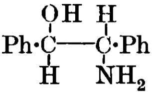
CXXXI.—*The Optically Active Diphenylhydroxyethylamines and* iso*Hydrobenzoins. Part I.*

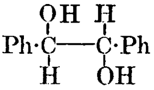
By JOHN READ and CATHERINE CASSELS STEELE.

THE constitution, $OH{\cdot}CHPh{\cdot}CHPh{\cdot}NH_2$, assigned to the diphenylhydroxyethylamines contains two dissimilar asymmetric carbon atoms and thus demands two externally compensated and four optically active stereoisomerides. A mixture of the two externally compensated bases is produced (i) in the reduction of benzoinoxime with sodium amalgam (Söderbaum, *Ber.*, 1895, **28**, 2523), and (ii) in the condensation of benzaldehyde and glycine (Erlenmeyer, *Annalen*, 1899, **307**, 97), diphenylhydroxyethylamine (m. p. 163°) predominating in the first reaction and *iso*diphenylhydroxyethylamine (m. p. 129—130°) in the second. Only the *iso*-base appears to have been resolved into optically active components (*Annalen*, 1904, **337**, 321; compare *Ber.*, 1899, **32**, 2378).

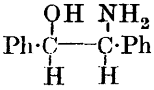
The base of m. p. 129—130° was originally regarded as *iso*diphenylhydroxyethylamine (I) by Erlenmeyer (*Annalen*, 1899, **307**, 97) because of its conversion by nitrous acid into *iso*hydrobenzoin; the latter substance, owing to its resolution into optically active components (*vide infra*), was assigned configuration (II). According to this scheme, diphenylhydroxyethylamine (m. p. 163°) would correspond configurationally to internally compensated hydrobenzoin (IV), thus possessing configuration (III) :


$Ph{\cdot}\overset{OH}{\underset{H}{C}}{-\!-}\overset{H}{\underset{NH_2}{C}}{\cdot}Ph$

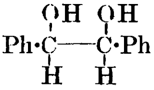
(I.)


$Ph{\cdot}\overset{OH}{\underset{H}{C}}{-\!-}\overset{H}{\underset{OH}{C}}{\cdot}Ph$

(II.)


$Ph{\cdot}\overset{OH}{\underset{H}{C}}{-\!-}\overset{NH_2}{\underset{H}{C}}{\cdot}Ph$

(III.)


$Ph{\cdot}\overset{OH}{\underset{H}{C}}{-\!-}\overset{OH}{\underset{H}{C}}{\cdot}Ph$

(IV.)

It was found later, however, that both of the externally compensated bases gave a mixture of *iso*hydrobenzoin and hydrobenzoin in this reaction, the former product predominating in each instance (*Annalen*, 1899, **307**, 130, 136). Erlenmeyer was in consequence led to postulate the intermediate formation of a diazo-compound, $Ph{\cdot}CH(OH){\cdot}C(\dot{:}N_2){\cdot}Ph$, containing only one asymmetric carbon atom in the molecule. The mechanism of the reaction has been discussed more recently by McKenzie and Richardson (J., 1923, **123**, 82).

We now describe the optical resolution of *dl*-diphenylhydroxyethylamine with *d*-oxymethylenecamphor and also with *d*-camphorsulphonic acid; the base appears to form a partly racemic salt with *d*-α-bromocamphorsulphonic acid. The optical rotatory powers of the two stereoisomeric bases show some remarkable contrasts: the respective values of $[\alpha]_D$ for *d*-diphenylhydroxyethylamine, *d*-diphenylhydroxyethylamine hydrochloride, and benzylidene-*d*-diphenylhydroxyethylamine were + 10·0° (alcohol), + 69·3° (water), and − 81·4° (alcohol); the corresponding values observed by us for the *d*-*iso*-base and its hydrochloride were + 125·0° and + 81·7°, whilst benzylidene-*d*-*iso*diphenylhydroxyethylamine gave $[\alpha]_D$ +56·0° (*Annalen*, 1904, **337**, 343). *d*-Diphenylhydroxyethylamine showed a strong mutarotation in acetone, $[\alpha]_D$ changing from + 15·1° to − 108·8° in 90 minutes; the corresponding change for the *l*-*iso*-base was from − 102·2° to − 90·3°; in this respect, the *iso*-base thus appears to provide the closer analogy to the constitutionally similar hydroxyhydrindamine, the optically active forms of which show a weak but distinct mutarotation in acetone (J., 1912, **101**, 769).

