made alkaline with sodium carbonate. The oil which separated was extracted twice with ether and the combined ethereal extracts washed with water and dried over anhydrous potassium carbonate. The ester hydrochloride separated as a fine crystalline precipitate upon addition of dry hydrogen chloride to the filtered ethereal solution. The collected precipitate was recrystallized from absolute ethanol; m. p. 190–191°.

Anal. Calcd. for $C_{13}H_{18}O_4N_2ClF$: N, 8.74. Found: N, 8.72.

Diethylaminoethyl-3-fluoro-4-aminobenzoate Hydrochloride.—A solution of 1 g. of diethylaminoethyl-3-fluoro-4-nitrobenzoate in 100 ml. of absolute ethanol absorbed the theoretical quantity of hydrogen in fifteen minutes using Adams platinum oxide catalyst at a pressure of 2 atmospheres at room temperature. The catalyst was recovered by filtration and the solvent removed by distillation *in vacuo*. The product after recrystallization from a mixture of alcohol and ether melted at 142–143°.

Anal. Calcd. for $C_{13}H_{20}O_2N_2ClF$: N, 9.64. Found: N, 10.24.

Procedure I.—Following the procedure of Blicke and Lilienfeld[5] the acid chloride hydrochlorides of 2-chloro-4-aminobenzoic acid,[6] 3-chloro-4-aminobenzoic acid[3] and 2-fluoro-4-aminobenzoic acid[4] were prepared. These unstable compounds were immediately esterified by reaction with the appropriate alkanol or alkanolamine hydrochloride.

Procedure II.—Hydrogen chloride was passed for three hours through a refluxing solution of 20 g. (0.1 mole) of 2-chloro-4-acetamidobenzoic acid in 200 cc. of the appropriate alkanol. The mixture was then poured onto ice and excess sodium carbonate. The precipitated ester was removed by filtration and purified by recrystallization.

Summary

The preparation of various esters of 2-chloro-4-aminobenzoic acid and the diethylaminoethyl esters of 3-chloro- and 2- and 3-fluoro-4-aminobenzoic acids has been described.

(6) Kunckell and Richartz, *Ber.*, **40**, 3395 (1907).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, WINTHROP CHEMICAL COMPANY, INC.]

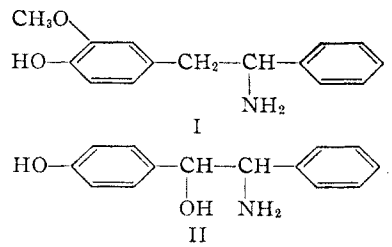
The Preparation of Substituted Diphenylethylamines and Diphenylethanolamines

BY WARREN D. McPHEE AND ERNST S. ERICKSON, JR.[1]

In 1943, Dodds, Lawson and Williams[1a] published a note on the morphine-like properties of diphenylethylamine and five related compounds. In a later publication[2] the study was extended to include nine compounds not previously tested, several of which had hydroxyl or methoxyl groups in the aromatic rings. The most active substances of the English workers were the hydrochlorides of α,β-diphenyl-β-hydroxyethylamine, α,β-diphenylethylamine and dimethyldesylamine. These three were tested clinically in a small number of patients, the first substance giving results which indicated that it might be useful as a general analgesic.

The present project was undertaken in order to ascertain the effect of alkoxyl and hydroxyl substituents in the β-phenyl groups of diphenylethylamine and diphenylethanolamine. After our synthetic work had been completed, there appeared a third publication[3] of the English group stating that α,β-diphenyl-β-hydroxyethylamine, which was the most active substance they had tested and which had been found to be effective in relieving pain due to pressure on nerves in patients with inoperable tumors, "has no universal analgesic action and cannot be used generally as a substitute for morphine." We had prepared α,β-diphenyl-β-hydroxyethylamine and under the conditions of our tests[4] this compound does not show analgesic activity. When the third publication[3] appeared, it was apparent, however, from the methods of synthesis that a different stereoisomer was studied in each series of tests. The English workers employed the isomer of m. p. 163° obtained from benzoin oxime while we studied the more easily prepared Erlenmeyer base of m. p. 129°.[5]

Pharmacological tests employing electrical stimulation in dogs indicate, however, that several of the compounds of the present series have definite analgesic properties. The most effective are the hydrochlorides of α-phenyl-β-(3-methoxy-4-hydroxyphenyl)-ethylamine (I) and α-phenyl-β-(4-hydroxyphenyl)-β-hydroxyethylamine (II).



