was replaced by a white turbidity. After standing for several hours, the mixture was filtered and the white powder washed with water, alcohol, and ether, in succession. The product, weighing 0.392 g. (60%), was insoluble in the usual organic solvents, both hot and cold, was only very slightly soluble in hot glacial acetic acid and was readily soluble in hot dimethylformamide from which it crystallized as an extremely fine powder. It did not melt below 300°. After air-drying, the product still contained 1.51% of water; the analytical sample was dried at 100° (0.1 mm.). On heating to boiling a mixture of a few crystals and aqueous ferric chloride, a dark green color appeared which changed to brown-green on standing at room temperature.

Anal. Calcd. for $C_7H_3N_3O_3$: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.62; 3.18; N, 25.63.

6-Acetamido-2,3-dihydroxypyrido(2,3)pyrazine.—By a procedure similar to the foregoing, there was obtained 5.37 g. of 6-amino-2,3-dihydroxypyrido(2,3)pyrazine from the reaction of 21.4 g. of 2,3,6-triaminopyridine oxalate with 100 ml. of ethyl oxalate. The yellow powder had a tendency to pass through filter paper when an aqueous suspension was filtered. This was overcome by making the aqueous mixture slightly acid with dilute hydrochloric acid and washing the product with very dilute acid rather than with pure water. Bernstein, *et al.*,[7] prepared the amine by a similar method but did not describe these difficulties. The amine did not melt below 300°.

Anal. Calcd. for $C_7H_6N_4O_2 \cdot 0.5H_2O$: C, 44.92; H, 3.77; N, 29.94; H_2O, 4.81. Found: C, 45.15; H, 3.50; N, 29.87; H_2O, 4.73.

The product lost its water of hydration when heated at 120° (0.1 mm.) for several hours.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.39; N, 31.45. Found: C, 47.19; H, 3.41; N, 31.32.

A mixture of 0.898 g. of 6-amino-2,3-dihydroxypyrido(2,3)-pyrazine and 100 ml. of acetic anhydride was heated under reflux for 139 hr. After chilling, the product which precipitated was collected by filtration and washed with methanol. The air-dried amide contained 1.00% water and did not melt below 300°. The analytical sample was dried at 120° (0.1 mm.).

Anal. Calcd. for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 48.87; H, 3.81; N, 25.55.

The product is presumed to be the 6-acetamido derivative inasmuch as analogous hydroxypyrido(2,3)pyrazines and quinoxalines are readily methylated, with methyl sulfate in alkaline solution, on a ring nitrogen which is not adjacent to a hydroxylic carbon rather than on one of the hydroxyl substituents.[8] This chemical property, coupled with their extreme insolubility and high melting points, suggests that the 2,3-dihydroxy pyrido(2,3)-pyrazines are predominantly cyclic amides, tautomeric with their enolic forms; the presence of the latter is indicated by their solubility in aqueous alkali and color reactions with ferric chloride.

6-Amino-2,3-diphenylpyrido(2,3)pyrazine Hydrochloride.—A mixture of 4.93 g. (0.025 mole) of 2,3,6-triaminopyridine dihydrochloride, 5.25 g. (0.025 mole) of benzil, 50 ml. of ethyl methyl ketone, 100 ml. of water, and 3 ml. of concentrated hydrochloric acid was heated under reflux for 5 hr. After adjusting the pH of the solution to 6–7 with ammonia water and chilling in a refrigerator overnight, the yellow salt which precipitated was separated by filtration and washed twice with a cold solution consisting of ethanol–butanone–water (1:1:2, by vol.). The product weighed 1.27 g. (15%) and melted at 291.5–293°, after recrystallization from glacial acetic acid. On recrystallization again from this solvent, the melting point of the yellow powder remained constant at 293.5–294.5°.

Anal. Calcd. for $C_{19}H_{14}N_4 \cdot HCl$: C, 68.17; H, 4.52; N, 16.74; Cl, 10.59. Found: C, 68.19; H, 4.55; N, 16.73; Cl, 10.54.

The 6-acetamido derivative melted at 265–266° in good agreement with the reported value.[4]

2,3-Dimethylpyrido(2,3)pyrazine.—A solution of 0.655 g. (0.006 mole) of 2,3-diaminopyridine and 1 ml. of diacetyl in 15 ml. of isopropyl alcohol was heated under reflux for 45 hr. The solvent was removed and the residue sublimed at 120–130° (14 mm.). The sublimate, obtained as yellow needles, on recrystallization from isopropyl ether, was isolated as a pink solid, 0.730 g. (75%), m.p. 141–142.5°. On recrystallization from the same solvent, the compound melted at 143.5–144°.[9]

Anal. Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.85; H, 5.61; N, 26.24.

