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Synthesis of 1-(2,3- and 3,4-Dimethoxyphenyl)-1-phenyldimethylamine

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As potential analgesic agents 1-(2,3-dimethoxyphenyl)-1-phenyldimethylamine (Ia) and 1-(3,4-dimethoxyphenyl)-1-phenyldimethylamine (Ib) were synthesized.

The synthesis was carried out by two routes, one started from 2,3- and 3,4-dimethoxybenzophenone(IIa,b), and the other from 2,3- and 3,4-dimethoxybenzaldehyde methylimide (IIIa,b). The starting materials, dimethoxybenzophenones(IIa, b), were obtained from 2,3-dimethoxybenzaldehyde and 3,4-dimethoxybenzaldehyde by the methods of Paulsen and Buu-Hoï.[2] The dimethoxybenzophenones (IIa,b) were hydrogenated by the method of Bercot–Vatteroni[3] using potassium borohydride to the corresponding benzhydrols(IVa,b). The benzhydrols(IVa,b) were halogenated with thionyl chloride to α-chlorodiphenylmethane

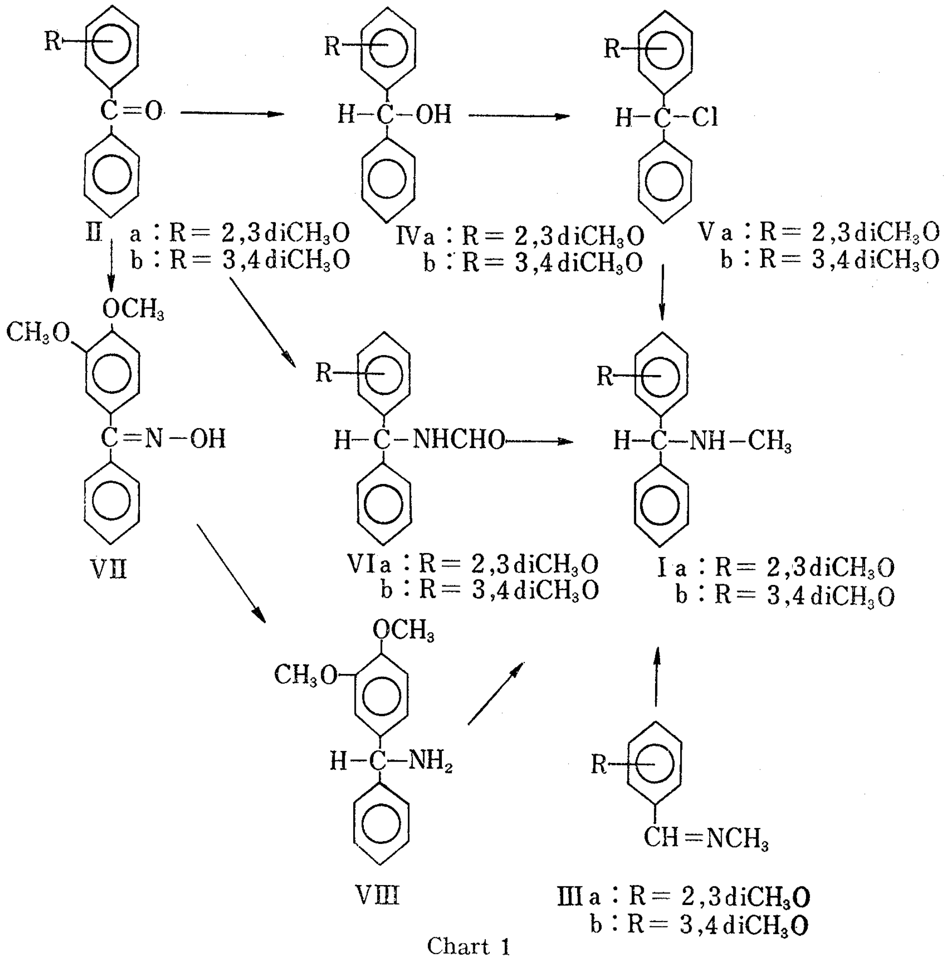

Chart 1

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[1] Location: *3-1, Tanabe-dori, Mizuho-ku, Nagoya.*

