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Mescaline Analogs. X. 3,4-Dimethyl-, 3,4-Dichloro-, and 3,5-Dimethoxy- 4-methyl- β -phenethylamines¹

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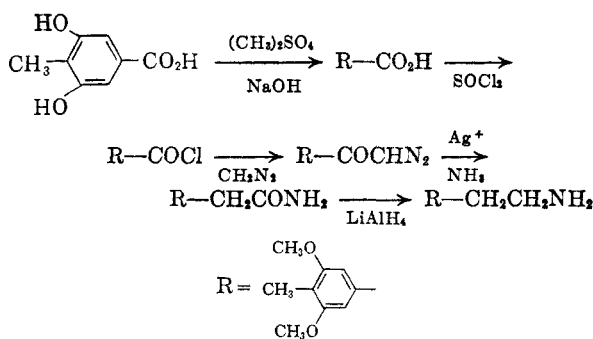
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In a continuation of a long-range study of the influence of ring substituents on β -phenethylamines on psychopharmacological activity,⁴ three new β -phenethylamines substituted in the 3-, 4-, or 5-positions of the ring were synthesized, and the effect of these compounds on normal cat behavior was examined. The sham rage response⁵ induced by 3,4,5-trimethyl-, 4-methyl-, 4-chloro-, and 3,5-dimethyl-4-methoxy- β -phenethylamines⁴ prompted investigation of other β -phenethylamines with these ring substituents.

The three new β -phenethylamines described in this communication, 3,4-dimethyl-, 3,4-dichloro-, and 3,5-dimethoxy-4-methyl-, all induced a strong rage response in cats. These findings confirmed previous observations that the substitution of methyl or chloro groups in the 3- and 4-positions of the β -phenethylamine molecule results in compounds which produce a rage syndrome in cats. Replacement of just the 4-methoxy group in mescaline (3,4,5-trimethoxy- β -phenethylamine) with methyl is sufficient to impart rage-producing properties to the compound, whereas mescaline itself does not induce rage.

3,4-Dimethyl- β -phenethylamine was synthesized from 3,4-dimethylbenzyl chloride by conversion to 3,4-dimethylphenylacetone nitrile and reduction with lithium aluminum hydride. 3,4-Dichloro- β -phenethylamine was obtained in a similar manner.

3,5-Dimethoxy-4-methyl- β -phenethylamine was synthesized from 3,5-dihydroxy-*p*-toluic acid⁶ by the following steps:



Details of the psychopharmacological properties of these compounds will be published elsewhere.

EXPERIMENTAL⁷

3,4-Dimethylbenzyl chloride. A rapid stream of dry hydrogen chloride gas was passed into a stirred mixture of 106 g. of *o*-xylene, 84 g. of 35% aqueous formaldehyde solution, and 450 ml. of concd. hydrochloric acid kept at $65 \pm 5^\circ$ for 6 hr. The organic layer was separated, the aqueous layer extracted with ether, and the combined organic layer was washed thoroughly with water and aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled through a 12-in. Vigreux column. After removal of unchanged *o*-xylene and a small intermediate fraction, 3,4-dimethylbenzyl chloride was collected as the fraction boiling at $113\text{--}116^\circ/22$ mm.; yield, 98.4 g. (64%). The structure of this chloromethyl compound has been demonstrated.⁸

3,4-Dimethylphenylacetone nitrile. To a stirred solution of 26 g. of sodium cyanide in 30 ml. of water was added a solution of 62 g. of 3,4-dimethylbenzyl chloride in 100 ml. of alcohol, and the resulting mixture was stirred and refluxed for 4 hr. The dark reaction mixture was filtered from inorganic salts, and most of the alcohol was removed from the filtrate by evaporation under reduced pressure. The residue was treated with water, and the crude oily product extracted with ether. The ether solution was washed three times with 50-ml. portions of 1:1 hydrochloric acid to remove foul-smelling isonitrile, then several times with water, and finally dried over anhydrous magnesium sulfate. After removal of ether, the residue was distilled under reduced pressure through a 12 in.-Vigreux column; b.p. $147\text{--}150^\circ/22$ mm.; yield, 44.6 g. (77%).

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.7; H, 7.6. Found: C, 82.4; H, 7.5.

