CCCLV.—*The Optically Active Diphenylhydroxyethylamines and* iso*Hydrobenzoins. Part IV. Di*-p-*methoxyphenylhydroxyethylamine and Di*-3:4-*methylenedioxyphenylhydroxyethylamine.*

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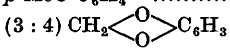
IN continuing an investigation of αβ-amino-alcohols of the type Ar·CH(OH)·CH(NH_2)·Ar and certain derived substances (J., 1927, 910; 1929, 2305; this vol., p. 2377), we have studied two such bases obtained by condensing glycine with anisaldehyde and piperonal, respectively (compare Erlenmeyer, *Annalen*, 1899, **307**, 70; 1904, **337**, 232).

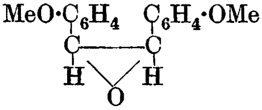
The resulting *dl*-di-*p*-methoxyphenylhydroxyethylamine and *dl*-di-3 : 4-methylenedioxyphenylhydroxyethylamine were resolved into optically active components by fractionally crystallising the *hydrogen* d-*tartrates*, and in each instance the diastereoisomeride of the form *d*A*l*B proved to be the less soluble. In the case of di-3 : 4-methylenedioxyphenylhydroxyethylamine, the more soluble salt, *d*A*d*B, was also isolated in a state of purity.

The following summary affords an interesting comparison of the physical properties of bases of the type Ar·CH(OH)·CH(NH_2)·Ar which we have now investigated; the values of $[\alpha]_D$, which were observed in absolute alcohol for the free bases and in water for their hydrochlorides, indicate a decided enhancement of the rotatory power as a result of substitution in the aromatic nuclei :

	M. p. of base :			Hydrochloride :	
Ar.	*dl*-.	*d*- or *l*-.	$[\alpha]_D$ of base.	$[\alpha]_D$.	$[M]_D$.
C_6H_5	163°	143°	+10·0°	+69·3°	+173°
C_6H_5 (*iso*-base)	129—130	115	−133·0	−83·7	−209
p-MeO·C_6H_4	135·5	111—112	−150·0	−99·0	−307
 $(3:4)\ CH_2{<}^{O}_{O}{>}C_6H_3$	159	164	−196·0	−131·0	−442

From their close structural relationship to the diphenylhydroxyethylamines, it was anticipated that the two substituted bases would yield the hydroanisoins and hydropiperoins, respectively, when treated with nitrous acid. Up to the present, the reaction has been applied only to *l*-di-*p*-methoxyphenylhydroxyethylamine. The yield of crystalline material (30%) was in this case about three times as great as from the optically active *iso*diphenylhydroxyethylamines, and since the substance was optically inactive it was at first supposed to be internally compensated hydroanisoin. Analysis, however, pointed to the replacement of the amino-group by hydroxyl, followed by elimination of water, rather than to formation of the expected glycol. The properties of the substance (m. p. 142—143°)

were distinct from those of either deoxyanisoin (m. p. 108—109°) or di-*p*-methoxydiphenylacetaldehyde (m. p. 104—105°) (*Annalen*, 1869, **151**, 40; *Ber.*, 1907, **40**, 1803; *Bull. Soc. chim.*, 1923, **33**, 1832); moreover, it showed no ability to form an oxime or a semicarbazone. It appears, therefore, to be a substituted ethylene oxide, *i.e.*, either αβ-di-*p*-methoxyphenylethylene oxide or a polymeric form of this substance. The melting point is 101° higher than that of *cis*-αβ-diphenylethylene oxide (m. p. 42°; this vol., p. 2381) and the substance is unaffected by hot dilute acid or alkali or by cold concentrated sulphuric acid (compare Meerwein, *Annalen*, 1913, **396**, 200). The compound thus showed no tendency to isomerise to the aldehyde or ketone, as observed in the case of methylphenylethylene oxide by Venus-Danilova (*J. Russ. Phys. Chem. Soc.*, 1929, **61**, 1479; compare Tiffeneau and Lévy, *Bull. Soc. chim.*, 1926, **39**, 763); its stability is even greater than that of the αβ-diphenylethylene oxides, which resist hydrolysis by dilute acid and resinify in contact with cold concentrated sulphuric acid (Böeseken and Elsen, *Rec. trav. chim.*, 1928, **47**, 694). Although the melting point and stability of the supposed oxide pointed to the possibility of polymerisation having occurred, the molecular weight in benzene was in agreement with the unimolecular formula. Since, further, the substance was optically inactive, even when produced by two distinct methods from an optically active base (*vide infra*), we regard it as the symmetrical *cis*-αβ-di-*p*-methoxyphenylethylene oxide,



