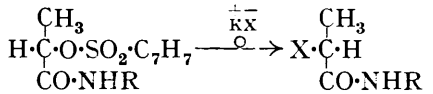
66. *Walden Inversion Reactions of* d-(+)α-p-*Toluenesulphonoxypropionic Acid and Amide and their Derivatives.*

By C. M. Bean, J. Kenyon, and H. Phillips.

The substitution reactions of acids are frequently complicated by the carboxyl group: Holmberg, for example (*J. pr. Chem.*, 1913, **87**, 456), showed that the sign of rotation of the malic acid obtained on hydrolysis of bromosuccinic acid depends on the experimental conditions employed, and demonstrated that malolactone is an intermediate product in the reaction. Intermediate lactone formation may also explain (Kenyon and Phillips, *Trans. Faraday Soc.*, 1930, **26**, 451) the difference in configuration of the products obtained from amino-acids and their esters under the action of either nitrous acid or nitrosyl bromide.

In such substitution reactions, the ionised carboxyl group can be considered to displace and react as though it were the entering anion. Additional evidence on the influence of carboxyl and related groups on the course of substitution reactions, and on the stereochemical factors that tend to augment or diminish this influence, has now been obtained by a study of the reactions of * *d*-(+)α-*p*-toluenesulphonoxypropionic acid, its amide, and some of its substituted amides. This series of compounds was chosen for investigation because it has been shown that the *p*-toluenesulphonoxy-group of the ethyl ester of the acid can be replaced by anions with inversion (Kenyon, Phillips, and Turley, J., 1925, **127**, 399), and also because the carboxyl and related groups in these compounds are conveniently situated for displacing the α-*p*-toluenesulphonoxy-group intramolecularly, when the experimental conditions are favourable.

As indicated below, the replacement of the α-*p*-toluenesulphonoxy-groups in the neutral compounds of this series—amide and anilide—by either the acetoxy- or the benzoyloxy-group was proved to occur with inversion.



d- *l*-

R = H; C_6H_5. X = O·CO·CH_3; O·CO·C_6H_5.

This was accomplished by preparing the *d*-α-acetoxy- and -benzoyloxy-derivatives from either *d*-(−)lactic acid or a derivative of this acid by the following reactions, which are unlikely to lead to configurative change: *d*-(+)α-acetoxypropionamide, *d*-(−)lactic acid ⟶ *d*-(+)α-acetoxypropionic acid ⟶ *d*-(+)α-acetoxypropionyl chloride ⟶ *d*-(+)α-acetoxypropionamide; *d*-(−)α-benzoyloxypropionamide, ethyl *d*-(+)lactate ⟶ *d*-(+)α-hydroxypropionamide ⟶ *d*-(−)α-benzoyloxypropionamide; *d*-(+)α-acetoxypropionanilide from *d*-(+)α-acetoxypropionyl chloride; *d*-(−)α-benzoyloxypropionanilide from *d*-(−)α-benzoyloxypropionylchloride. Attempts to prepare *d*-α-acetoxy- or -benzoyl-

* The signs (+) and (−) are used in place of the terms dextrorotatory and lævorotatory; the letters *d*- and *l*- denote configurations. It is assumed that (−) lactic acid has a *d*-configuration and, in the theoretical portion of the paper, that all the experiments were made on *d*-compounds.

oxy-propion-β-naphthalide by reactions unlikely to lead to configurative change were unsuccessful. As in some of the reactions of ethyl *d*-(+)α-*p*-toluenesulphonoxypropionate (Kenyon, Phillips, and Turley, *loc. cit.*), many of the above replacement reactions occurred with little racemisation: α-acetoxypropionamide, for example, being obtained from ethyl *d*-(+)lactate, α_{5461} + 10·66° (*l*, 1), and from *d*-(+)α-*p*-toluenesulphonoxypropionamide (prepared from a sample of this ester) with α_{5461} + 17·8° and α_{5461} − 16·9° (*l*, 1) respectively.

d-(+)α-*p*-Toluenesulphonoxypropionic acid does not undergo similar reactions with either potassium acetate, benzoate or thiocyanate, because its salts readily hydrolyse into *d*-(−)lactic acid and *p*-toluenesulphonic acid. With lithium chloride in acetone or aqueous acetone, *d*-(+)α-*p*-toluenesulphonoxypropionic acid reacted smoothly to give α-chloropropionic acid. The rotations of the α-chloro-acids obtained under the various experimental conditions employed are in Table I.

TABLE I.

Rotatory power of α-*p*-toluenesulphonoxypropionic acid used. $[\alpha]_{5461}$ in methyl alcohol (*c*, 5).*	Form in which the sulphonate was present.	Reaction medium.	Proportion of lithium chloride, mols.	Rotatory power of α-chloropropionic acid † produced, α_{5461} (*l*, 1).	Result.
+ 57·0°	Acid	Dry acetone (40 c.c.), 1 c.c. water	1·2	− 15·82°	Inversion
− 24·3	,,	Moist acetone (50 c.c.)	1·2	+ 7·55	,,
− 24·3	,,	Acetone–water (20 c.c., 1 : 1)	3·0	+ 7·45	,,
+ 25·0	,,	Water (20 c.c.)	1·2	− 4·31	,,
+ 25·0	,,	*N*/10-HCl (20 c.c.)	1·2	− 4·65	,,
+ 25·0	K salt	Moist acetone (20 c.c.)	1·2	+ 9·55	No inversion
+ 57·0	,,	Moist acetone (20 c.c.)	1·2	+ 16·78	,,
+ 25·0	NH_4 salt	Moist acetone (20 c.c.)	1·2	+ 7·12	,,
− 20·1	Ba salt	Moist acetone (40 c.c.)	1·2	− 6·19	,,
+ 25·0	Aniline salt	Moist acetone	1·2	+ 4·43	,,

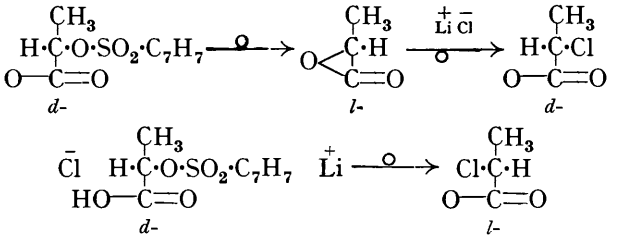
* For the optically pure acid, $[\alpha]^{25°}_{5461}$ 57·8° (Kenyon, Phillips, and Turley, *loc. cit.*).

