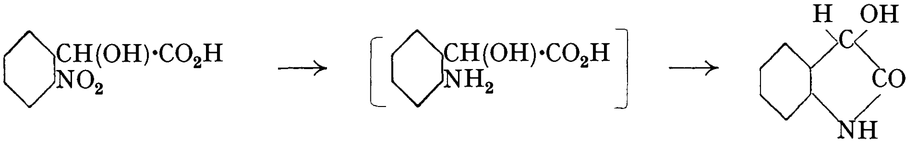
23. *Optical Activity in the Indole Group.*

By Alex. McKenzie and Peter A. Stewart.

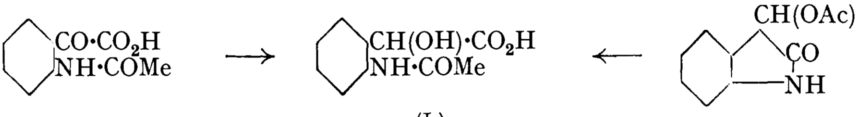
The primary objective of the present research was the isolation of the optically active dioxindoles. But, before it was possible to accomplish this successfully, some preliminary investigation of *r*-dioxindole and of certain compounds related to it was indispensable.

The conclusion was drawn by Heller (*Ber.*, 1904, **37**, 938) that *r*-*o*-aminomandelic acid is incapable of existence, transforming immediately into its lactam, dioxindole, thus :



We have now isolated r-o-*aminomandelic acid* by reducing the barium salt of *r*-*o*-nitromandelic acid with ferrous sulphate and baryta, the barium salt of the amino-acid being then converted into the sodium salt, and the latter decomposed by slightly less than the calculated amount of dilute sulphuric acid. The *r*-amino-acid exhibits the characteristics of a compound possessing an amino- and a carboxyl group, but it is unstable in the presence of mineral acid; thus, when its sodium salt (1 mol.) was decomposed by dilute sulphuric acid (1 mol.), the product was *r*-dioxindole.

The *r*-amino-acid gave a monoacetyl derivative, which was identical with the compound prepared according to Suida (*Ber.*, 1878, **11**, 584) by the reduction of the acetylisatinic acid derived from isatin :



(I.)

The acetyl group is thus attached to nitrogen. According to Suida the acetyl derivative (I) is identical with that formed by the action of baryta on monoacetyldioxindole, and since Heller and Lauth (*Ber.*, 1929, **62**, 343) have shown that the acetyl group in the latter is attached to oxygen, it seems that an interesting migration of the acetyl group had taken place by the action of baryta. When the sodium salt of the amino-acid was benzoylated, a monobenzoyl derivative, identical with that formed from *r*-dioxindole, was obtained.

The resolution of *r*-*o*-nitromandelic acid by means of brucine was easily carried out. The numerical values for the rotatory powers of the *antimerides* are very high, even when compared with the high values for the mandelic acids, and they show a marked decrease with elevation of temperature, a similar decrease having also been observed with the mandelic acids (Roger, J., 1932, 2168). The (+)*acetyl* derivative and the *ethyl* (+)ester were also highly optically active. When *r*-*o*-nitromandelic acid was heated with (—)menthol according to the method of Marckwald and McKenzie involving fractional esterification of the antimerides, the unesterified acid was dextrorotatory, whereas *r*-mandelic acid under similar experimental conditions gives a lævorotatory acid.

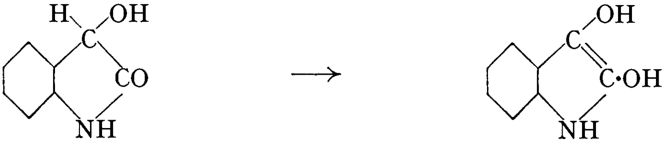
Our experience on the reduction of *r*-*o*-nitromandelic acid either with zinc and acetic acid or with tin and hydrochloric acid held out little hope that such methods, involving as they do the use of an acid medium, would be of service when applied for the preparation of the optically active dioxindoles.

(—)*o*-Nitromandelic acid was accordingly reduced by ferrous sulphate and baryta in the manner outlined for the *r*-isomeride. The sodium salt of the amino-acid was lævorotatory in water and gave the (—)*amino*-acid. A change of sign of rotation took place when the salt was decomposed by additional mineral acid, the product being (+)*dioxindole.* Under the conditions described in the experimental section the change required 29 hours at the ordinary temperature. By the similar procedure, (+)o-*aminomandelic acid* and (—)*dioxindole* were prepared.

The rotation of (—)*o*-aminomandelic acid in *N*-hydrochloric acid fell from $[\alpha]_{5461}$ — 151° to zero when the solution was kept at the ordinary temperature for 312 hours. Since isatide was then isolated, it was clear that the (—)*o*-amino-acid was first transformed into (+)dioxindole, which was oxidised to isatide. Heller (*loc. cit.*) mentions that *r*-dioxindole is transformed into isatide by hydrochloric acid, and we have observed that isatide is also formed from *r*-*o*-aminomandelic acid in the presence of hydrochloric acid.