This constitution is supported by the observation that the same substance results when *dl*- or *l*-di-*p*-methoxyphenylhydroxyethyltrimethylammonium iodide is heated with silver oxide and water (*Ber.*, 1910, **43**, 885; this vol., p. 2381).

Substituted ethylene oxides have occasionally been obtained by the action of mild dehydrating agents, such as mineral acids, on the corresponding glycols, but in such cases the oxide generally appears to be dimeric (see, for example, Limpricht and Schwanert, *Annalen*, 1871, **160**, 192; Breuer and Zincke, *Annalen*, 1879, **198**, 155; Lévy, *Bull. Soc. chim.*, 1921, **29**, 827; McKenzie and Roger, J., 1924, **125**, 2149). The formation of unimolecular oxides by the action of perbenzoic acid on the corresponding ethylenic compounds in chloroform has been studied by Prilejaieff and by Tiffeneau (*Compt. rend.*, 1924, **179**, 979). No unimolecular oxides have been isolated by Tiffeneau, McKenzie, and their collaborators, either in the dehydration of glycols of the type $R'R'C(OH)\cdot CH(OH)R$ or in deaminations of amino-alcohols of the type $RRC(OH)\cdot CH(NH_2)R$ (*i.e.*, semipinacolinic deaminations) or $RRC(OH)\cdot CH_2\cdot NH_2$ (in both of which R may vary; see McKenzie and Lesslie, *Ber.*, 1929, **62**, 289). It appears that little attention has been devoted to amino-alcohols of the type now under notice, *i.e.*, $RCH(OH)\cdot CH(NH_2)R$, but it is possible that a dimeric oxide is produced in the deamination of the diphenylhydroxyethylamines (this vol., p. 2381). The possibility of the existence of such oxides as an intermediate phase in the dehydration of *l*-α-1-naphthyl-ββ-dibenzylethylene glycol, $(CH_2Ph)_2C(OH)\cdot CH(OH)\cdot C_{10}H_7$, and of *d*-α-phenyl-ββ-dibenzylethylene glycol, $(CH_2Ph)_2C(OH)\cdot CH(OH)Ph$, when optically active ketones are formed, has been discussed by McKenzie and Roger (*Ber.*, 1929, **62**, 272). Further, McKenzie and Lesslie (*loc. cit.*) consider that there is no evidence indicating the intermediate formation of an oxide during the deamination of the optically active amino-alcohols which they have studied; it has also been pointed out by McKenzie and Wills (J., 1925, **127**, 284) that Paal and Weidenkaff (*Ber.*, 1906, **39**, 2062) were unjustified in claiming that *as*-diphenylethylene oxide is formed in the deamination of β-amino-αα-diphenylethanol.

The formation of an oxide by the direct action of nitrous acid on di-*p*-methoxyphenylhydroxyethylamine is thus novel and of some theoretical significance. It is remarkable that an optically active base should furnish an inactive oxide, both in this way and through the corresponding quaternary ammonium hydroxide. It is hoped to prepare the corresponding *trans*-oxide from the stereoisomeride of the above base which will perhaps be obtained by reducing anisoin-oxime with sodium amalgam.

The oily product which is formed, together with the crystalline oxide, in the reaction between di-*p*-methoxyphenylhydroxyethylamine and nitrous acid appears to contain some hydroanisoin, but it has not yet been fully examined.

