.)

5-*Substituted* 2-*Acetoalkylamido*-4′-*methyldiphenyl Sulphones.*—The toluene-*p*-sulphonyl derivatives of *p*-methyl-, *p*-methoxy-, *p*-chloro-, and *p*-bromo-*N*-methyl- and *N*-ethyl-aniline were all prepared by normal methods. Rearrangement to the *o*-amino-sulphone was carried out by heating it at 100° with an equal weight of 96% sulphuric acid for 2 hours; when the mixture was cooled and poured into water the sulphones were precipitated. The following 2-amino-4′-methyldiphenyl sulphones were obtained : *N*-acetyl-*N* : 5-dimethyl-, prisms, m. p. 168° (lit., 138°; Halberkaan, *Ber.*, 1921, **54**, 1835) (Found : C, 64·5; H, 5·8. Calc. for $C_{17}H_{19}O_3NS$: C, 64·4; H, 6·0%); *N*-acetyl-5-methyl-*N*-ethyl-, needles (alcohol), m. p. 145°; *N*-acetyl-5-methoxy-*N*-methyl-, prisms (alcohol), m. p. 138°; 5-*methoxy*-N-*ethyl*-, prisms (alcohol), m. p. 94° (Found : C, 63·1; H, 6·3; N, 4·8. $C_{16}H_{19}O_3NS$ requires C, 63·0; H, 6·2; N, 4·6%); N-*acetyl*-5-*methoxy*-N-*ethyl*-, prisms (alcohol), m. p. 145° (Found : C, 62·6; H, 6·1; N, 4·3. $C_{18}H_{21}O_4NS$ requires C, 62·2; H, 6·0; N, 4·0%); 5-*chloro*-N-*methyl*-, needles (alcohol), m. p. 155° (Found : C, 57·1; H, 4·8; N, 5·1. $C_{14}H_{14}O_2NClS$ requires C, 56·9; H, 4·7; N, 4·7%); 5-*chloro*-N-*acetyl*-N-*methyl*-, needles (alcohol), m. p. 159° (Found : C, 57·0; H, 4·7; N, 4·4. $C_{16}H_{16}O_3NClS$ requires C, 56·9; H, 4·7; N, 4·2%); 5-*chloro*-N-*ethyl*-, needles (alcohol), m. p. 136° (Found : C, 58·1; H, 5·1; N, 4·8. $C_{15}H_{16}O_2NClS$ requires C, 58·2; H, 5·2; N, 4·5%); 5-*chloro*-N-*acetyl*-N-*ethyl*-, plates (alcohol), m p. 153° (Found : C, 58·0; H, 5·4; N, 3·7. $C_{17}H_{18}O_3NClS$ requires C, 58·0; H, 5·2; N, 4·0%); 5-*bromo*-N-*methyl*-, needles (alcohol), m. p. 161° (Found : C, 50·0; H, 4·3. $C_{14}H_{14}O_2NBrS$ requires C, 49·7; H, 4·2%); 5-*bromo*-N-*acetyl*-N-*methyl*-, needles (alcohol), m. p. 173° (Found : C, 50·1; H, 4·3. $C_{16}H_{16}O_3NBrS$ requires C, 50·3; H, 4·2%); 5-*bromo*-N-*ethyl*-, needles (alcohol), m. p. 141° (Found : C, 50·9; H, 4·8. $C_{15}H_{16}O_2NBrS$ requires C, 50·9; H, 4·6%); 5-*bromo*-N-*acetyl*-N-*ethyl*-, needles (alcohol), m. p. 144° (Found : C, 51·5; H, 4·6. $C_{17}H_{18}O_3NBrS$ requires C, 51·6; H, 4·6%).

