262. *The Optically Active Diphenylhydroxyethylamines and* iso*Hydrobenzoins. Part VI. The Di-*o*-methoxyphenylhydroxyethylamines and Related Substances.*

By Norman A. B. Wilson and John Read.

In continuing researches on compounds of the type Ar·CH(OH)·CH(NH_2)·Ar (cf. Read and Campbell, J., 1930, 2674) it was hoped to extend the method of condensing aldehydes with glycine (Erlenmeyer, *Annalen*, 1906, **337**, 232) to the preparation of a comprehensive series of this kind, since the reaction concerned had provided an entry to the *iso*-series of such αβ-amino-alcohols derived from benzaldehyde, *o*-methoxybenzaldehyde, anisaldehyde and piperonal. The failure of the condensation with salicylaldehyde (Erlenmeyer, *loc. cit.*) suggested an inhibitive effect due to the possible formation of a chelate complex by the sodium derivatives of *o*-hydroxyaldehydes (cf. Brady and Bodger, J., 1932, 952). It is now found, however, that the condensation fails also with the following aldehydes: *m*-methoxy-, *o*- and *m*-nitro-, *p*-dimethylamino-, veratric, benzoylsalicylic, 1- and 2-naphthoic, and with œnanthal; moreover, Ingersoll (private communication) reports failures with *p*-tolualdehyde, furfural, and cinnamic aldehyde. It does not appear possible to deduce from these observations any general rule concerning the applicability of the reaction, unless perhaps a fresh mechanism is postulated (cf. Erlenmeyer, *loc. cit.*).

The amino-alcohol furnished by *o*-methoxybenzaldehyde in this condensation is now shown to belong, as anticipated, to the *iso*-series, since the quaternary ammonium iodides obtained from the *dl*- and the *l*-form each furnished the internally compensated *cis*-form of αβ-*di*-o-*methoxyphenylethylene oxide*, m. p. 127—128°, when distilled with silver oxide and water (J., 1930, 2378, 2680). The stereoisomeric *di*-o-*methoxyphenylhydroxyethylamine*, corresponding to the *trans*-oxide, was obtained in very small yield by reducing di-*o*-methoxybenzoinoxime with sodium and alcohol, the main product being *α-aminodi*-(o-*methoxybenzyl*). Because of the curious results observed in the deamination of the diphenylhydroxyethylamines (J., 1930, 2380) and *l*-di-*p*-methoxyphenylhydroxyethylamine (*ibid.*, p. 2674), the action of nitrous acid on *l-iso*-di-*o*-methoxyphenylhydroxyethylamine was studied carefully. The oily, optically inactive product appeared to consist of a

mixture of the hydrobenzoin, the ethylene oxide, and di-*o*-methoxyphenylacetaldehyde. The aldehyde was diagnosed by comparison of its semicarbazone with a synthesised specimen. There was no evidence of the production of di-*o*-methoxydeoxybenzoin in the deamination. Although the reaction appears to follow an unusual course, there is no difficulty in interpreting the formation of the aldehyde in terms of the mechanism depicted for the semipinacolinic deamination by McKenzie (see, *e.g.*, *J. Soc. Chem. Ind.*, 1931, **50**, 926). Further evidence is here provided of the complex nature of the deamination of αβ-amino-alcohols of the symmetrical type, Ar·CH(OH)·CH(NH_2)·Ar.