EXPERIMENTAL.

*Synthesis of Di-*p*-methoxyphenylhydroxyethylamine.*—Aminoacetic acid (37 g.) was dissolved in water (200 c.c.) and mixed with anisaldehyde (196 g. or 175 c.c.) and methylated spirit (200 c.c.). A solution of sodium hydroxide (40 g. in 200 c.c. of water) was added, and the mixture kept at 50° for 10 hours. The resulting crystalline material (30 g.) was washed several times with cold water and once with methylated spirit; upon recrystallisation from absolute alcohol, *anisylidene*-dl-*di*-p-*methoxyphenylhydroxyethylamine* formed fine colourless needles, m. p. 116° (Found: C, 73·2; H, 6·4. $C_{24}H_{25}O_4N$

requires C, 73·6; H, 6·4%). The substance (20 g.) was hydrolysed by heating it on the water-bath for several hours with 2*N*-hydrochloric acid (500 c.c.). Anisaldehyde separated on cooling and was removed with ether. The aqueous layer was freed from ether and treated with ammonia in excess: the ensuing precipitate of *dl*-di-*p*-methoxyphenylhydroxyethylamine (10·1 g.; 75% yield) formed glistening prisms, m. p. 135·5°, when recrystallised from alcohol. The *chloroplatinate* separated from dilute hydrochloric acid in bright yellow leaflets, m. p. 171° (decomp.) [Found: Pt, 20·4. $(C_{16}H_{19}O_3N)_2,H_2PtCl_6$ requires Pt, 20·4%].

The *monoacetyl* derivative was prepared by adding acetic anhydride (0·4 c.c.) to a hot solution of the base (1 g.) in ethyl acetate; long fine needles separated over-night, and after recrystallisation from the same solvent melted at 145—147° (Found: C, 68·3; H, 6·8. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7%). The *diacetyl* derivative was formed by boiling a solution of the base (1 g.) in acetic anhydride (10 c.c.) for 10 minutes; it crystallised from acetone in colourless prisms, m. p. 169—171° (Found: C, 67·0; H, 6·5. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·5%). The *benzylidene* derivative, prepared by adding a slight excess of benzaldehyde to a solution of the base in hot alcohol, separated from absolute alcohol in colourless needles, m. p. 125—126° (Found: C, 76·0; H, 6·5. $C_{23}H_{23}O_3N$ requires C, 76·4; H, 6·4%). The salicylidene derivative formed pale yellow needles, m. p. 134—135°.

Optical Resolution of dl-*Di*-p-*methoxyphenylhydroxyethylamine.*—*d*-α-Bromocamphor-π-sulphonic acid, *d*-camphor-10-sulphonic acid, and *d*-oxymethylenecamphor all yielded vitreous and very soluble products when brought into reaction with the base; also, the hydrogen *d*-tartrate of the base was obtained from absolute alcohol as a syrup. Resolution was ultimately achieved through the last-named salt in the following way.

dl-Di-*p*-methoxyphenylhydroxyethylamine (40 g.), dissolved in hot ethyl acetate (300 c.c.), was mixed with a solution of *d*-tartaric acid (22·4 g.; 1 mol.) in hot methylated spirit. The crystalline separation which resulted upon cooling had α_D − 0·43°, $[\alpha]_D$ − 21·0° (*c* 1·0250, water) *; after two recrystallisations from moist acetone this material yielded pure l-*di*-p-*methoxyphenylhydroxyethylamine hydrogen* d-*tartrate* (19·9 g.) in plates, m. p. 110—111°, α_D − 1·42°, $[\alpha]_D$ − 66·7, $[M]_D$ − 294° (*c* 1·0645, water). The salt crystallised with one molecule of water (Found for the air-dried salt: C, 54·3; H, 6·1. $C_{20}H_{25}O_9N,H_2O$ requires C, 54·4; H, 6·2%). *l*-Di-*p*

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* All the values of α recorded in this paper were observed in a 2-dcm. tube at the ordinary temperature (about 15°).

