TABLE II

Compound	M.p., °C.	Yield, %	Formula	Calcd. C	Calcd. H	Found C	Found H
II[a]	150[b]	70	$C_{14}H_{18}N_2O_2S\cdot HCl$	53.40	6.08	53.65	6.15
V[c,d,e]	241[f]	60	$C_{14}H_{18}N_4S_2\cdot 2HCl$	49.02	5.58	48.81	5.49
VIII[d,g,h]	113[b]	60	$C_{15}H_7N_3O_2S_2\cdot 2HCl$	48.44	4.87	48.50	5.04
X[a,i]	154[b]	60	$C_{13}H_{16}Cl_2N_2OS\cdot HCl$	43.88	4.81	43.97	4.84

[a] Reaction solvent, dilute acetone. [b] From dry acetone. [c] For III, see ref. 9. [d] Dinitro free amine reduced in low pressure hydrogenator in presence of catalytic amount of platinum oxide; diamine not converted to salt owing to hygroscopic nature. [e] Reaction solvent, ethyl acetate. [f] From acetone–dimethylformamide. [g] For VI, see ref. 11. [h] Reaction solvent, chloroform. [i] For IX dihydrochloride, see ref. 8.

Anal. Calcd. for $C_{11}H_6N_6O_4S$: C, 41.51; H, 1.90. Found: C, 41.72; H, 2.16.

2-(2,4-Dinitrophenyl)-thiobenzimidazole (XIII).—The procedure for XI, using 2-benzimidazolethiol, 2,4-dinitrobromobenzene and sodium hydroxide, gave a 70% yield of yellow product, m.p. 231–232°. It was recrystallized from alcohol.

Anal. Calcd. for $C_{13}H_8N_4O_4S$: C, 49.42; H, 2.73. Found: C, 49.41; H, 3.00.

Nuclear Substituted 2-Amino-1-(2-pyridyl)propanes[1]

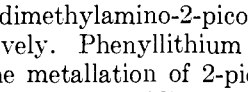
ALFRED BURGER AND HELEN HU ONG

Department of Chemistry, University of Virginia, Charlottesville, Va.

Received October 10, 1962

The postulate that histaminic activity may be expected if in a system, $-CH=N-C(=CH)-CH_2CH_2-NH_2$,[2] both the aliphatic and heterocyclic nitrogen atoms are members of a chelated ring,[3] has been made the basis of a working hypothesis for several attempts to produce hypotensive amines,[4,5] and to delineate the essential molecular fragment for histaminic properties.[2,3] Branching of the carbon chain α to the aliphatic amino group should render the resulting compounds more refractory to enzymatic deamination, and this prediction has indeed been realized in some cases.[6] However, the histaminic depressor properties of 2-amino-1-(2-pyridyl)-propane are lost when an ethyl group is introduced into position 5, or methyl into position 6 of the pyridine nucleus; these alkylpyridine derivatives exhibit, instead, marked analgetic activity.[6,7] In thiazolyl-2-aminopropane, two nuclear methyl groups intensified the analgetic effect,[8] while in methylpyrazolylethylamines the low depressor activity of the nuclear unsubstituted derivative was abolished by introduction of a C-methyl group.[5,6]

An explanation of these qualitative changes in activity is still lacking. The nuclear alkyl groups could perhaps change the distribution ratios of the resulting compounds, or somehow interfere with the stability of six-membered chelate rings. In the present study, the synthesis of two additional nuclear substituted 2-amino-1-(2-pyridyl)propanes is described. The 6-dimethylamino group in I should facilitate hydrogen bridging from the nuclear to the aliphatic nitrogen atoms.