I

II

The action of these compounds appears to be somewhat different from that of morphine. The substances exert a prolonged effect at peak activity whereas the effect of morphine tapers off quite regularly from the peak.

The first synthetic approach considered was the condensation of suitably substituted aromatic aldehydes with phenylnitromethane to form substituted α-nitrostilbenes and reduction of the latter to substituted diphenylethylamines. While

(1) At present, Ensign, U. S. N. R.

(1a) Dodds, Lawson and Williams, *Nature*, **151**, 614 (1943).

(2) Dodds, Lawson and Williams, *Proc. Roy. Soc.* (London), **B132**, 119 (1944).

(3) Dodds, Lawson and Williams, *Nature*, **154**, 514 (1944).

(4) The pharmacological tests were carried out under the direction of Dr. T. J. Becker of these Laboratories and will be reported elsewhere.

(5) *Cf.* Read and Steele, *J. Chem. Soc.*, 910 (1927).

this scheme is simple enough, the reduction of the nitrostilbenes gave considerable trouble. This difficulty has been encountered by others. Reichert and Hoffmann[6] found it advisable to reduce the nitrostilbenes in the presence of palladium-on-charcoal in pyridine to the oxime stage, after which sodium amalgam was used to carry the reduction to the corresponding amines. In a later paper Reichert[7] achieved a one-step reduction of 3,4-methylenedioxy-α'-nitrostilbene to the desired amine by use of a high ratio of platinum oxide catalyst in glacial acetic and concentrated sulfuric acids. There have been similar reductions of β-nitrostyrenes to phenylethylamines,[8] all employing especially large amounts of catalyst in acetic and sulfuric acid mixtures. We did not find these reductive procedures practicable and so this synthetic scheme was abandoned.

The method adopted is outlined

$$\mathrm{ArCHO} + \mathrm{C_6H_5CH_2COONa} \longrightarrow \mathrm{ArCH{=}C(C_6H_5)COONa} \longrightarrow \mathrm{ArCH_2CH(C_6H_5)COOH} \longrightarrow \mathrm{ArCH_2CH(C_6H_5)CONH_2} \longrightarrow \mathrm{ArCH(NH_2){-}CH(C_6H_5)}$$

The aldehydes used were vanillin, piperonal, anisaldehyde, *p*-hydroxybenzaldehyde, protocatechualdehyde, veratraldehyde and "ethyl vanillin." The Perkin condensation gave fair yields in all cases except that of protocatechualdehyde. The reaction of the latter was dropped, and the desired amine was obtained by demethylating α-phenyl-β-(3-methoxy-4-hydroxyphenyl)-ethylamine.

Reduction of the substituted α-phenylcinnamic acids proceeded smoothly in sodium carbonate solution with Raney nickel in essentially quantitative yield. The resulting acids were converted with thionyl chloride to acid chlorides which, without purification, were treated in dioxane with aqueous ammonia; the corresponding amides were formed in high yield in a pure state. The Hofmann reaction to form the amines gave yields of about 60%.

The acids having free hydroxyl groups could not be converted to amides without protecting the group by benzylation. After benzylation they could be carried through the amide and amine stages readily. The amine hydrochlorides were easily debenzylated by catalytic hydrogenolysis.