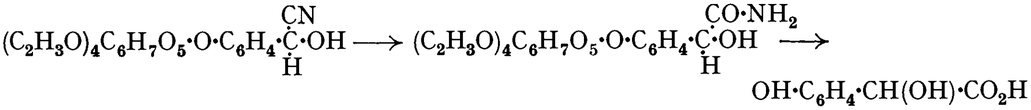
The optically active dioxindoles are prone both to decomposition and to racemisation, and with the exception of the antimeric *N*-hydroxydioxindoles we have not obtained any derivatives of them where the optical activity was retained. Thus, the action of phenylhydrazine on the (+)antimeride gave isatin-β-phenylhydrazone, whilst acetyl chloride gave *r*-*O*-acetyldioxindole, and benzoyl chloride gave *r*-dibenzoyldioxindole. Even a few drops of alcoholic potash (0·5*N*) added to an ethyl-alcoholic solution brought about almost at once the disappearance of rotatory power with the formation of isatide. With less alcoholic potash, however, a gradual fall of rotatory power was observed (see experimental section). The addition of further alkali caused the precipitation of a white solid, which was probably the potassium derivative of *r*-dioxindole. Pyridine also caused the complete racemisation of (+)dioxindole.

It seems likely enough that the fall in rotatory power observed with a trace of alcoholic potash might have been due to the migration of a hydrogen atom to the oxygen atom of the adjacent carbonyl group with the formation of enolic dioxindole, which contains no asymmetric carbon atom, thus :



An interesting point arose when a trace of alcoholic potash was added to an ethyl-alcoholic solution of *r*-dioxindole. It was impossible to recover the *r*-dioxindole, isatide being obtained instead, whereas *r*-dioxindole can be recovered from its ethyl-alcoholic solution in the absence of alcoholic potash. The deduction which we draw from these observations is that the trace of alcoholic potash acts catalytically to form enolic dioxindole (Baeyer's " Hydroisatin "), which then undergoes oxidation readily to isatide. Again, the dioxindoles melt indefinitely, since they undergo transformation into isatide on rise of temperature; it seems probable that here also enolic dioxindole is formed as an intermediate phase.

One of the early attempts to realise an asymmetric synthesis had helicin as its starting point (E. Fischer and Slimmer, *Sitzungber. K. Akad. Wiss. Berlin*, 1902, **28**, 597; *Ber.*, 1903, **36**, 2575). Hydrogen cyanide combined quantitatively with tetra-acetylhelicin to form a crystalline cyanohydrin which had all the appearance of uniformity and had thus apparently been formed by an addition which was entirely one-sided. But this is not an asymmetric synthesis in the sense of the term as used by Fischer, Marckwald, McKenzie, and others. This cyanohydrin was then converted into the amide, which was hydrolysed by dilute hydrochloric acid to give *o*-hydroxymandelic acid :

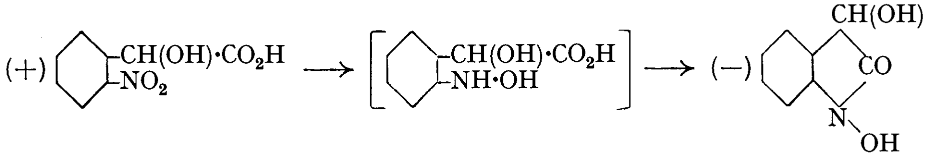


$$(C_2H_3O)_4C_6H_7O_5{\cdot}O{\cdot}C_6H_4{\cdot}\overset{CN}{\underset{H}{C}}{\cdot}OH \longrightarrow (C_2H_3O)_4C_6H_7O_5{\cdot}O{\cdot}C_6H_4{\cdot}\overset{CO{\cdot}NH_2}{\underset{H}{C}}{\cdot}OH \longrightarrow OH{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CO_2H$$

The rotatory power of the hydroxy-acid obtained in this manner was so small that Fischer and Slimmer did not claim to have effected an asymmetric synthesis. The highest value quoted for a product which was not analysed was $[\alpha]_D^{20^\circ}$ + 1·9° in ether, but unfortunately the observed angle of rotation is not recorded. It may justifiably be assumed, however, that the solution examined gave so small an angle of rotation that evidence for optical activity could not be accepted as definite.

In the light of these experiments the isolation of optically active *o*-hydroxymandelic acid from sodium (—)*o*-aminomandelate was of some interest. The value in ether was $[\alpha]_D^{15^\circ}$ — 53·8°.

The reduction of (+)*o*-nitromandelic acid by zinc dust and ammonium hydroxide was accompanied by a change of sign of rotation, the product being (—)*N*-hydroxydioxindole :



The antimeric (+)*N*-hydroxydioxindole was isolated in a similar manner.

EXPERIMENTAL.