methoxyphenylhydroxyethylamine, obtained by adding ammonia to an aqueous solution of this salt, crystallised from absolute alcohol in needles, m. p. 111—112°, α_D $-$ 2·87°, $[\alpha]_D$ $-$ 150° (*c* 0·9520, absolute alcohol). Owing to its pronounced solubility, the salt *d*A*d*B could not be obtained pure, but a fraction from the mother-liquors having $[\alpha]_D$ + 35·6° (water) yielded an optically impure dextro-base having α_D + 1·18°, $[\alpha]_D$ + 58·4° (*c* 1·0110, absolute alcohol).

The hydrochloride, crystallised from ethyl acetate, had m. p. 188—190°, α_D $-$ 1·15°, $[\alpha]_D$ $-$ 99·0°, $[M]_D$ $-$ 307° (*c* 0·5805, water). The *monoacetyl* derivative separated from ethyl acetate in needles, m. p. 128—129°, α_D $-$ 0·17°, $[\alpha]_D$ $-$ 16·9° (*c* 0·5025, absolute alcohol) (Found: C, 68·3; H, 6·8. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7%). The *diacetyl* derivative crystallised in prisms from aqueous acetone and had m. p. 160—161°, α_D + 1·04°, $[\alpha]_D$ + 44·6° (*c* 1·1650, absolute alcohol) (Found: C, 67·0; H, 6·5. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·5%). The *benzylidene* derivative crystallised from alcohol in fine colourless needles, m. p. 136°, α_D $-$ 0·89°, $[\alpha]_D$ $-$ 88·1° (*c* 0·5050, absolute alcohol) (Found: C, 76·0; H, 6·5. $C_{23}H_{23}O_3N$ requires C, 76·4; H, 6·4%). The *d*- and *l*-camphor-10-sulphonates of the *l*-base proved to be vitreous substances, but when kept for 2 months in a desiccator the salt *d*A*l*B crystallised; when recrystallised from ethyl acetate, it formed colourless needles, m. p. 163°, $[\alpha]_D$ $-$ 76·9° (*c* 1·0, water). This pure salt was used to seed the mixture of diastereoisomerides obtained from the *dl*-base, but no crystallisation could be induced.

Action of Nitrous Acid on l-*Di*-p-*methoxyphenylhydroxyethylamine.*—A solution of the pure *l*-base (5 g.) in the calculated quantity of *N*-sulphuric acid (18·3 c.c.) was diluted with water (50 c.c.) and cooled in ice. After titration with sodium nitrite (1·26 g. in 50 c.c. of water; 1 mol.), the solution was kept in ice for ½ hour; *N*-sulphuric acid (36·6 c.c.; 2 mols.) was added and the liquid was heated on the water-bath for 2 hours and boiled under reflux for ½ hour. The oily layer was separated and dissolved in ether, and the aqueous layer was kept over-night. Crystalline material (0·3 g.) separated from the aqueous layer, and the oil (2·7 g.) gave a further yield (1 g.) of the same material, m. p. 135—140°, on treatment with ether and light petroleum. The combined fractions, when recrystallised from absolute alcohol, yielded colourless needles, m. p. 142—143°, which exhibited no optical activity when dissolved in acetone (*c* 2·2) (Found: C, 74·3; H, 5·9. $C_{16}H_{18}O_4$ requires C, 70·0; H, 6·6. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). This *substance* was regained unchanged when boiled for 3 hours with 7·5% sulphuric acid or 8% sodium hydroxide solution, and it was even unaffected when left in contact with cold concentrated sulphuric acid for 6 hours.

The dark brown, partly crystalline syrup (10 g.) obtained as a by-product in a series of such preparations yielded a further fraction (1·5 g.) of the above substance, m. p. 142—143°, when treated with acetic anhydride. The filtrate was boiled for 5 minutes and poured into water; no crystalline material was formed, but the resulting oil appeared to contain about 20% of hydroanisoin in the form of diacetate [Found: $CH_3 \cdot CO$, 4·9. Calc. for $C_{16}H_{16}O_4(CO \cdot CH_3)_2$: $CH_3 \cdot CO$, 24·0%].