2,3-Diphenyl(2,3)pyrazine, prepared in the same fashion, melted somewhat higher (141–142°) than the reported value[4] (136–138°).

(8) C. L. Leese, and H. N. Rydon, *J. Chem. Soc.*, 303 (1955).

(9) V. Petrow and J. Saper, *ibid.*, 1389 (1948).

2,6-Dialkylpiperazines. I. Synthesis of *cis*-2,6-Dimethylpiperazine Derivatives

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In connection with pharmacological research on 3,8-diazabicyclo[3.2.1]octane derivatives (I),[1,2] we became interested in studying the behavior of 2,6-dimethylpiperazines (II) structurally related to I. A survey of the literature showed that class II was only represented by *cis*-2,6-dimethylpiperazine (V)[3-5] and 1,2,4,6-tetramethylpiperazine (II, R, R' = CH_3).[4] Convenient key intermediates to II appeared to be 4-benzyl-*cis*-2,6-dimethylpiperazine (III), II, R = H; R' = $CH_2C_6H_5$, and its 1-benzyl isomer (IV), II, R = $CH_2C_6H_5$, R' = H. We wish to point out that, starting from III or IV, it is possible to obtain N-monosubstituted or N,N'-disubstituted 2,5-dimethylpiperazine of definite structure ruling out any ambiguity on the position of the N-substituents. In addition, V can be now synthesized in high yield through a new convenient method.

Experimental

N-Benzyl-α-bromopropionamide (VI).—Although this product was described by Bischoff,[6] details of the preparation are given because a different procedure was employed. To a cooled solution of 900 g. of benzylamine in 300 ml. of chloroform, 74 g. of α-bromopropionyl bromide was added dropwise with stirring. The reaction mixture was stirred an additional 3 hr. at room temperature, water was added to dissolve the benzylamine hydrobromide, the organic layer was shaken with water and dried over sodium sulfate. The solvent was concentrated to the point of incipient crystallization, and an equal volume of petroleum ether (b.p. 34–60°) was added. After standing overnight, 73 g. (88%) of VI, m.p. 88–91°, was collected. The analytical sample was crystallized from 2-propanol, m.p. 96–97°, lit.[6] m.p. 92°.

Anal. Calcd. for $C_{10}H_{12}BrNO$: C, 49.60; H, 4.99; Br, 33.0; N, 5.87. Found: C, 46.53; H, 5.15; Br, 33.05; N, 5.60.

2,2'-Iminodipropionic Ethyl Ester Benzylamide (VII).—To a stirred solution of 105 g. (0.43 mole) of VI, 43.5 g. (0.43 mole) of triethylamine, and 500 ml. of toluene, a solution of 50.4 g. (0.43 mole) of *dl*-α-alanine ethyl ester[7] in 50 ml. of toluene was added at room temperature, and the mixture was refluxed 18 hr. with stirring. After cooling, triethylamine hydrobromide was filtered, and the solvent was evaporated under reduced pressure. The residue was suspended in 10% HCl, the unchanged VI (~10 g.) was extracted with ether, the acid solution was made basic with sodium carbonate, and the separated oil was extracted with ether. The extract was dried over sodium sulfate, the solvent was evaporated, the oily residue was distilled, and the fraction boiling at 155–160° (0.5 mm.) was collected. The yield was 80 g. (65%); infrared spectrum 3310 cm.$^{-1}$ (>NH stretching), 1740–1190 cm.$^{-1}$ (–COOR), 1685 cm.$^{-1}$ (amide), 1540 cm.$^{-1}$ (amide II), and 740–700 cm.$^{-1}$ (CH out of plane of phenyl group).

(1) G. Cignarella, E. Occelli, G. Maffii, and E. Testa, *J. Med. Chem.*, **6**, 26 (1963).

(2) G. Cignarella, E. Occelli, G. Maffii, and E. Testa, *ibid.*, **6**, 764 (1963).

(3) C. Stoehr, *J. prakt. Chem.*, **47** [2], 514 (1893); Beilstein, Vol. XXIII, p. 19.

(4) W. J. Pope and J. Read, *J. Chem. Soc.*, **105**, 219 (1914).

(5) W. R. Langdon and W. W. Levis, U. S. Patent 2,911,407 (Nov. 3, 1959); *Chem. Abstr.*, **54**, 3465e (1960).

(6) C. A. Bischoff, *Ber.*, **31**, 3236 (1898).

(7) R. W. Chambers and F. H. Carpenter, *J. Am. Chem. Soc.*, **77**, 1542 (1955).

Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.80; H, 7.97; N, 10.07. Found: C, 64.89; H, 7.52; N, 10.36.