The method outlined by Heller and Spielmeyer (*Ber.*, 1925, **58**, 834) for the preparation of *r*-*o*-nitromandelonitrile was found to be more satisfactory than those previously described (Heller, *Ber.*, 1904, **37**, 938; 1906, **39**, 2334; Reissert and Hessert, *Ber.*, 1924, **57**, 964). The following procedure is convenient for the preparation of *r*-*o*-nitromandelic acid.

o-Nitrobenzaldehyde (50 g.) was suspended in glacial acetic acid (100 g.) kept at 0°, and a solution of potassium cyanide (33 g.) in water (66 c.c.) was gradually added. After 4—5 hours, sufficient water was added to complete the separation of the crystals, which were removed and hydrolysed by concentrated hydrochloric acid. The *r*-*o*-nitromandelic acid obtained, crystallised from water, formed colourless prisms (48 g.), m. p. 137—138°.

Reduction of r-o-*Nitromandelic Acid.*—(a) *With zinc and acetic acid.* This reaction (Heller, *Ber.*, 1904, **37**, 938) was in our hands unsatisfactory; *e.g.*, only about 0·3 g. of pure *r*-dioxindole (prisms from water) was obtained from 5 g. of the acid. Our product was identical with a specimen obtained by the reduction of isatin with sodium hydrosulphite (Marschalk, *Ber.*, 1912, **45**, 582). In accordance with Heller's observations, *r*-dioxindole is readily oxidised in aqueous solution to form isatide. *r*-Dioxindole melts indefinitely at about 170° with preliminary softening; the molten mass readily absorbs oxygen, becoming solid and then giving the m. p. of isatide.

(b) *With tin and hydrochloric acid.* *r*-*o*-Nitromandelic acid (10 g.) was warmed with concentrated hydrochloric acid (60 c.c.) and granulated tin (20 g.); *r*-dioxindole hydrochloride (3 g.), m. p. 156° (decomp.), was isolated after removal of the tin as sulphide (Found : Cl, 18·7. Calc. for $C_8H_7O_2N,HCl$: Cl, 19·1%). When the hydrochloride was crystallised thrice from water, it was transformed into *r*-dioxindole.

(c) *With ferrous sulphate and barium hydroxide.* 300 C.c. of a warm aqueous solution of barium *r*-*o*-nitromandelate, prepared by neutralising 30 g. of the acid with barium hydroxide, were added to a warm solution of ferrous sulphate (275 g.) in water (255 c.c.). After the addition of a warm solution of barium hydroxide (330 g.) in water (1 l.), the mixture was stirred for 1 hour, boiled for ½ hour, and filtered hot. On cooling, plates of barium *r*-*o*-aminomandelate separated, and a further quantity of this salt was obtained by boiling the residue thrice with water, precipitating the excess of barium hydroxide as carbonate, and concentrating the liquors. The barium *r*-*o*-aminomandelate (22 g.) was converted into the sodium salt by boiling with the calculated quantity of sodium carbonate and then removing the barium carbonate. The aqueous solution of the sodium salt was decomposed at 40° by slightly less than the calculated quantity of dilute sulphuric acid; the amino-acid (11 g.) then separated.

r-o-*Aminomandelic acid* forms prisms, m. p. 144° (decomp.) (Found: C, 57·7; H, 5·5. $C_8H_9O_3N$ requires C, 57·5; H, 5·4%).

When the sodium salt was acidified at 40° by dilute sulphuric acid containing twice the amount necessary for decomposition, the needles which were deposited in 82% yield gave in ethyl-alcoholic solution a faint transient violet coloration on the addition of ammonia. When the needles were moistened with hot barium hydroxide, they assumed a violet coloration which was slowly evanescent. These colour reactions as well as the m. p. were identical with the behaviour of an authentic specimen of *r*-dioxindole.

When a solution of *r-o*-aminomandelic acid in an excess of dilute hydrochloric acid was evaporated under diminished pressure at the ordinary temperature, a solid, m. p. 243—246° (decomp.), separated, which in pyridine gave a violet coloration with barium hydroxide, and a ruby-red coloration on heating with ethyl alcohol–sodium carbonate. When shaken with concentrated sulphuric acid and benzene, it caused the sulphuric acid to assume a green coloration. This solid was isatide.

By acetylation in cold aqueous suspension with acetic anhydride, *r-o*-aminomandelic acid gave *r-o*-acetamidomandelic acid, crystallising from water in needles, m. p. 142—143° (Found: C, 57·6; H, 5·5. Calc. for $C_{10}H_{11}O_4N$: C, 57·4; H, 5·3%). It gave no depression in m. p. on admixture with an authentic specimen prepared by converting *N*-acetylisatin (Camps, *Arch. Pharm.*, 1899, **237**, 587) into acetylisatinic acid (Aeschlimann, J., 1926, 2907), and reducing the latter by sodium amalgam (Suida, *loc. cit.*).

r-o-*Benzamidomandelic acid*, prepared by benzoylating sodium *r-o*-aminomandelate by benzoyl chloride and caustic soda, crystallised from benzene–ethyl alcohol in needles, m. p. 146° (Found: C, 66·4; H, 5·0. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8%). It was also formed from *r*-dioxindole (2 g.) by boiling under reflux for 1 hour with 2*N*-caustic soda (25 c.c.), cooling, and then benzoylating with benzoyl chloride (6 g.). The main product was the benzoyl acid; another substance, m. p. 217°, formed in small quantity, was not further examined.

r-o-β-*Naphtholazomandelic acid*, prepared from sodium *r-o*-aminomandelate by diazotisation and coupling of the diazonium solution with β-naphthol, crystallised from glacial acetic acid in red needles, m. p. 205—206° (decomp.) (Found: C, 66·9; H, 4·4. $C_{18}H_{14}O_4N_2$ requires C, 67·1; H, 4·4%).