The synthesis of diphenylethanolamines was carried out according to the scheme

$$\mathrm{ArH} + \mathrm{C_6H_5CH_2COCl} \longrightarrow \mathrm{Ar{-}COCH_2C_6H_5} \longrightarrow \mathrm{ArCOCC_6H_5} \longrightarrow \mathrm{Ar{-}CH(OH){-}CH(NH_2){-}C_6H_5}$$
$$\|$$
$$\mathrm{NOH}$$

where Ar represents 3,4-dihydroxyphenyl and *p*-hydroxyphenyl. The Friedel–Crafts reactions were carried out by modifications of published procedures. Before nitrosation of the ketones, the hydroxy groups were protected by benzylation. On reduction, the isonitroso group was carried to the amino stage and the benzyl group cleaved. The ketone was reduced on longer treatment.

(6) Reichert and Hoffmann, *Arch. Pharm.*, **274**, 153, 217 (1936).

(7) Reichert, *ibid.*, **274**, 505 (1936).

(8) Kindler, Brandt and Gehlhaar, *Ann.*, **511**, 209 (1934); Schales, *Ber.*, **68**, 1579 (1935); Kindler and Brandt, *Arch. Pharm.*, **273**, 478 (1935).

Experimental[9]

As an illustration, the preparation of α-phenyl-β-(3-methoxy-4-hydroxyphenyl)-ethylamine hydrochloride is given. The tables give the properties of the other products which were made in substantially the same way.

α-Phenyl-3-methoxy-4-hydroxycinnamic Acid.—A solution of 131 g. (0.86 mole) of vanillin and 150 g. (0.95 moles) of sodium phenylacetate in 600 cc. (6.38 moles) of acetic anhydride was refluxed for five hours. Then 150 cc. (8.33 moles) of water was added dropwise to the solution at a rate sufficient to maintain the solution at reflux. Upon cooling, a tan solid separated and was washed thoroughly with water. The tan solid was dissolved in 1800 cc. of 6% sodium hydroxide and the solution was refluxed for one hour. Acidification of this solution to *p*H 2 with concentrated hydrochloric acid yielded 137 g. (59% yield) of slightly yellow solid, m. p. 186–187°.

α-Phenyl-β-(3-methoxy-4-hydroxyphenyl)-propionic Acid.—A solution of 175.8 g. (0.65 mole) of α-phenyl-3-methoxy-4-hydroxycinnamic acid in an equivalent amount of 10% sodium carbonate was diluted to 860 cc. with water. The reduction was carried out at 300–450 lb./sq. in. pressure and 100° with Raney nickel catalyst and required four hours. After removal of the catalyst, the solution was acidified to *p*H 2 with 4 *N* hydrochloric acid. The white precipitate was washed thoroughly with water. One hundred and sixty-six grams (94% yield) of white powder, m. p. 142–143°, was obtained.

α-Phenyl-β-(3-methoxy-4-benzyloxyphenyl)-propionic Acid.—A mixture of 118 g. (0.434 mole) of α-phenyl-β-(3-methoxy-4-hydroxyphenyl)-propionic acid, 195 g. (1.54 moles) (148 cc.) of benzyl chloride, 3.5 g. (0.021 mole) of potassium iodide, 17.4 g. (0.435 mole) of sodium hydroxide in 100 cc. of water, and 500 cc. of 95% ethanol was brought to reflux. Refluxing was continued for three hours, during which time a solution of 86.8 g. (2.17 moles) of sodium hydroxide in 300 cc. of water was added dropwise with stirring. The solution was refluxed an additional hour, then evaporated to one-half its original volume and 500 cc. of water was added. The aqueous solution was extracted with ether and acidified to *p*H 2 with 4 *N* hydrochloric acid. The solid which precipitated was recrystallized from 50% aqueous methanol; yield 100 g. (64%)

