TABLE I

Amine	Ketone or aldehyde	Yield crude, %	M.p. crude, °C.	(Recryst.), m.p.
9-Aminofluorene	Fluorenone	98	82–83	83–84
3β-Acetoxy-20-amino-5-pregnene acetate	5-Pregnenolone	71	181–185	185–188
Benzylamine	Benzaldehyde	80[a]	236–237[a]	237[a]
Cyclohexylamine	Cyclohexanone	73[a]	157–160[a]	160–161[a]
β-Phenylethylamine	Phenylacetaldehyde	39[a]	70–105[a]	118–120[a]

[a] 2,4-Dinitrophenylhydrazone.

and the solution was made strongly acid with 10% sulfuric acid. After boiling the solution for 30 minutes, an excess of cold water was added, and the resulting white suspension was extracted with ether. The ethereal solution was washed with water, dried over sodium sulfate and evaporated to dryness, leaving crude 5-pregnenolone as a yellowish crystalline powder, m.p. 181–185°; yield 340 mg. (71%). Recrystallization from aqueous methanol gave colorless needles, m.p. 185–188°. The mixed melting point with an authentic sample, m.p. 188–190°, was 186–189°. During the course of this reaction the 3-acetoxy group was hydrolyzed.

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Synthesis of 4-Hydroxy- and 4-Ethoxy-3,5-dimethoxy-β-phenethylamines[1]

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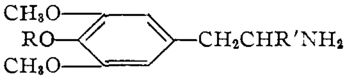
Some of the physiological properties of both 4-hydroxy-3,5-dimethoxy-β-phenethylamine (I) and 4-ethoxy-3,5-dimethoxy-β-phenethylamine (II) have been reported by Noteboom[4]; although a synthesis of the latter compound from 4-hydroxy-3,5-dimethoxybenzyl alcohol is given in the patent literature,[5] the synthesis and chemical and physical properties of compounds I and III do not appear to have been described. We have found that the synthesis of these phenethylamines from syringaldehyde proceeds readily and in good yield.



I, $R = R' = H$
II, $R = C_2H_5$; $R' = H$
III, $R = H$; $R' = CH_3$

Syringaldehyde, which was obtained from 2,6-dimethoxyphenol by the method of Pearl,[6] was condensed with nitromethane in the presence of methylamine to give 4-hydroxy-3,5-dimethoxy-β-nitrostyrene. Subsequent reduction with lithium aluminum hydride[7] afforded 4-hydroxy-3,5-dimethoxy-β-phenethylamine (I). Similarly, condensation of syringaldehyde with nitroethane gave 1-(4-hydroxy-3,5-dimethoxyphenyl)-2-nitropropene which was reduced to *dl*-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-aminopropane (III) with lithium aluminum hydride.

4-Ethoxy-3,5-dimethoxybenzaldehyde was prepared by the action of diethyl sulfate and sodium hydroxide on syringaldehyde. Condensation of 4-ethoxy-3,5-dimethoxybenzaldehyde with nitromethane in the presence of methylamine failed to give 4-ethoxy-3,5-dimethoxy-β-nitrostyrene; however, this intermediate was obtained readily when the condensation was carried out in acetic acid solution in the presence of ammonium acetate.[8] An attempted condensation of syringaldehyde with nitromethane by the acetic acid–ammonium acetate method gave only tarry decomposition products. In the case of 3,4,5-trimethoxybenzaldehyde, which can be obtained readily by either methylation of syringaldehyde with methyl sulfate and sodium hydroxide or from trimethylgallic acid,[9] the methylamine-catalyzed reaction gave a high-melting polymeric product instead of the desired 3,4,5-trimethoxy-β-nitrostyrene, while catalysis with ammonium acetate gave the desired product in good yield. The amine-catalyzed condensation of these benzaldehydes with nitromethane is preferred when a free phenolic hydroxyl is present; the acetic acid–ammonium acetate method is superior for condensation of 3,4,5-trialkoxybenzaldehydes with nitromethane.

In distinct contrast to results obtained with tyramine hydrochloride and 4-hydroxy-3-methoxy-β-phenethylamine hydrochloride, 4-hydroxy-3,5-dimethoxy-β-phenethylamine hydrochloride, in ethanol solution, failed to undergo ring hydrogenation in the presence of Adams catalyst. In this respect, its behavior is more like the completely alkylated trihydroxyphenethylamines. Alternate methods for hydrogenating this class of compounds are currently being examined.