[2] A. Paulsen, *Acta Polytech. Scand., Chem. Met. Ser.*, **6**, 94 (1960); *Chem. Abstr.*, **55**, 22319 (1961); N.P. Buu-Hoï, E. Lescot, Jr. and N.D. Xuong, *J. Org. Chem.*, **23**, 1261 (1958).

[3] M. Bercot-Vatteroni and P. Bercot, *Compt. Rend.*, **258**, (23), 5660 (1964); *Chem. Abstr.*, **61**, 5546 (1964).

derivatives(Va,b), which on reaction with methylamine in a sealed tube afforded the 1-dimethoxyphenyl-1-phenyldimethylamines(Ia,b).

The diphenyldimethylamines(Ia,b) were also obtained from the benzophenones(IIa,b) by means of the Leuckart reaction. The benzophenones (IIa,b) were reacted with formamide and yielded formamide compounds(VIa,b), which were hydrogenated with lithium aluminum hydride to the diphenyldimethylamines (Ia, b).

3,4-Dimethoxybenzophenone oxime(VII)$^{4)}$ was reduced in the presence of Raney nickel catalyst under pressure to corresponding amine (VIII), which by formylation and subsequent reduction with Adams platinum afforded 3,4-dimethoxy derivate of the diphenyldimethylamine(Ib).

As an alternate route, the diphenyldimethylamines(Ia,b) were also prepared from dimethoxybenzaldehyde methylimides(IIIa,b). The methylimides(IIIa,b) were prepared from the corresponding benzaldehyde by the method of Moffett.$^{5)}$ The imides(IIIa,b) were subjected to the Grignard reaction with bromobenzene to yield the diphenyldimethylamines(Ia,b) in good yield. This method was proved to be more convenient than the method starting from the benzophenones(IIa,b).

The diphenyldimethylamines(Ia,b) were crystallized as their hydrochlorides. The infrared spectra of the free amines(Ia,b) showed characteristic N–H stretching absorptions at 3344 and 3314 cm^{-1} respectively. The hydrochlorides showed no N–H absorption band in this region, and presented broad strong bands near 2675 and 2694 cm^{-1} respectively indicating ammonium stretching absorption.$^{6)}$

Experimental$^{7)}$

α-Chloro-2,3-dimethoxydiphenylmethane(Va)——One gram of 2,3-dimethoxybenzhydrol(IVa) was added n small portions to 2.5 g of thionyl chloride with stirring. The mixture was warmed on a water bath for 1 hr. The excess thionyl chloride was removed by repeated evaporation with benzene. The residual oil was distilled giving 0.7 g (65.1%) of colorless liquid, bp 143° (0.25 mmHg). *Anal.* Cacld. for $C_{15}H_{15}O_2Cl$: C, 68.57; H, 5.71. Found: C, 68.41; H, 5.87. IR cm^{-1}: ν_{C-H} 2934, 2820 (NaCl).

1-(2,3-Dimethoxyphenyl)-N-formyl-1-phenylmethylamine(VIa)——A mixture of 1 g of 2,3-dimethoxybenzophenone(IIa) and 4.5 g of formamide was heated to reflux on an oil bath for 6.5 hr under nitrogen. The mixture was cooled and poured onto 15 ml of water. The oily substance which appeared was extracted with benzene and dried over Na_2SO_4. The solvent was removed by distillation and the residue was crystallized from EtOH to colorless plates of mp 186—188°. Yield, 0.6 g (53.6%). *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.93; H, 6.42; N, 5.22. IR cm^{-1}: ν_{N-H} 3275 (KBr); $\nu_{C=O}$ 1650 (KBr).