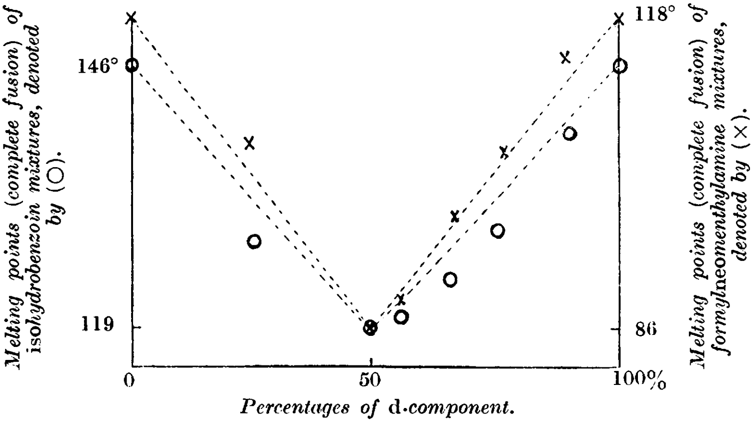
Upon treatment with nitrous acid, *dl*-diphenylhydroxyethylamine gave a mixture containing hydrobenzoin, *dl*-*iso*hydrobenzoin, and probably deoxybenzoin; the crude products obtained similarly from *l*-diphenylhydroxyethylamine, *l*-*iso*diphenylhydroxyethylamine and *d*-*iso*diphenylhydroxyethylamine had $[\alpha]_D$ + 38·9°, − 47·1°, and + 49·7°, respectively, in alcohol. When fractionally crystallised, these optically active preparations yielded pure *d*- or *l*-*iso*-hydrobenzoin, having m. p. 146° and $[\alpha]_D$ ± 90° approximately. The broad quantitative resemblance between the rotatory powers of the three crude products accords with Erlenmeyer's suggestion of the intermediate formation of a diazo-compound, but the results may be held alternatively to denote the occurrence of a Walden inversion affecting the enantiomorphously disposed groups $\cdot CH(NH_2)Ph$ of formulæ (I) and (III), the same equilibrium being reached from the two sides. The oily material formed in the reactions may contain diphenylacetaldehyde, produced as a result of concomitant semipinacolinic deamination (compare McKenzie and Roger, J., 1924, **125**, 844). Since *l*-diphenylhydroxyethylamine and *d*-*iso*diphenylhydroxyethylamine both yield *d*-*iso*hydrobenzoin, it may be inferred that the group $Ph\cdot CH(OH)\cdot$ has a similar spatial disposition in the molecules of these two bases: for example, if formula (I) is *d*-*iso*diphenylhydroxyethylamine, (III) is *l*-diphenylhydroxyethylamine. It appears that the optically active *iso*hydrobenzoins are less soluble than either *dl*-*iso*hydrobenzoin or hydrobenzoin.

The reaction with nitrous acid thus affords no decisive evidence concerning the molecular configurations of the stereoisomeric bases. We suggest, however, that diphenylhydroxyethylamine probably possesses the more symmetric configuration (III), on account of (*a*) the low rotatory power of the free base, (*b*) the remarkable change in rotatory power upon annulling the electropositive influence of the amino-group, and (*c*) the comparative ease with which this base yields condensation products containing heterocyclic ring-systems (compare *Ber.*, 1896, **29**, 1210; *Annalen*, 1904, **337**, 352). The *iso*-base would thus correspond to configuration (I), as suggested by Erlenmeyer on grounds which are no longer tenable (*vide supra*).

