LXXXVIII.—*Optically Active Derivatives of Phenylaminoacetic Acid.*

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THE semipinacolinic deamination of tertiary amino-alcohols has been applied by McKenzie, Roger, and Wills (J., 1926, 779) for the preparation of optically active ketones. It was desirable that optically active desylamine hydrochloride should be prepared in order that the behaviour of nitrous acid towards the amino-alcohols derived from it by means of Grignard reagents could be studied. This was one of the reasons why the present research was undertaken.

The resolution of *r*-desylamine gave unpromising results at first. The nicely-crystalline product from the interaction of *r*-desylamine hydrochloride and sodium hydrogen *d*-tartrate in aqueous solution did not lend itself to recrystallisation. Moreover, *d*-camphor-10-sulphonic acid and *d*-α-bromocamphorsulphonic acid also gave unsatisfactory results. It was thought possible that phthalyl derivatives of phenylaminoacetic acid might serve the purpose, and that *l*-α-phthalimidophenylacetyl chloride would give optically active desylamine hydrochloride through the intermediate stages of desylphthalimide and desylphthalamic acid:

$$NH_2\cdot CHPh\cdot CO_2H \longrightarrow C_8H_4O_2{:}N\cdot CHPh\cdot CO_2H \longrightarrow$$
$$C_8H_4O_2{:}N\cdot CHPh\cdot COCl \longrightarrow C_8H_4O_2{:}N\cdot CHPh\cdot COPh \longrightarrow$$
$$CO_2H\cdot C_6H_4\cdot CO\cdot NH\cdot CHPh\cdot COPh \longrightarrow NH_2\cdot CHPh\cdot COPh,HCl.$$

The optically active α-phthalimidophenylacetic acid cannot be obtained by heating *l*-phenylaminoacetic acid with phthalic anhydride at 160—170°, presumably owing to the racemisation which occurs at this temperature. After preliminary experiments with various alkaloids, the resolution of the *r*-phthalyl acid was successfully accomplished by morphine. When, however, the acid chloride of the *l*-acid was acted on by benzene and aluminium chloride, the product was *r*-desylphthalimide.

l-α-Phthalimidophenylacetic acid, when hydrolysed with caustic soda under the conditions described in the experimental section, gave a dextrorotatory dicarboxylic acid with the probable constitution $CO_2H\cdot C_6H_4\cdot CO\cdot NH\cdot CHPh\cdot CO_2H$.

The next stage was to start with *r*-desylphthalamic acid. This was resolved by morphine, but we were not satisfied at the time that the desylamine hydrochloride obtained by hydrolysing the *l*-acid was optically pure, and subsequent experiments confirmed this view. The concentrated hydrochloric acid used in the hydrolysis was apparently the racemising agent. It was further found that *l*-desylphthalamic acid gives on dehydration *r*-desylphthalimide.

It remained, therefore, to revert to the resolution of *r*-desylamine itself. By the application of *l*-mandelic acid and *d*- and *l*-$\gamma\gamma\gamma$-trichloro-β-hydroxybutyric acids—substances which have not hitherto been used for the resolution of *r*-bases—the optically active desylamine hydrochlorides are now accessible in sufficient quantity to enable them to be applied for our studies on the migration of groups.

The *d*- and *l*-desylamines have a certain interest on account of their connexion with the *d*- and *l*-benzoins. When *d*-desylamine hydrochloride was acted on by nitrous acid, a mixture of *r*- and *d*-benzoins was formed, so that the following change was effected :

$$d\text{-Ph}\cdot\text{CH}(\text{NH}_2)\cdot\text{COPh,HCl} \xrightarrow{(\text{HNO}_2)} d\text{-Ph}\cdot\text{CH}(\text{OH})\cdot\text{COPh}.$$

When the free base, which is very unstable, was liberated from the *d*-hydrochloride, the sign of rotation was unaltered. Its optical activity in ethyl-alcoholic solution was evanescent at the ordinary temperature, a result which we attribute—in part at least—to racemisation rather than to decomposition.

Experimental.

Action of Phthalic Anhydride on l-*Phenylaminoacetic Acid.*—2 G. of *l*-phenylaminoacetic acid were heated for 2½ hours with freshly-distilled phthalic anhydride (2 g.) at 160—170°. The product was crystallised first from glacial acetic acid and then from benzene. The resulting acid (3 g.) was optically inactive in acetone and in benzene : it consisted of *r*-α-phthalimidophenylacetic acid, m. p. 170·5—171·5° (Ulrich, *Ber.*, 1904, **37**, 1685).