Reduction of r-o-*Nitroacetylmandelic Acid.*—*r-o*-Nitromandelic acid was acetylated by acetyl chloride to give r-o-*nitroacetylmandelic acid*, separating from chloroform–light petroleum (b. p. 60—80°) in colourless prisms, m. p. 102—103° (Found: C, 50·0; H, 3·8. $C_{10}H_9O_6N$ requires C, 50·2; H, 3·8%). Reduction with various reagents was unsuccessful, except with zinc dust and glacial acetic acid, which gave *O*-acetyldioxindole but unfortunately in very small yield. The reduction of (+)*o*-nitroacetylmandelic acid, m. p. 95—96° (p. 108), was not attempted.

r-o-*Nitrophenylmethoxyacetic Acid.*—An intimate mixture of *r-o*-nitromandelic acid (8·5 g.) and dry silver oxide (20 g.) was added gradually with cooling to methyl iodide (34·5 g.), and the reaction completed by heating for 1 hour on the water-bath. The oil (8·7 g.) isolated was saponified with a solution of potassium hydroxide (4·4 g.) in water (30 c.c.). r-o-*Nitrophenylmethoxyacetic acid* (dried under diminished pressure at 60°) crystallised from water in plates, m. p. 81—82°. Yield, 8 g. (Found: C, 51·0; H, 4·5. $C_9H_9O_5N$ requires C, 51·2; H, 4·3%).

Ethyl r-o-*Nitrobenzoylmandelate.*—Benzoyl chloride (18 c.c.) was added gradually to a solution of ethyl *r-o*-nitromandelate (10 g.) in pyridine (50 g.) kept at 0°. After addition of dilute hydrochloric acid the resulting ethyl *r-o*-nitrobenzoylmandelate separated from ethyl alcohol–light petroleum (b. p. 60—80°) as rectangular prisms (11·5 g.), m. p. 76—77° (Found: C, 62·0; H, 4·7. Calc. for $C_{17}H_{15}O_6N$: C, 62·0; H, 4·6%). Heller (*Ber.*, 1906, **39**, 2334) obtained this compound by a different method.

The reduction of ethyl *r-o*-nitrobenzoylmandelate with stannous chloride and hydrochloric acid gave *O*-benzoyldioxindole in 83% yield.

Resolution of r-o-*Nitromandelic Acid.*—100 G. of brucine (1 mol.) were added with stirring to a hot solution of 50 g. of the acid (1 mol.) in water (2 l.). After 16 hours, crystals (A, 68 g.) had separated, and from the filtrate crystals (B, 60 g.) were deposited after 36 hours longer. On crystallising A thrice from water, the homogeneous brucine (−)*o*-nitromandelate (46 g.) crystallised with $4H_2O$ as hexagonal plates (m. p. 91—92°), which after heating under diminished pressure at 80° had m. p. 137° (decomp.) and then gave in acetone ($l = 2$, $c = 2·4305$) $\alpha_{5461}^{20·5°}$ $-$ 16·63°, $[\alpha]_{5461}^{20·5°}$ $-$ 342°. The brucine was removed by precipitating the aqueous solution of this salt with ammonia, the filtrate being then acidified by hydrochloric acid. The resulting acid, obtained by extraction with ether, was crystallised once from chloroform, yielding 13 g. of (−)o-*nitromandelic acid* in colourless hexagonal plates, m. p. 100—101° (Found : C, 48·5; H, 3·7. $C_8H_7O_5N$ requires C, 48·7; H, 3·6%). Its rotatory power was determined in acetone (l = 2, c = 1·5785, t = 20°) :

λ	6708	6563	5893	5461	4861	4358
α	− 10·21°	− 10·89°	− 14·79°	− 18·74°	− 28·90°	− 48·35°
[α]	− 323°	− 345°	− 468°	− 594°	− 915°	−1532°

In acetone (l = 2, c = 1·8955), $\alpha^{20^\circ}_{5791}$ − 18·56°, $[\alpha]^{20^\circ}_{5791}$ − 490°.

The three successive filtrates from which A had been crystallised gave acids with $[\alpha]_{5791}$ − 268°, − 473°, and − 483° respectively in acetone (c = 2) after removal of the brucine.