Bodewig (*Annalen*, 1876, **182**, 279) found that the crystals separating from ethereal solutions of optically inactive *iso*hydrobenzoin were hemihedral, and by means of a mechanical separation of *d*- and *l*-crystals Erlenmeyer (*Ber.*, 1897, **30**, 1531) obtained specimens exhibiting optical activity in alcoholic solution. The polarimetric data are not precise, and no melting points are quoted, but apparently the maximum rotation observed was $[\alpha]_D - 7{\cdot}30°$. Since we now record maximum values of $[\alpha]_D + 90{\cdot}5°$ and $- 89{\cdot}7°$ for *d*- and *l*-*iso*hydrobenzoin, respectively, it appears that the selected crystals contained not more than 54% of the *l*-component. The fission of *dl*-*iso*hydrobenzoin into optically active components by Erlenmeyer has been accepted for thirty years as a standard example of optical resolution by Pasteur's first method of so-called "spontaneous separation of enantiomers" (compare A. Werner, "Lehrbuch der Stereochemie," 1904, p. 62). It now appears that the formation of well-defined enantiomorphous crystals is not necessarily indicative of a complete optical resolution by this method. The melting-point curve of mixtures of *d*- and *l*-*iso*hydrobenzoin (Fig. 1) departs so markedly from the rectilinear form, when the temperatures of complete fusion are plotted, as to be incompatible with the existence of a conglomerate; the curve conforms, in fact, to Roozeboom's Fig. 11 (*Z. physikal. Chem.*, 1899, **28**, 510), thus indicating the formation of mixed crystals.

It is thus shown that mixed crystals derived from externally compensated organic substances may crystallise in enantiomorphously developed forms. In the light of these observations, it now seems justifiable to advance formyl-*dl*-*neo*menthylamine as a second example of the kind. This substance also yields *d*- and *l*-oriented crystals with hemihedral facets, which, again, display only a slight optical activity in solution; whilst pure formyl-*d*-*neo*menthylamine exhibits no hemihedry (J., 1926, 2228, 2219). Although in this case the melting-point curve (Fig. 1) does not depart so markedly from the conglomerate type as the above-mentioned curve, yet a certain similarity to Roozeboom's Fig. 11 is manifest; moreover, it is clear that a crystal containing a slight excess of one enantiomeride exhibits hemihedral facets, whilst crystals of the pure optically active forms do not. Consequently, if formyl-*dl*-*neo*menthylamine deposited a conglomerate of crystals of the pure *d*- and *l*-forms, these crystals would be holohedral and crystallographically identical; since this is not so, the hemihedral crystals which are actually deposited must be regarded as mixed crystals rather than as a conglomerate. When sufficient material becomes available, it will thus be of particular interest to secure a crystallographic examination of pure *d*- and *l*-*iso*hydrobenzoin, which may also prove to be holohedral. Meanwhile, it becomes necessary to revise the opinions which have hitherto prevailed concerning the applicability of Pasteur's method of optical resolution by the mechanical separation of *d*- and *l*-oriented crystals.

FIG. 1.



EXPERIMENTAL.

Optical Resolution of dl-*Diphenylhydroxyethylamine by Condensation with* d-*Oxymethylenecamphor.*—The *dl*-base (m. p. 163°) was prepared from benzoinoxime by the method of Goldschmidt and Polonowska (*Ber.*, 1887, **20**, 492). An oily separation of the condensation product occurred almost at once upon mixing equivalent weights of the base and *d*-oxymethylenecamphor, dissolved, respectively, in warm 50% acetic acid and methylated spirit. After the mixture had been kept for 10 minutes on the water-bath, the product was isolated and freed from unchanged material in the usual way (J., 1913, **103**, 1516). The resulting viscid syrup crystallised partly when kept in a desiccator; in absolute alcohol (c = 1·2) it had $[\alpha]_D$ + 143°. After three recrystallisations from ether–light petroleum, the solid portion yielded pure d-*diphenylhydroxyethylamino*-d-*methylenecamphor*, consisting of small, colourless prisms, m. p. 146°, $[\alpha]_D$ + 235°. The oily fractions furnished by the mother-liquors consisted of somewhat impure *l*-diphenylhydroxyethylamino-*d*-methylenecamphor, and gave values of $[\alpha]_D$ ranging from + 99·5° to + 101·5°.