† Only two rotations for α-chloropropionic acid in the homogeneous state appear to be recorded in the literature: α_{5893} − 2·36° (*l*, 1) (Frankland and Garner, J., 1914, **105**, 1101; acid obtained by the hydrolysis of α-chloropropionyl chloride); α_{5893} + 2·15° (*l*, 1) [Levene and Haller, *J. Biol. Chem.*, 1929, **81**, 707; acid obtained by the oxidation of (−)αγ-dimethylallyl chloride].

From the experiments of Kenyon, Phillips, and Turley (*loc. cit.*), and subsequent unpublished work, it can be concluded that ethyl (+)α-chloropropionate has the same configuration as ethyl (+)lactate. Since (+)α-chloropropionic acid gives ethyl (+)α-chloropropionate on esterification, it must be configuratively similar to ethyl (+)lactate. Hence *d*-(+)α-*p*-toluenesulphonoxypropionic acid obtained by the hydrolysis of ethyl *d*-(+)α-*p*-toluenesulphonoxypropionate [prepared from ethyl *d*-(+)lactate by methods unlikely to lead to configurative change; Kenyon, Phillips, and Turley, *loc. cit.*] has the same configuration as (+)α-chloropropionic acid. It is thus possible to determine, as recorded in Table I, which of the α-chloropropionic acids were produced with inversion. The conclusion reached is that the *d*-(+)α-*p*-toluenesulphonoxypropionic acid reacts with lithium chloride with inversion, but its salts give configuratively similar acids.

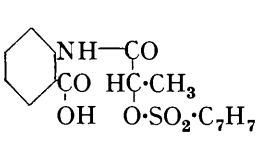
Although the salts of *d*-(+)α-*p*-toluenesulphonoxypropionic acid yield *d*-(+)α-chloropropionic acids, it is probable that inversion reactions occur during their formation. As indicated in the scheme on p. 305, the ionised carboxyl groups of these salts compete successfully with the chlorine anions, and give rise to a lactone with inversion of configuration. This lactone in turn reacts with lithium chloride with inversion so that the resulting α-chloropropionic acid is the product of two consecutive inversion reactions and is therefore configuratively similar to the original salt. On the other hand, the non-ionised carboxyl group of the acid does not compete with the entering chlorine anions, which react in the

usual manner with the *d*-acid and replace the α-*p*-toluenesulphonoxy-group with inversion. A further example of a double inversion reaction, probably involving the intermediate

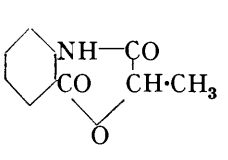


formation of the lactone, is afforded by the interaction of the ammonium salt of the *d*-acid with potassium acetate. This gave *d*-(+)α-acetoxypropionic acid in marked contrast to the *l*-(−)α-acetoxy-derivatives obtained from the neutral *d*-(+)α-*p*-toluenesulphonoxypropionamides. Attempts to establish the formation of lactone by replacement of the *p*-toluenesulphonoxy-group of the ammonium salt of the acid in two stages, (*a*) eliminating ammonium *p*-toluenesulphonate by heating a dry chloroform solution of the salt, (*b*) treating the filtered chloroform solution supposed to contain the lactone with lithium chloride, did not give a conclusive result, since the amount of ammonium *p*-toluenesulphonate isolated was never equal to the calculated amount possible and the quantity of α-chloropropionic acid produced was always very small.

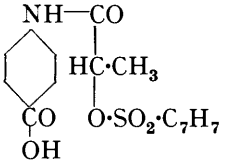
More conclusive evidence of the interference by carboxyl groups in substitution reactions was obtained, however, by a study of the reactions of *d*-(+)α-*p*-toluenesulphonoxy-*N*-*o*-carboxyphenylpropionamide (I) and also those of its *p*-isomeride (III).



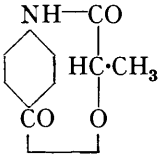
(I.)



(II.)



(III.)



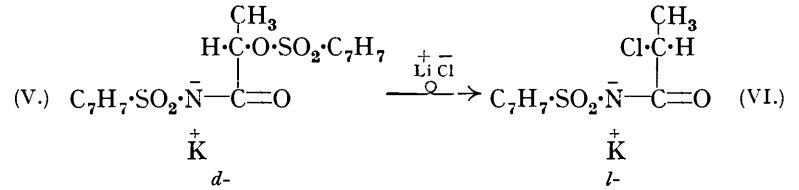
(IV.)

When (I) reacted with lithium chloride in ethyl-alcoholic solution, *l*-(−)α-chloro-*N*-*o*-carboxyphenylpropionamide was produced with inversion, as was shown by preparing the corresponding *d*-(+)amide from *d*-(+)α-chloropropionyl chloride and anthranilic acid. When, however, the sodium salt of (I) reacted with lithium chloride, under the same experimental conditions, the lactone of α-hydroxy-*N*-*o*-carboxyphenylpropionamide (II) was the sole product. This lactone was also prepared by warming a solution of the amide (I) in dilute aqueous sodium carbonate. Its rotatory power is very high, an optically impure specimen having $[\alpha]_D$ − 449° in ethyl-alcoholic solution. (−)*cis*-Hydrocarbostyril-3 : 3′-spirone-6 : 6′-disulphonic acid (Leuchs, Conrad, and von Katinszky, *Ber.*, **1922**, **55**, 2131), a structurally similar compound, also possesses an unusually high rotatory power.