Crystallisation of B thrice from water gave the homogeneous brucine (+)*o*-nitromandelate, needles (35 g.) which when dried in air contained $2H_2O$. When dried under diminished pressure at 80°, it had m. p. 137° (decomp.). In acetone (l = 2, c = 2·336), $\alpha^{20^\circ}_{5461}$ + 13·61°, $[\alpha]^{20^\circ}_{5461}$ + 291°.

(+)o-*Nitromandelic acid* from the brucine salt crystallised from chloroform in colourless hexagonal plates, m. p. 100—101° (Found : C, 48·9; H, 3·8. $C_8H_7O_5N$ requires C, 48·7; H, 3·6%). Yield, 10 g. The rotation in acetone was in agreement with that for its antimeride (l = 2, c = 1·896) : $\alpha^{20^\circ}_{5791}$ + 18·59°, $[\alpha]^{20^\circ}_{5461}$ + 490°. The rotatory power decreases with rise of temperature : in acetone (l = 2, c = 1·8965),

λ.	$\alpha^{1\cdot5^\circ}$.	$[\alpha]^{1\cdot5^\circ}$.	α^{20°.	$[\alpha]^{20^\circ}$.	α^{40°.	$[\alpha]^{40^\circ}$.
5461	+23·92°	+ 631°	+22·54°	+ 594°	+21·14°	+ 557°
4358	+62·67	+1652	+58·54	+1543	+54·86	+1446

The three successive filtrates from which B had been crystallised gave acids with $[\alpha]_{5791}$ + 256°, + 444°, and + 477° respectively in acetone (c = 2).

(+)o-*Nitroacetylmandelic acid*, prepared by acetylating (+)*o*-nitromandelic acid with acetyl chloride, formed colourless prisms, m. p. 95—96°, from benzene (Found : C, 50·1; H, 3·8. $C_{10}H_9O_6N$ requires C, 50·2; H, 3·8%). In acetone (l = 2, c = 2·09), $\alpha^{20\cdot5^\circ}_{D}$ + 12·10°, $[\alpha]^{20\cdot5^\circ}_{D}$ + 289°; $\alpha^{20^\circ}_{5461}$ + 15·34°, $[\alpha]^{20^\circ}_{5461}$ + 367°.

Ethyl (+)o-*nitromandelate*, prepared from the (+)acid, is a pale yellow oil, b. p. 165—166°/4 mm. (Found : C, 53·2; H, 5·1. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9%), whereas the isomeric *r*-ester is a solid, m. p. 49—50° (Heller, *Ber.*, 1904, **37**, 938). In acetone (l = 2, c = 2·9645), $\alpha^{20\cdot5^\circ}_{D}$ + 17·91°, $[\alpha]^{20\cdot5^\circ}_{D}$ + 302°; $\alpha^{20^\circ}_{5461}$ + 22·78°, $[\alpha]^{20^\circ}_{5461}$ + 384°. In pyridine (l = 2, c = 2·9385), $\alpha^{16\cdot5^\circ}_{5461}$ + 17·75°, $[\alpha]^{16\cdot5^\circ}_{5461}$ + 302°. When the latter solution was kept for 9 days at the ordinary temperature, the rotatory power remained unaltered. The ester itself became dark-coloured on keeping.

Fractional Esterification of r-o-*Nitromandelic Acid by* (−)*Menthol.*—The *r*-acid (6 g.) was esterified at 150—155° by (−)menthol (6 g.) for 1¼ hours. The ethereal solution of the product was shaken with sodium bicarbonate. The unesterified acid (2·4 g.) obtained from the alkaline solution by acidification with hydrochloric acid and extraction with ether was dextrorotatory in acetone (l = 2, c = 7·3065), $\alpha^{20\cdot5^\circ}_{5461}$ + 4·3°, $[\alpha]^{20\cdot5^\circ}_{5461}$ + 29·4°.

The Optically Active o-*Aminomandelic Acids.*—(−)o-*Aminomandelic acid.* (−)*o*-Nitromandelic acid (7·5 g.) was reduced with barium hydroxide and ferrous sulphate as described for the *r*-isomeride to form barium (−)*o*-aminomandelate (7·6 g.), which is considerably more soluble in water than is the *r*-salt. This salt was then converted into the sodium salt, which is very soluble in water and crystallises in rectangular plates. (−)o-*Aminomandelic acid*, obtained by decomposing the sodium salt with dilute sulphuric acid in an amount slightly less than that calculated for 1 mol. of salt, crystallises from water in prisms, m. p. 159° (decomp.) (Found : C, 57·6; H, 5·6. $C_8H_9O_3N$ requires C, 57·5; H, 5·4%). In *N*-caustic soda (l = 1, c = 1·63, t = 20°) :

λ	6708	6563	5893	5791	5461	5106	4861	4358
α	− 1·87°	− 2·01°	− 2·61°	− 2·85°	− 3·18°	− 3·84°	− 4·14°	− 5·54°
[α]	−115°	−123°	−160°	−175°	−195°	−236°	−254°	−340°

In ammonium hydroxide (0·95*N*) (l = 1, c = 1·227) : $\alpha^{20^\circ}_{5461}$ − 2·34°, $[\alpha]^{20^\circ}_{5461}$ − 191°; $\alpha^{20^\circ}_{5791}$ − 2·08, $[\alpha]^{20^\circ}_{5791}$ − 170°.