TABLE I

SUBSTITUTED α-PHENYLCINNAMIC ACIDS

Substituents	M. p., °C.	Yield, %	Recrystallization solvent
4-Methoxy[a]	188–189	38	Alcohol
3,4-Methylenedioxy[b]	235–236	50	Acetic acid
3,4-Dimethoxy[c]	223–224	35	Acetic acid
3-Methoxy-4-hydroxy[d]	186–187	59	Acetic acid
3-Ethoxy-4-hydroxy[e]	186–186.5	26	Methanol
4-Hydroxy[f]	220–223	67[h]	Dilute alcohol
3,4-Dihydroxy[g]	205–206	24[h]	Water

[a] Oglialoro, *Gazz. chim. ital.*, **9**, 533 (1879). [b] Bodroux, *Compt. rend.*, **153**, 350 (1911). [c] Kauffmann, *Ber.*, **52**, 1432 (1919). [d] Dey and Row, *Quart. J. Indian Chem. Soc.*, **1**, 277 (1925). [e] Calcd. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67. Found: C, 71.83; H, 5.38. [f] Prepared by Mr. A. Besozzi by the method of Zincke and Geibel, *Ann.*, **349**, 107 (1906). [g] Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 69.62; H, 4.49. [h] Yield of unrecrystallized acid suitable for reduction.

(9) Microanalyses by the Misses Esther Bass, Alice Rainey and Patricia Curran.

TABLE II

SUBSTITUTED α,β-DIPHENYLPROPIONIC ACIDS

Substituted β-phenyl	M. p., °C.	Yield, %	Recryst. solvent	Analyses, % Calcd. C	Calcd. H	Found C	Found H
4-Methoxy[a]	116–118	96					
3,4-Methylenedioxy	126–127	95	Benzene	71.10	5.22	71.51	5.16
3,4-Dimethoxy	98–99	98	Dilute alcohol	71.31	6.34	71.63	6.27
3-Methoxy-4-hydroxy	142–143	94	Dilute alcohol	70.57	5.92	70.42	5.91
3-Ethoxy-4-hydroxy	145–146	96	Benzene	71.31	6.34	71.40	6.06
4-Hydroxy[b]	176–178	92	Alcohol				
3-Methoxy-4-benzyloxy	114–115	64[c]	Dilute alcohol	76.22	6.12	76.19	6.3
3-Ethoxy-4-benzyloxy	105–106	78	Dilute alcohol	76.57	6.44	76.58	6.53
4-Benzyloxy	131–132	98[c]	Acetone	79.49	6.07	80.02	6.38

[a] Faltis, Wrann and Kuhas, *Ann.*, **497**, 69 (1932). [b] Bakunin, *Gazz. chim. ital.*, **25**, I, 186 (1895). [c] Yield of unrecrystallized acid suitable for next reaction.

TABLE III

SUBSTITUTED α,β-DIPHENYLPROPIONAMIDES

Substituted β-phenyl	M. p., °C.	Yield, %	Recryst. solvent	Analyses, %N Calcd.	Found
4-Methoxy	161–162	98	Alcohol	5.49	5.46
3,4-Methylenedioxy	144.5–145	89	Benzene–Skellysolve C	5.20	5.34
3,4-Dimethoxy	131–132	78	Benzene	4.91	5.03
3-Methoxy-4-benzyloxy	142–143	89	Ethyl acetate	3.88	3.93
3-Ethoxy-4-benzyloxy	139–140	90[a]	Benzene	3.73	3.67
4-Benzyloxy	165–165.5	95[a]	Methanol	4.23	4.22

[a] Yield of unrecrystallized amide suitable for Hofmann reaction.

The analytical sample was recrystallized from aqueous alcohol; m. p. 114–115°.

α-Phenyl-β-(3-methoxy-4-benzyloxyphenyl)-propionamide.—A mixture of 87.1 g. (0.24 mole) of α-phenyl-β-(3-methoxy-4-benzyloxyphenyl)-propionic acid and 150 cc. (2.25 moles) of thionyl chloride was refluxed for ten minutes. The excess thionyl chloride was removed *in vacuo* and the residue was dissolved in 500 cc. of anhydrous dioxane. The dioxane solution was added dropwise with vigorous stirring to 1 liter of concentrated ammonium hydroxide. The white precipitate was washed thoroughly with water and air-dried. A yield of 77.6 g. (89%) was obtained; m. p. 140–142°. Recrystallization from ethyl acetate gave a m. p. of 142–143°.