I, R = 6-N(CH$_3$)$_2$
II, R = 3-CH$_3$

The synthesis of I and II started with the metallation of 6-dimethylamino-2-picoline, and 2,3-lutidine, respectively. Phenyllithium had been fairly satisfactory for the metallation of 2-picoline, but had given lower yields with 2,6-lutidine, and had failed with 4-picoline and 2,4-lutidine.[6] The much more stable methyllithium was therefore employed in the present cases. Treatment of the lithium derivatives with acetonitrile gave the corresponding lithium picolyl ketimines, and attempts were made to reduce these adducts *in situ* to the amines I and II. This direct route was unsuccessful, and the adducts were therefore hydrolyzed to 6-dimethylamino- and 3-methyl-2-pyridylacetone, respectively. Reduction of the oximes of these ketones furnished the amines, I and II, in good yields. The infrared spectrum of 2-amino-1-(3-methyl-2-pyridyl)-propane (II) contained an N–H stretching band at 3250 cm.$^{-1}$, slightly lower than that expected for free NH_2, and perhaps indicative of intramolecular hydrogen bonding.

In early experiments designed to synthesize (3-methyl-4-pyridyl)acetone, 3,4-lutidine was treated with phenyllithium, and after the color of the mixture had lightened, acetonitrile was added as above. However, the oily reaction product contained no carbonyl group. Fractionation furnished two isomers, $C_{13}H_{13}N$, which boiled at 113–115° (2.2 mm.) (III) and at 124-129° (2.2 mm.) (IV), respectively, and gave different picrates. This suggested that 3,4-lutidine had been phenylated, and that III and IV represent two of the three structures, 4-benzyl-3-methyl-, 3,4-dimethyl-2-phenyl-, or 3,4-dimethyl-6-phenylpyridine. Since the melting point of the picrate of 6-phenyl-3,4-lutidine[9] differs from those of the picrates of III and IV, the first two structures must be assigned to our compounds.

A C-methyl determination for III indicated the presence of only one methyl group while the values obtained for IV were inconclusive. This discrepancy should be weighed against the experience that the analysis for aromatically bound methyl groups often yields only a fraction of the expected values.[10] Oxidation of both III and IV produced only benzoic acid, and no pyridinecarboxylic acids could be found. If III is 4-benzyl-3-methylpyridine, oxidation to benzoic acid

(1) This research has been supported by a Grant, B-1445, from the Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service.

(2) L. A. Walter, W. H. Hunt and R. J. Fosbinder, *J. Am. Chem. Soc.*, **63**, 2771 (1941).

(3) C. Niemann and J. T. Hays, *ibid.*, **64**, 2288 (1942).

(4) R. G. Jones, M. J. Mann, and K. C. McLaughlin, *J. Org. Chem.*, **19**, 1428 (1954).

(5) H. M. Lee and R. G. Jones, *J. Pharmacol. Exptl. Therap.*, **95**, 71 (1949).

(6) A. Burger and G. E. Ullyot, *J. Org. Chem.*, **12**, 342 (1947).

(7) E. J. Fellows and G. E. Ullyot in "Medicinal Chemistry," C. M. Suter, ed., Vol. I, John Wiley & Sons, New York, N. Y., 1951, p. 390.

(8) M. Erne, F. Ramirez, and A. Burger, *Helv. Chim. Acta*, **34**, 143 (1951).

(9) G. J. Janz and W. J. H. McCulloch, *J. Am. Chem. Soc.*, **77**, 3143 (1955).

(10) F. Pregl and J. Grant, "Quantitative Organic Microanalyses," The Blakiston Co., Philadelphia, Pa., 1946, p. 169.

is readily understandable; if IV is 2-phenyl-3,4-dimethylpyridine, the failure to oxidize to 2-phenylcinchomeronic acid is less readily appreciated. However, Chichibabin[11] and later Tronova and Nikonova[12] had found that the oxidation of either 2-phenyl- or 2-benzylpyridine in neutral or alkaline solution gave only benzoic acid while in acidic medium a very small amount of α-picolinic acid also could be demonstrated. The failure of III and IV to furnish pyridinecarboxylic acids may well be attributed to the lowered resistance to oxidation of their more highly methyl-substituted pyridine rings. Control experiments in oxidizing 3,4-lutidine and cinchophen gave the expected pyridinecarboxylic acids in good yields.