This behaviour of optically active phenylaminoacetic acid, $\text{C}_6\text{H}_5\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}_2\text{H}$, is in marked contrast with that of *d*-β-amino-β-phenylpropionic acid, $\text{C}_6\text{H}_5\cdot\text{CH}(\text{NH}_2)\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, from which *d*-β-phthalimido-β-phenylpropionic acid is readily prepared when the amino-acid is heated with phthalic anhydride (McKenzie and Tudhope, J., 1924, **125**, 928), no racemisation occurring in the latter case.

Resolution of r-α-*Phthalimidophenylacetic Acid.*—Morphine (30·7 g.) was dissolved by heating with ethyl alcohol (2850 c.c.), the solution cooled to 30°, and the *r*-acid (28·5 g.) added. The acid dissolved readily. The morphine salt (36·5 g.), which had separated over-

night, was crystallised once from ethyl alcohol (2900 c.c.), and the resulting needles were dissolved in boiling water (2500 c.c.), and decomposed, while the solution was still warm, by concentrated hydrochloric acid. The acid precipitated was crystallised once from aqueous acetone, washed with ice-cold water, and dried in a vacuum over sulphuric acid. It was then optically pure, repeated crystallisation failing to raise the value of its specific rotation. Yield: 10 g.

l-α-*Phthalimidophenylacetic acid*, $C_8H_4O_2{:}N{\cdot}CHPh{\cdot}CO_2H$, forms glassy needles, m. p. 192—193° (Found: C, 68·3; H, 4·0; N, 5·1. $C_{16}H_{11}O_4N$ requires C, 68·3; H, 3·9; N, 5·0%). In acetone: $l = 2$, $c = 3{\cdot}5385$, $\alpha_D^{14·5°}$ −3·67°, $[\alpha]_D^{14·5°}$ −51·9°. In methyl alcohol: $l = 2$, $c = 4{\cdot}588$, $\alpha_D^{17·5°}$ −1·86°, $[\alpha]_D^{17·5°}$ −20·3°; $l = 2$, $c = 2{\cdot}251$, $\alpha_{5461}^{12·5°}$ −1·11°, $[\alpha]_{5461}^{12·5°}$ −24·7°.

Conversion of l-α-*Phthalimidophenylacetic Acid into* r-*Desylphthalimide.*—The *l*-acid (3 g.) was heated on the water-bath with thionyl chloride (20 g.) for 3 hours, and the excess of thionyl chloride removed; the residual oil gradually crystallised when kept in a vacuum over soda-lime. This acid chloride was then heated for 3 hours with dry thiophen-free benzene (30 c.c.) and aluminium chloride (3 g.), and the product was decomposed by dilute sulphuric acid. The solid obtained from the benzene solution was crystallised from pyridine–ethyl alcohol, and the crystals obtained (1·5 g.) were identified as *r*-desylphthalimide.

The racemisation observed must have occurred during the Friedel and Crafts reaction, since the acid chloride is lævorotatory. The product obtained by heating the *l*-acid (1 g.) for 2 hours with thionyl chloride (5 g.) gave in benzene ($l = 2$, $c = 3{\cdot}33$), α_D −4·68°.

Action of Potassium Hydroxide on l-α-*Phthalimidophenylacetic Acid.*—The *l*-acid (3 g.) was neutralised at the ordinary temperature by dissolving it gradually in 247·4 c.c. of caustic potash ($N/10 \times 0{\cdot}863$). After 1 hour the solution was acidified by dilute hydrochloric acid, and the precipitated acid collected (m. p. 177—179°). It was *dextrorotatory*, its rotation in acetone ($l = 2$, $c = 1{\cdot}266$) being α_D + 2·25°, $[\alpha]_D$ + 88·9°. Yield: 2·4 g. After crystallisation from aqueous acetone, it gave in acetone ($l = 2$, $c = 1{\cdot}2525$), α_D + 2·55°, $[\alpha]_D$ + 101·8°. The compound was now apparently homogeneous because, after two further crystallisations from aqueous acetone, it was unaltered in its specific rotation. The amount of alkali (of the strength given above) required to form the potassium salt from 3 g. of *l*-α-phthalimidophenylacetic acid is 123·63 c.c., whereas the amount actually added was 247·4 c.c. The amount of alkali required to effect the change