3,4-Dimethyl- β -phenylethylamine. To a stirred solution of 11.7 g. of lithium aluminum hydride in 250 ml. of dry absolute ether was added slowly a solution of 29 g. of 3,4-dimethylphenylacetone nitrile at a rate which caused the ether to reflux. The mixture was then stirred and heated under reflux for 0.5 hr., cooled in an ice bath, and hydrolyzed by slow and cautious addition of water until decomposition of the reaction complex was complete. Inorganic matter was removed by filtration, the filtrate was dried (anhydrous magnesium sulfate), filtered again, and treated with alcoholic hydrogen chloride to precipitate the 3,4-dimethyl- β -phenethylamine as its hydrochloride salt; yield, 21 g. (57%); recrystallization from hot alcohol afforded colorless plates, m.p. $222\text{--}223^\circ$.

Anal. Calcd. for $C_{10}H_{13}N$: Cl, 19.1; N, 7.55. Found: Cl, 19.0; N, 7.47.

3,4-Dichlorophenylacetone nitrile. A mixture of 100 g. of α ,3,4-trichlorotoluene,⁹ 130 ml. of ethanol, 33.4 g. of sodium cyanide, and 40 ml. of water was stirred and heated under

(7) Melting points are uncorrected.

(8) G. Vavon, J. Bolle, and J. Calin, *Bull. soc. Chim.*, [5] 6, 1025 (1939).

(9) From Eastman Organic Chemicals.

(1) This research was supported by Battelle Memorial Institute funds and by Public Health Service Grant M-1588.

(2) Battelle Memorial Institute.

(3) The University of Alabama Medical School.

(4) F. Benington, R. D. Morin, L. C. Clark, Jr., and R. P. Fox, *J. Org. Chem.*, 23, 1979 (1958).

(5) S. Norton and E. J. deBeer, *Ann. N. Y. Acad. Sci.*, 65, 249 (1956).

(6) Obtained from Aldrich Chemical Co., Milwaukee, Wis.

reflux for 3.5 hr. Most of the ethanol was distilled under reduced pressure, and the dark residue was added to 500 ml. of water. The crude nitrile was extracted with ether, washed with 1:1 hydrochloric acid and water, dried (anhydrous magnesium sulfate), ether removed, and distilled under reduced pressure; b.p. 115–130°/0.5 mm. (reported,¹⁰ b.p. 170°/12 mm.); yield, 71.5 g. (76%). The distillate gradually solidified, and melted at 45–46° after recrystallization from petroleum ether.

Anal. Calcd. for $C_8H_8Cl_2N$: Cl, 38.2; N, 7.53. Found: Cl, 37.8; N, 7.34.

3,4-Dichloro-β-phenethylamine. To a stirred solution of 16.9 g. of lithium aluminum hydride in 300 ml. of dry absolute ether was added gradually a solution of 37.2 g. of 3,4-dichlorophenylacetone in 100 ml. of dry ether. The reaction mixture was then refluxed for an additional hour, cooled, hydrolyzed cautiously with water, and filtered from inorganic matter. The dried ether solution was treated with dry hydrogen chloride to precipitate 3,4-dichloro-β-phenethylamine hydrochloride, which was recrystallized from methanol-ether; yield, 7.5 g. (17%); m.p. 178–179°.

Anal. Calcd. for $C_8H_{10}Cl_2N$: Cl, 47.0; N, 6.18. Found: Cl, 46.9; N, 6.14.

3,5-Dimethoxy-4-methylbenzoic acid. To a stirred solution of 40 g. of 3,5-dihydroxy-p-toluic acid in 57 g. of sodium hydroxide and 250 ml. of water were added three 33-ml. portions of methyl sulfate at such a rate that the temperature remained below 30° during addition of the first portion, at 30 to 35° during the second, and at 40 to 45° during the third.¹¹ The mixture was then boiled under reflux for 2 hr., treated with a solution of 20 g. of sodium hydroxide in 30 ml. of water, and boiled for an additional 2 hr. Acidification with dilute hydrochloric acid precipitated the crude product, which was purified by recrystallization from acetone; yield, 30.5 g. (65%); m.p. 216–217°; (reported¹² m.p., 213–214°).