α-Phenyl-β-(3-methoxy-4-benzyloxyphenyl)-ethylamine Hydrochloride.—A mixture of 74.0 g. (0.205 mole) of α-phenyl-β-(3-methoxy-4-benzyloxyphenyl)-propionamide, 274 cc. of 40% sodium hydroxide, 42.7 g. (0.267 mole) of bromine and 500 cc. of water was refluxed for two hours. Upon cooling, the alkaline solution was extracted with ether, the extract dried over anhydrous sodium sulfate and the hydrochloride precipitated with ethereal hydrogen chloride. The 61.1 g. of brown-orange solid, m. p. 193–196°, was triturated with 100 cc. of hot ethyl acetate to yield 51 g. (67%) of light yellow solid, m. p. 199–200°. A sample recrystallized from methanol–dioxane melted at 203–204°.

The three amines having methoxyl groups in the ring were distilled after extraction and drying. Their constants are given in Table IV.

α-Phenyl-β-(3-methoxy-4-hydroxyphenyl)-ethylamine Hydrochloride.—Fifty grams (0.135 mole) of α-phenyl-β-(3-methoxy-4-benzyloxyphenyl)-ethylamine hydrochloride was dissolved in 400 cc. of hot methanol. The solution was hydrogenated in two portions at 55° and 20–60 lb./sq. in. pressure with palladium-on-charcoal catalyst. After removal of the catalyst, the solution was evaporated to dryness *in vacuo*. The residue was washed well with ether, yielding 37.5 g. (99%) of a slightly tan solid, m. p. 219–220° with sintering at 218°. This product was not purified further for the demethylation, but was recrystallized from 50% methanol–ethyl acetate for animal testing. The purified product melted at 219–220°.

TABLE IV

SUBSTITUTED α,β-DIPHENYLETHYLAMINES

Substituted β-phenyl	B. p., °C.	Press., mm.	Yield, %	Analyses, %N Calcd.	Found
4-Methoxy[a]	150–151	0.8	67	6.16	6.14
3,4-Methylenedioxy[a]	169–170	0.8	55	5.81	6.02
3,4-Dimethoxy[a]	193–194	1.7	50	5.44	5.28
4-Hydroxy[a]	[b]		89	6.57	6.58

[a] Reichert and Hoffmann, *Arch. Pharm.*, **274**, 153 (1936). [b] M. p. 161–162°, recrystallized from ethyl acetate; prepared by catalytic debenzylation.

α-Phenyl-β-(3,4-dihydroxyphenyl)-ethylamine Hydrochloride.—A solution of 21.0 g. (0.075 mole) of α-phenyl-β-(3-methoxy-4-hydroxyphenyl)-ethylamine hydrochloride in 120 cc. of glacial acetic acid and 45 cc. of 55% hydrobromic acid was refluxed for four hours, cooled and made alkaline with ammonium hydroxide. The white precipitate was filtered, washed and dried. The dry base was suspended in methanol and excess ethereal hydrogen chloride was added. Evaporation of the clear brown solution yielded a brown gum, which on trituration with ethyl acetate resulted in 17 g. (85%) of pink solid, m. p. 225–227° with sintering at 224°. The hydrochloride was recrystallized three times from methanol–ethyl acetate, forming 13.3 g. (67% yield) of white crystals, m. p. 225–226°.

α,β-Diphenyl-β-hydroxyethylamine Hydrochloride.—This compound was made by a procedure adapted from Read and Campbell,[10] using 75 g. (1 mole) of glycine, 340 g. (3.2 moles) of benzaldehyde, 80 g (2 moles) of sodium hydroxide, 400 cc. of methanol and 400 cc. of water. The crude benzal derivative was hydrolyzed in a solution of 50 cc. of concentrated hydrochloric acid in 500 cc. of water. The cooled solution was extracted with ether, then made basic with ammonia. The base precipitated as a white solid. It was washed with water and recrystallized from methanol, yielding 52.8 g. (21%) of white crystals, m. p.