The structure of III as 4-benzyl-3-methylpyridine was further supported by its ultraviolet absorption spectrum which failed to display any significant absorption in the region of 220–350 mμ to which conjugation could be assigned. Both 2- and 4-benzylpyridine,[13] examined for comparison, behaved similarly. By contrast, IV absorbed strongly at 235 and 272 mμ, and 2-phenylpyridine[14] at 245 and 277 mμ. Stringent proof for the structures of III and IV by hydrogenation of their pyridine nuclei and exhaustive methylation has not been undertaken because the phenyldimethyl- and benzylmethylpentadiene derivatives expected from these steps are unknown.

2-Amino-1-(6-dimethylamino-2-pyridyl)propane dihydrochloride was studied pharmacologically by Dr. Ralph Tedeschi of Smith Kline and French Laboratories to whom we are grateful for permission to quote his test results. On oral administration, the compound produced significant antipyretic, analgetic, and antiphlogistic effects at 100, 50 and 25 mg./kg. in rats in the Randall and Selitto procedure. No side effects were observed at the 25 mg./kg. dose, while slight to moderate CNS stimulation occurred at 50 mg./kg., and marked CNS stimulation at 100 mg./kg., manifested by exophthalmia, salivation, hypersensitivity to touch, polyurea, hyperpnea, erection of the penis, hypertonia, Straub tail (when touched) and increased motor activity. The compound produced a significant antiphlogistic effect in 40% of the rats at 100 mg./kg. and a significant analgetic effect in 80% of the animals tested. Oral analgetic activity in fasted rats as determined by a modified D'Amour–Smith procedure[15] resulted in a peak effect of 14.8% at 25 mg./kg. after 60 minutes. In one dog anesthetized with pentobarbital and arranged to record mean arterial blood pressure and heart rate, the compound produced a marked, sustained hypertension following an intravenous dose of 5.0 mg./kg. The effects of peripheral vagal stimulation and angiotensin appeared to be augmented while the responses of the remaining autonomic standards, including histamine, were not significantly altered.

Experimental[16]

(3-Methyl-2-pyridyl)acetone.—A solution of 42 g. of freshly distilled, dry 2,3-lutidine in 150 ml. of dry ether was added, with stirring and under nitrogen, to a solution[17] of 0.45 mole of methyllithium. After the end of the addition (90 min.) the solution was refluxed for another 3 hr., and a solution of 20 g. of dry acetonitrile in 100 ml. of dry ether then was dropped in. After 8 hr. boiling, the greenish-yellow mixture was poured into 200 g. of crushed ice, hydrolyzed with ice-cold 18% hydrochloric acid, and worked up. The yellow oily ketone (38 g., 65%) boiled at 61–62° (0.5 mm.).

The **picrate** crystallized from ethanol as yellow prisms, m.p. 149.5–151°.

Anal. Calcd. for $C_{15}H_{14}N_4O_8$: C, 47.62; H, 3.73. Found: C, 47.73; H, 3.60.

The **oxime** was prepared by allowing a mixture of 3 g. of the ketone, 2.5 g. of hydroxylamine hydrochloride, 5 g. of sodium acetate and 15 ml. of water to stand at 25° for 24 hr. with occasional shaking. The mobile yellow oil gradually crystallized on cooling. The colorless needles (2.6 g., 78%) melted at 93.5–95°.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.82; H, 7.36. Found: C, 65.44; H, 7.12.

2-Amino-1-(3-methyl-2-pyridyl)propane.—To a stirred slurry of 11.5 g. of powdered lithium aluminum hydride in 300 ml. of dry ether was added slowly a solution of 11 g. of (3-methyl-2-pyridyl)acetoxime in 150 ml. of dry ether. The mixture turned greenish and boiled. After refluxing for 8 hr., it was decomposed cautiously with 11 ml. of water, then 11 ml. of 15% sodium hydroxide solution and finally 33 ml. of water. The precipitate was filtered, washed with ether (100 ml.), and the ether filtrate was dried over potassium hydroxide for 40 hr. and fractionated. The main fraction (6 g., 66%) boiled at 62–64° (0.6 mm.), 52.5–53.5° (0.3 mm.), as an almost colorless oil.

The **bis-dilituarate** was prepared by dissolving the components in the minimum amount of water. It crystallized on cooling as a slightly tan powder which was recrystallized from hot water and darkened above 260° without melting. This powder was a monohydrate which did not lose water at 78° (0.5 mm.) for 48 hr., but could be dried at 143° (0.5 mm.) over phosphorus pentoxide after 36 hr.