2-*Acetomethylamido*-5 : 4′-*dimethyldiphenyl Sulphone in Ethyl* (+)-*Tartrate.*—(*a*) The sulphone (3 g.) was dissolved in ethyl (+)-tartrate (10 c.c.). After 5 hours at room temperature the sulphone was precipitated by addition of water, filtered off, washed thoroughly with water, and dried *in vacuo*; 1·336 g. in chloroform (15 c.c.) had α^{18} −0·20°, rising to zero, half-life period = 19 minutes.

(*b*) The sulphone (5 g.) was crystallised from ethyl (+)-tartrate (7 c.c.). When crystallisation

appeared to be complete, the crystals were carefully drained as free from ethyl tartrate as possible, washed with a little alcohol, then washed thoroughly with water, and dried *in vacuo*. It was essential not to scratch or in any way agitate the crystals while they were still in contact with ethyl tartrate, as this caused precipitation of lævorotatory material from the mother-liquors. The material remaining in the mother-liquors was precipitated and treated as in (*a*) above. Crystals: 2·034 g. in 15 c.c. of chloroform had α^{17} +0·17°, falling to zero, half-life period = 19 minutes. Precipitate: 1·271 g. in 15 c.c. of chloroform had α^{16} −0·15°, half-life period of mutarotation = 19 minutes.

Effect of increase of temperature. The sulphone (5 g.) was crystallised from ethyl (+)-tartrate (7 c.c.) at 84°, and samples were kept in the ester solution at 42° and 84° for several hours without crystallisation taking place; the several fractions were then recovered in the appropriate manner. The samples treated at 84° possessed negligible rotations (*ca.* ±0·01° for 10% solutions in chloroform). The 42° sample had $[\alpha]^{17}$ −0·5° (*c*, 12 in chloroform).

2-*Acetomethylamido*-5 : 4′-*dimethyldiphenyl Sulphone in Other Asymmetric Solvents.*—(a) *Ethyl* (−)-*tartrate.* The sulphone (3 g.) was recrystallised from ethyl (−)-tartrate (5 c.c.). Crystals: 0·438 g. in 15 c.c. of chloroform had α^{20} −0·05°, rising to zero in 1 hour. Precipitate: 1·6446 g. in 15 c.c. of chloroform had α^{19} +0·13° falling to zero in 2 hours.

(b) (−)-*Menthyl acetate.* A solution of 3 g. in 20 c.c. was allowed to crystallise completely; the crystals were filtered off and washed with cold methanol: 1·03 g. in 15 c.c. of chloroform had α^{20} +0·08°, falling to −0·10° in 80 minutes, the final lævorotation being presumably due to the presence of residual menthyl acetate.

(c) (+)- *and* (−)-sec.-*Octyl alcohol.* Solutions of 3 g. of the sulphone in 10 c.c. each of the alcohols were allowed to crystallise; the crystals, representing almost the whole of the solute, were in both cases optically inactive.

2-*Acetoethylamido*-5 : 4′-*dimethyldiphenyl Sulphone in Ethyl* (+)-*Tartrate.*—The compound (3 g.) was crystallised from ethyl (+)-tartrate (10 c.c.). Crystals: 1·8164 g. in 15 c.c. of chloroform had α^{22} +0·11°, falling to zero, half-life period *ca.* 6 hours. Precipitate: 1·254 g. in 15 c.c. of chloroform had α^{20} −0·08°, rising to zero.

A solution of 1 g. in 10 c.c. of ethyl (+)-tartrate was kept for a few days, and the solute recovered by precipitation with water; 1·5177 g. in 15 c.c. of chloroform had α^{20} −0·08°, rising to zero.

Other Compounds of Type (I) *in Ethyl* (+)-*Tartrate.*—The compounds were in turn crystallised from ethyl (+)-tartrate (3 g. in 5—10 c.c.), giving two fractions, crystals, A, and precipitate from the mother-liquors, B. Samples (1 g.) of the sulphones were also kept in solution in ethyl (+)-tartrate (10 c.c.) for some hours and then the solute was recovered by precipitation with water to give fraction C. The observed rotations for the various fractions in chloroform solution (15 c.c.) of all these compounds are tabulated below.