$$C_6H_4\begin{<}\begin{matrix}CO\\CO\end{matrix}\end{>}N{\cdot}CHPh{\cdot}CO_2H \xrightarrow{2KOH} CO_2K{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}CHPh{\cdot}CO_2K$$

is 247·26 c.c. It would therefore appear that the dextrorotatory dicarboxylic acid, $CO_2H{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}CHPh{\cdot}CO_2H$, was formed by hydrolysing *l*-α-phthalimidophenylacetic acid under the conditions quoted.

Resolution of r-*Desylphthalamic Acid.*—270 C.c. of water were added to a solution of a mixture of 27 g. of the *r*-acid (Neumann, *Ber.*, 1890, **23**, 995) and 22·7 g. of morphine in 270 c.c. of ethyl alcohol. After 3 hours at the ordinary temperature, crystallisation started on stirring. The glassy prisms (23·5 g.), which separated over-night, were crystallised twice from 50% aqueous alcohol. Yield: 12·2 g. After decomposition of the salt by dilute sulphuric acid, the acid was extracted with ether. Yield: 6·1 g. It was almost pure, giving in acetone ($l = 2$, $c = 2{\cdot}4965$), $\alpha_D^{18°}$ −7·85°, $[\alpha]_D^{18°}$ −157·2°. It was finally crystallised from ether.

l-*Desylphthalamic Acid*, $CO_2H{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}CHPh{\cdot}COPh$, is sparingly soluble in water, benzene, and light petroleum. It separates from ether in feathery needles, m. p. 155—157° (decomp.). In acetone: $l = 2$, $c = 2{\cdot}545$, $\alpha_D^{18°}$ −8·10°, $[\alpha]_D^{18°}$ −159·1°.

l-Desylphthalamic acid underwent dehydration to *r*-desylphthalimide under the following conditions. A solution of 1·3 g. of the acid in acetone–water was evaporated to dryness on the water-bath, a bright yellow mixture of solid and oil being obtained. The solution in acetone was only slightly lævorotatory, and from it colourless crystals of *r*-desylphthalimide (0·6 g.) separated gradually.

Hydrolysis of l-*Desylphthalamic Acid.*—The *l*-acid (1·7 g.) was evaporated to dryness on the steam-bath with concentrated hydrochloric acid (50 c.c.), and the aqueous solution of the residual solid was extracted 4 times with ether. The aqueous solution was evaporated to dryness, and the resulting desylamine hydrochloride (1 g.) was examined polarimetrically in ethyl alcohol: $l = 2$, $c = 3{\cdot}4685$, α_D −7·52°, $[\alpha]_D$ −108·4°. After one crystallisation from a mixture of water (10 c.c.) and concentrated hydrochloric acid (25 c.c.), the value for $[\alpha]_D$ was increased to −110·3° ($c = 2{\cdot}9765$), and after one crystallisation more from the same solvent, to −114° ($c = 3{\cdot}269$). From those values alone it was clear that some racemisation must have occurred during the formation of desylamine hydrochloride, the racemising agent presumably being the concentrated hydrochloric acid employed (compare Fitger, "Racemisierungserscheinungen bei optisch-aktiven Sulphidsäuren," Lund, 1924). It was also proved that the racemisation was pronounced: the mother-liquor, from which the crystals giving $[\alpha]_D$ −114° had been removed, was evaporated to dryness, and the desylamine hydrochloride obtained in this manner gave the following low value in ethyl alcohol: $l = 1$, $c = 1{\cdot}572$, α_D −0·57°, $[\alpha]_D$ −36·3°.