In *N*-hydrochloric acid (l = 1, c = 1·954) : $\alpha^{16^\circ}_{5461}$ − 2·96°, $[\alpha]^{16^\circ}_{5461}$ − 151°. This solution gradually lost its optical activity when kept at 16° :

Hours	19½	43½	67½	163	312
α_{5461}	−0·41°	−0·15°	−0·09°	−0·04°	0·00°

From the resulting solution a colourless, sparingly soluble substance separated. It had m. p. 243—245° (decomp.), gave a violet coloration when barium hydroxide was added to its solution in pyridine, and an evanescent ruby-red coloration on heating with ethyl alcohol–sodium carbonate. These properties are exhibited by isatide.

Finely powdered (—)*o*-aminomandelic acid (1·2 g.) was suspended in water (16 c.c.) and then shaken at 0° with acetic anhydride (1·5 c.c.) until it had all dissolved. (—)o-*Acetamidomandelic acid* (0·8 g.) separated from benzene–acetone in needles, m. p. 160° (Found: C, 57·2; H, 5·5. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3%). In acetone ($l = 2$, $c = 1·0325$), $\alpha_D^{20^\circ}$ − 3·89°, $[\alpha]_D^{20^\circ}$ − 188°, $[\alpha]_{5461}^{20^\circ}$ − 4·69°, $[\alpha]_{5461}^{20^\circ}$ − 227°.

(—)o-β-*Naphtholazomandelic acid*, prepared from sodium (—)*o*-aminomandelate by diazotisation and coupling of the diazonium solution with β-naphthol, crystallised from glacial acetic acid in red needles, m. p. 190—191° (decomp.) (Found: C, 66·7; H, 4·5; N, 9·1. $C_{18}H_{14}O_4N_2$ requires C, 67·1; H, 4·4; N, 8·7%).

(+)o-*Aminomandelic acid*, prepared from sodium (+)*o*-aminomandelate, formed prisms, m. p. 159° (decomp.) (Found: C, 57·6; H, 5·6. $C_8H_9O_3N$ requires C, 57·5; H, 5·4%). In ammonium hydroxide (0·95*N*) ($l = 1$, $c = 1·178$), $\alpha_{5461}^{20^\circ}$ + 2·24°, $[\alpha]_{5461}^{20^\circ}$ + 190°. In pyridine ($l = 1$, $c = 2·685$), $\alpha_{5461}^{17^\circ}$ + 6·92°, $[\alpha]_{5461}^{17^\circ}$ + 258°; $\alpha_{5791}^{17^\circ}$ + 5·98°, $[\alpha]_{5791}^{17^\circ}$ + 223°.

The latter solution gradually dropped in dextrorotatory power and finally became lævorotatory. It became gradually reddish-brown, and polarimetric readings could not eventually be taken for λ_{5461} and λ_{5791}. The readings for λ_{6563} are only approximate, but the lævorotation seems to remain constant after 270 hours.

Hours	5	70½	95½	119	145
$[\alpha]_{5461}$	+254°	+182°	+144°	+110°	—
$[\alpha]_{5791}$	+220°	+162°	+134°	+ 99°	+ 66°

Hours	167	174	241	246½	264½	270	287
$[\alpha]_{5791}$	+ 44°	+ 31°	—	—	—	—	—
$[\alpha]_{6563}$	+ 37°	+ 37°	− 5°	− 24°	− 28°	− 45°	− 45°

The residue obtained after removal of the pyridine was lævorotatory in ethyl alcohol.

Action of Dilute Sulphuric Acid on (—)o-*Aminomandelic Acid*.—0·1755 G. of the acid (1 mol.) was made up to 10 c.c. with dilute sulphuric acid (½ mol.): $l = 1$, $c = 1·755$, $\alpha_{5461}^{16^\circ}$ − 2·48°, $[\alpha]_{5461}^{16^\circ}$ − 141°. The solution gradually changed its sign of rotation from lævo to dextro:

Time	8 (mins.)	18	40	2 (hrs.)	4	6	23	26	29	48
$\alpha_{5461}^{16^\circ}$	−2·45°	−2·39°	−2·24°	−1·72°	−1·10°	−0·70°	+0·37°	+0·43°	+0·50°	+0·50°

When the rotatory power had reached a constant value, (+)dioxindole was isolated from the solution.