4-Benzyl-*cis*-2,6-dimethyl-3,5-diketopiperazine (VIII).—VII (75 g.) was heated at 200–205° for 3 hr. under atmospheric pressure, and the ethyl alcohol formed was collected. The residual viscous oil was distilled, collecting the fraction (65 g.) boiling at 150–170° (0.6 mm.). The crude product was dissolved in ethanol, and an ether solution of dry HCl was added to precipitate the hydrochloride of VII which was filtered and suspended in sodium carbonate solution. The liberated base was extracted with ether, the solvent was evaporated, and the residue was distilled to yield 53.4 g. (85%) of VIII, b.p. 150–155° (0.6 mm.). On standing, the product solidified, m.p. 62–63° (petroleum ether).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.21; H, 6.94; N, 12.06. Found: C, 67.18; H, 7.12; N, 12.07.

The hydrochloride crystallized from ethanol, m.p. 212–214°.

Anal. Calcd. for $C_{13}H_{17}ClN_2O$: C, 58.10; H, 6.37; Cl, 13.19; N, 10.42. Found: C, 57.95; H, 6.57; Cl, 13.54; N, 10.32.

The infrared spectrum of VIII showed bands at 3280 $m.^{-1}$ (>NH stretching), 1730–1675 $cm.^{-1}$ (>CO of imidic group), and 740–700 $cm.^{-1}$ (CH out of plane of phenyl group). The *cis* configuration of VIII was demonstrated by the n.m.r. spectrum[8] which showed absorption at 1.41 δ (doublet, 6H, methyl hydrogens), 1.58 δ (singlet, 1H, hydrogen attached to nitrogen), 3.57 δ (quartet, 2H, hydrogens bonded to the carbons of the ring), 4.90 δ (singlet, 2H, methylene hydrogens), and 7.27 δ (multiplet, 5H, aromatic hydrogens). The presence of a doublet at 1.41 δ and of a quartet at 3.57 δ is consistent with an identical orientation of the 2,6-C–H bonds.

4-Benzyl-*cis*-2,6-dimethylpiperazine (III).—A solution of 44.5 g. of VIII in 500 ml. of anhydrous ether was added with stirring to a suspension of 44 g. of lithium aluminum hydride in 500 ml. of ether, and the mixture was refluxed for 6 hr. On cooling, the reaction mixture was decomposed by adding dropwise 135 ml. of water and by stirring the mass for 1 hr. at room temperature. The inorganic salts were filtered, thoroughly washed with ether, and the filtrates were dried over sodium sulfate. After removing the solvent, the oily residue was distilled and the fraction, b.p. 85–86° (0.6 mm.), was collected, yield 38 g. (95%), $n^{20}D$ 1.5363.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.86; N, 13.71. Found: C, 76.63; H, 10.04; N, 13.61.

The dipicrate crystallized from 70% ethanol, m.p. 245–247°.

Anal. Calcd. for $C_{25}H_{26}N_8O_{14}$: C, 45.31; H, 3.95; N, 16.91. Found: C, 44.95; H, 4.10; N, 17.17.

1-Benzyl-*cis*-2,6-dimethylpiperazine (IV).—A solution of 30 g. of 1-benzoyl-*cis*-2,6-dimethylpiperazine (X) in 300 ml. of ether was added dropwise with stirring to a cooled suspension of 30 g. of lithium aluminum hydride in 300 ml. of ether. The mixture was refluxed for 6 hr., then cooled at −5° and cautiously decomposed with 90 ml. of water. The mass was stirred for 1 hr. at room temperature, the inorganic salts were filtered and washed with ether. The filtrate was collected and dried over sodium sulfate; the solvent was evaporated, and the residue was distilled to yield 25.8 g. (92%) of IV, b.p. 97–98° (0.6 mm.), $n^{20}D$ 1.5473.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.86; N, 13.71. Found: C, 76.40; H, 10.09; N, 13.51.

***cis*-2,6-Dimethylpiperazine (V).**—A solution of 10.2 g. of III (or IV) in 50 ml. of ethanol was hydrogenated at atmospheric pressure over 3 g. of 10% palladium-on-carbon. After 5 hr., the theoretical amount of hydrogen had been consumed, and the reduction was stopped. The catalyst was filtered and the filtrate was distilled at atmospheric pressure collecting the fraction (4.8 g.) boiling at 140–145°. The product solidified at room temperature and after crystallization from ether melted at 115–116° (lit.[1] m.p. 110–111°), yield 84%. The n.m.r. spectrum[8] showed absorption at 0.92 δ (doublet, 6H, methyl hydrogens), 1.04 δ (singlet, 3H, hydrogen attached to nitrogen), and 2.30–2.80 δ (multiplet, 6H, hydrogens attached to the carbons of piperazine ring).