Sodium N-*Acetyl*-N-*methyl*-p-*toluidine*-3-*sulphonate in Asymmetric Solvents.*—*N*-Methyl-*p*-toluidine was prepared by the method of Halberkaan (*loc. cit.*), and its acetyl derivative sulphonated and acetylated by the method of Mills and Kelham (*loc. cit.*). The hydrated salt melted at 84°.

(a) *Ethyl* (+)-*tartrate.* A solution of the salt (2 g.) in ethyl tartrate (5 c.c.) was kept at room temperature for 5 hours, and the solute recovered by precipitation with moist ether (use of dry ether led to difficulty in obtaining a solid precipitate). The salt was freed from ethyl tartrate by extraction with ether in a Soxhlet apparatus: 1·267 g. in 15 c.c. of water had α^{18} −0·08°, rising to zero, half-life period 150 minutes.

(b) (+)-sec.-*Butyl alcohol.* The salt (2 g.) was recrystallised from moist (+)-*sec.*-butyl alcohol (7·5 c.c.). The crystals were filtered off at the pump and washed with ether several times: 1·562 g. in 15 c.c. of water had α^{18} −0·07°, rising to zero in about 5 hours.

5-*Nitro*-2-*methylaminobenzenesulphonanilide.*—2-Chloro-5-nitrobenzenesulphonanilide was boiled for 48 hours in methanolic solution with an excess of methylamine carbonate; the *methylamino*-compound formed needles, m. p. 169°, from alcohol (Found: C, 51·0; H, 4·4; N, 13·8. $C_{13}H_{13}O_4N_3S$ requires C, 50·7; H, 4·2; N, 13·7%); its *acetyl* derivative (III) formed prisms, m. p. 222°, from dioxan (Found: C, 51·8; H, 4·4; N, 12·2. $C_{15}H_{15}O_5N_3S$ requires C, 51·6; H, 4·4; N, 12·0%). Crystallisation from ethyl (+)-tartrate gave an inactive product (*c*, 10 in dioxan).

Substituents.		A. Initial α.	A. Wt., g.	B. Initial α.	B. Wt., g.	C. Initial α.	C. Wt., g.	Half-life period.
X = OMe	Y = Me ...	−0·10°	0·432	−0·11°	0·962	−0·08°	0·746	41 mins.
	Y = Et ...	+0·03	0·494	−0·10	1·065	—	—	very large
X = Cl	Y = Me ...	−0·20	1·078	−0·10	0·975	−0·04	0·955	3 mins.
	Y = Et ...	nil	0·958	+0·14	0·756	+0·16	0·937	120 mins.
X = Br	Y = Et ...	−0·13	0·720	+0·12	0·750	—	—	30 mins.

Sodium 5-*Nitro*-2-*methylaminobenzenesulphonate.*—Dry *p*-nitro-*N*-acetyl-*N*-methylaniline (21·6 g.) was sulphonated with chlorosulphonic acid (13 g.) at 120—135° for 4 hours with stirring. The product was dissolved in water, neutralised with sodium carbonate, and evaporated to dryness. Crystallisation from 90% aqueous alcohol gave the hydrated *salt* as yellow needles (Found: C, 30·0; H, 3·8. $C_7H_7O_5N_2SNa,1·5H_2O$ requires C, 29·9; H, 3·6%). Acetylation gave the N-*acetyl* derivative, the hydrated salt being dehydrated at 100° (Found: C, 36·3; H, 3·2; N, 9·5. $C_9H_9O_6N_2SNa$ requires C, 36·5; H, 3·0; N, 9·5%).