Experimental.

dl-iso*Di-o-methoxyphenylhydroxyethylamine.*—This base was prepared from aminoacetic acid (37 g.) and *o*-methoxybenzaldehyde (196 g.) according to the general method of Erlenmeyer (*Annalen*, 1906, **337**, 232) with certain modifications suggested by the work of Read and Campbell (J., 1930, 2676) on *iso*diphenylhydroxyethylamine. The resulting crude crystalline *o*-methoxybenzylidene-*dl*-di-*o*-methoxyphenylhydroxyethylamine (140 g.) was hydrolysed with hot 2*N*-hydrochloric acid. After recrystallisation from methyl alcohol, *dl-iso*di-*o*-methoxyphenylhydroxyethylamine melted at 136°. 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, from which it crystallised in colourless needles, m. p. 180° (Found: C, 68·3; H, 6·7. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7%); it did not react with nitrous acid (cf. J., 1929, 2305). The diacetyl derivative, formed by boiling the base with excess of acetic anhydride, separated from acetone in colourless prisms, m. p. 152°. The *benzylidene* derivative, prepared in hot alcohol, formed colourless needles, m. p. 131° (Found: C, 73·5; H, 6·3. $C_{23}H_{23}O_3N$ requires C, 73·7; H, 6·4%).

Optical Resolution of dl-iso*Di-o-methoxyphenylhydroxyethylamine.*—The *dl*-base (13 g.) was mixed in hot aqueous solution with *d*-camphor-10-sulphonic acid (11·1 g., 1 equiv.). The resulting crystalline salt (13 g.) had $[\alpha]_D$ − 19·1° (*c* 1·3, water). Two recrystallisations from acetone gave pure l-iso*di-o-methoxyphenylhydroxyethylamine* d-*camphor-10-sulphonate* (9 g.), m. p. 109°, $[\alpha]_D$ − 43·3° (*c* 1·0, water). The salt crystallises slowly from water in large, transparent doubly-terminated prisms (Found: C, 57·5; H, 7·1. $C_{26}H_{35}O_7NS,2H_2O$ requires C, 57·5; H, 7·2%). The diastereoisomeric salt, *d*A*d*B, could not be obtained pure. The *d*-α-bromocamphor-π-sulphonate of the *dl*-base was an uncrystallisable syrup; the hydrogen *d*-tartrate, after 12 successive fractional crystallisations from moist acetone, yielded a base having only $[\alpha]_D$ − 25·3° (*c* 1·1, alcohol).

l-iso*Di-o-methoxyphenylhydroxyethylamine.*—The free base, obtained by adding ammonia to a solution of the above *d*-camphor-10-sulphonate, crystallised from methyl alcohol in transparent needles, m. p. 111°, $[\alpha]_D$ − 52·7° (*c* 0·9, alcohol). The hydrochloride failed to crystallise. The monoacetyl derivative separated from ethyl acetate in leaflets, m. p. 146°, $[\alpha]_D$ + 3·8° (*c* 1·7, alcohol). The *diacetyl* derivative crystallised from aqueous acetone in needles, m. p. 170°, which showed no perceptible optical rotation in absolute alcohol (*c*, 1·5) (Found: C, 66·8; H, 6·6. $C_{20}H_{23}O_5N$ requires C, 66·8; H, 6·6%). The *salicylidene* derivative was deposited from light petroleum in brilliant yellow needles, m. p. 106°, $[\alpha]_D$ − 24·0° (*c* 2·7, alcohol) (Found: C, 73·1; H, 6·0. $C_{23}H_{23}O_4N$ requires C, 73·6; H, 6·0%).

cis-αβ-*Di-o-methoxyphenylethylene Oxide.*—This substance was prepared by the general method of Read and Campbell (J., 1930, 2381). Upon methylation, *dl-iso*di-*o*-methoxyphenylhydroxyethylamine (20 g.) yielded dl-iso*di-o-methoxyphenylhydroxyethyltrimethylammonium iodide* (34 g.), forming colourless prisms from ethyl acetate, m. p. 183—184° (Found: I, by titration, 28·8. $C_{19}H_{26}O_3NI$ requires I, 28·7%). When heated under reflux with water and its own weight of fresh silver oxide, this substance (15 g.) decomposed into trimethylamine and cis-αβ-*di-o-methoxyphenylethylene oxide*; when steam-distilled and recrystallised from aqueous alcohol, the oxide formed feathery needles, m. p. 127—128° (Found: C, 75·0; H, 6·5; *M*, cryoscopic in benzene, 245, 244, 251. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·2%; *M*, 256). *l-iso*Di-*o*-methoxyphenylhydroxyethylamine yielded an optically inactive oxide identical in all respects with the above oxide obtained from the *dl*-base.