Like the *d*-(+)*o*-amide (I), the *p*-amide (III) and also its aniline salt reacted with lithium chloride in ethyl-alcoholic solution, *l*-(−)α-chloro-*N*-*p*-carboxyphenylpropionamide being produced with inversion. All attempts, however, to obtain this chloro-amide by the interaction of the sodium salt of (III) with lithium chloride failed. The only definite product isolated was a sulphur-free, white, amorphous substance, which gave analytical data in agreement with (IV). This substance was obtained also by heating an aqueous solution of the sodium salt of the amide (III) at 100° for some hours. In view of its insolubility in common solvents and its amorphous character, it appears probable that this substance is a linear condensation product.

Its formation is possibly the result of end-on association, favoured by the presence of

dipoles and followed by intermolecular inversion reactions, and illustrates how the course of a reaction can be determined by the molecular configuration of the reacting molecules. This reaction can be contrasted with the reaction of the *o*-isomeride (I), in which the molecular configuration favours lactone formation by intramolecular reaction. The reactions of *d*-(+)α-*p*-toluenesulphonoxy-*N*-*p*-toluenesulphonylpropionamide (V) and its sodium salt provide examples of the influence of the size of a potential entering anion on the course of a reaction.



Although the salts of this compound contain an ionised acidic group conveniently situated to favour intramolecular reaction, such reactions do not occur, probably because the *p*-toluenesulphonylimide group is too large to approach close enough to the α-carbon atom to enable it to replace the α-*p*-toluenesulphonoxy-group. Thus the *d*-*p*-toluenesulphonylamide and its potassium and lithium salts reacted with lithium chloride in alcoholic solution to give *l*-(−)α-chloro-*N*-*p*-toluenesulphonylpropionamide (VI) with inversion, as was proved by preparing the corresponding *d*-(+)amide by the interaction of *d*-(+)α-chloropropionyl chloride with sodium *p*-toluenesulphonamide.

As a possible example of the course of a reaction being determined by the molecular configuration of an external entering anion, the reaction between the salts of *p*-toluenesulphinic acid and alkyl halides can be quoted. Such reactions do not give rise to sulphinic esters, as might be expected, but to sulphones. The reason for this may be that the sulphur atom of the *p*-toluenesulphinate anion, being situated at the apex of a tetrahedron (Phillips, J., 1925, **127**, 2252), can approach more nearly to the carbon atom at the centre of the tetrahedron of which the halogen atom occupies the apex than can either of the anionic oxygen atoms.

When heated in ethyl-alcoholic solution, the potassium salt of (V) gave *d*-(+)α-ethoxy-*N*-*p*-toluenesulphonylpropionamide, the configuration of which was proved by preparing it from ethyl *d*-(+)α-ethoxypropionate. This reaction of the *p*-toluenesulphonylpropionamide is a further example of the tendency of sulphonic esters to undergo fission at the O–S linkage in the presence of alcohols and to give rise to ethyl *p*-toluenesulphonate, which ethylates the hydroxy-compound simultaneously produced (Phillips, J., 1923, **123**, 44).

Experimental.

Partial Resolution of α-p-*Toluenesulphonoxypropionic Acid.*—To an ice-cold solution of *dl*-α-*p*-toluenesulphonoxypropionic acid (15 g.) and quinine (20 g.) in acetone (25 c.c.), ethyl acetate (75 c.c.) was added, and the mixture cooled in ice. The quinine salt (18 g.) obtained proved too unstable to be recrystallised; when decomposed with dilute sulphuric acid, it gave (+)α-*p*-toluenesulphonoxypropionic acid, $[\alpha]_{5461}$ + 27·2° (*l*, 2; *c*, 5·00) in methyl alcohol. The filtrate, after decomposition, yielded the (−)acid with approximately the same rotatory power. The rotatory power of the *d* + *dl*-acid increases slowly when it is recrystallised from benzene and light petroleum, but the optically pure acid is more readily obtained from *d*-lactic acid by Kenyon, Phillips, and Turley's method (*loc. cit.*).

d-(+)α-p-*Toluenesulphonoxypropionyl Chloride.*—*d*-(+)α-*p*-Toluenesulphonoxypropionic acid (15 g., $[\alpha]_{5461}$ + 48·5° in methyl alcohol) and thionyl chloride (20 c.c.) were heated together for 3 hours, and the excess of reagent removed at 100° under diminished pressure. The residual *d*-(+)α-p-*toluenesulphonoxypropionyl chloride*, b. p. 140—145° < 0·1 mm., set to a mass of phenol-like crystals (13·5 g.), m. p. 53°, with $[\alpha]_{5461}$ + 3·69° (*l*, 2; *c*, 4·607) in benzene solution (For complete hydrolysis, 0·3082 g. required 0·1400 g. of sodium hydroxide. Calc., 0·1411 g.).

d-(+)α-*Chloropropionyl Chloride from* l-(−)α-p-*Toluenesulphonoxypropionyl Chloride.*—*l*-(−)α-*p*-Toluenesulphonoxypropionyl chloride {10 g., $[\alpha]_{5461}$ − 42·4°, supercooled, from (−)acid, $[\alpha]_{5461}$ − 24·3° in methyl alcohol} and lithium chloride (3 g., 1·6 mols.) in dry acetone (30 c.c.)

were heated under reflux for 5 hours. The (+)α-chloropropionyl chloride produced was converted into ethyl (+)α-chloropropionate by the addition of ethyl alcohol (5 c.c.) and a little potassium carbonate. When isolated in the usual manner, it (0·75 g.) had b. p. 135—137°, $\alpha_{5461}^{18°}$ + 1·17° (*l*, 0·25).