(−)-*Brucine* 5-*Nitro*-2-*acetomethylamidobenzenesulphonate.*—The sodium salt (1·5 g.) in water (4 c.c.) was treated with a solution of brucine (2·3 g.) in water (10 c.c.) containing acetic acid (0·41 g.). The solution became deep red and on storage the *brucine* salt separated (Found: C, 57·4; H, 5·5; N, 8·4. $C_{32}H_{36}O_{10}N_4S$ requires C, 57·5; H, 5·1; N, 8·4%). The salt was recrystallised from water, alcohol, in which it was sparingly soluble, and nitrobenzene (readily soluble). The rotation in each case was

0·0° (*c*, 10 in chloroform). No change in rotation occurred on further recrystallisation from water; no mutarotation was observed. A saturated solution of the brucine salt in chloroform was treated with the theoretical quantity of alcoholic sodium ethoxide at 0°. The precipitated sodium salt was optically inactive. The zero value for the rotation of the brucine salt may be due to optical activation of the acid so that its rotation exactly counterbalances that of the brucine; but, in the absence of mutarotation or optical activity in the recovered acid, no definite conclusion can be drawn from anomalous rotation (cf. Kharasch *et al.*, *J. Amer. Chem. Soc.*, **1934**, **56**, 1646).

(+)-*Quinidine 5-Nitro-2-acetomethylamidobenzenesulphonate.*—The sodium salt (8·88 g.) in water (35 c.c.) was treated with quinidine (9·72 g.) in water (25 c.c.) containing acetic acid (1·8 g.). The precipitated yellow viscous oil slowly crystallised to pale yellow prisms of the quinidine salt (10 g.). The rotation ($[\alpha]^{20}$ +210·5°) was not raised by repeated crystallisation from ethyl acetate; no mutarotation was observed. Extraction of a chloroform solution of the salt with dilute ammonia solution gave an optically inactive solution of the ammonium salt.

4-Substituted 2-Acetomethylamido-4'-methyldiphenyl Sulphones.—The appropriate *o*-nitroaryl halides were condensed with sodium *p*-tolylsulphide, the thio-ethers were oxidised (hydrogen peroxide in acetic acid) to sulphones, and the nitro-groups then reduced to amino-groups with stannous chloride in aqueous-alcoholic hydrochloric acid. Acetylation of the amino-sulphones, followed by methylation with methyl sulphate and alcoholic sodium ethoxide, gave the required compounds. The following substituted 4'-methyldiphenyl sulphides have not previously been described: 2-*nitro*-4-*methoxy*-, orange prisms (from methanol), m. p. 96° (Found: C, 61·3; H, 4·6. $C_{14}H_{13}O_3NS$ requires C, 61·1; H, 4·8%); 4-*bromo*-2-*nitro*-, elongated orange prisms (from dioxan), m. p. 124° (Found: C, 48·6; H, 3·3. $C_{13}H_{10}O_2NBrS$ requires C, 48·2; H, 3·1%). The following substituted 4'-methyldiphenyl sulphones are also new: 2-*acetomethylamido*-, prisms (from alcohol), m. p. 121° (Found: C, 63·5; H, 5·0. $C_{16}H_{17}O_3NS$ requires C, 63·4; H, 5·3%); 2-*acetomethylamido*-4-*methyl*-, needles (from alcohol), m. p. 161° (Found: C, 64·5; H, 5·7; N, 4·5. $C_{17}H_{19}O_3NS$ requires C, 64·4; H, 6·0; N, 4·5%); 2-*nitro*-4-*methoxy*-, needles (from alcohol), m. p. 127° (Found: C, 54·8; H, 4·2. $C_{14}H_{13}O_5NS$ requires C, 54·8; H, 4·2%); 2-*amino*-4-*methoxy*-, small needles (from benzene), m. p. 153° (Found: C, 60·7; H, 5·5. $C_{14}H_{15}O_3NS$ requires C, 60·7; H, 5·4%); 2-acetamido-4-methoxy-, needles (from alcohol), m. p. 115°; 2-*acetomethylamido*-4-*methoxy*-, prisms (from methanol), m. p. 147° (Found: C, 61·3; H, 5·8; N, 4·4. $C_{17}H_{19}O_4NS$ requires C, 61·3; H, 5·7; N, 4·2%); 4-*chloro*-2-*amino*-, white platelets (from alcohol), m. p. 137° (Found: C, 55·6; H, 4·3. $C_{13}H_{12}O_2NClS$ requires C, 55·4; H, 4·3%); 4-*chloro*-2-*acetamido*-, needles (from methanol), m. p. 129° (Found: C, 55·8; H, 4·3. $C_{15}H_{14}O_3NClS$ requires C, 55·7; H, 4·3%); 4-*chloro*-2-*acetomethylamido*-, prisms (from acetic acid), m. p. 175° (Found: C, 57·1; H, 4·6; N, 4·3. $C_{16}H_{16}O_3NClS$ requires C, 56·9; H, 4·8; N, 4·2%); 4-*bromo*-2-*nitro*-, white needles (from alcohol), m. p. 132° (Found: C, 43·9; H, 2·9. $C_{13}H_{10}O_4NBrS$ requires C, 43·8; H, 2·8%); 4-*bromo*-2-*amino*-, prisms (from alcohol), m. p. 154° (Found: C, 47·7; H, 3·8. $C_{13}H_{12}O_2NBrS$ requires C, 47·9; H, 3·7%); 4-*bromo*-2-*acetamido*-, white prisms (from methanol), m. p. 132° (Found: C, 49·0; H, 4·1. $C_{15}H_{14}O_3NBrS$ requires C, 49·0; H, 3·8%); 4-*bromo*-2-*acetomethylamido*-, white prisms (from alcohol), m. p. 160° (Found: C, 50·2; H, 4·2; N, 4·0. $C_{16}H_{16}O_3NBrS$ requires C, 50·3; H, 4·2; N, 3·7%).