1-(2,3-Dimethoxyphenyl)-1-phenyldimethylamine(Ia)——a) From α-Chloro-2,3-dimethoxydiphenylmethane(Va): A solution of 5 g of the chloromethane(Va) and 8 g of 30% methylamine in 50 ml of MeOH was kept in a sealed tube for 1 week. The reaction mixture was evaporated and the residue was dissolved into 50 ml of 10% HCl and washed with ether. The acidic solution was made basic with 10% NaOH and extracted with ether and dried over K_2CO_3. After removing the solvent the residue was distilled giving 3.1 g (63.3%) of colorless liquid, bp 145—146° (0.1 mmHg). *Anal.* Calcd. for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.44; H, 7.45; N, 5.40. IR cm^{-1}: ν_{N-H} 3344 (NaCl): ν_{C-H} 2942, 2826 (NaCl).

Hydrochloride: Colorless prisms (from MeOH), mp 243—244° (decomp.). *Anal.* Calcd. for $C_{16}H_{19}O_2N \cdot HCl$: C, 65.42; H, 6.81; N, 4.77. Found: C, 65.62; H, 7.05: N, 4.67. IR cm^{-1}: $\nu_{NH_2^+}$ 2675, 2514, 2384 (KBr).

b) From 1-(2,3-Dimethoxyphenyl)-N-formyl-1-phenylmethylamine(VIa): A mixture of 5 g of the N-formyl compound (VIa), 5 g of lithium aluminum hydride and 100 ml of anhyd. ether was refluxed for 2 hr with stirring. The reaction mixture was poured onto 100 ml of ice water and extracted with ether. The ether extracts were dried over Na_2SO_4. After removing the solvent the residue was distilled giving 2.8 g (59.0%) of colorless liquid, bp 158—159° (0.3 mmHg), which was identified with the sample obtained above method a) by IR comparison and mixed mp determination of the free amine and the hydrochloride.

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4) A.H. Bhatkhande and B.V. Bhide, *J. Univ. Bombay*, (*N.S.*), **24**, A,5, 11 (1955); *Chem. Abstr.*, **51**, 11325 (1957).

5) R.B. Moffett and W.M. Hoehn, *J. Am. Chem. Soc.*, **69**, 1792 (1947).

6) K. Nakanishi, "IR Absorption Spectroscopy –Practical–", Nankodo, Tokyo, 1960, p. 47.

7) All melting points were not corrected.

c) From 2,3-Dimethoxybenzaldehyde methylimide (IIIa): To a solution of phenylmagnesium bromide prepared from 15.7 g of bromobenzene, 2.4 g of magnesium and 30 ml of anhyd. ether, a solution of 4.5 g of 2,3-dimethoxybenzaldehyde methylimide (IIIa) in 10 ml of anhyd. ether was slowly added with stirring. After refluxing and stirring for 30 min, the mixture was cooled and poured onto a mixture of 25 ml of concd. HCl and the minimum amount of ice. The layers were separated, the aqueous layer was washed with ether and made basic with 20% NaOH. The suspension of magnesium hydroxide was extracted with ether, which was washed with water and dried over K_2CO_3. After removing the solvent, the residue was destilled giving 3.8 g (58.8%) of colorless liquid, bp 158—159° (0.3 mmHg), which was identified with the sample obtained above method a) by IR comparison and mixed mp determination of the free amine and the hydrochloride.

***α*-Chloro-3,4-dimethoxydiphenylmethane (Vb)**——This compound was prepared from 3,4-dimethoxybenzhydrol (IVb) in the same manner as for (Va). Yield, 63.4%. Colorless liquid, bp 140° (0.06 mmHg). *Anal.* Calcd. for $C_{15}H_{15}O_2Cl$: C, 68.57; H, 5.71. Found: C, 68.21; H, 5.92. IR cm^{-1}: $\nu_{\text{C-H}}$ 2832, 2804 (NaCl).