d-(+)α-*Acetoxypropionamide from* l-(−)α-p-*Toluenesulphonoxypropionamide.*—A solution of *l*-(−)α-*p*-toluenesulphonoxypropionamide (10 g., $[\alpha]_{5461}$ − 37·8° in ethyl alcohol *) and fused potassium acetate (4·5 g.) in ethyl alcohol (25 c.c.) was heated under reflux for 1·5 hours and then evaporated to dryness. The residue was mixed with acetone, and the filtered solution dried with sodium sulphate. The resulting d-(+)α-*acetoxypropionamide* (3 g.), after three distillations, b. p. 128—131° < 0·1 mm., had constancy of rotatory power, $\alpha_{5461}^{18°}$ + 4·26° (*l*, 0·25), $n_D^{20°}$ 1·4565 (supercooled), m. p. 59—60° (needles) (Found : N, 10·9. $C_5H_9O_3N$ requires N, 10·7%). It is very soluble in water but only sparingly in ether.

l-(−)α-*Acetoxypropionamide from Ethyl* l-(−)*Lactate.*—Ethyl *l*-(−)lactate † (20 g.; α_{5461} − 10·66°, *l* 1) was saponified with sodium hydroxide (8 g.) in the minimum amount of water and the syrupy sodium *l*-lactate obtained on evaporation was mixed with a slight excess of cold hydrochloric acid. The product was mixed with acetone (50 c.c.) and *iso*propyl ether (50 c.c.) and sufficient sodium sulphate to remove the water. The dry *l*-lactic acid, after removal of the solvents, was mixed with acetyl chloride (25 g.), and the product fractionated under reduced pressure; the *l*-(−)α-acetoxypropionic acid (17 g.) had b. p. 135—136°/24 mm. and $\alpha_{5461}^{18°}$ − 47·8° (*l*, 1). This acid (17 g.), mixed with thionyl chloride, yielded *l*-α-acetoxypropionyl chloride (18 g.), b. p. 78°/22 mm. A portion (5 g.) in dry methylene chloride (30 c.c.) was treated with dry ammonia, a large excess being avoided. Filtration and evaporation yielded l-(−)α-*acetoxypropionamide* (3 g.), b. p. 104—105° < 0·1 mm., m. p. 59—60° alone and when mixed with the amide prepared as described above, α_{5461} − 17·7° (*l*, 1 in supercooled state) (Found : N, 10·7%).

l-(+)α-*Benzoyloxypropionamide from* d-(+)α-p-*Toluenesulphonoxypropionamide.*—*d*-(+)α-*p*-Toluenesulphonoxypropionamide (5 g., $[\alpha]_{5461}$ + 37·4° in ethyl alcohol) was heated at 100° for 4 hours with potassium benzoate (4 g.) and water (20 c.c.) : on cooling, d-(+)α-*benzoyloxypropionamide* (3·5 g.) separated in short needles, m. p. 118—125°. After crystallisation from methyl alcohol and *iso*propyl ether, it was obtained in tablets (1·7 g.), m. p. 127—128°, $[\alpha]_{5461}$ + 66·6°, $[\alpha]_{5790}$ + 56·8° (*l*, 2; *c*, 4·74) in ethyl alcohol (Found : N, 7·4. $C_{10}H_{11}O_3N$ requires N, 7·3%).

l-(+)α-*Benzoyloxypropionamide from Ethyl* l-(−)*Lactate.*—The lactate (15 g.; α_{5461} − 10·66°, *l* 1) was saturated with ammonia at 0° and left over-night at room temperature in a closed bottle. After removal of unchanged ester by distillation under diminished pressure, *l*-lactamide (6 g.), m. p. 72°, was obtained. This was mixed with pyridine (10 g.) and freshly distilled benzoyl chloride (10 g.) : after addition of dilute hydrochloric acid the l-(+)α-*benzoyloxypropionamide* was extracted with chloroform and crystallised from ethyl alcohol. It had m. p. 125—126°, and $[\alpha]_{5461}$ + 61·8°, $[\alpha]_{5790}$ + 53·7° (*l*, 2; *c*, 5·359) in ethyl alcohol (Found : N, 7·1%).

l-(−)α-p-*Toluenesulphonoxypropionanilide.*—Aniline (10 c.c.) was triturated with *l*-(−)α-*p*-toluenesulphonoxypropionyl chloride (3 g. from optically pure acid; Kenyon, Phillips, and Turley, *loc. cit.*) in dry ether. The anilide (4 g.) separated from aqueous ethyl alcohol in oblong plates, m. p. 132°, $[\alpha]_{5461}$ − 104·2°, $[\alpha]_{5790}$ − 91·5° (*l*, 2; *c*, 1·733) in ethyl alcohol.

d-(+)α-*Acetoxypropionanilide from* l-(−)α-p-*Toluenesulphonoxypropionanilide.*—The anilide (4 g., $[\alpha]_{5461}$ − 41° in ethyl alcohol) was heated with an alcoholic solution of potassium acetate (1·4 mols.) for 1 hour. d-(+)α-*Acetoxypropionanilide* was obtained by evaporation of the solvents and trituration of the dry residue with cold water. When either the proportion of potassium acetate or the period of heating was increased, lactanilide was produced. The crude acetate, m. p. 104°, $[\alpha]_{5461}$ + 5·37° (in ethyl alcohol), when crystallised (charcoal) from ethyl alcohol gave the optically inactive acetate, m. p. 124°; from the filtrate, the (+)acetate, $[\alpha]_{5461}$ + 12·7° in ethyl alcohol (*l*, 2; *c*, 2·200) was obtained (Found : N, 6·9. $C_{11}H_{13}O_3N$ requires N, 6·8%).

l-(−)α-*Acetoxypropionanilide* (Found : N, 6·9%), m. p. 121°, $[\alpha]_{5461}$ − 12·2° (*l*, 2; *c*, 1·026) in ethyl alcohol, was obtained as the more soluble fraction when the crude anilide ($[\alpha]_{5461}$ − 2·38°) from the interaction of aniline (7 c.c.) and (−)acetoxypropionyl chloride [3 g., from ethyl (−)lactate, α_{5461} − 6·76°, *l* 1] was recrystallised from ethyl alcohol.