Synthesis of αβ-*Di*-p-*methoxyphenylethylene Oxide.*—A more drastic method of methylation than the treatment described by Rabe and Hallensleben (*Ber.*, 1910, **43**, 885) for the diphenylhydroxyethylamines was found to be necessary in preparing the quaternary ammonium iodides of *dl*- and *l*-di-*p*-methoxyphenylhydroxyethylamine. Satisfactory results were eventually obtained by applying Wallach's method of methylating bases (*Annalen*, 1898, **300**, 284).

(1) A solution of the *dl*-base (20 g.) in dry methyl alcohol (75 c.c.) was boiled under reflux for an hour with methyl iodide (6·75 c.c.; 1·5 mols.); the mixture was then warmed on the water-bath for 10 minutes with an atomic proportion of sodium (1·7 g.) dissolved in a little dry methyl alcohol. The whole treatment was repeated, and finally the mixture was boiled gently for an hour after the addition of a third quantity (6·75 c.c.) of methyl iodide. The heavy, dark yellow syrup obtained by distilling off the methyl alcohol was stirred with a little cold water in order to remove sodium iodide; the residual material upon treatment with absolute alcohol deposited hard glistening prisms of dl-*di*-p-*methoxyphenylhydroxyethyltrimethylammonium iodide*, m. p. 155° (decomp.) (Found: I, by titration, 28·1. $C_{19}H_{26}O_3NI$ requires I, 28·7%).

The heavy syrup (20 g.) obtained in the last reaction was boiled under reflux with water and its own weight of freshly precipitated silver oxide for 2 hours. Trimethylamine was evolved. The reaction mixture was cooled, acidified, and extracted with ether. The semicrystalline mass (5·5 g.) deposited from the ether yielded wholly crystalline material (2·5 g.) upon further treatment with ether and light petroleum. A solution of this product in absolute alcohol deposited glistening leaflets, m. p. 142—143° (Found: C, 74·7; H, 6·1. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). There was no depression of melting point on mixing this compound with the substance obtained by the action of nitrous acid on the *l*-base, although the two specimens showed distinctive crystalline forms. On recrystallising the needles obtained in the first reaction, and seeding the cooling solution with leaflets from the second reaction, a crop of leaflets separated. The converse recrystallisation was also carried out, so that needles were obtained on seeding a specimen resulting from the second reaction. The two preparations were thus chemically identical, although dimorphous.

(2) The *l*-base (10 g.) was converted into the quaternary ammonium iodide by the method described above. The crude product (14·4 g.) separated from absolute alcohol in well-defined colourless prisms, m. p. 145° (decomp.), α_D $-$ 1·07°, $[\alpha]_D$ $-$ 34·6° (*c* 1·5475, methyl alcohol). When treated with silver oxide and hot water, the iodide (10 g.) gave an optically inactive, semi-crystalline syrup (2·8 g.), which yielded glistening leaflets (1·0 g.), m. p. 142—143°, when recrystallised from absolute alcohol. This substance was optically inactive in solution and identical with the substance formed by the action of (*a*) nitrous acid on *dl*-di-*p*-methoxyphenylhydroxyethylamine, and (*b*) silver oxide and hot water on the *dl*-quaternary ammonium iodide.

The oxide was found to be unimolecular in benzene solution (Found : *M*, 257, 245, 258. $C_{16}H_{16}O_3$ requires *M*, 256).