4-Substituted 2-Acetomethylamido-4'-methyldiphenyl Sulphones in Ethyl (+)-*Tartrate.*—Solutions of the compounds (2 g.) in the ester (15 c.c.) were kept at room temperature for several hours, and the solute then recovered by precipitation with water. In each case the recovered material was optically inactive. The unsubstituted sulphone (IV; X = H) (2 g.) was crystallised from ethyl (+)-tartrate (5 c.c.). Both the crystals which separated and the material remaining in the mother-liquors were optically inactive in chloroform solution.

4-Nitro-2-acetomethylamido-4'-methyldiphenyl Sulphide.—2-Chloro-5-nitro-*N*-methylacetanilide was condensed with sodium *p*-tolyl sulphide; the *sulphide* formed dull yellow prisms, m. p. 157° from alcohol, (Found: C, 60·8; H, 5·1. $C_{16}H_{16}O_3N_2S$ requires C, 60·8; H, 5·1%). Oxidation with hydrogen peroxide in acetic acid gave the *sulphone*, white platelets (from alcohol), m. p. 171° (Found: C, 55·3; H, 4·6. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·6%). The latter compound was crystallised from ethyl (+)-tartrate; both the crystals and the material recovered from the mother-liquors were optically inactive.

Methyl 2-Chloro-N-benzoyl-6'-methyldiphenylamine-2'-carboxylate (prisms, m. p. 169°) *in Asymmetric Solvents.*—(a) *Ethyl* (+)-*tartrate.* The compound (3 g.) was crystallised from ethyl (+)-tartrate (10 c.c.). Crystals: 1·1022 g. in 15 c.c. of chloroform had α^{20} −0·11°, rising to zero, half-life period = 8 minutes. Precipitate: 0·4623 g. in 15 c.c. of chloroform had α^{20} −0·27°, rising to zero, half-life period = 8 minutes. A solution of the compound (2 g.) in ethyl (+)-tartrate (30 c.c.) was kept for several hours, and the solute precipitated by addition of water; 1·0899 g. in 15 c.c. of chloroform had α^{22} −0·32°, rising to zero, half-life period = 8 minutes.