(+)*Dioxindole*.—A solution of 3·4 g. of sodium (—)*o*-aminomandelate (1 mol.) in 25 c.c. of water was acted upon at 30° by 14·4 c.c. of dilute sulphuric acid containing twice the amount necessary for the decomposition of the sodium salt. Precautions should be taken to prevent oxidation. After 1 day at the ordinary temperature under diminished pressure, optically pure (+)dioxindole (1·1 g.) separated. (+)*Dioxindole* gives in ethyl-alcoholic solution a faint transient violet coloration on the addition of ammonia. When (+)dioxindole was moistened with hot barium hydroxide, it assumed a pronounced violet coloration. It crystallises from water in prisms which when heated rapidly have m. p. 167—168° with preliminary softening (Found: C, 64·2; H, 5·0. $C_8H_7O_2N$ requires C, 64·4; H, 4·7%). In acetone ($l = 1$, $c = 2·099$), $\alpha_{5461}^{20^\circ}$ + 0·84°, $[\alpha]_{5461}^{20^\circ}$ + 40°; $\alpha_D^{20^\circ}$ + 0·71°, $[\alpha]_D^{20^\circ}$ + 34°. In ethyl alcohol ($l = 1$, $c = 1·964$), $\alpha_{5461}^{20·5^\circ}$ + 1·09°, $[\alpha]_{5461}^{20·5^\circ}$ + 55·5°; $\alpha_{5791}^{20·5^\circ}$ + 1·0°, $[\alpha]_{5791}^{20·5^\circ}$ + 51°. The solution in acetone did not change in rotatory power after several days, but when it was kept in a closed flask for a few weeks, isatide gradually separated from it.

(—)*Dioxindole*, prepared from sodium (+)*o*-aminomandelate, forms prisms, m. p. 167—168° with preliminary softening (Found: C, 64·1; H, 4·7. $C_8H_7O_2N$ requires C, 64·4; H, 4·7%). In acetone ($l = 1$, $c = 2·091$, $t = 20°$):

λ	6708	6563	6162	5893	5461	5106
α	− 0·50°	− 0·56°	− 0·62°	− 0·70°	− 0·83°	− 0·91°
$[\alpha]$	−24°	−27°	−30°	−33·5°	−40°	−43·5°

Action of Phenylhydrazine on (+)*Dioxindole*.—A mixture of (+)dioxindole (0·3 g.), phenylhydrazine (1 g.), and ethyl alcohol (6 c.c.) was refluxed for 6 hours. On cooling, yellow needles, m. p. 208°, separated. These were optically inactive in benzene, and the m. p. was not depressed on admixture with isatin-β-phenylhydrazone (Fischer, *Ber.*, 1884, **17**, 577; Heller, *Ber.*, 1904, **37**, 938).

Action of Alcoholic Potash on (+)*Dioxindole.*—To an ethyl-alcoholic solution of (+)dioxindole (l = 1, c = 1·964) giving α_{5461} + 1·09°, three drops of alcoholic potash (0·5*N*) were added. The optical activity vanished almost at once, and, when the solution was evaporated to dryness under diminished pressure, the residue, m. p. 245—246° (decomp.), was isatide. Under similar conditions, *r*-dioxindole and three drops of alcoholic potash (0·8*N*) gave isatide. *r*-Dioxindole, used alone, was recovered unchanged.

A gradual fall of rotation was, however, observed when an ethyl-alcoholic solution of (+)dioxindole was made less alkaline than above: thus, when three drops of alcoholic potash (0·2*N*) were added to a solution (l = 1, c = 1·99) giving $\alpha^{20°}_{5461}$ + 1·11°, the following observations were made:

Time	2 (mins.)	3	7	12	22	37
$\alpha^{20°}_{5461}$	+0·95°	+0·80°	+0·77°	+0·72°	+0·64°	+0·58°
Time	47 (mins.)	62	1½ (hrs.)	2	20	24
$\alpha^{20°}_{5461}$	+0·53°	+0·48°	+0·42°	+0·38°	+0·24°	+0·24°

Acetylation of (+)*Dioxindole.*—Acetyl chloride (0·8 c.c.) was added gradually to (+)dioxindole (1 g.) at 0°, the colour changing to green and then to black. The mixture was kept at the ordinary temperature over-night and then triturated with water. The violet solid was recrystallised from water in presence of charcoal, colourless prisms, m. p. 130°, being obtained. In acetone these were optically inactive, and the m. p. was not depressed on admixture with authentic *r*-*O*-acetyldioxindole prepared by acetylating *r*-dioxindole with acetyl chloride.

Benzoylation of (+)*Dioxindole.*—Benzoyl chloride (2·2 c.c.) was added gradually at 0° to a solution of (+)dioxindole (1·2 g.) in pyridine. The product was crystallised from ethyl alcohol, needles (0·75 g.), m. p. 171—172°, and optically inactive in acetone, being obtained. The m. p. was not depressed on admixture with authentic *r*-dibenzoyldioxindole, prepared by benzoylating *r*-dioxindole either by the Schotten–Baumann method or by the action of benzoyl chloride in the presence of pyridine.

Action of Pyridine on (+)*Dioxindole.*—A solution of (+)dioxindole in pyridine which gave (l = 1, c = 2·253) $\alpha^{16°}_{5461}$ + 1·76°, $[\alpha]^{16°}_{5461}$ + 78°, gradually became optically inactive:

Hours	2½	20	44	93	188	331	433	501	551
$\alpha^{16°}_{5461}$	+1·66°	+1·43°	+1·20°	+0·80°	+0·44°	+0·13°	+0·04°	0·00°	0·00°

The optically inactive solution was evaporated to small bulk under diminished pressure and dilute sulphuric acid was added. A small amount of isatin was isolated.