* Kenyon, Phillips, and Turley (*loc. cit.*) give $[\alpha]_{5461}^{25°}$ + 40·4° for the optically pure *d*-amide in ethyl alcohol at the same concentration (*c*, 5).

† By calculation from data given by Wood, Such, and Scarf (J., 1923, **123**, 600), the rotation of optically pure ethyl lactate is $\alpha_{5893}^{18·9°}$ 11·65°, $\alpha_{5461}^{20°}$ 13·3° (*l*, 1).

d-(−)α-*Benzoyloxypropionanilide from* l-(+)α-p-*Toluenesulphonoxypropionanilide*.—The anilide (2·5 g., $[\alpha]_{5461}$ − 41° in ethyl alcohol), anhydrous potassium benzoate (1·5 g.), and absolute alcohol (20 c.c.) were heated under reflux for 3·5 hours. The *d*-(−)α-benzoyloxypropionanilide, isolated in the usual manner, had m. p. 160°, $[\alpha]_{5461}$ − 21·2°, and after recrystallisation from ethyl alcohol m. p. 160°, $[\alpha]_{5461}$ − 12·0°, (*l* 2; *c*, 0·7735) in ethyl alcohol.

l-(+)α-*Benzoyloxypropionanilide from Ethyl* l-(−)*Lactate*.—Dry *l*-lactic acid (20 g., from ethyl *l*-lactate, α_{5461} − 10·66°, *l* 1) was gently warmed with benzoyl chloride (25 g.) until the evolution of hydrogen chloride ceased, and the crude product was extracted with *iso*propyl ether. From the washed and dried extract, a mixture of α-benzoyloxypropionic and benzoic acids was isolated, which was warmed with thionyl chloride, the bulk of benzoyl chloride removed at 15 mm., and the residue distilled at low pressure. l-(+)α-*Benzoyloxypropionyl chloride* (5 g.) was obtained as a mobile liquid with a choking odour: b. p. 98° < 0·1 mm., $n_D^{20°}$ 1·5232, $[\alpha]_{5790}$ + 43·7°, $[\alpha]_{5461}$ + 51·3° (*l*, 1) (0·3190 g. required 0·1784 g. of sodium hydroxide for complete hydrolysis. Calc., 0·1806 g.). This chloride (2 g.) and aniline (3 g.) gave *l*-(+)α-benzoyloxypropionanilide, m. p. 160° (mixed with the anilide prepared from the sulphonate, m. p. 159—160°), $[\alpha]_{5461}$ + 15·0° (*l*, 2; *c*, 1·025) in ethyl alcohol.

l-(−)α-p-*Toluenesulphonoxypropiono*-β-*naphthalide*.—An ethereal solution of β-naphthylamine (in excess) was added to *l*-(−)α-*p*-toluenesulphonoxypropionyl chloride (2·8 g., from the optically pure acid; Kenyon, Phillips, and Turley, *loc. cit.*), and the solvent allowed to evaporate. After trituration with dilute hydrochloric acid the residue (6·1 g.) separated from ethyl alcohol in needles, m. p. 128° (Found: N, 3·6. $C_{20}H_{19}O_4NS$ requires N, 3·8%), $[\alpha]_{5780}$ − 108·5°, $[\alpha]_{5461}$ − 123·8° (*l*, 2; *c*, 1·023) in ethyl alcohol.

dl-α-p-*Toluenesulphonoxy*-N-p-*Toluenesulphonylpropionamide*.—*dl*-α-*p*-Toluenesulphonoxypropionyl chloride (35 g.) in ether (200 c.c.) was mixed with dry sodium *p*-toluenesulphonamide (150 g.; > 2 mols.). Heat was evolved, and after occasional shaking during 1 hour the ether was allowed to evaporate completely and the residue mixed with dilute hydrochloric acid; the dough-like insoluble product was washed with water and mixed with ice-cold potassium carbonate solution. *p*-Toluenesulphonamide was dissolved from the resulting crystalline precipitate by means of acetone (350 c.c.) and the insoluble potassio-α-*p*-toluenesulphonoxy-*N*-*p*-toluenesulphonylpropionamide with hydrochloric acid yielded dl-α-p-*toluenesulphonoxy*-N-p-*toluenesulphonylpropionamide*, which formed granular crystals, m. p. 137°, from benzene and light petroleum (Found: N, 3·65. $C_{17}H_{19}O_6NS_2$ requires N, 3·5%). Titration with 0·1*N*-sodium hydroxide and phenolphthalein gave equiv., 390. Calc., 396). An aqueous solution of the ammonium salt of this compound, mixed with potassium chloride solution, yielded the potassio-derivative as crystalline needles.

l-(−)α-p-*Toluenesulphonoxy*-N-p-*toluenesulphonylpropionamide*.—(−)α-*p*-Toluenesulphonoxypropionyl chloride {50 g., from (−)acid with $[\alpha]_{5461}$ − 34° in methyl alcohol}, was treated with sodium *p*-toluenesulphonamide as in the preceding experiment. The dough-like product obtained by the addition of hydrochloric acid was thoroughly washed with water, allowed to dry, and dissolved in chloroform (150 c.c.), in which *p*-toluenesulphonamide is but sparingly soluble. The syrup obtained after evaporation of the chloroform was dissolved in hot ethyl alcohol (360 c.c.) containing potassium carbonate (14 g.); *potassium* α-p-*toluenesulphonoxy*-N-p-*toluenesulphonylpropionamide* then crystallised. This was washed with a small amount of water to remove potassium carbonate, and the residue (57 g.) added to warm dry acetone (300 c.c.), in which the potassium salt of the *dl*-amide is almost insoluble. This (18 g.) was removed and the acetone filtrate was concentrated to 100 c.c., mixed with an equal volume of ethyl alcohol, and allowed to crystallise spontaneously. Long needles of the potassium salt of the *l*-amide (22 g.) were obtained, m. p. 160° (decomp.), and $[\alpha]_{5461}$ − 79·4° (*l*, 2; *c*, 1·306) in acetone (Found: N, 3·3. $C_{17}H_{18}O_6NS_2K$ requires N, 3·2%). On decomposition with dilute hydrochloric acid and extraction with methylene chloride the *l*-amide was obtained as a vitreous mass which would not crystallise.