(b) *Ethyl* (−)-*tartrate.* The compound (3 g.) was recrystallised from ethyl (−)-tartrate (8 c.c.). Crystals: 1·322 g. in 15 c.c. of chloroform had α^{21} +0·14°, falling to zero in 30 minutes. Precipitate: insufficient for examination.

Methyl 4: 6-Dichloro-N-benzoyldiphenylamine-2-carboxylate (prisms, m. p. 119°) in *Ethyl* (+)-*Tartrate.*—The compound (3 g.) was crystallised from ethyl (+)-tartrate (9 c.c.). Crystals: 20·25 g. in 15 c.c. of chloroform had α^{19} −0·09°, rising to zero, half-life period = 5 minutes. Precipitate: 0·57 g. in 15 c.c. of chloroform had α^{19} −0·03°, rising to zero. A solution of the compound (2 g.) in ethyl (+)-tartrate (20 c.c.) was kept for 24 hours, and the solute precipitated with water; 1·55 g. in 15 c.c. of chloroform had α^{20} −0·11°, rising to zero.

N-*o*-*Chlorophenylbenzimino* o-*carbomethoxyphenyl ether* prisms (from methanol), m. p. 89° (Found: C, 68·6; H, 4·4. $C_{21}H_{16}O_3NCl$ requires C, 68·9; H, 4·4%), and *methyl 2-chloro-N-benzoyldiphenylamine-2'-carboxylate*, prisms, m. p. 123° (Found: C, 68·9; H, 4·5. $C_{21}H_{16}O_3NCl$ requires C, 68·9; H, 4·4%), were prepared.

Methyl 2-Chloro-N-benzoyldiphenylamine-2'-carboxylate in Ethyl (+)-*Tartrate.*—The compound (3 g.) was crystallised from ethyl (+)-tartrate (10 c.c.). The crystals were optically inactive. Precipitate: 1·653 g. in 15 c.c. of chloroform had α^{17} −0·13°, rising to zero, half-life period = 15 minutes.

A solution of the compound (1 g.) in ethyl (+)-tartrate (5 c.c.) was kept for several hours, and the solute precipitated : 0·955 g. in 15 c.c. of chloroform had α^{19} −0·10°, rising to zero.

Crystallisation of α-Benzyldeoxybenzoin from Ethyl (+)-Tartrate.—α-Benzyldeoxybenzoin (30 g.) was crystallised from ethyl (+)-tartrate (170 c.c.) to give crystals, $[\alpha]^{20}$ −2·11° (*c*, 5 in chloroform), which were then crystallised from more tartrate (200 c.c.) and then successively from four 50-c.c. portions; the succeeding fractions had $[\alpha]^{20}$ −2·3°, −3·8°, −5·2°, −5·7°, −5·7°, −5·7°. The α-benzyldeoxybenzoin recovered from the mother-liquors of the first three crystallisations was combined and crystallised from ethyl (+)-tartrate (30 c.c.) to give crystals (5·8 g.), $[\alpha]^{20}$ +5·7° (*c*, 5 in chloroform), and a precipitate from the mother-liquors (0·3 g.), $[\alpha]^{19}$ +17° (*c*, 2 in chloroform). In a parallel experiment with a different sample of ethyl (+)-tartrate a less soluble fraction was obtained, having $[\alpha]^{21}$ −20°; the soluble fraction had $[\alpha]^{21}$ +20°. The sample, $[\alpha]^{19}$ +17° (0·5 g.), was recrystallised from alcohol (20 c.c.); the crystals (0·3 g.) had $[\alpha]^{20}$ +5·8°, and the material recovered from the mother-liquors had $[\alpha]^{20}$ +30·9°. Similarly, the lævorotatory material of $[\alpha]^{21}$ −20° gave crystals of $[\alpha]^{20}$ −14° and a precipitate from the mother-liquors of $[\alpha]^{20}$ −34°. Owing to the small amount of material available it was not possible to carry this separation further. An attempt at separation by chromatographic analysis of a benzene solution of the active material on a column of activated alumina was unsuccessful.