Reduction of (+)o-*Nitromandelic Acid with Zinc Dust and Ammonium Hydroxide.*—Preliminary experiments on the reduction of *r*-*o*-nitromandelic acid with zinc dust and sulphuric acid on the lines adopted by Reissert (*Ber.*, 1908, **41**, 3921) for the preparation of *N*-hydroxyoxindole from *o*-nitrophenylacetic acid gave unsatisfactory yields of *N*-hydroxydioxindole. Reduction with zinc dust and ammonium hydroxide was more promising (Kalle and Co., D.R.-P. 184,693, 184,694, 189,841, 191,855; Heller, *Ber.*, 1909, **42**, 470), and this method was accordingly applied to (+)*o*-nitromandelic acid.

(+)*o*-Nitromandelic acid (5 g.) was dissolved in water (32 c.c.), 15 g. of aqueous ammonia (15%) and ammonium chloride (2·5 g.) added, and then zinc dust (5 g.) gradually with stirring (1 hour), the temperature being kept below 35°. The filtrate from the solid was acidified by hydrochloric acid (Congo-red). After several days under diminished pressure at the ordinary temperature (—)N-*hydroxydioxindole* [(—)*trioxindole*] (2 g.) separated; needles, m. p. 159° (decomp.), from light petroleum (b. p. 60—80°)–ethyl alcohol (Found: C, 58·4; H, 4·5. $C_8H_7O_3N$ requires C, 58·2; H, 4·3%). In acetone (l = 1, c = 2·3, t = 20°):

λ	6708	6563	5893	5461	5106	4861	4358
α	— 0·88°	— 0·92°	— 1·15°	— 1·36°	— 1·52°	— 1·69°	— 2·05°
[α]	—38°	—40°	—50°	—59°	—66°	—73·5°	—89°

(+)N-*hydroxydioxindole*, prepared from (—)*o*-nitromandelic acid, forms prisms, m. p. 159° (decomp.), from water (Found: C, 58·1; H, 4·5. $C_8H_7O_3N$ requires C, 58·2; H, 4·3%). In acetone (l = 1, c = 1·251), $\alpha^{20°}_{5461}$ + 0·74°, $[\alpha]^{20°}_{5461}$ + 59°. The addition of a few drops of alcoholic potash to an ethyl-alcoholic solution of (+)*N*-hydroxydioxindole caused the deposition of the potassium derivative.

The optically active *N*-hydroxydioxindoles give a blue coloration with ferric chloride, and gradually reduce Fehling's solution at the ordinary temperature.

(—)o-*Hydroxymandelic Acid.*—A solution of sodium (—)*o*-aminomandelate (10·7 g.) in water (130 c.c.) was mixed with a solution of sodium nitrite (4 g.) in water (20 c.c.) and gradually added within 1 hour to 2*N*-sulphuric acid (115 c.c.) at 0°. The solution was heated until the evolution of nitrogen ceased, filtered from some resin, and extracted with ether, the ethereal solution dried, and the resulting oil (4·5 g.), which contained no nitrogen, kept for 9 days over calcium chloride under diminished pressure.

(—)o-*Hydroxymandelic acid* is a viscous oil which gives a blue coloration with ferric chloride (Found : C, 56·9; H, 5·0. $C_8H_8O_4$ requires C, 57·1; H, 4·8%). In acetone ($l = 2, c = 2{\cdot}7285$), $\alpha_{\mathrm{D}}^{20^\circ} - 3{\cdot}58^\circ$, $[\alpha]_{\mathrm{D}}^{20^\circ} - 65{\cdot}6^\circ$; $\alpha_{5461}^{20^\circ} - 4{\cdot}18^\circ$, $[\alpha]_{5461}^{20^\circ} - 76{\cdot}6^\circ$. In ethyl ether ($l = 2, c = 2{\cdot}7345$), $\alpha_{\mathrm{D}}^{15^\circ} - 2{\cdot}94^\circ$, $[\alpha]_{\mathrm{D}}^{15^\circ} - 53{\cdot}8^\circ$; $\alpha_{5461}^{15^\circ} - 3{\cdot}44^\circ$, $[\alpha]_{5461}^{15^\circ} - 62{\cdot}9^\circ$.

Similarly, *dl*-*o*-hydroxymandelic acid (6 g.) was prepared from sodium *r*-*o*-aminomandelate (13 g.) as a viscous oil. On reduction with hydriodic acid, it gave *o*-hydroxyphenylacetic acid, crystallising from water in needles, m. p. 141—141·5° (Found : C, 63·4; H, 5·4. Calc. for $C_8H_8O_3$: C, 63·1; H, 5·3%); Baeyer and Fritsch (*Ber.*, 1884, **17**, 973) give m. p. 137°, and Stoermer (*Annalen*, 1900, **313**, 83) m. p. 144—145°.

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