Deamination of l-iso*Di-o-methoxyphenylhydroxyethylamine.*—A solution of the *l*-base (5 g.) in *N*-sulphuric acid (18·3 c.c., 1 equiv.) 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 (36·5 c.c.) was added, and the liquid heated on the water-

bath for 2 hours and boiled under reflux for ½ hour. The resulting deep yellow oil (3·5 g.) was soluble in ether and insoluble in light petroleum. It reduced Fehling's solution appreciably, was optically inactive (*c* 2·0, alcohol), and did not give Liebermann's reaction (cf. McKenzie and Luis, *Ber.*, 1932, **65**, 800). The analytical values fell between those required by αβ-di-*o*-methoxyphenylethylene oxide, or the isomeric aldehyde or ketone (see below), and di-*o*-methoxyhydrobenzoin (Found : C, 72·4; H, 6·2; N, absent. Calc. for $C_{16}H_{16}O_3$: C, 75·0; H, 6·2%. Calc. for $C_{16}H_{18}O_4$: C, 70·0; H, 6·6%).

The oil (1·5 g.) gave a semicarbazone (0·6 g.) which crystallised from absolute alcohol in colourless needles, m. p. 203—204°, and gave analytical results agreeing with the semicarbazone of either di-*o*-methoxyphenylacetaldehyde or di-*o*-methoxydeoxybenzoin (Found : C, 64·8; H, 6·0. Calc. for $C_{17}H_{19}O_3N_3$: C, 65·2; H, 6·1%). As shown below, it was the former substance. Acetyl determinations were made on the fully acetylated oil (Gildemeister and Hoffmann, "The Volatile Oils," 1913, I, 575) [Found : COMe, 7·4, 7·4. Calc. for MeO·C_6H_4·CH(OAc)·CH(OAc)·C_6H_4·OMe : COMe, 24·1%]. The evidence points to the oil consisting approximately of 30% of the hydrobenzoin (from the acetyl value), 34% of the aldehyde (from the yield of semicarbazone), and 36% of unidentified material, presumably the ethylene oxide. Any of the last substance present would apparently be in the unimolecular form (Found : *M*, cryoscopic in benzene, 249, 279, 271. Calc. for $C_{16}H_{18}O_4$: *M*, 274. Calc. for $C_{16}H_{16}O_3$: *M*, 256. Calc. for $C_{32}H_{32}O_6$: *M*, 512).

Di-o-methoxydeoxybenzoinsemicarbazone.—*o*-Methoxybenzaldehyde was obtained quantitatively by methylating salicylaldehyde with methyl sulphate (3 mols.) in presence of 12·5% aqueous sodium hydroxide (6 equivs.) at 80° with vigorous stirring. The derived benzoin (Irvine, J., 1901, **79**, 669), when distilled with twice its weight of zinc dust at 250—300°/70 mm. in an atmosphere of carbon dioxide (Irvine and Moodie, unpublished), yielded a pale yellow, oily distillate, which crystallised partly on keeping. When treated with semicarbazide acetate (J., 1922, **121**, 1876), this furnished a 50% yield of *di-o-methoxydeoxybenzoinsemicarbazone*, crystallising from alcohol in colourless prisms, m. p. 196° (Found : C, 64·9; H, 6·1. $C_{17}H_{19}O_3N_3$ requires C, 65·2; H, 6·1%). A mixture of this substance with the semicarbazone (m. p. 203—204°) of the reducing substance obtained in the above deamination melted indefinitely at about 186°.