l-(−)α-*Ethoxy*-N-p-*toluenesulphonylpropionamide from Potassium* l-α-p-*Toluenesulphonoxy*-N-p-*toluenesulphonylpropionamide*.—The *l*-potassium salt (5 g., $[\alpha]_{5893}$ −79·4° in acetone) in absolute alcohol (50 c.c.) was heated under reflux for 11 hours, the solvent removed, and the residue mixed with dilute hydrochloric acid. The resulting (−)α-*ethoxy*-N-p-*toluenesulphonylpropionamide* ($[\alpha]_D$ − 12·64°) separated from benzene and light petroleum in rectangular plates, m. p. 80—81°, $[\alpha]_{5893}$ − 10·0° (*l*, 2; *c*, 0·9985) in ethyl alcohol (Found: C, 53·9; H, 6·25; N, 5·2; equiv., 275. $C_{12}H_{17}O_4NS$ requires C, 53·2; H, 6·3; N, 5·2%; equiv., 271). The corresponding ethoxy-derivative prepared from optically inactive materials also had m. p. 80—81°.

l-(−)α-*Ethoxy*-N-p-*toluenesulphonylpropionamide from Ethyl* l-(−)*Lactate*.—Ethyl *l*-lactate (17 g.; $[\alpha]_{5893}$ − 8·7°, *l* 1), ethyl iodide (40 g.), and dry silver oxide (28 g.; 1·6 mols.) were heated together for 2 hours and the resulting ethyl *l*-α-ethoxypropionate (15 g.) was saponified with sodium hydroxide. The *l*-α-ethoxypropionic acid (12 g.), b. p. 104—105°/25 mm., obtained was warmed with thionyl chloride, and the *l*-α-ethoxypropionyl chloride redistilled twice, b. p. 40—49°/20 mm. This (5 g.) was dissolved in ether (30 c.c.) and mixed with sodium-*p*-toluenesulphonamide (12 g.). The *l*-(−)α-ethoxy-*N*-*p*-toluenesulphonylpropionamide (3 g.) thus prepared had m. p. 65—70°, $[\alpha]_{5893}$ − 21·4°. After crystallisation from benzene and light petroleum it had m. p. 79—80° (80—81° when mixed with the compound prepared by the action of ethyl alcohol on potassium *l*-α-*p*-toluenesulphonoxy-*p*-toluenesulphonylpropionamide) and $[\alpha]_{5893}$ − 21·0° (*l*, 2; *c*, 3·25) in ethyl alcohol.

d-(+)α-*Chloro*-N-p-*toluenesulphonylpropionamide from* l-(−)α-p-*Toluenesulphonoxy*-N-p-*toluenesulphonylpropionamide*.—Optically pure *l*-(−)α-*p*-toluenesulphonoxy-*N*-*p*-toluenesulphonylpropionamide (7 g.), lithium chloride (2 g.), and alcohol (50 c.c.) were heated under reflux for 3 hours. The resulting *d*-(+)α-chloro-*N*-*p*-toluenesulphonylpropionamide had m. p. 109° and $[\alpha]_{5461}$ + 17·7° : it separated from benzene and light petroleum in hairy crystals, m. p. 118°, $[\alpha]_{5461}$ + 29·7° (*l*, 2; *c*, 2·236) in ethyl alcohol. Further crystallisation did not alter appreciably either the m. p. or the rotatory power.

The lithium derivative of optically pure *l*-α-*p*-toluenesulphonoxy-*N*-*p*-toluenesulphonylpropionamide on similar treatment gave α-chloro-*N*-*p*-toluenesulphonylpropionamide having m. p. 118°, $[\alpha]_D$ + 23·2°, $[\alpha]_{5461}$ + 28·2° (*l*, 2; *c*, 4·1885) in ethyl alcohol.

d-(+)α-*Chloro*-N-p-*toluenesulphonylpropionamide from Ethyl* d-(+)α-*Chloropropionate*.—Ethyl *d*-(+)α-chloropropionate, b. p. 139—144°, α_{5893} + 7·68° (*l*, 1), prepared from ethyl *l*-lactate (50 g.; α_{5461} − 6·5°, *l* 1), pyridine (40 g.), and thionyl chloride (55 g.), was saponified with cold sodium hydroxide solution, and the resulting *d*-α-chloropropionic acid converted by means of thionyl chloride into *d*-α-chloropropionyl chloride * (24 g.), b. p. 110—120°, α_{5893} + 0·8°, which (15 g.) in ethereal solution with sodium *p*-toluenesulphonamide (2 mols.) gave *d*-(+)α-chloro-*N*-*p*-toluenesulphonylpropionamide (45 g.), m. p. 90—100°, $[\alpha]_{5461}$ + 6·5°. After crystallisation from benzene and light petroleum, it had $[\alpha]_{5461}$ + 13·7° (*l*, 2; *c*, 1·9275) in ethyl alcohol, m. p. 117—118°, either alone or mixed with any of the three specimens of this compound prepared as described above.