When dissolved in rectified spirit and titrated with bromine (1 mol.), *d*-diphenylhydroxyethylamino-*d*-methylenecamphor readily yielded the hydrobromide of the corresponding *d*-base (J., 1913, **103**, 448). After evaporation to small bulk on the water-bath, the product was shaken with water and benzene : the aqueous layer deposited d-*diphenylhydroxyethylamine hydrobromide* upon evaporation to dryness. This salt crystallises from acetone in long, transparent needles, m. p. 192°, $[\alpha]_D$ + 59·0°, $[M]_D$ + 173° in aqueous solution (c = 0·5) (Found : Br, 26·9. $C_{14}H_{15}ON,HBr$ requires Br, 27·2%).

d-*Diphenylhydroxyethylamine*, obtained by precipitating an aqueous solution of the hydrobromide with dilute ammonia, melted at 143° and had $[\alpha]_D$ + 10·0°, when dissolved in absolute alcohol (c = 0·65). No mutarotation was noticed in absolute alcohol, but in acetone (c = 0·2) the original value, $[\alpha]_D$ + 15·1°, changed to − 108·8° in 1·5 hours, and attained the constant value, − 120·8°, in 6 hours. That the low optical rotation of the free base was not due to partial racemisation was shown by the fact that the *hydrochloride* prepared from it had $[\alpha]_D$ + 69·3°, $[M]_D$ + 173°, in aqueous solution (c = 0·65).

Benzylidene-d-*diphenylhydroxyethylamine* crystallises from aqueous alcohol in colourless, transparent prisms, m. p. 109°, $[\alpha]_D$ − 81·4° in absolute alcohol (c = 0·5).

When dissolved in rectified spirit and titrated with bromine, crude *l*-diphenylhydroxyethylamino-*d*-methylenecamphor, having $[\alpha]_D$ + 101·5°, yielded a lævorotatory salt, which after three recrystallisations from acetone gave a specimen of pure l-*diphenylhydroxyethylamine hydrobromide*, m. p. 192°, $[\alpha]_D$ − 59·0°, $[M]_D$ − 173°, in aqueous solution (c = 0·65).

dl-*Diphenylhydroxyethylamine hydrobromide*, prepared for comparison, crystallised from acetone in small needles, m. p. 184°; it is considerably more soluble than the optically active components.

Benzylidene-dl-*diphenylhydroxyethylamine* separates from ether–light petroleum in long, fine, translucent needles, m. p. 120·5°.

Crystallisation of dl-*Diphenylhydroxyethylamine with Optically Active Acids.*—1. Hot aqueous solutions of the hydrochloride of the *dl*-base (2 mols.) and ammonium *d*-bromocamphorsulphonate (1 mol.) were mixed and allowed to cool. The resulting glistening plates, m. p. 210° (decomp.), appeared to consist of dl-*diphenylhydroxyethylamine* d-*bromocamphorsulphonate* (Found: *M*, by titration, 525. $C_{24}H_{30}O_5NBrS$ requires *M*, 524). The salt was obtained in almost quantitative yield, and the original separations showed values of $[M]_D$ ranging from about + 330° to + 350° in dilute aqueous solution (0·1264 g., made up to 20 c.c., gave α_D + 0·84°, $[\alpha]_D$ + 66·5°, $[M]_D$ + 348°). After one or two recrystallisations from aqueous alcohol, the molecular rotation fell to $[M]_D$ + 273° (0·1018 g., made up to 20 c.c., gave α_D + 0·53°, $[\alpha]_D$ + 52·1°); this value, which is practically coincident with that of the acid ion in dilute aqueous solution (J., 1910, **97**, 2201), was unaffected by further recrystallisation. Specimens of the base liberated from fractions of this salt, and also from the original aqueous filtrate, exhibited no appreciable optical rotation when dissolved in absolute alcohol (0·13 g. in 20 c.c.) and examined in a 2-dcm. tube. The variations in the rotatory power of the *d*-bromocamphorsulphonate thus appear to be attributable to tautomerism on the part of the acid (compare J., 1914, **105**, 800).