1(4)-Benzoyl-4(1)-benzyl-*cis*-2,6-dimethylpiperazine (IX, XI).—To a cooled suspension of 0.1 mole of 4(1)-benzyl-*cis*-2,6-dimethylpiperazine (III, IV) in 300 ml. of 5% sodium hydroxide, 0.12 mole of benzoyl chloride was added with stirring. The reaction mixture was stirred for 2 hr. at room temperature and acidified with hydrochloric acid. The unreacted benzoyl chloride was extracted with ether. The acid layer was made basic with sodium carbonate, and the viscous separated oil was thoroughly extracted with ether. After drying over sodium sulfate, the solvent was evaporated and the residue was distilled by the technique of Ronco, *et al.*,[9] obtaining IX in 86% yield, b.p. 190–195° (1 mm.).

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.87; H, 7.84; N, 9.08. Found: C, 77.52; H, 9.02; N, 9.31.

XI, b.p. 200° (1 mm.) was obtained in 90% yield.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.87; H, 7.84; N, 9.08. Found: C, 78.11; H, 8.03; N, 8.89.

1(4)-Benzoyl-*cis*-2,6-dimethylpiperazine (X, XII).—A solution of 0.1 mole of IX (XI) in 500 ml. of absolute ethanol was hydrogenated at 60° and 51.65 kg. of initial hydrogen pressure/$cm.^2$ in the presence of 10 g. of 10% palladium-on-carbon. The catalyst was filtered, the solvent was evaporated, and the residue was distilled. X, b.p. 128–130° (0.5 mm.) was isolated in 87% yield. On standing, the product solidified and after two crystallizations from ether melted at 110–112°, (lit.[1] m.p. 109–110° for a hypothetical 1-benzoyl-2,6-dimethylpiperazine to which, however, the structure was assigned without adequate proof).

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.30; N, 12.83. Found: C, 71.39; H, 8.42; N, 12.66.

Infrared spectrum of X (in $CHCl_3$) showed, besides bands at 3400 (>NH) and 1610 $cm.^{-1}$ (–CON<), strong absorption at 1430 $cm.^{-1}$. The n.m.r. spectrum[8] showed absorption at 1.28 δ (doublet, 6H, methyl hydrogens), 1.45 δ (singlet, 1H, hydrogen bonded to nitrogen), 2.74 δ (doublet, 6H, methylene hydrogens), 4.12 δ (multiplet, 2H, hydrogens bonded to the carbon of the piperazine ring), and 7.29 δ (singlet, 5H, aromatic hydrogens).

The **D-tartrate** was obtained by evaporating to dryness an ethanol solution of equimolar amount of the base and D-tartaric acid. The solid product was purified by crystallization from ethanol, m.p. 198–200°.

Anal. Calcd. for $C_{13}H_{18}N_2O \cdot C_4H_6O_6$: C, 55.42; H, 6.57; N, 7.60. Found: C, 55.21; H, 6.67; N, 7.63.

XII, b.p. 160° (1 mm.), was isolated in 82% yield. On standing, the product solidified and was crystallized from ether, m.p. 117–119° (lit.[1] m.p. 117° for the hypothetical 4-benzoyl-2,6-dimethylpiperazine). Infrared spectrum (in $CHCl_3$) showed bands at 3400 $cm.^{-1}$ (>NH), 1620 $cm.^{-1}$ (–CON<), and characteristic strong bands at 1430–1450, 1275, and 1085 $cm.^{-1}$. The n.m.r. spectrum[8] showed absorption at 0.97 δ (doublet, 6H, methyl hydrogens), 1.32 δ (singlet, 1H, hydrogen attached to nitrogen), 2.65 δ (multiplet, 6H, methylene hydrogens), 4.00 δ (multiplet, 2H, hydrogens bonded to the carbon of the piperazine ring), and 7.31 δ (singlet, 5H, aromatic hydrogens).

By evaporating to dryness an equimolar amount of the base and D-tartaric acid, a gummy residue was obtained which, after boiling in acetone-ethanol, separated a **di-D-tartrate**, m.p. 223–225°.[10] The product crystallized from ethanol, m.p. 228–229°.

Anal. Calcd. for $C_{13}H_{18}N_2O \cdot 2C_4H_6O_6$: C, 61.41; H, 7.21; N, 9.55. Found: C, 61.43; H, 7.28; N, 9.42.

(8) The n.m.r. spectrum was obtained using a Varian A-60 spectrometer operating at 60 Mc., in carbon tetrachloride with tetramethylsilane as internal reference; the chemical shifts are reported as δ values.

(9) K. Ronco, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, **39**, 2088 (1957).

(10) By this procedure, Pope and Read[1] isolated a D-tartrate, m.p. 227–228°. However, these authors erroneously attributed to it the formula of a mono salt.

p-Vinylphenyl Glycosides of Cellobiose and Maltose

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During the course of an immunochemical investigation currently being undertaken in this Laboratory, it became desirable to synthesize glycosides derived from *p*-vinylphenol and certain

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