The action of concentrated hydrochloric acid on *l*-desylphthalamic acid was accordingly examined as follows. 0·5 G. of the *l*-acid was added to 25 c.c. of hydrochloric acid (*d* 1·2) and kept for 10 days in the ice-chest. The *l*-acid was practically undissolved, and the value for its specific rotation had not fallen after this treatment. On the other hand, the racemisation was very pronounced under the following conditions at the ordinary temperature. Dry hydrogen chloride was passed into a solution of the *l*-acid (0·7 g.) in ether (100 c.c.). There was no separation of desylamine hydrochloride, and 30 c.c. of hydrochloric acid (*d* 1·2) were added. After 4 days with occasional shaking, the lower layer was evaporated to dryness, and the resulting solid had the following rotation in ethyl alcohol: $l = 2$, $c = 1·62$, α_D −2°, $[\alpha]_D$ −62°. The ethereal layer was evaporated at the ordinary temperature and the desylphthalamic acid thus obtained exhibited only a slight lævorotation in acetone: $l = 2$, $c = 1·008$, α_D −0·23°, $[\alpha]_D$ −11°.

Resolution of r-*Desylamine Hydrochloride.*—(1) *Resolution with* l-*mandelic acid.* A solution of 15 g. of *r*-desylamine hydrochloride (Pschorr and Brüggemann, *Ber.*, 1902, **35**, 2740) in 130 c.c. of water was mixed with 75 c.c. of an aqueous solution of ammonium *l*-mandelate prepared from 9 g. of *l*-mandelic acid. The voluminous, colourless precipitate was drained off, and dissolved in boiling rectified spirit; the solution became orange-red. On cooling, yellow needles separated. These, after being washed with rectified spirit, became colourless (7 g.) and gave in acetone, in which the salt is somewhat sparingly soluble at the ordinary temperature, ($l = 2$, $c = 2·076$), α_D −2·38°, $[\alpha]_D$ −57·3°. The solution was yellow. The acetone was expelled by warming on the water-bath, the residue being an oil with the colour of port wine. The remainder of the mandelate was crystallised from rectified spirit; the crystals (3·8 g.) obtained had the following rotation in acetone: $l = 2$, $c = 1·426$, α_D −1·64°, $[\alpha]_D$ −57·5°. The salt was thus apparently homogeneous; it melted at 149—150° with decomposition to an orange-coloured solution. It was decomposed by dilute hydrochloric acid, the mandelic acid was removed completely by extraction with ether, and the aqueous layer containing the desylamine hydrochloride was evaporated to dryness. After one crystallisation from ethyl alcohol, the hydrochloride was optically pure.

d-*Desylamine hydrochloride*, $C_6H_5·CH(NH_2)·CO·C_6H_5,HCl$, is more soluble in ethyl alcohol than is the *r*-isomeride. It separates in glassy prisms, which decompose with rapid evolution of gas at 230° (Found: C, 67·9; H, 5·6; N, 5·8; Cl, 14·1. $C_{14}H_{14}ONCl$ requires C, 67·9; H, 5·7; N, 5·7; Cl, 14·3%). In ethyl alcohol: $l = 2$, $c = 2·538$, $\alpha_D^{16°}$ + 11·33°, $[\alpha]_D^{16°}$ + 223·2°.

(2) *Resolution with* l-γγγ-*trichloro*-β-*hydroxybutyric acid.* 52 G. of the *l*-chloro-acid (McKenzie and Plenderleith, J., 1923, **123**, 1090) were neutralised by ammonia, and added to an aqueous solution of *r*-desylamine hydrochloride (62 g.). The flocculent crystals, which separated quickly from the solution (1500 c.c.), were collected, and after drying over concentrated sulphuric acid were crystallised from 1 litre of rectified spirit, the solution assuming an orange-red tint. Over-night at about 8°, colourless needles (35 g.) had deposited. These were decomposed by dilute hydrochloric acid, and extracted with ether, the *l*-chloro-acid being recovered from the ethereal solution. The aqueous solution was then evaporated until crystallisation started. The desylamine hydrochloride (18 g.) which separated on cooling was almost optically pure. The pure *d*-desylamine hydrochloride was obtained after two crystallisations from ethyl alcohol.

(3) *Resolution with* d-γγγ-*trichloro*-β-*hydroxybutyric acid.* The l-*desylamine hydrochloride* obtained resembled the enantiomorphous form in crystalline appearance, melting point, and optical rotatory power. In each one of these resolutions, the desylamine hydrochloride obtained had the opposite sign of rotation from that of the optically active acid employed.

