20 hr. The product was isolated in the manner described for 2. During the final ether extractions, some ether-insoluble solid separated and was removed by filtration. The dried weight was 2.3 g., m.p. 230–240°; λ_{max} 315 mμ (ε 11,100). This solid is undoubtedly the enamine **7** but was not further characterized. Evaporation of the ether extracts gave 1.7 g. of solid, m.p. 170–178°. This residue was combined with 0.55 g. of crude product from a similar half-scale reaction. The combined crude products were dissolved in benzene and added to a column of 190 g. of Florisil[11] prewet with benzene. The column was eluted with benzene and increasing amounts of ether in benzene. When the column was eluted with 15–20% ether in benzene, 0.65 g. (6%) of crystalline material was obtained. Two recrystallizations of this material from benzene gave 0.43 g. (4%) of colorless prisms, m.p. 205.6–207.2°, $[\alpha]_D$ +29.7°; λ_{max} 254 mμ (ε 4100); λ_{max} 2.99, 3.45, 6.33, 6.38, 6.82, 7.00, 7.12 μ.

Anal. Calcd. for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; N, 8.23. Found: C, 77.43; H, 9.31; N, 8.01.[13]

17β-Acetoxyandrost-4-eno[3,2-*d*]-2′-methylpyrimidine (10). A.—A solution of sodium ethoxide in ethanol was prepared from 0.69 g. (0.030 mole) of sodium metal and 20 ml. of anhydrous ethanol and added to a mixture of 6.32 g. (0.020 mole) of 2-hydroxymethylenetestosterone[8] (**9**), 2.82 g. (0.030 mole) of acetamidine hydrochloride, and 50 ml. of anhydrous ethanol. The mixture was allowed to stand for 0.5 hr. at room temperature and then refluxed for 6 hr. The crude product was isolated as usual to give 1.25 g. of an amber oil. This oil was combined with 0.3 g. of oil from a similar half-scale reaction. The combined crude products were dissolved in benzene and added to a column of 80 g. of Florisil[11] prewet with benzene. The column was eluted with benzene and gradually increasing amounts of ether in benzene. When the column was eluted with 20% ether in benzene, 0.76 g. (7%) of oil was obtained, λ_{max} 227 mμ (ε 10,600), 250 mμ (5500), 301 mμ (10,400).

A mixture of 0.69 g. of this oil, 4 ml. of pyridine, and 4 ml. of acetic anhydride was heated for 10 min. on a steam bath and then poured into water. The mixture stood for several hr. and the solid was removed by filtration. There was obtained 0.59 g. (6%) of colorless solid, m.p. 150–165°. Repeated recrystallizations from hexane gave colorless prisms, m.p. 170.4–171.8°; $[\alpha]_D$ +143.4°; λ_{max} mμ (11,700), 256 mμ (5300), 302 mμ (12,600); λ_{max} 3.45, 5.76, 6.14, 6.37, 6.46, 6.96 μ.

Anal. Calcd. for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.60; H, 8.51; N, 7.43.

B.—A mixture of 3.16 g. (0.0100 mole) of 2-hydroxymethylenetestosterone,[8] 1.16 g. (0.012 mole) of acetamidine hydrochloride, 1.73 ml. (0.0125 mole) of triethylamine, and 10 ml. of dimethylformamide was refluxed for 2 hr. The solution was poured into 330 ml. of *N* hydrochloric acid and the crude product isolated in the manner described above. There was obtained 0.96 g. of an amber oil. This oil was converted to the acetate **10** by the above procedure and the crude oily product was chromatographed on Florisil.[11] After preliminary elution with benzene, a mixture of 15% ether in benzene removed the crystalline acetate **10** identical with the product previously described.

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(13) Since our preparation was completed, this compound has been reported, m.p. 205–206°, $[\alpha]_D$ +28°, see ref 4c.

New Compounds

Some Substituted Pyrido(2,3)pyrazines

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Several pyrido(2,3)pyrazines have been prepared by condensing 2,3-diaminopyridine or 2,3,6-triaminopyridine with either an α-diketone or ethyl oxalate; one product, lead 6-aminopyrido-(2,3)-pyrazine-2,3-dicarboxylate, was obtained *via* permanganate oxidation of 6-amino-2,3-dimethylpyrido(2,3)pyrazine.

Experimental

All melting points are corrected. 2,3-Diaminopyridine, m.p. 112–113°, was prepared by Raney nickel reduction[2] of 2-amino-5-chloro-3-nitro-pyridine[3] and purified by sublimation at about 130° (17 mm.). The oxalate and hydrochloride salts of 2,3,6-triaminopyridine were prepared by reducing 2,6-diamino-3-nitrosopyridine with hydrogen sulfide. The nitroso compound was obtained by nitrosating 2,6-diaminopyridine dihydrochloride with sodium nitrite in aqueous acetic acid. The over-all procedure was a combination of the methods of Titov[4] and Engelman.[5] 6-Amino(2,3)-pyrazine, obtained in 44% yield from the reaction of diacetyl and 2,3,6-triaminopyridine, melted at 272–273° after recrystallization from water; a melting point above 250° has been reported by Korte.[6]

6-Acetamido-2,3-dimothylpyrido(2,3)pyrazine.—The amide was prepared by heating 6-amino-2,3-dimethylpyrido(2,3)-pyrazine[7] (m.p. 231–231.5°) with acetic anhydride and recrystallized twice from isopropyl alcohol. The white fluffy product collapsed at 179–180.5° to a yellow semisolid mass which turned orange-red at 187° and melted, forming a red liquid, at 200°. Further recrystallization did not change the melting characteristics.

Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.04; H, 5.59; N, 25.91. Found: C, 61.01; H, 5.63; N, 25.80.

Lead 6-Amino(2,3)pyrazine-2,3-dicarboxylate.—A solution of 6.7 g. of potassium permanganate in 100 ml. of hot water was added dropwise, with stirring, over a period of about 150 min. to a refluxing solution of 1.74 g. (0.01 mole) of 6-amino-2,3-dimethylpyrido(2,3)pyrazine in 67 ml. of water containing 8 ml. of 10% aqueous sodium hydroxide. The precipitate of manganese dioxide was removed by filtration and the yellow filtrate neutralized with dilute nitric acid. An aqueous solution containing 12 g. of lead acetate trihydrate was added. After standing in an ice bath for several hr., the mixture was filtered and the yellow powder washed well with water. The salt weighed 4.80 g. (74%) and did not melt below 300°.

Anal. Calcd. for $C_9H_4N_4O_4Pb$: C, 16.72; H, 0.62; N, 8.67; Pb, 64.09. Found: C, 16.85; H, 0.68; N, 8.78; Pb, 64.04.

2,3-Dihydroxypyrido(2,3)pyrazine.—A mixture of 0.437 g. (0.004 mole) of 2,3-diaminopyridine and 5 ml. of ethyl oxalate was heated under reflux for 2 hr. Ether was added and the mixture filtered. The brown powder, after washing with ether, was dissolved in hot dilute aqueous sodium hydroxide and the solution was treated with decolorizing carbon. On neutralizing the filtrate with dilute hydrochloric acid to pH 7, its pink color

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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]

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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°).

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).

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