Anal. Calcd. for $C_{17}H_{20}N_8O_{16}$: C, 41.12; H, 4.06. Found: C, 40.84; H, 4.54.

6-Dimethylamino-2-picoline.—A solution of 20 g. of 6-amino-2-picoline in 100 ml. of anhydrous ether was added dropwise under nitrogen to a stirred slurry of 10 g. of sodium hydride (50%, in mineral oil) in 150 ml. of dry ether, and the mixture was refluxed for 5 hr. A solution of 16 g. of dimethyl sulfate in 50 ml. of dry ether was added, the mixture was boiled for 2 hr., and then 10 g. of sodium hydride was added again and refluxing continued for 4 hr. This was followed by another addition of 20 g. of dimethyl sulfate, refluxing for 3 hr., and decomposing with 300 g. of ice. The aqueous layer was washed with three 100 ml. portions of ether, the combined ether solutions were extracted with cold 18% hydrochloric acid, the acid layer was made alkaline with 40% sodium hydroxide solution, and the alkaline mixture was extracted continuously with ether for 24 hr. The residual oil from the dried ether extract was boiled with 20 g. of acetic anhydride for 1 hr., cooled, and the mixture was fractionated. The yield of colorless mobile tertiary amine, b.p. 97.5–99.5° (7–8 mm.), was 9.5 g. (41%).

The yellow **picrate** crystallized from ethanol, m.p. 162–163°.

Anal. Calcd. for $C_{14}H_{15}N_5O_7$: C, 46.02; H, 4.14. Found: C, 45.88; H, 4.18.

An attempt to methylate 6-amino-2-picoline with formaldehyde and formic acid led only to a high-boiling deliquescent material which melted at 41–45° and was not further identified. In analogy with a similar experience of Chichibabin and Kmunyantz[18] the material could be bis(6-dimethylamino-2-methyl-5-pyridyl) methane.

(6-Dimethylamino-2-pyridyl)acetone.—A solution of 8 g. of 6-dimethylamino-2-picoline in 100 ml. of anhydrous ether was dropped with stirring into 400 ml. of a 0.57 *N* solution of methyllithium, refluxed for 4 hr., and then 6 g. of acetonitrile in 30 ml. of ether was added. After stirring and refluxing for 10 hr. the cooled mixture was decomposed with 40 g. of ice and worked up as usual. Fractionation of the reaction product gave, besides 6 g. of unchanged starting material, 2.1 g. (19%) of a yellow oil, b.p. 107–108° (0.5 mm.).

(11) A. E. Chichibabin, *Ber.*, **37**, 1373 (1904).

(12) B. V. Tronova and L. S. Nikonova, *J. Russ. Phys. Chem. Soc.*, **61**, 541 (1929); *Chem. Abstr.*, **23**, 4614 (1929).

(13) K. E. Crook and S. M. McElvain, *J. Am. Chem. Soc.*, **52**, 4006 (1930).

(14) J. C. W. Evans and C. F. H. Allen, *Org. Syn.*, **18**, 70 (1938).

(15) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

(16) All melting points are corrected. Microanalyses by Mrs. Dolores Ellis and Miss Winnie Sheffield.

(17) C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).

(18) A. E. Chichibabin and I. L. Knunyantz, *Ber.*, **62**, 3048 (1929).

The **picrate** crystallized from ethanol as shiny platelets, m.p. 136.5–137.5° (after slight sintering).

Anal. Calcd. for $C_{16}H_{17}N_5O_8$: C, 47.17; H, 4.20. Found: C, 46.95; H, 4.23.

The **oxime** was prepared as described for (3-methyl-2-pyridyl)-acetoxime above. It could not be crystallized. The infrared absorption spectrum confirmed the structure of the oily material.

