Stereochemical Studies. Part I. The Relative Configurations of (−)-Aminophenylacetic Acid (α-Phenylglycine) and (−)-Mandelic Acid.

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(−)-Aminophenylacetic acid (α-phenylglycine) has been converted by a series of reactions into (−)-1-phenyl-1-toluene-*p*-sulphonamidoethane, which was also obtained by the action of toluene-*p*-sulphonyl chloride on (−)-1-phenylethylamine. The (−)-amino-acid is thus configurationally related to (−)-1-phenylethylamine and must belong to the D_s-series of amino-acids.

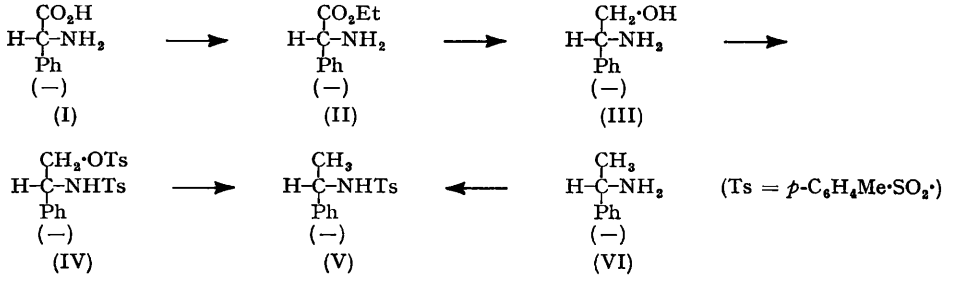
Identity of the D_s- and D_g-standards being accepted, it follows that the deamination of (−)-aminophenylacetic acid, with nitrous acid, to give L(+)-mandelic acid, is accompanied by inversion.

(−)-Aminophenylacetic acid (α-phenylglycine) was originally assigned to the D_s-configurational series by methods based on optical comparisons (Lutz, *Ber.*, 1932, **65**, 1609; Reihlen and Knöpfle, *Annalen*, 1936, **523**, 199; and Reihlen, Knöpfle, and Sapper, *ibid.*, 1938, **534**, 247). This has been confirmed chemically, by a somewhat circuitous sequence of reactions with incompletely resolved material, by Kuna, Ovakimian, and Levene (*J. Biol. Chem.*, 1941, **137**, 337).

Optical methods applied by Clough (*J.*, 1918, **113**, 534), Freudenberg and his co-workers, and others all pointed to configurational correspondence between (−)-mandelic acid and D(−)-lactic acid. Recently this has been proved chemically by Mislow (*J. Amer. Chem. Soc.*, 1951, **73**, 3954) who completed the chain of relations between the two hydroxy-acids. (−)-Mandelic acid, therefore, belongs to the D_g-series.

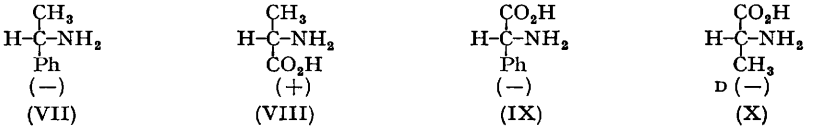
The identity of the D$_S$- and the D$_g$-(and L$_s$- and L$_g$-)standards for α-amino-acids and α-hydroxy-acids is supported by the kinetic studies of Brewster, Hughes, Ingold, and Rao (*Nature*, 1950, **166**, 178) and proved from *X*-ray evidence on the structure of L-threonine (Shoemaker, Donohue, Schomaker, and Corey, *J. Amer. Chem. Soc.*, 1950, **72**, 2328) and L-hydroxyproline (Zussman, *Acta Cryst.*, 1951, **4**, 72). It follows, therefore, that (−)-aminophenylacetic acid and (−)-mandelic acid are configurationally related and that both belong to the D-series. According to the kinetic studies of Brewster, Hiron, Hughes, Ingold, and Rao (*ibid.*, p. 179), however, the two acids of *opposite* sign are configurationally related, and deamination of the (−)-amino-acid with nitrous acid to give (+)-mandelic acid takes place with *retention* of configuration. As the relative configurations of the two acids have an important bearing on the stereochemical mechanism of pinacolic deaminations and dehydrations, we thought it desirable again to investigate, by chemical methods, the configurations of both acids. The work of Mislow (*loc. cit.*), however, anticipated our study of mandelic acid, so our investigation of (−)-aminophenylacetic acid only is reported.