Experimental[10]

4-Ethoxy-3,5-dimethoxybenzaldehyde.—Syringaldehyde was obtained in 50% yield from 2,6-dimethoxyphenol by the procedure of Pearl.[6] The action of ethyl iodide and anhydrous potassium carbonate on syringaldehyde, in accordance with the procedure of Head and Robertson,[11] failed to give 4-ethoxy-3,5-dimethoxybenzaldehyde. In an alternate scheme, a mixture of 21.9 g. of syringaldehyde and 45 ml. of water was heated to boiling and 36 ml. of aqueous sodium hydroxide (15 g. of NaOH in 75 ml. of solution) was then added to the boiling suspension. The sodium salt of syringaldehyde which separated redissolved in the mixture on further heating and stirring. Diethyl sulfate (23 g.) was then added to the boiling solution over a period of 10 minutes, and refluxing was continued for an additional hour. The boiling mixture was treated alternately with four 5.0-g. portions of diethyl sulfate and four 6-ml. portions of aqueous alkali. The oily product, which separated on cooling, was extracted with ether. After drying the ether layer over anhydrous magnesium sulfate and decolorizing with Norite, the solvent was removed under diminished pressure. A light yellow, crystalline, crude product remained as a residue; yield 21.8 g. (86%), m.p. 51–52°. Recrystallization from ether gave light yellow plates melting at 52–53°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.7; H, 6.5. Found: C, 62.9; H, 6.7.

3,4,5-Trimethoxybenzaldehyde.—Syringaldehyde was methylated by means of methyl sulfate and alkali by the procedure of Buck[12]; 21.9 g. of syringaldehyde afforded 21.2 g. of 3,4,5-trimethoxybenzaldehyde, m.p. 72–74° (lit.[9] 75–76°).

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[1] This research is supported by Battelle Memorial Institute and in part by Public Health Service Grant No. M-600 (R).

[2] Battelle Memorial Institute.

[3] The Fels Research Institute.

[4] L. Noteboom, *Proc. Acad. Sci. Amsterdam*, **37**, 562 (1934).

[5] H. Jensch, German Patent 526,172 (1929).

[6] I. A. Pearl, THIS JOURNAL, **70**, 1747 (1948).

[7] F. A. Ramirez and A. Burger, *ibid.*, **72**, 2781 (1950).

[8] L. C. Raiford and D. E. Fox, *J. Org. Chem.*, **9**, 170 (1944).

[9] K. H. Slotta and H. Heller, *Ber.*, **63**, 3029 (1930).

[10] All melting points are uncorrected.

[11] F. S. H. Head and A. Robertson, *J. Chem. Soc.*, 2434 (1930).

[12] J. S. Buck, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 619.

4-Hydroxy-3,5-dimethoxy-β-nitrostyrene.—A mixture of 26.2 g. of syringaldehyde, 10 ml. of redistilled nitromethane, 100 ml. of methanol and 10 ml. of 3% methanolic methylamine was allowed to stand in the dark at room temperature for 48 hours. The yellow crystalline mass was collected on a filter, washed with both methanol and ether and dried in a vacuum oven at room temperature; yield 31.5 g. (97%), m.p. 164–165° dec. Recrystallization from methanol gave yellow prisms, m.p. 167° dec.[13]

Anal. Calcd. for $C_{10}H_{11}NO_5$: C, 53.4; H, 4.9. Found: C, 53.2; H, 5.0.

4-Hydroxy-3,5-dimethoxy-β-phenethylamine Hydrochloride (I).—The reduction of 30 g. of 4-hydroxy-3,5-dimethoxy-β-nitrostyrene with a slurry of 22 g. of lithium aluminum hydride in 1000 ml. of absolute ether by the procedure of Ramirez and Burger[7] gave 45.8 g. (81%) of 4-hydroxy-3,5-dimethoxy-β-phenethylamine picrate, m.p. 231–231.5°, after recrystallization from acetic acid.

Anal. Calcd. for $C_{16}H_{18}O_{10}N_4$: C, 45.2; H, 4.2. Found: C, 45.3; H, 4.3.

The crude picrate (40 g.) was converted to the hydrochloride by treatment with a boiling mixture of 250 ml. of hydrochloric acid and 100 ml. of water. After cooling, the precipitated picric acid was extracted successively with one 75-ml. portion of nitrobenzene, two 50-ml. portions of nitrobenzene, and then with two 50-ml. portions of benzene. After treatment with Norite, the nearly colorless solution was concentrated under reduced pressure to give a total of 16.4 g. (78%) of 4-hydroxy-3,5-dimethoxy-β-phenethylamine hydrochloride, m.p. 258–259°, after recrystallization from methanol–ethyl acetate.

Anal. Calcd. for $C_{10}H_{16}ClNO_3$: N, 6.0; Cl, 15.2. Found: N, 5.6; Cl, 15.0.

dl-1-(**4-Hydroxy-3,5-dimethoxyphenyl**)-**2-aminopropane Picrate** (III).—Reduction of 15.2 g. of 1-(4-hydroxy-3,5-dimethoxyphenyl)-2-nitropropane, m.p. 101–102°,[14] which was obtained by condensation of syringaldehyde with nitroethane in the presence of a methanol solution of methylamine, was carried out with a slurry of 12.5 g. of lithium aluminum hydride in 600 ml. of absolute ether essentially as described previously. The main reaction was accompanied by the formation of a highly-colored side product. The ethereal slurry of the product-complex was decomposed by means of 2 *N* sulfuric acid and the aqueous layer brought to a *p*H of 6 by the addition of solid lithium carbonate. The hot aqueous solution of the base was treated with a saturated solution of 19.0 g. of picric acid in boiling ethanol and placed in the refrigerator overnight. The bright-yellow picrate was collected on a filter, washed with water and dried; yield 13.9 g. (48%). After recrystallization from ethanol, a sample melted at 225° dec.