(10) Read and Campbell, *J. Chem. Soc.*, 2674 (1930).

TABLE V

SUBSTITUTED α,β-DIPHENYLETHYLAMINE HYDROCHLORIDES

Substituted β-phenyl	M. p., °C.	Yield, %	Recryst. solvent	Analyses, %N Calcd.	Found
4-Methoxy[a]	212–213	44	Benzene	5.31	5.26
3,4-Methylenedioxy[a]	255–256	50	Alcohol	5.04	5.30
3,4-Dimethoxy	176–177	43		4.77	4.91
3-Methoxy-4-hydroxy[b]	219–220	99	MeOH–EtOAc	5.01	5.11
3-Ethoxy-4-hydroxy[b]	217–218	73	EtOAc–MeOH	4.77	4.82
4-Hydroxy	255–256	56	EtOAc–MeOH	5.61	5.73
3,4-Dihydroxy	225–226	67	EtOAc–MeOH	5.27	5.17
3-Methoxy-4-benzyloxy	203–204	67	Dioxane–MeOH	3.97	3.84
3-Ethoxy-4-benzyloxy	211–212	42	Dioxane–EtOAc	3.65	3.62
4-Benzyloxy	208–209	59	Dioxane	4.12	4.33

[a] Reichert and Hoffmann, *Arch. Pharm.*, **274**, 153 (1936). [b] Prepared by hydrogenolysis of the corresponding benzyloxy amine hydrochloride.

124–126°. Ten grams of the base was dissolved in ether and excess ethereal hydrogen chloride was added. The crystalline hydrochloride was washed with ether and dried; weight 10 g.; m. p. 201–202° with sintering from 199°.

Anal. Calcd. for $C_{14}H_{16}ONCl$: N, 5.61. Found: N, 5.56.

Benzyl *p*-Hydroxyphenyl Ketone.—This was prepared from 12.2 g. (0.13 mole) of phenol, 37 g. (0.28 mole) of aluminum chloride, 100 cc. of nitrobenzene and 17.2 cc. (0.13 mole) of phenylacetyl chloride at 80–90° for ninety minutes. The product was isolated by extraction with ether followed by extraction with dilute sodium hydroxide solution and acidification. The yield was 16.8 g. (61%) of tan solid, m. p. 139–142° with sintering from 132°.[11]

Benzyl *p*-Benzyloxyphenyl Ketone.—The product above (164 g., 0.774 mole) was benzylated in the usual manner with 98 cc. (0.852 mole) of benzyl chloride, 57.6 g. (0.542 mole) of sodium carbonate, 6.44 g. (0.039 mole) of potassium iodide and 800 cc. of 95% alcohol in eight hours. The product was washed with water and alcohol and dried. The yield was 205 g. (88%) of ketone, m. p. 136–137°, of sufficient purity for the next reaction. Recrystallization from benzene did not change the m. p.

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.66; H, 5.86.

α-Isonitrosobenzyl *p*-Benzyloxyphenyl Ketone.—A suspension of 10 g. of the ketone in 200 cc. of dry ether was nitrosated with a large excess of amyl nitrite (10 cc.) and dry hydrogen chloride. The nitrosated product is soluble in ether and is readily separated from the starting material by filtration. The filtrate was treated with two volumes of Skellysolve A and 5.5 g. (51% yield) of the isonitroso ketone crystallized; m. p. 126–127°, with sintering from 122°. Recrystallization from benzene raised the m. p. to 131–132°.

Anal. Calcd. for $C_{21}H_{17}O_3N$: N, 4.23. Found: N, 4.21.