Ethyl l-(−)*Lactate from* l-(−)α-p-*Toluenesulphonoxypropionic Acid*.—l-(−)α-*p*-Toluenesulphonoxypropionic acid † (19 g., $[\alpha]_{5790}$ − 47·6° in methyl alcohol), fused potassium acetate (7·7 g.), and absolute alcohol (30 c.c.) were heated under reflux for 12 hours, the solvent removed, and the residue neutralised with sodium carbonate solution. The last traces of moisture having been removed, the mixture of salts was heated under reflux (8 hours) with ethyl *p*-toluenesulphonate (31·2 g.) and absolute alcohol (50 c.c.) to esterify the lactic acid produced. Dry ether (50 c.c.) was then added, the precipitated salts removed by filtration, the filtrate evaporated, and the ethyl lactate fractionally distilled, b. p. 46°/15 mm., until its rotatory power remained unchanged on redistillation. This reaction was carried out also in aqueous and in glacial acetic acid solutions, portions of the same specimen of (−)α-*p*-toluenesulphonoxypropionic acid being used; the rotatory powers (α_{5461}, *l* 1) of the three samples of ethyl *l*-lactate obtained were: from absolute alcohol, −10·07°; water, − 10·60°; glacial acetic acid, − 10·80°.

l-(−)α-*Acetoxypropionic Acid from* l-(−)α-p-*Toluenesulphonoxypropionate*.—*l*-(−)α-*p*-Toluenesulphonoxypropionic acid (10 g., $[\alpha]_{5893}$ − 34° in methyl alcohol) was dissolved in the calculated volume of a standardised solution of ammonia in dry acetone. The resulting solution was heated with potassium acetate (4·2 g.) for 45 minutes and an acetone solution of hydrogen chloride was then added in slight excess (Congo-red), followed by anhydrous sodium sulphate. When distilled, the dry acetone solution gave *l*-(−)α-acetoxypropionic acid (2 c.c.), b. p. 136—137°/16 mm., α_{5461} − 26·2° (*l*, 1) (Found: equiv., 132. Calc., 132).

d-(+)α-*Chloropropionic Acid from* l-(−)α-p-*Toluenesulphonoxypropionic Acid*.—*l*-α-*p*-Toluenesulphonoxypropionic acid (10 g., $[\alpha]_{5461}$ − 24·3° in methyl alcohol), lithium chloride (2 g.), and moist acetone (50 c.c.) were heated under reflux for 2 hours, the solvent removed, and ether (50 c.c.) and anhydrous sodium sulphate added. The α-chloropropionic acid (2 g.) obtained was distilled under reduced pressure, b. p. 88°/17 mm., and subsequently at atmospheric pressure (180—181°) until constancy of rotatory power was reached. The purity of the final

* This chloride has previously been isolated by Frankland and Garner (*loc. cit.*) with $\alpha_{5893}^{18°}$ + 0·2° (*l*, 1).

† Kenyon, Phillips, and Turley (*loc. cit.*) give $[\alpha]_{5790}^{25°}$ + 48·7° for the optically pure acid in methyl alcohol at the same concentration (*c*, 5).

product was verified by titration with alkali. This reaction was repeated in a number of other solvents : the results are in Table I.

In the experiment in which 0·1*N*-hydrochloric acid was used as the reaction solvent, the calculated quantity of calcium carbonate necessary to neutralise the hydrochloric acid was added before the chloro-acid was isolated by dilution of the reaction mixture with *iso*propyl ether and addition of sufficient anhydrous sodium sulphate to combine with any water present.

l-(−)α-*Chloropropionic Acid from Salts of* l-(−)α-p-*Toluenesulphonoxypropionic Acid and Lithium Chloride.*—These reactions were carried out in acetone solutions to which in the first place the sulphonate (10 g.) was added, followed by the calculated amount of the appropriate base. After the addition of lithium chloride (1·2 mols.) the solution was heated under reflux for about 2 hours. A very slight excess of concentrated hydrochloric acid, mixed with acetone, and then *iso*propyl ether and anhydrous sodium sulphate were added to the reaction mixtures and the α-chloropropionic acid produced was isolated by distillation, the purity of each specimen being checked by determination of its equivalent. The rotatory powers of the α-chloro-acids obtained are in Table I.

l-(−)α-p-*Toluenesulphonoxy*-N-o-*carboxyphenylpropionamide.*—*l*-α-*p*-Toluenesulphonoxypropionyl chloride {20 g., from (−)acid, $[\alpha]_{5461}$ − 40·2° in methyl alcohol} in dry ether (70 c.c.) was triturated with anthranilic acid (25 g.); the resulting l-α-p-*toluenesulphonoxy*-N-o-*carboxyphenylpropionamide* (30 g.) separated from benzene–light petroleum in oblong plates or rods, m. p. 131°, $[\alpha]_{5893}$ − 102·4° (*l*, 2; *c*, 1·660) in ethyl alcohol. Solutions of this (−)amide in organic solvents, notably benzene, showed a violet fluorescence. The *dl*-amide forms hexagonal plates, m. p. 150—151° (Found : equiv., 360. $C_{17}H_{17}O_6NS$ requires equiv., 363).

d-(+)α-*Chloro*-N-o-*carboxyphenylpropionamide from* l-(−)p-*Toluenesulphonoxy*-N-o-*carboxyphenylpropionamide.*—The (−)amide (5 g.), prepared as described above, lithium chloride (1 g.), and alcohol (50 c.c.) were heated under reflux for 8 hours; the resulting α-chloro-*N*-*o*-carboxyphenylpropionamide, m. p. 146—148°, had $[\alpha]_{5893}$ + 3·5° in ethyl alcohol and was completely soluble in dilute sodium carbonate solution. It separated from benzene and light petroleum in flat plates, m. p. 148°, $[\alpha]_{5893}$ + 3·34° (*l*, 2; *c*, 5·094) in chloroform.