Benzyl α-Benzyldeoxybenzoin-2-carboxylate.—Methyl deoxybenzoin-2-carboxylate (32 g.) was dissolved in methanol (60 c.c.) containing sodium (5·1 g.) and alkylated with benzyl chloride (29 g., 2 mols.). The *benzyl* ester formed large white needles, m. p. 75° (Found : C, 83·1; H, 5·6. $C_{29}H_{24}O_3$ requires C, 82·9; H, 5·7%). Hydrolysis gave the *acid*, white prisms (from acetic acid), m. p. 171° (Found : C, 79·7; H, 5·4. $C_{22}H_{18}O_3$ requires C, 80·0; H, 5·5%).

Brucine (+)-α-Benzyldeoxybenzoin-2-carboxylate.—Brucine (16·8 g.) and the foregoing acid (11·3 g.) were dissolved in ethyl acetate (80 c.c.); the crystals which separated on cooling had $[\alpha]^{20}$ −15·3° (*c*, 5 in chloroform). Three crystallisations from ethyl acetate (200 c.c.) gave 7 g. of salt with $[\alpha]^{20}$ −12·1°.

(+)-α-Benzyldeoxybenzoin-2-carboxylic acid obtained by decomposition of the brucine salt with dilute hydrochloric acid had $[\alpha]^{20}$ +27·5° (*c*, 5 in chloroform). The *methyl* ester, obtained by esterification with excess of diazomethane, had $[\alpha]^{20}$ +29·3° (*c*, 4 in methanol), and, after 48 hours' refluxing in methanol, $[\alpha]^{20}$ +31·8° (*c*, 3 in methanol). The ester formed prisms, m. p. 110° (Found : C, 80·0; H, 5·7. $C_{23}H_{20}O_3$ requires C, 80·3; H, 5·8%).

Racemisation of (+)-α-Benzyldeoxybenzoin-2-carboxylic Acid.—A sample of the acid, $[\alpha]^{20}$ +4·85°, was heated at 100° for 33 hours with excess of aqueous-alcoholic sodium ethoxide; it was then optically inactive (*c*, 2 in chloroform). On crystallisation of some of the same sample of acid from acetic acid the crystals were found to be optically inactive (*c*, 2 in chloroform).

Methyl α-Benzyldeoxybenzoin-2-carboxylate in Ethyl (+)-Tartrate.—On crystallisation of the ester (4·7 g.) from ethyl (+)-tartrate (9 c.c.) both the crystals and the precipitate from the mother-liquors were optically inactive (*c*, 8 in chloroform).

αα′-Dinitrodibenzyl.—This was prepared by Schmidt's method (*Ber.*, 1901, **34**, 3540). From 30 g. of stilbene were obtained 12 g. of the higher-melting isomer, m. p. 235°, and 7 g. of the lower-melting isomer, m. p. 142—146°.

αα′-Dinitrodibenzyl in Ethyl (+)-Tartrate.—(a) *High-melting isomer.* This compound (3 g.) was recrystallised from ethyl (+)-tartrate (45 c.c.), some nitrogen dioxide being evolved. Crystals : 0·9467 g. in 15 c.c. of nitrobenzene had α^{20} −0·28°, rising to zero in an hour. When this experiment was repeated with 3 g. of the solute in 60 c.c. of ester, care being taken to avoid decomposition, no optical activity was detected in the crystals even when crystallisation was slow (solution kept in a bath of water slowly cooled from 84° to room temperature).

(b) *Low-melting isomer.* The compound (2 g.) was recrystallised from ethyl (+)-tartrate (10 c.c.) below 140° (conversion into the other isomer takes place above 152°); both the crystals and the material recovered from the mother-liquors were optically inactive and melted at 147°.

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