We have converted (−)-aminophenylacetic acid into an amine of known configuration by a two-stage reduction using lithium aluminium hydride (see Karrer *et al.*, *Helv. Chim. Acta*, 1948, **31**, 1617; 1951, **34**, 2202; 1953, **36**, 122, for similar reductions in the aliphatic series). The conversions and the steric relations are shown in the annexed scheme.



Reduction of the (−)-ester (II) in ether with lithium aluminium hydride gave the (−)-amino-alcohol (III), $[\alpha]_D^{19}$ −25·5°. The (−)-sulphonic ester (IV), which is insoluble in ether, was reduced with lithium aluminium hydride in tetrahydrofuran, to give a quantitative yield of the (−)-toluene-*p*-sulphonamide (V), $[\alpha]_D^{19}$ −78·8°. The same compound was obtained by treating the pure (−)-amine (VI), $[\alpha]_D$ −40·1°, with toluene-*p*-sulphonyl chloride, then having $[\alpha]_D^{20}$ −79·3°. Hence (−)-aminophenylacetic acid (I) is configurationally related to (−)-1-phenylethylamine (VI) and the conversion of (I) into (V) was effected without significant racemisation.

Leithe (*Ber.*, 1931, **64**, 2827) has shown that (−)-1-phenylethylamine is configurationally related to L-alanine as (VII) and (VIII). Therefore, (−)-aminophenylacetic acid and



D-alanine are related as (IX) and (X). (−)-Aminophenylacetic acid and (−)-mandelic acid are, therefore, configurationally related, and deamination of the (−)-amino-acid to (+)-mandelic acid must lead to overall inversion of configuration.

Brewster, Hiron, Hughes, Ingold, and Rao (*loc. cit.*) state that deamination by the S_N1 mechanism proceeds with racemisation and "possibly with some excess of inversion, unless a configuration-holding group, such as the α-carboxylate ion group, is present, when configuration is retained." It is difficult to see how this rule applies to aminophenylacetic acid, for it has been shown by McKenzie and Clough (*J.*, 1909, 777) and by McKenzie and Wills (*J.*, 1925, 291) that the action of nitrous acid on (+)-aminophenylacetic acid and on its configurationally related (+)-ester follows the same steric course.

Experimental

2-Amino-2-phenylethanol.—Aminophenylacetic acid (Ingersoll and Adams, *J. Amer. Chem. Soc.*, 1922, **44**, 2933) was esterified (McKenzie and Wills, *loc. cit.*), and the ester (16 g.) in dry ether (250 c.c.) was added slowly to lithium aluminium hydride (9·7 g.) in dry ether (200 c.c.). The mixture was then refluxed on the water-bath for 3 hr. The excess of hydride was decomposed by adding water until the precipitated aluminium hydroxide coagulated in the water layer. The ether layer and extracts were dried ($MgSO_4$) and evaporated. The residual oil, which distilled at 144—147°/14 mm., solidified and had m. p. 47—49°. The amino-alcohol gave a hydrochloride, m. p. 139—140° (cf. Gabriel and Colman, *Ber.*, 1914, **47**, 1867, who give m. p. 137—138°) (Found: C, 70·0; H, 7·9. Calc. for $C_8H_{11}ON$: C, 70·1; H, 8·0%).

*2-Phenyl-2-toluene-*p*-sulphonamidoethyl Toluene-*p*-sulphonate.*—2-Amino-2-phenylethanol (5 g.) in pyridine (15 c.c.) was added to toluene-*p*-sulphonyl chloride (13·5 g.) in pyridine (25 c.c.), and the mixture heated on the water-bath for 30 min. and then left overnight at room temperature. The pyridine was removed under reduced pressure. The residual oil solidified. Treatment with Norit and recrystallisation from aqueous alcohol gave the *toluene-*p*-sulphonamido*-ester as colourless needles, m. p. 143—144° (12·5 g., 77%) (Found: C, 59·1; H, 5·2; N, 3·2. $C_{22}H_{23}O_5NS_2$ requires C, 59·3; H, 5·2; N, 3·1%).