Di-o-methoxyphenylacetaldehydesemicarbazone.—Di-*o*-methoxybenzoin, m. p. 101·5°, was reduced with sodium amalgam (Irvine and Moodie, J., 1907, **91**, 538). The resulting di-*o*-methoxyhydrobenzoin (9 g., m. p. 153°) was boiled with 20% sulphuric acid : the ensuing pale yellow, mobile syrup (7·5 g.) when stirred with absolute alcohol (2 c.c.) yielded colourless prisms (6·6 g.) of *di-o-methoxyhydrobenzoin anhydride*, m. p. 175·5° (Found : C, 74·7; H, 6·4. $C_{32}H_{32}O_6$ requires C, 75·0; H, 6·2%). This substance was unaffected when boiled with concentrated aqueous sodium hydroxide. The mother-liquors, upon treatment with alcoholic semicarbazide acetate, yielded *di-o-methoxyphenylacetaldehydesemicarbazone*, which crystallised from absolute alcohol in colourless needles, m. p. 204° (Found : C, 65·2; H, 6·1. $C_{17}H_{19}O_3N_3$ requires C, 65·2; H, 6·1%). A mixture of this substance with the semicarbazone of the reducing substance formed in the above deamination (m. p. 203—204°) also melted at 204°, and the two preparations were identical in all respects.

Attempts to prepare the Stereoisomeric Di-o-methoxyphenylhydroxyethylamine.—Di-*o*-methoxybenzoinoxime (10 g.), m. p. 143° (J., 1901, **74**, 669), was reduced only with great difficulty by sodium (30 g.) and alcohol (350 c.c.). The syrupy product yielded a crude crystalline hydrogen tartrate (12·6 g.) having $[\alpha]_D$ — 42·9° (*c* 1·6, water). The solution of this material in alcohol–ethyl acetate gave a very small crop of crystals, which after repeated crystallisation from this solvent furnished small colourless prisms (0·8 g.), m. p. 160°, of l-*di-o-methoxyphenylhydroxyethylamine hydrogen* d-*tartrate*, $[\alpha]_D$ — 66·0° (*c* 0·5, water) (Found : C, 56·1; H, 6·2. $C_{20}H_{25}O_9N$ requires C, 56·7; H, 5·9%). The constant optical rotation corresponds to the value $[M]_D$ — 321° for the basic ion. The amount of the salt *l*B*d*A was too small to permit of the isolation and characterisation of the free base.

The original mother-liquor obtained in the above process was evaporated to dryness; the residue, after four recrystallisations from alcohol, yielded crystals (5·5 g.) having $[\alpha]_D$ + 10·2° (*c* 3·6, water). The derived base, *α-aminodi-*(*o-methoxybenzyl*), crystallised from light petroleum in small needles, m. p. 60° (Found : C, 74·8; H, 7·5. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·5%). The value, $[M]_D$ + 41·5°, for the above hydrogen *d*-tartrate of the base is identical with that of the acidic ion in dilute aqueous solution : the base was accordingly optically inactive. The *acetyl* derivative, obtained by using acetic anhydride, crystallised from aqueous alcohol in soft needles, m. p. 156° (Found : C, 72·2; H, 6·9. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·0%). The

salicylidene derivative separated from light petroleum in pale yellow prisms, m. p. 83·5° (Found : C, 76·5; H, 6·4. $C_{23}H_{23}O_3N$ requires C, 76·5; H, 6·4%).