2. When evaporated to dryness on the water-bath, an alcoholic solution of equivalent weights of *dl*-diphenylhydroxyethylamine and *d*-camphorsulphonic acid yielded a colourless, crystalline solid. The crude product melted indefinitely at about 190°, and had $[\alpha]_D$ +17·8° in dilute aqueous solution; separations consisting of small prisms were readily deposited from solutions in acetone or chloroform. Five successive recrystallisations from these solvents furnished a pure specimen of d-*diphenylhydroxyethylamine* d-*camphorsulphonate*, m. p. 193°; 0·1213 g., made up to 20 c.c. with water, gave α_D + 0·62°, $[\alpha]_D$ + 51·5°, $[M]_D$ + 227° (Found: *M*, by titration, 447. $C_{24}H_{31}O_5NS$ requires *M*, 445). The calculated molecular rotatory power for the basic ion is thus + 175°, a value which is in excellent agreement with $[M]_D$ + 173°, recorded above for the hydrobromide of the *d*-base. In accordance with this conclusion, specimens of the free base and of the hydrobromide, prepared from the salt *d*A*d*B, gave optical rotations practically identical with those already recorded.

Owing to its pronounced solubility, the pure diastereoisomeric salt, *d*A*l*B, could not be isolated. An impure fraction, having $[M]_D$ + 38°, yielded a specimen of crude *l*-diphenylhydroxyethylamine hydrochloride having $[M]_D$ − 13°; this value is practically identical with the calculated value for the basic ion of the fraction in question, and thus it appears that both diastereoisomerides give the normal rotatory powers in dilute aqueous solution.

Action of Nitrous Acid on dl- *and* l-*Diphenylhydroxyethylamine.*—1. A dilute ice-cooled aqueous solution of *dl*-diphenylhydroxyethylamine hydrochloride was treated with the calculated amount of sodium nitrite solution, the reaction being completed on the water-bath. By repeated fractional crystallisation of the partly crystalline product from ether, fractions were isolated which melted at 134° and 118°, and appeared to consist of hydrobenzoin (m. p. 138°) and *iso*hydrobenzoin (m. p. 119°), respectively.

2. *l*-Diphenylhydroxyethylamine hydrobromide upon similar treatment yielded a partly crystalline product, which was extracted with ether and examined polarimetrically in absolute alcohol: 0·2366 g. in 20 c.c. gave α_D + 0·92°, $[\alpha]_D$ + 38·9°. The crude product was purified by recrystallisation from light petroleum; the first fraction melted indefinitely between 117° and 130°, and had $[\alpha]_D$ + 41·9° in absolute alcohol.

Action of Nitrous Acid on l- *and* d-iso*Diphenylhydroxyethylamine.*—1. *dl-iso*Diphenylhydroxyethylamine (*Annalen*, 1899, **307**, 120) upon resolution with *d*-tartaric acid (*Annalen*, 1904, **337**, 321) gave a separation which after one recrystallisation from boiling water consisted of l-iso*diphenylhydroxyethylamine hydrogen* d-*tartrate*, m. p. 177°, $[\alpha]_D$ − 42·6°, $[M]_D$ − 155°, in water ($c = 0·5$). l-iso-*Diphenylhydroxyethylamine*, m. p. 115°, obtained from this salt by precipitation with aqueous ammonia, gave $[\alpha]_D$ − 125·0° in absolute alcohol * ($c = 0·65$), no mutarotation being observed. In acetone solution ($c = 0·6$), a slight mutarotation occurred, the original value, $[\alpha]_D$ − 102·2°, changing to − 90·3° in 3 hours. The *hydrochloride* had $[\alpha]_D$ − 81·7°, $[M]_D$ − 204°, in aqueous solution ($c = 0·65$).

When treated with nitrous acid in the cold, as described above, *l-iso*diphenylhydroxyethylamine hydrochloride yielded a partly crystalline product having $[\alpha]_D$ − 47·1° in absolute alcohol ($c = 1·05$). A wholly crystalline fraction from ether–light petroleum had m. p. 114—125°, $[\alpha]_D$ − 48·0°; a final purification from hot alcohol yielded a crystalline separation having m. p. 138—142°, $[\alpha]_D$ − 79·7°.