*Reduction of 2-Phenyl-2-toluene-*p*-sulphonamidoethyl Toluene-*p*-sulphonate with Lithium Aluminium Hydride.*—The toluene-*p*-sulphonate (10 g.) in dry tetrahydrofuran (50 c.c.) was added gradually with stirring to lithium aluminium hydride (4·5 g.) in tetrahydrofuran (200 c.c.) The mixture was refluxed on the water-bath for 1 hr. Most of the solvent was distilled off, dry ether added, and the excess of hydride decomposed with water. The ether layer was dried ($MgSO_4$) and distilled. The residual oil, which solidified, was purified by precipitation from benzene with light petroleum (b. p. 60—80°). *1-Phenyl-1-toluene-*p*-sulphonamidoethane* crystallised from aqueous ethanol as colourless needles, m. p. 81—82° alone or mixed with the specimen described below (Found: C, 65·3; H, 6·0; N, 5·0; S, 11·7. $C_{15}H_{17}O_2NS$ requires C, 65·45; H, 6·2; N, 5·1; S, 11·6%).

*1-Phenyl-1-toluene-*p*-sulphonamidoethane.*—Toluene-*p*-sulphonyl chloride in pyridine was added to a slight excess of 1-phenylethylamine in pyridine. The mixture was kept at room temperature for 3 hr., then evaporated under reduced pressure, and an ether solution of the residue was washed several times with dilute hydrochloric acid. The compound was isolated in the usual way as needles, m. p. 81—82°, from aqueous ethanol.

(−)-*1-Phenyl-1-toluene-*p*-sulphonamidoethane.*—This *compound*, prepared as described above from (−)-1-phenylethylamine (*Org. Synth.*, 1937, **17**, 76), formed needles (from benzene–light petroleum or aqueous ethanol), m. p. 98—99°, $[\alpha]_D^{20}$ −79·3° (*c*, 2·004; *l*, 2; in C_6H_6) (Found: C, 65·3; H, 6·0; N, 5·0; S, 11·6%). The (+)-isomer, prepared in the same way from the (+)-amine, had m. p. 98—99°, $[\alpha]_D^{21}$ +79·6° (*c*, 2·003; *l*, 2; in C_6H_6).

(−)-*2-Amino-2-phenylethanol.*—(−)-Aminophenylacetic acid (Ingersoll and Adams, *loc. cit.*) was esterfied and the (−)-ester (15 g.) reduced in ether with lithium aluminium hydride (9 g.) as described for the racemic compound. The resulting (−)-*2-amino-2-phenylethanol* (8·25 g., 55%), however, was not distilled but, crystallised from benzene, had m. p. 75—76°, $[\alpha]_D^{19}$ −25·5° (*c*, 9·00; *l*, 2; in MeOH) [cf. Kuna, Ovakimian, and Levene, *loc. cit.*, who give $[\alpha]_D^{25}$ −15·0° (*c*, 9·06; *l*, 2; in MeOH)] (Found: C, 70·2; H, 7·9%). The (−)-amino-alcohol forms a hydrochloride, m. p. 168—169° (from ethanol–ether), $[\alpha]_D^{19}$ −25·5°, $[M]_D^{19}$ −44·3° (*c*, 2·00; *l*, 1) (cf. Reihlen, Knöpfle, and Sapper, *loc. cit.*, who resolved the racemic amino-alcohol with tartaric acid and obtained $[M]_D$ −39° to −40°).

(−)-*2-Phenyl-2-toluene-*p*-sulphonamidoethyl Toluene-*p*-sulphonate.*—The (−)-amino-alcohol (5 g.) was treated with toluene-*p*-sulphonyl chloride (13·5 g.) as already described. The resulting *compound* (12 g., 74%) crystallised from ethanol as needles, m. p. 171—172°, $[\alpha]_D^{19}$ −56·3 (*c*, 2·00; *l*, 2; in acetone) (Found: C, 59·2; H, 5·3; N, 3·1%).

This (−)-toluene-*p*-sulphonate (5 g.) was reduced in tetrahydrofuran, as described for the racemic compound, to (−)-1-phenyl-1-toluene-*p*-sulphonamidoethane (2·6 g., 84%), needles (from aqueous ethanol), m. p. and mixed m. p. 98—99°, $[\alpha]_D^{19}$ −78·8° (*c*, 2·00; *l*, 2; in C_6H_6) (Found: C, 65·4; H, 6·1; N, 4·9; S, 11·3%).

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