Anal. Calcd. for $C_{17}H_{20}N_4O_{10}$: C, 46.4; H, 4.6. Found: C, 46.4; H, 4.9.

The amine picrate was treated with hot dilute hydrochloric acid and was extracted with nitrobenzene in accordance with the procedure described for the preparation of I. Concentration of the aqueous solution of the amine hydrochloride to a small volume gave a rather dark sirupy solution from which the hydrochloride did not crystallize despite repeated attempts.

4-Ethoxy-3,5-dimethoxy-β-nitrostyrene.—A mixture of 14.7 g. of 4-ethoxy-3,5-dimethoxybenzaldehyde, 7.2 ml. of redistilled nitromethane, 50 ml. of glacial acetic acid and 4.4 g. of ammonium acetate was refluxed for 30 minutes, as described by Raiford and Fox[8] for the preparation of 3,4-dimethoxy-β-nitrostyrene. Upon cooling to room temperature, the product crystallized in large, stout yellow needles melting at 100–102°; yield 11.5 g. (65%), m.p. 108–109° after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 57.0; H, 5.9. Found: C, 56.8; H, 6.1.

4-Ethoxy-3,5-dimethoxy-β-phenethylamine Picrate (II).—The preceding nitrostyrene (11.0 g.) was reduced by treatment with a slurry of 8.6 g. of lithium aluminum hydride in 500 ml. of absolute ether and worked up as described previously. The crude, yellow crystalline picrate weighed 19.7 g. (84%), m.p. 182–183° after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{22}N_4O_{10}$: C, 47.6; H, 4.9. Found: C, 47.5; H, 4.8.

The picrate was converted to the hydrochloride of II by treatment with hot dilute hydrochloric acid in the manner already described. The conversion of 15.1 g. of picrate yielded 7.6 g. (90%) of hydrochloride, m.p. 165–166°, after recrystallization from methanol–ethyl acetate. Jensch reported a m.p. of 165°.[5]

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Purification and Physical Properties of 2,6-Lutidine and 2,4,6-Collidine

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2,6-Lutidine and 2,4,6-collidine are presently commercially available, presumably in a state of relatively high purity. Accordingly, when we decided to include these two compounds in a study we had been making of the base strengths of substituted pyridine bases, it appeared convenient to utilize the commercial products, purified in the conventional manner by fractionation.

The materials thus obtained appeared to be of satisfactory homogeneity by the usual criteria. However, the pK_a values deviated considerably from the values expected on the basis of simple additivity. Such deviations had been observed previously for these two bases, but had been attributed by the investigators to steric effects.[1]

Certain anomalies in the data led us to question this explanation and to examine instead the homogeneity of our purified samples. We therefore undertook a study of the isolation and properties of pure 2,6-lutidine and 2,4,6-collidine. The results revealed that the purity of the commercial samples available to us were much lower than had been expected—with Eastman Kodak and Matheson samples of 2,4,6-collidine exhibiting purities of but 55–65%.

Commercial 2,6-lutidine is generally contaminated with 3- and 4-picoline, all of which possess boiling points within 1°. It has been purified by azeotropic distillation with phenol[2] and by selective reaction of the impurities with ethyl tosylate.[3]

We had previously observed that the heat of reaction of boron trifluoride with 2,6-lutidine is far less than that of the corresponding reactions with 3- and 4-picoline. Consequently this reaction appeared to offer a simple and convenient procedure for the selective removal of these contaminants. A sample of commercial 2,6-lutidine (Reilly Tar and Chemical Corp.) was therefore treated with

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[13] F. Mauthner and G. Szonyi, *J. prakt. Chem.*, **92**, 200 (1915), reported a melting point of 115–116° for this compound. This value appears rather low when compared with the melting points of other closely related 3,4,5-substituted nitrostyrenes of this series. The products from a number of different runs always melted in the range of 165–167°, whether crude or recrystallized; analytical data and chemical properties of the 4-hydroxy-3,5-dimethoxy-β-nitrostyrene obtained in this work support the correctness of the structure assigned.

[14] M. Kulka and H. Hibbert, THIS JOURNAL, **65**, 1180 (1943), reported a melting point of 103–104° for this compound.

[1] A. Gero and J. J. Markham, *J. Org. Chem.*, **16**, 1835 (1951).

[2] E. A. Coulson, J. L. Hales, E. C. Holt and J. B. Ditcham, *J. Appl. Chem.* (*London*), **2**, 71 (1952).

[3] J. A. Cathcart and D. D. Reynolds, THIS JOURNAL, **73**, 3504 (1951).