α-Phenyl-β-(4-hydroxyphenyl)-β-hydroxyethylamine Hydrochloride.—A suspension of 23 g. (0.07 mole) of the isonitroso ketone in 150 cc. of methanol was reduced in the presence of palladium-on-charcoal catalyst at 55° and 50 lb. pressure. After three moles of hydrogen was absorbed, 12 cc. (0.07 mole) of 5.8 *N* alcoholic hydrogen chloride was introduced and hydrogenation was continued until a fourth mole was taken up. The reduction required twenty-one hours. The solution was filtered and concentrated. The addition of ether yielded 11.4 g. (62%) of white crystalline amine hydrochloride, m. p. 186–187° (dec.).

Anal. Calcd. for $C_{14}H_{16}O_2NCl$: N, 5.27. Found: N, 5.00.

Benzyl 3,4-Dihydroxyphenyl Ketone.—A mixture of 110 g. (1 mole) of catechol, 136 g. (1 mole) of phenylacetic acid and 101 g. (0.66 mole) of phosphorus oxychloride was stirred for two hours at 90–100°, at the end of which time a thick, dark brown paste resulted and stirring was difficult. Two hundred and fifty grams of water was introduced and the mixture was refluxed for an hour. Upon cooling, the red-brown oil gave a red-orange solid which was washed with hot benzene and dried. The yield was 134 g. (59%); m. p. 168–170°, with sintering from 162°.[12]

Benzyl 3,4-Dibenzyloxyphenyl Ketone.—The benzylation was carried out as above, using 130 g. (0.57 mole) of the dihydroxy ketone, 159 g. (1.25 moles) of benzyl chloride, 170 g. (1.6 moles) of sodium carbonate, 4.7 g. (0.03 mole) of potassium iodide and 500 cc. of alcohol. Recrystallization from alcohol afforded 153 g. (66% yield) of product, m. p. 91.5–93°. A second recrystallization gave m. p. 92.5–93°.

Anal. Calcd. for $C_{28}H_{24}O_3$: C, 82.33; H, 5.92. Found: C, 82.39; H, 5.83.

α-Isonitrosobenzyl 3,4-Dibenzyloxyphenyl Ketone.—The nitrosation was similar to the previous one, except that excess gaseous methyl nitrite and hydrogen chloride were passed into a suspension of 15 g. (0.037 mole) of ketone in 250 cc. of dry ether for forty minutes during refluxing. The isonitroso ketone was recrystallized from methanol; yield 12 g. (75%); m. p. 138–139°, with shrinking from 136°.

Anal. Calcd. for $C_{28}H_{23}O_4N$: N, 3.20. Found: N, 3.19.

α-Phenyl-β-(3,4-dihydroxyphenyl)-β-hydroxyethylamine Hydrochloride.—Twelve grams (0.0275 mole) of the isonitroso ketone was reduced in 150 cc. of 67% aqueous methanol containing an equivalent of hydrochloric acid, in the presence of palladium-on-charcoal catalyst. Debenzylation and reduction of the isonitroso group proceeded at room temperature, and the ketone was reduced at 55°. The entire process required ten hours. The solution was filtered and evaporated to dryness. Recrystallization from benzene–ethanol yielded 3.1 g. (43%) of white crystals, m. p. 172–173° (dec.).

Anal. Calcd. for $C_{14}H_{16}O_3NCl$: N, 4.97. Found: N, 4.89.

Summary

Seven substituted α,β-diphenylethylamine hydrochlorides and three substituted α,β-diphenyl-β-hydroxyethylamine hydrochlorides have been prepared and tested for analgesic properties. The most active compound of the first group is α-phenyl-β-(3-methoxy-4-hydroxyphenyl)-ethylamine hydrochloride. α-Phenyl-β-(3,4-dihydroxyphenyl)-β-hydroxyethylamine hydrochloride is the most effective of the second group of substances.

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(11) Weise, *Monatsh.*, **26**, 986 (1905), reported m. p. 142°.

(12) Finzi, *ibid.*, **26**, 1133 (1905), reported m. p. 173°.