2-Amino-1-(6-dimethylamino-2-pyridyl)propane.—A solution of 5 g. of crude (6-dimethylamino-2-pyridyl)acetoxime in 30 ml. of anhydrous ether was reduced with 8 g. of lithium aluminum hydride as described above. The colorless oily reaction product weighed 3.6 g. (78%) and boiled at 94–96° (1.3 mm.). The dihydrochloride crystallized from methanol–ether as a somewhat hygroscopic colorless material, m.p. 241–242.5° dec.

Anal. Calcd. for $C_{10}H_{19}Cl_2N_3$: C, 47.62; H, 7.59. Found: C, 47.63; H, 7.44.

Reaction of 3,4-Lutidine with Phenyllithium.—A solution of 26 g. of dried redistilled 3,4-lutidine in 100 ml. of anhydrous ether was dropped into a stirred solution of 0.25 *N* phenyllithium,[19] and the mixture was stirred at 25° for 19 hr. After hydrolysis with 100 g. of ice it was extracted with cold 18% hydrochloric acid, and the basic fraction liberated by alkalinization and extraction with ether. The dried extracts were fractionated. Besides 9 g. of unchanged starting material, a yellowish oil (8.1 g.), b.p. 102–123° (1.6–1.7 mm.) was obtained. This was refractionated to give two products, III and IV.

III (presumably 4-benzyl-3-picoline) weighed 2.1 g. The colorless oil had a bitter odor, b.p. 113–115° (2.2 mm.). Its *picrate* crystallized as fine needles from ethanol, m.p. 204–205°.

Anal. Calcd. for $C_{19}H_{16}N_4O_7$: C, 55.33; H, 3.91. Found: C, 55.55; H, 4.19.

IV (presumably 2-phenyl-3,4-lutidine) weighed 2.3 g., b.p. 124–129° (2.2 mm.). The *hydrochloride* crystallized as colorless needles from methanol, m.p. 235–236° dec.

Anal. Calcd. for $C_{13}H_{14}ClN$: C, 71.06; H, 6.42. Found: C, 70.98; H, 6.45.

The *picrate* crystallized from ethanol as yellow leaflets, m.p. 172.5–174.5°.

Anal. Calcd. for $C_{19}H_{16}N_4O_7$: C, 55.33; H, 3.91. Found: C, 55.21; H, 4.10.

Oxidation Experiments.—(a) To a stirred mixture of the oily III (1.5 g.) and 30 ml. of water, 9 g. of powdered potassium permanganate was added at 20° in 0.5 g. portions over a period of 4 hr. The solution was filtered, concentrated to 10 ml., acidified to pH 1 with nitric acid, and the precipitate was filtered and recrystallized from water. It weighed 0.58 g. (68%) and was identified as benzoic acid by its melting and mixture melting points and infrared spectrum. No basic or other product could be isolated from the filtrates *via* a copper salt or after treatment of buffered evaporation residues with diazomethane.

(b) The oily fraction IV was oxidized likewise. The only product to be isolated was benzoic acid, yield, 65.5%.

(c) A solution of 3 g. of III in 400 ml. of 5% sulfuric acid was oxidized, in small portions, with 7 g. of potassium permanganate, first with cooling, then at 25° for 1 hr. It was cleared with 2 g. of sodium bisulfite, acidified with hydrochloric acid, and 0.16 g. of a colorless precipitate (identified as benzoic acid) was filtered.

(19) R. G. Jones and H. Gilman, "Organic Reactions," Vol. VI, John Wiley & Sons, New York, N. Y., 1951, p. 353.

The Synthesis of S^{35}-(1,2-Dichlorovinyl)-L-Cysteine[1a]

R. F. DERR[1b] AND M. O. SCHULTZE[1c]

Department of Agricultural Biochemistry, University of Minnesota, St. Paul 1, Minnesota

Received October 16, 1962

In their search for the toxic factor in trichloroethylene-extracted soybean oil meal which induces aplastic anemia[2,3] in cattle, McKinney, *et al.*, synthesized a cysteine derivative[4,5] which when fed in small amounts produces this blood dyscrasia in calves. Based on the method of synthesis and other evidence they identified their product as S-(*trans*-1,2-dichlorovinyl)L-cysteine (DCVC). In this laboratory the extremely high toxicity of DCVC for calves has been amply confirmed,[6] as little as 2 mg./kg. of body weight injected intravenously being sufficient to induce fatal aplastic anemia. Among other species the rat is much more resistant and does not develop a blood dyscrasia[7]; *Escherichia coli* B is highly susceptible.[8]

For studies on the metabolism of DCVC in various species and of the interaction of the whole or fragments of this molecule with components of biological systems, radioactively labeled DCVC of high specific activity was required. Inasmuch as the D-isomer of DCVC is biologically less active than its enantiomorph,[9] synthesis of the radioactively labeled L-isomer is a prerequisite for meaningful biochemical studies.

