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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[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.

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

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RECEIVED JUNE 10, 1954

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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[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).

TABLE I

PHYSICAL CONSTANTS OF 2,6-LUTIDINE AND 2,4,6-COLLIDINE

	2,6-Lutidine		2,4,6-Collidine	
	Present	Literature	Present	Literature
B.p., °C.	143.4 (740 mm.)	144.0 (760 mm.)[a]	170.2 (749 mm.)	170.3 (760 mm.)[b]
F.p., °C.	-6.07[c]	-5.9[a]	-44.46[c]	-46[d]
$n^{20}\text{D}$	1.4971	1.4971[a]	1.4981	....
$n^{25}\text{D}$	1.4953	1.4953[b,a]	1.4959	1.4959,[b] 1.4964[d]
$d^{25}{}_4$	0.9183	0.9183[e]	0.9100	0.9103[d]
pK_a (25°)	6.74	6.62[f]	7.59	7.45[f]

[a] E. A. Coulson and J. I. Jones, *J. Soc. Chem. Ind.*, **65**, 169 (1946). A. C. Bratton and J. R. Bailey, THIS JOURNAL, **59**, 175 (1937); G. Errera, *Ber.*, **34**, 3700 (1901). [c] From cooling curve corrected to zero impurity. [d] K. H. Engel, ref. 6. [e] T. Eguchi, *Bull. Chem. Soc.* (*Japan*), **2**, 176 (1927). [f] A. Gero and J. J. Markham, ref. 1, uncorrected for activity effects.

approximately 6 mole % of boron trifluoride and the unreacted 2,6-lutidine distilled away from the much less volatile addition compounds. The purity of the resulting sample was established as 99.8 mole % from the cooling curve.[4] The pK_a value, 6.74, was in good agreement with the value estimated on the basis of additivity. Physical constants are summarized in Table I.

2,4,6-Collidine has been purified by recrystallization of its mercuric chloride complex[5] and of its hydrochloride.[6] Assuming that the impurities present might be isomeric pyridine bases without two alkyl substituents in the α-positions, it appeared possible that these impurities might likewise be removed by treatment with boron trifluoride. However, the treatment improved the samples only slightly. Recrystallization of the hydrochloride, prepared from the product resulting from the boron trifluoride treatment, yielded a pure sample. A cooling curve determination indicated this sample to be better than 99 mole % pure. The pK_a value was determined to be 7.59, in excellent agreement with the calculated additive value. The physical constants are summarized in Table I.

The purification of 2,4,6-collidine was followed by changes in the infrared spectra. The results indicated that the commercial samples contained only 55–65% of the 2,4,6-collidine. The principal impurities, as determined from the spectra, appear to be 3,5-dimethylpyridine,[7] with strong peaks at 11.8 and 14.2 μ, and 2,3,6-collidine with a strong peak at 12.3 μ.[2] The 3,5-dimethylpyridine is present to the extent of approximately 5% and is removed by a single treatment with boron trifluoride. The isomeric collidine with substituents in both α-positions is not removed by this treatment, but is removed by recrystallization of the hydrochloride from absolute ethanol.

It was observed that brief exposure of 2,4,6-collidine to the atmosphere resulted in a considerable increase in the refractive index of the base and in the appearance in the infrared spectrum of two new sharp peaks at 12.75 and 13.15 μ. These peaks disappeared upon addition of calcium hydride and reappeared upon addition of water. 2,6-Lutidine did not exhibit this behavior. It therefore appears that 2,4,6-collidine possesses an unusual affinity for water.

Experimental Part

2,6-Lutidine.—Commercial 2,6-lutidine was fractionated through a 70-plate column and a narrow boiling center fraction utilized for the purification. To 529 g. of this fraction there was added 21 g. of boron trifluoride (6.3 mole %) and the mixture was redistilled through the column, until little material other than the addition compound remained in the flask. The product distilled at a constant temperature and all fractions exhibited a constant refractive index (Table I).

Previous attempts to purify 2,6-lutidine had utilized fractional crystallization. Material of 99.4–99.6% purity had been obtained by this method, but with a recovery of only 22% of the original material. In contrast, without any special effort to obtain the maximum possible yield, the boron trifluoride procedure resulted in a recovery of approximately 80% of material of 99.8% purity.

2,4,6-Collidine.—The following procedure was applied to both Eastman Kodak and Matheson samples. No significant difference was observed.

Since rectification through the 70-plate column at atmospheric pressure appeared to result in some decomposition, the preliminary purification was carried out by a distillation at reduced pressure through a 40-cm. Vigreux column. The infrared spectrum indicated no significant change in the original material except for the removal of water.

To 430 g. of a middle fraction there was added slowly, with cooling to 0°, 45 g. of boron trifluoride–ethyl etherate, approximately 10 mole %. The product was then distilled through the Vigreux column at 40 mm. The infrared spectrum showed the absence of the bands at 14.2 and 11.8 μ, presumably due to 3,5-dimethylpyridine. Redistillation of the product through a Todd column containing a stainless steel spiral did not result in any significant improvement in the purity.

An equal volume, 300 cc., of dry benzene was mixed with 290 g. of the middle fraction of the above distillation and dry hydrogen chloride was added, keeping the reaction mixture cold in an ice-bath. The product, 370 g., was filtered and recrystallized from 580 cc. of absolute ethanol. A total of 160 g. (43% recovery) of white needles was obtained (m.p. 286–287° in sealed capillary). Two additional recrystallizations resulted in a recovery of 90% in each operation, but the products showed no significant improvement in purity. The free base was regenerated by treating an aqueous solution of the hydrochloride with aqueous sodium hydroxide, extracting with benzene, drying over magnesium sulfate, and distilling under reduced pressure (b.p. 75.0° at 38.8 mm.). A comparison of the infrared spectrum of this product with those of the commercial materials indicated the presence of no more than 55–65% of 2,4,6-collidine in the original products.

Acknowledgment.—This study was assisted by a grant from the National Science Foundation.

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[4] The procedure used was a modification of that described by Rossini and co-workers, *J. Research Natl. Bur. Standards*, **26**, 591 (1941).

[5] F. C. Garrett and J. A. Smythe, *J. Chem. Soc.*, 763 (1903).

[6] K. H. Engel, U. S. Patent 2,426,442, Aug. 26, 1947; *C. A.*, **42**, 226 (1948).

[7] The infrared spectrum of 3,5-dimethylpyridine was not available. However, on the basis of a correlation we have made of the infrared spectra of pyridine with analogous benzene compounds, the peaks at 14.2μ and 11.8 are attributed to 3,5-dimethylpyridine, b.p. 169.8° (760 mm.).