In a further experiment, carried out at 70° instead of at 0°, a slight excess of sodium nitrite solution was added gradually to *l-iso*diphenylhydroxyethylamine hydrochloride in a dilute aqueous solution containing one equivalent of free hydrochloric acid. Upon cooling, the product consisted of a brown oil, together with a less amount of small, glistening needles having $[\alpha]_D$ − 80·7° in absolute

---

* Erlenmeyer (*loc. cit.*), using either *d*-tartaric acid or helicin as the resolving agent, observed $[\alpha]_D$ ±109·7°; by using *d*-camphorsulphonic acid, values of $[\alpha]_D$ as high as +130° for the free base have been observed in this laboratory.

alcohol ($c = 0{\cdot}65$), m. p. 137—138°. After recrystallisation from ether–light petroleum, the needles gave $[\alpha]_D - 89{\cdot}1°$, m. p. 144°. A final recrystallisation from absolute alcohol yielded small, transparent prisms or leaflets, m. p. 146°, $[\alpha]_D - 89{\cdot}7°$; these appeared to consist of l-iso*hydrobenzoin* (Found: C, 78·4; H, 6·6. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%). A mixture of this substance with the crystals melting at 138—142°, mentioned above, melted at 138—142°.

2. The crude *d*-*iso*diphenylhydroxyethylamine obtained by adding ammonia to the mother-liquors from the above resolution with *d*-tartaric acid, when crystallised from aqueous alcohol yielded a final (fourth) small fraction having $[\alpha]_D + 125{\cdot}5°$ (absolute alcohol); the preceding fractions consisted of the optically impure *d*-*iso*-base. More of this base was prepared by mixing sodium *l*-tartrate (1 mol.), hydrochloric acid (1 mol.), and *dl*-*iso*diphenylhydroxyethylamine hydrochloride (2 mols.) in an appropriate quantity of hot water. The ensuing crystalline separation, when recrystallised from hot water, had $[\alpha]_D + 43{\cdot}4°$ in dilute aqueous solution, and thus consisted of d-iso*diphenylhydroxyethylamine hydrogen* l-*tartrate,* m. p. 177°. The corresponding base had $[\alpha]_D + 125{\cdot}5°$ (absolute alcohol).

Upon treating *d*-*iso*diphenylhydroxyethylamine with nitrous acid in the usual way at 0°, the resulting partly crystalline product had $[\alpha]_D + 49{\cdot}7°$ in absolute alcohol. In preparing pure *d*-*iso*hydrobenzoin, it was found advantageous, in a further experiment, to add two equivalents of *N*-hydrochloric acid to the reaction mixture before heating on the water-bath to expel the nitrogen. The crystalline deposit formed upon cooling the liquid (0·7 g. from 5·5 g. of base) was readily separated from the accompanying oil: it had $[\alpha]_D + 77{\cdot}0°$ (absolute alcohol), m. p. 135—139°. Recrystallisation from absolute alcohol yielded small, glistening prisms or leaflets of d-iso*hydrobenzoin,* m. p. 146°, $[\alpha]_D + 90{\cdot}5°$ in absolute alcohol ($c = 0{\cdot}65$). In view of the sharp melting point and the close agreement of these values with the corresponding data for *l*-*iso*hydrobenzoin, the preparations may be regarded as optically pure.

Melting-point Curve of Mixtures of d- *and* l-iso*Hydrobenzoin.*—Solid mixtures of known composition were made by mixing and evaporating measured volumes of standard alcoholic solutions of the two components. The equimolecular mixture had a sharp melting point (119°). With the single exception indicated below, the other mixtures melted over a range of at least 5°, and the recorded temperature is that of complete fusion. In all instances, the result was checked by remelting the mixture after it had solidified. The melting points were as follows for mixtures containing the stated percentages of the *d*-enantiomeride : 100, 146°; 90, 139°; 75, 129°; 65, 124°; 55, 119—120°; 50, 119°; 25, 128°. The melting point of pure *dl-iso*hydrobenzoin must thus be accepted as 119°; the values quoted in the literature range from 119° to 122°.

We express our indebtedness to the Department of Scientific and Industrial Research for a maintenance grant to one of the authors (C. C. S.). The research is being continued.

UNITED COLLEGE OF ST. SALVATOR AND ST. LEONARD,
UNIVERSITY OF ST. ANDREWS.
[*Received, March 2nd*, 1927.]