ω-Diazo-3,5-dimethoxy-4-methylacetophenone. A mixture of 30 g. of 3,5-dimethoxy-4-methylbenzoic acid, 30 ml. of dry benzene, and 22 ml. of thionyl chloride was refluxed for 2 hr. After removal of benzene and excess thionyl chloride, the residue was distilled under reduced pressure to yield 21 g. (64%) of 3,5-dimethoxy-4-methylbenzoyl chloride, b.p. 107–110°/0.5 mm. A solution of this acid chloride was added to a cooled (ice bath) and stirred solution of 0.316 mole of diazomethane (generated from *N*-nitroso-*N*-methylurea and 45% potassium hydroxide and assayed against benzoic acid) in 680 ml. of dry ether. After stirring for 20 hr. at room temperature, the diazoketone had separated as a yellow solid. Collection of this solid and concentration of the filtrate by evaporation yielded a total of 19.6 g. (90%) of the pure diazoketone; m.p. 138–139° dec.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5. Found: C, 59.7; H, 5.7.

3,5-Dimethoxy-4-methylphenylacetamide. To a mixture of 19 g. of *ω*-diazo-3,5-dimethoxy-4-methylacetophenone and 100 ml. of dioxane was added 200 ml. of concd. ammonium hydroxide and 20 ml. of 10% aqueous silver nitrate. The mixture was heated on a steam bath under a reflux condenser for 16 hr. when evolution of nitrogen, brisk at first, was complete. The hot reaction mixture was treated with Norite, filtered, and concentrated by evaporation whereupon the crude solid amide crystallized on cooling. Recrystallization of the crude product from alcohol-water yielded 10.5 g. (58%) of pure 3,5-dimethoxy-4-methylphenylacetamide, m.p. 166–167°.

(10) C. E. Kwartler and P. Lucas, *J. Am. Chem. Soc.*, **68**, 2395 (1946) reported this compound as an oil rather than the crystalline solid which we obtained.

(11) See F. Mauthner, *Org. Syntheses*, Coll. Vol. I, 537 (1943) for methylation of gallic acid.

(12) K. Yamaguchi, *J. Chem. Pharm. Soc. (Japan)*, **62**, 491 (1952).

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.2; H, 7.2. Found: C, 63.2; H, 7.4.

3,5-Dimethoxy-4-methyl-β-phenethylamine. To a stirred solution of 6.8 g. of lithium aluminum hydride in 200 ml. of dry absolute ether was added a slurry of 10 g. of 3,5-dimethoxy-4-methylphenylacetamide in 125 ml. of hot dry reagent benzene, using part of the benzene to rinse in the last of the amide. The resulting mixture was stirred and refluxed for 1 hr., cooled in an ice bath, and hydrolyzed by slow and cautious addition of water. The ether solution of the amine obtained after filtration from inorganic matter and drying (anhydrous magnesium sulfate) was treated with dry hydrogen chloride to precipitate the product as its hydrochloride salt; yield, 8.9 g. (80%); m.p. 233–235°. Recrystallization from ethanol-ethyl acetate raised the melting point to 244–245°.

Anal. Calcd. for $C_{11}H_{15}ClNO_2$: C, 57.0; H, 7.8; Cl, 15.3. Found: C, 56.2; H, 8.0; Cl, 15.2.

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Nobiletin from the Peel of the Valencia Orange (*Citrus sinensis* L.)¹

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During an investigation of the constituents of orange peel, a substance was isolated which was identified as nobiletin by physical and chemical properties, elemental analysis, and degradation products.

Nobiletin was first isolated by Tseng² from the Chinese drug chen-pi which, in turn, was made from the peel of a variety of mandarin (*Citrus nobilis*, Lour.). In the original work the isolation was made by a rather tedious process from a cold methanolic extract of the drug but in the present study the juice of fresh orange peel was utilized.

The structural formula for nobiletin was partly elucidated by Tseng² and Robinson and Tseng,³ who isolated veratric acid and acetoveratrone (as the oxime) from the alkaline hydrolysis mixture. On the basis of this and other evidence, Robinson and Tseng came to the conclusion that nobiletin was 3', 4', 5, 6, 7, 8-hexamethoxyflavone. This view was supported later by syntheses carried out by Horii,⁴ Sreerama Murti and Seshadri,⁵

(1) Presented before the Symposium on Chemistry of the Citrus Fruit Industry at the Miami meeting of the American Chemical Society, April, 1957.

(2) K. Tseng, *J. Chem. Soc.*, 1003 (1938).

(3) R. Robinson and K. Tseng, *J. Chem. Soc.*, 1004 (1938).

(4) Z. Horii, *J. Pharm. Soc. Japan*, **60**, 614, Abstracts 246 (1940); *Chem. Abstr.* **35**, 7964 (1941).

(5) V. V. Sreerama Murti and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **27-A**, 217 (1948).