Lactone of α-*Hydroxy*-N-o-*carboxyphenylpropionamide from the Sodium Salt of* l-α-p-*Toluenesulphonoxy*-N-o-*carboxyphenylpropionamide.*—The (−)amide (2·5 g.), prepared as described above, was neutralised in alcohol (20 c.c.) with sodium ethoxide, lithium chloride (1 g.) added, and the clear solution heated under reflux for 3·5 hours. No acidic substance could be isolated from the resulting, faintly alkaline solution; the chief product was a neutral compound (1·2 g.), which separated from alcohol in colourless needles, m. p. 236—238°, $[\alpha]_{5893}$ − 449° (*l*, 2; *c*, 0·9720) in ethyl alcohol. It was insoluble in sodium carbonate solution, but dissolved slowly in hot sodium hydroxide solution; it could be sublimed near its m. p. It was identified as the *lactone* of *α-hydroxy*-N-o-*carboxyphenylpropionamide* (Found : C, 62·9; H, 4·7. $C_{10}H_9O_3N$ requires C, 62·9; H, 4·7%). The lactone was prepared also by warming a solution of the amide in dilute aqueous sodium carbonate : optically active amide gave a (−)lactone, m. p. 237°, and the *dl*-amide a lactone, m. p. 186°.

d-(+)α-*Chloro*-N-o-*carboxyphenylpropionamide from* d-(+)α-*Chloropropionyl Chloride.*—A dry ethereal solution of *d*-α-chloropropionyl chloride (α_{5893} + 0·8°; *l*, 1; preparation, see p. 307) was triturated with an excess of anthranilic acid. The *d*-α-chloro-*N*-*o*-carboxyphenylpropionamide produced separated from benzene and light petroleum in plates, $[\alpha]_{5893}$ + 1·5° (*l*, 2; *c*, 4·1315) in chloroform, m. p. 147—148° [alone or when mixed with the (+)α-chloro-amide prepared as described above].

l-(+)α-p-*Toluenesulphonoxy*-N-p-*carboxyphenylpropionamide.*—*l*-α-*p*-Toluenesulphonoxypropionyl chloride {20 g., from (−)acid, $[\alpha]_{5893}$ − 29·9° in methyl alcohol} was converted into the *N*-*p*-carboxyphenylpropionamide by interaction with *p*-aminobenzoic acid. After crystallisation from acetic acid, the product (34 g.) had m. p. 166—167°, $[\alpha]_{5893}$ − 51·3° (*l*, 2; *c*, 4·7205) in ethyl alcohol. The corresponding *dl*-compound formed plates, m. p. 171° (Found : equiv., 366. $C_{17}H_{17}O_6NS$ requires equiv., 363).

d-(+)α-*Chloro*-N-p-*carboxyphenylpropionamide from* l-(−)α-p-*Toluenesulphonoxy*-N-p-*carboxyphenylpropionamide.*—The *l*-sulphonate (5 g.), prepared as described above, lithium chloride (1 g.), and absolute alcohol (50 c.c.) were heated under reflux for 2 hours. The resulting *d*-(+)α-chloro-*N*-*p*-carboxyphenylpropionamide (2·8 g.) separated from alcohol in rectangular plates, m. p. 230—231°, $[\alpha]_{5893}$ + 35·2° (*l*, 2; *c*, 3·325) in ethyl alcohol.

The "Lactone" of α-*Hydroxy*-N-p-*carboxyphenylpropionamide.*—Sodium *l*-(−)α-*p*-toluenesulphonoxy-*N*-*p*-carboxyphenylpropionamide {3 g.; prepared from *l*-(−)α-*p*-toluenesulphonoxypropionic acid with $[\alpha]_{5790}$ − 29·9° in methyl alcohol} in water (20 c.c.) was heated on the steam-

bath for 4 hours. The "*lactone*" (1 g.) (Found : C, 59·8; H, 4·8; N, 7·2. $C_{10}H_9O_3N$ requires C, 62·8; H, 4·7; N, 7·3%) separated in an extremely fine state of division and was filtered off with difficulty. It decomposed between 270° and 290° and was insoluble in all the common solvents except pyridine, in which it had $[\alpha]_{5893}$ — 161° (*l*, 2; *c*, 0·301).

d-(+)α-*Chloro*-N-p-*carboxyphenylpropionamide from the Aniline Salt of* l-(—)α-p-*Toluenesulphonoxy*-N-p-*carboxyphenylpropionamide.*—*l*-(—)α-*p*-Toluenesulphonoxy-*N*-p-carboxyphenylpropionamide {2 g., $[\alpha]_{5893}$ — 51·3° in ethyl alcohol, prepared from *l*-(—)α-*p*-toluenesulphonoxypropionic acid with $[\alpha]_{5790}$ — 29·9° in methyl alcohol}, aniline (1·7 g.), absolute alcohol (20 c.c.), and lithium chloride (1 g.) were heated under reflux for 3 hours. The resulting *d*-(+)α-chloro-*N*-*p*-carboxyphenylpropionamide, crystallised from alcohol, had m. p. 230—233°, $[\alpha]_{5893}$ + 18·0° (*l*, 2; *c*, 4·1640) in ethyl alcohol.

d-(+)α-*Chloro*-N-p-*carboxyphenylpropionamide from* d-(+)α-*Chloropropionyl Chloride.*—*d*-α-Chloropropionyl chloride (2·5 g.; preparation, see p. 306), dissolved in dry ether, was triturated with *p*-aminobenzoic acid (7 g.). The resulting *d*-(+)α-chloro-*N*-*p*-carboxyphenylpropionamide after crystallisation from alcohol had $[\alpha]_{5893}$ + 19·7° (*l*, 2; *c*, 4·424) in ethyl alcohol and m. p. 232°, either alone or when mixed with the α-chloro-amide prepared by the interaction of lithium chloride with either *l*-(—)α-*p*-toluenesulphonoxy-*N*-*p*-carboxyphenylpropionamide or its aniline salt.

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