1-(3,4-Dimethoxyphenyl)-N-formyl-1-phenylmethylamine (VIb)——This compound was prepared from 3,4-dimethoxybenzophenone (IIb) in the same manner as for (VIa), and recrystallized from EtOH to colorless plates of mp 97°. Yield, 59.7%. *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.93; H, 6.42; N, 5.22. IR cm^{-1}: $\nu_{\text{N-H}}$ 3251 (KBr); $\nu_{\text{C=O}}$ 1671 (KBr).

1-(3,4-Dimethoxyphenyl)-1-phenyldimethylamine (Ib)——a) From 3,4-Dimethoxybenzaldehyde Methylimide (IIIb), α-Chloro-3,4-dimethoxydiphenylmethane (Vb) and 1-(3,4-Dimethoxyphenyl)-N-formyl-1-phenylmethylamine (VIb): This compound (Ib) was prepared from IIIb, Vb and VIb in the almost same manner as for Ia. bp 153° (0.2 mmHg), colorless liquid. *Anal.* Calcd.for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.55; H, 7.50; N, 5.77. IR cm^{-1}: $\nu_{\text{N-H}}$ 3314 (KBr); $\nu_{\text{C-H}}$ 2944; 2830 (KBr); $\nu_{\text{C-N}}$ 1418 (KBr).

Hydrochloride: Colorless prisms (from EtOH–ether), mp 191—192°. *Anal.* Calcd. for $C_{16}H_{19}O_2N\cdot HCl$: C, 65.42; H, 6.81; N, 4.77. Found: C, 65.65; H, 7.26; N, 5.15. IR: $\nu_{\text{NH}_2^+}$ 2694 (KBr).

b) From 1-(3,4-Dimethoxyphenyl)-1-phenylmethylamine (VIII): A mixture of 3 g of the amide (VIII), 2.2 g of paraformaldehyde and 20 ml of 70% MeOH was catalytically reduced in the presence of 0.2 g of Adams platinum for 48 hr. The reaction mixture was filtered and evaporated to an oily residue, which was dissolved into ether. The ether solution was dried over Na_2SO_4. After removing the solvent the residue was distilled giving 2.0 g (63.0%) of colorless liquid, bp 163° (0.4 mmHg), which was identified with the sample obtained above method a) by IR comparison and mixed mp determination of the free amine and the hydrochloride.

1-(3,4-Dimethoxyphenyl)-1-phenylmethylamine (VIII)——One gram of 3,4-dimethoxybenzophenone oxime (VII) was catalytically reduced in 20 ml of MeOH at 90 kg/cm^2 pressure in the presence of 0.5 g of W-2 Raney nickel catalyst for 6.5 hr. After removal of the catalyst, the solvent was evaporated to oily residue, which was dissolved into 20 ml of 10% HCl and filtered. The filtrate was made alkaline with K_2CO_3 and extracted with benzene. The extract was washed with water and dried over K_2CO_3. After removing the solvent the residue was crystallized from petroleum ether to colorless needles of mp 64—65°. Yield, 0.6 g (63.5%). *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.07; H, 7.04; N, 5.76. Found: C, 74.07; H, 7.17; N, 5.90. IR cm^{-1}: $\nu_{\text{N-H}}$ 3336, 3276 (KBr); $\nu_{\text{C-H}}$ 2940, 2832 (KBr).

Hydrochloride: Colorless needles (from MeOH), mp 231—232° (decomp.). *Anal.* Calcd. for $C_{15}H_{17}O_2$: $N\cdot HCl$: C, 64.40; H, 6.44; N, 5.01. Found: C, 64.30; H, 6.77; N, 4.87. IR cm^{-1}: $\nu_{\text{NH}_3^+}$ 2712, 2622, 2078 (KBr); $\delta_{\text{NH}_3^+}$ 1561 (KBr).

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