Action of Nitrous Acid on d-*Desylamine Hydrochloride.*—10 C.c. of hydrochloric acid (2*N*) were added to a solution of 1·4 g. of *d*-desylamine hydrochloride in 20 c.c. of water. A solution of 1·2 g. of sodium nitrite in 15 c.c. of water was then gradually added (15 mins.), the temperature being kept at 0°. After 5 hours at 0°, a further addition of sodium nitrite (0·6 g. in 10 c.c.) was made. Over-night in the ice-chest, a yellow, somewhat oily, solid (0·95 g.) was obtained which in ethyl alcohol gave: $l = 2$, $c = 1{\cdot}25$, $\alpha_D + 0{\cdot}76°$, $[\alpha]_D + 30{\cdot}4°$. The product was crystallised from ethyl alcohol, and the colourless, gritty crystals which separated were examined in ethyl alcohol: $l = 2$, $c = 1{\cdot}178$, $\alpha_D + 0{\cdot}71°$, $[\alpha]_D + 30{\cdot}1°$. This product was partly racemised *d*-benzoin. It melted indefinitely at 127—131°, and reduced Fehling's solution.

For comparison, *l*-benzoin, prepared from *l*-mandelamide and magnesium phenyl bromide (McKenzie and Wren, J., 1908, **93**, 309), was examined in ethyl-alcoholic solution: $l = 2$, $c = 1{\cdot}155$, $\alpha_D^{16°} -3{\cdot}06°$, $[\alpha]_D^{16°} -132{\cdot}5°$. There was, therefore, considerable racemisation in the displacement of the amino-group in *l*-desylamine hydrochloride.

d-*Desylamine.*—The instability of *r*-desylamine is clear from the work of Braun (*Ber.*, 1889, **22**, 557), Neumann (*loc. cit.*), and Pschorr and Brüggemann (*loc. cit.*). We confirmed the observations of the last-named authors, obtaining by crystallisation from ether a

colourless solid, m. p. 110° (decomp.). This specimen became yellow when kept. The *d*-base exhibits a similar instability.

18·5 C.c. of sodium carbonate (*N*/2) were added slowly with constant stirring to a solution of 2·5 g. of *d*-desylamine hydrochloride in 40 c.c. of water. The bulky, colourless precipitate was filtered off, washed three times with water, dried between filter-paper, and transferred to a desiccator, where it was kept over-night. The solid (1·5 g.) had now become bright yellow. It was found, however, to contain a small amount of the hydrochloride. To the filtrate from which this 1·5 g. had separated, and which had been kept over-night, 1·5 c.c. of sodium carbonate (*N*/2) were added. After ½ hour, the solid which had separated was collected, and dried over-night in a vacuum. It amounted to 0·4 g. and was colourless. It melted indefinitely at 82—86°, becoming bright yellow. 0·2504 G. was made up to 20 c.c. with ethyl alcohol and then gave α_D + 5·02° ($l = 2$), whence $[\alpha]_D$ + 200·5°. After 2 hours at the ordinary temperature, this value had fallen to + 4·20°; after 3 hours, the value was + 3·96°; after 21 hours, + 1·46°, and after 72 hours, + 0·28°. This drop in rotation was apparently mainly due to racemisation and not to decomposition, since, when an excess of hydrochloric acid was added to the solution giving α_D + 0·28° and the solution then evaporated to dryness, *r*-desylamine hydrochloride, m. p. 243—245° (decomp.), was obtained.

The *d*-base was liberated from *d*-desylamine hydrochloride (1·5 g.) in aqueous solution by the addition of caustic soda in slightly under the calculated amount. An oil was first deposited, and this solidified in a freezing mixture. It was washed twice with water, and dried over-night in a vacuum over sulphuric acid. The yellow product melted indefinitely, mainly between 87—89° with preliminary softening. Yield: 0·9 g. 0·2497 G. was made up to 20 c.c. with ethyl alcohol, and the rotation taken 5 minutes after the addition of the alcohol was begun. The progress of the racemisation is indicated by the following figures ($l = 2$):

Time (hours)	—	1	1½	2	3½
α_D	+4·60°	+4·50°	+4·40°	+4·27°	+3·94°
Time (hours)	4½	5½	7½	24	48
α_D	+3·75°	+3·60°	+3·34°	+1·76°	+0·62°

One of us (N. W.) acknowledges her indebtedness to the Carnegie Trust for the award of a Teaching Fellowship.

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UNIVERSITY OF ST. ANDREWS. [*Received, December 23rd,* 1927.]