dl-iso*Di*-o-*chlorophenylhydroxyethylamine*.—*o*-Chlorobenzylidene-*dl-iso*di-*o*-chlorophenylhydroxyethylamine, prepared in 46% yield from *o*-chlorobenzaldehyde and aminoacetic acid, by Erlenmeyer's method, crystallised from aqueous alcohol in faintly yellow prisms, m. p. 62°. Upon hydrolysis, this substance gave dl-iso*di*-o-*chlorophenylhydroxyethylamine*, which separated from aqueous alcohol in colourless needles, m. p. 151·5° (Found : C, 59·9; H, 4·7. $C_{14}H_{13}ONCl_2$ requires C, 59·6; H, 4·7%). The following were also prepared : the *monoacetyl* derivative, needles, m. p. 160° (Found : C, 59·3; H, 4·7. $C_{16}H_{15}O_2NCl_2$ requires C, 59·3; H, 4·6%); *diacetyl* derivative, needles, m. p. 184° (Found : C, 59·2; H, 4·7. $C_{18}H_{17}O_3NCl_2$ requires C, 59·0; H, 4·6%); *benzylidene* derivative, prisms, m. p. 146·5° (Found : C, 67·9; H, 4·6. $C_{21}H_{17}ONCl_2$ requires C, 68·1; H, 4·6%); *salicylidene* derivative, fine, yellow prisms, m. p. 130·5° (Found : C, 65·1; H, 4·4. $C_{21}H_{17}O_2NCl_2$ requires C, 65·3; H, 4·4%).

The hydrogen *d*-tartrate, *d*-camphor-10-sulphonate, *l*-menthoxyacetate, and *d*-methylenecamphor derivatives of the *dl*-base were crystalline substances whose optical rotations altered only slightly after repeated fractional crystallisation. The regenerated base was optically inactive, with the exception of a specimen from a fraction of the *d*-camphor-10-sulphonate which had been recrystallised six times : this had m. p. 152—152·5°, $[\alpha]_D$ + 3·5° (*c* 2·0, alcohol). The *d*-α-bromocamphor-π-sulphonate, *d*-camphor-10-sulphonylsalicylidene derivative (J., 1934, 233), and the acetylated *d*-methylenecamphor derivative were uncrystallisable syrups. Thus, no practicable optical resolution of the base was achieved : a similar conclusion has been reached by Ingersoll (private communication).

The Direct Preparation of Hydrobenzoins from Aldehydes.—Kaufmann and also Elbs and Brand (*Z. Elektrochem.*, 1898, **4**, 461; 1902, **8**, 784) obtained hydrobenzoins and certain other alcohols by the electrolytic reduction of aldehydes and ketones; but in the work now summarised use was made of a simplified technique due to Law (J., 1906, **89**, 1512; 1907, **91**, 748). Benzaldehyde and anisaldehyde gave quantitative yields of mixtures of hydro- and *iso*hydrobenzoin and -anisoin respectively, the *iso*-compound being the second to separate in each instance. It was not possible to obtain the hydroanisoins in a crystalline form suitable for detailed goniometric examination. In other cases no product crystallised, and the reaction mixture was diluted with water and extracted with ether. *m*-Methoxybenzaldehyde furnished *m*-methoxybenzyl alcohol, b. p. 115°/1·2 mm., 255°/760 mm.; m-*methoxybenzyl* 3 : 5-*dinitrobenzoate* crystallised from alcohol–ethyl acetate in pale yellow prisms, m. p. 124° (Found : C, 54·8; H, 3·6. $C_{15}H_{12}O_7N_2$ requires C, 54·8; H, 3·7%). *o*-Nitro-, *m*-nitro- and *p*-dimethylaminobenzaldehyde gave rise to resins; 1-naphthaldehyde was partly converted into the corresponding acid; *o*-methoxybenzaldehyde furnished the corresponding acid and alcohol. In none of these instances could any of the hydrobenzoin be isolated. Catalytic reduction of the corresponding benzils and benzoins was not investigated (*J. Amer. Chem. Soc.*, 1929, **51**, 2163; 1930, **52**, 4495; 1931, **53**, 3115, 3510).

We express our thanks to the Carnegie Trust for the Universities of Scotland for a Scholarship awarded to one of us (N. A. B. W.).

THE UNIVERSITY, ST. ANDREWS. [*Received, May 20th,* 1935.]