S^{35} from BaS^{35} was incorporated into DCVC by the sequence of reactions.

$$BaS^{35} + 2H^+ \rightarrow H_2S^{35} + Ba^{++} \quad (1)$$

$$H_2S^{35} + KOH \rightarrow KS^{35}H + H_2O \quad (2)$$

$$C_6H_5CH_2Cl + KS^{35}H \rightarrow \underset{\text{(I)}}{C_6H_5CH_2S^{35}H} + KCl \quad (3)$$

$$\underset{\text{(II)}}{\text{L-}CH_2ClCHNH_2COOH.HCl} + C_6H_5CH_2S^{35}H \xrightarrow{\text{NaOEt}} \underset{\text{(III)}}{\text{L-}C_6H_5CH_2S^{35}CH_2CHNH_2COOH} \quad (4)$$

$$\text{(III)} \xrightarrow[2.\ CHCl=CCl_2]{1.\ Na + NH_3} \underset{\text{(IV)}}{\text{L-}CHCl=CClS^{35}CH_2CHNH_2COONa} \quad (5)$$

S^{35}-Benzyl-L-cysteine (III) and DCVC, the latter obtained by acidifying aqueous solutions of (IV), were isolated in crystalline form, recrystallized and their identity was compared with that of authentic non-radioactive specimens by melting point, absorption spectra, and chromatography, using the ninhydrin and iodoplatinate reactions and the radioactivity to locate the compounds, and as criteria of purity.

Oral or parenteral administration of S^{35}-DCVC led to rapid excretion of radioactivity in the urine and feces, which was maintained at a low level for a long time. The data shown in Fig. 1 were obtained with a male rat weighing 217 g. which was injected intraperitoneally with 2.56 mg. of DCVC and 6 million counts per minute of total radioactivity. A similar animal to which the same amount of S^{35}-DCVC was given by stomach tube had a 1.5-fold higher excretion of radioactivity in the feces during the first 24 hours. Thereafter it was

(1) (a) Paper No. 4889, Scientific Journal Series, Minnesota Agricultural Experiment Station. Supported in part by the U. S. Atomic Energy Commission (Contract AT (11-1)-364). An abstract of oral report appeared in *Fed. Proc.*, **19**, 7 (1960); (b) postdoctorate trainee USPH Training Grant No. 2G-345; (c) to whom correspondence should be addressed.

(2) W. R. Pritchard, C. E. Rehfeld, and J. H. Sautter, *J. Am. Vet. Med. Assoc.*, **121**, 1 (1952).

(3) V. Perman, C. E. Rehfeld, J. H. Sautter, and M. O. Schultze, *J. Agr. Food Chem.*, **4**, 959 (1956).

(4) L. L. McKinney, F. B. Weakley, A. C. Eldridge, R. E. Campbell, J. C. Cowan, J. C. Picken, Jr., and H. E. Biester, *J. Am. Chem. Soc.*, **79**, 3932 (1957).

(5) L. L. McKinney, *et al.*, *ibid.*, **81**, 909 (1959).

(6) M. O. Schultze, P. Klubes, V. Perman, N. S. Mizuno, F. W. Bates, and J. H. Sautter, *Blood*, **14**, 1015 (1959).

(7) M. O. Schultze, *Fed. Proc.*, **21**, 5 (1962).

(8) R. G. Daniel and M. O. Schultze, *Arch. Biochem. Biophys.*, **93**, 56 (1961).

(9) J. C. Picken, Jr., personal communication, 1958; R. G. Daniel, Ph.D. thesis, University of Minnesota, 1962.