Synthesis of dl-*Di*-3 : 4-*methylenedioxyphenylhydroxyethylamine.*—A condensation conducted as above, in which piperonal was used in place of anisaldehyde and the temperature was kept at 60°, readily yielded a crystalline deposit of *piperonylidene*-dl-*di*-3 : 4-*methylenedioxyphenylhydroxyethylamine*; this substance separated from ethyl acetate in pale yellow needles, m. p. 177° (Found : C, 67·8; H, 4·5. $C_{24}H_{19}O_7N$ requires C, 68·1; H, 4·5%). The hydrolysis was first attempted by the same method as before, but a yield of only 70% of impure base resulted, and the large excess of acid led to the formation of a dark brown oily by-product which was insoluble in ether. On reducing the volume of acid to the calculated quantity, a yield of 85% of a purer base was obtained. A partial hydrolysis was also effected by suspending the piperonylidene derivative in warm rectified spirit and adding bromine (1 mol.). The alcohol was evaporated from the clear colourless solution, and the hydrobromide of the base was extracted from the residue with hot water; the addition of aqueous ammonia to this solution gave a yield of 60% of the base. The brown oily by-product was possibly a brominated piperonal. When decolourised in absolute alcohol with animal charcoal and recrystallised from ethyl acetate, the base formed colourless prisms, m. p. 159°. The *chloroplatinate* separated from dilute hydrochloric acid in deep yellow leaflets, m. p. 184° (decomp.) [Found : Pt, 19·4. $(C_{16}H_{15}O_5N)_2,H_2PtCl_6$ requires Pt, 19·3%].

Optical Resolution of dl-*Di*-3 : 4-*methylenedioxyphenylhydroxyethylamine.*—Upon mixing molecular proportions of the *dl*-base and *d*-tartaric acid, dissolved separately in warm methylated spirit, a crystalline separation occurred at once, and further crystalline material was obtained upon concentrating the mother-liquor. The first three fractions had $[\alpha]_D$ − 40·0°, + 81·2°, and + 67·0° (*c* 1·0, water), respectively. Five recrystallisations of the first fraction from aqueous acetone furnished pure l-*di*-3 : 4-*methylenedioxyphenylhydroxyethylamine hydrogen* d-*tartrate* in fine silky needles, m. p. 208° (decomp.), α_D − 2·28°, $[\alpha]_D$ − 104·2°, $[M]_D$ − 470° (*c* 1·0930, water) (Found : C, 53·1 ; H, 4·6. $C_{20}H_{21}O_{11}N$ requires C, 53·2 ; H, 4·7%). By recrystallising the combined second and third fractions six times from aqueous acetone, pure d-*di*-3 : 4-*methylenedioxyphenylhydroxyethylamine hydrogen* d-*tartrate* was obtained in minute leaflets, m. p. 145°, α_D + 1·80°, $[\alpha]_D$ + 117·1°, $[M]_D$ + 549° (*c* 0·7680, water) (Found : C, 51·4 ; H, 5·0.

$$C_{20}H_{21}O_{11}N,H_2O$$

requires C, 51·2 ; H, 4·9%). The free, optically active bases were obtained by decomposing hot aqueous solutions of these diastereoisomeric salts with ammonia : *l*-di-3 : 4-methylenedioxyphenylhydroxyethylamine had m. p. 164°, α_D − 2·87°, $[\alpha]_D$ − 196° (*c* 0·7320, absolute alcohol) ; the *d*-base had m. p. 164°, α_D + 1·79°, $[\alpha]_D$ + 196° (*c* 0·4575, absolute alcohol). From 20 g. of the *dl*-base, 3·9 g. of the *l*-base and 1·9 g. of the *d*-base were obtained, corresponding, respectively, to 39% and 19% of the calculated yields. The *diacetyl* derivative of the *l*-base crystallised from ethyl acetate in needles, m. p. 222—224° (decomp.), α_D − 0·22°, $[\alpha]_D$ − 38·5° (*c* 0·2850, absolute alcohol) (Found : C, 62·6 ; H, 5·0. $C_{20}H_{19}O_7N$ requires C, 62·3 ; H, 5·0%). The hydrochloride of the *l*-base formed a vitreous mass when obtained from aqueous solution by evaporation ; it gave α_D − 3·06°, $[\alpha]_D$ − 131°, $[M]_D$ − 442° (*c* 1·1690, water).

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