Synthesis of 5-Amino-1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide and Related 5'-Deoxyimidazole Ribonucleosides

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5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (1, AICA ribonucleoside) was converted in two steps to 5-amino-1-(5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (3) which was hydrogenated in the presence of Pd/C to yield 5-amino-1-(5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (4). The dehydration of 4 yielded 5-amino-1-(5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carbonitrile (7). The compounds 3, 4, and 7 were deblocked with formic acid to furnish 5-amino-1-(5-deoxy-5-iodo-β-D-ribofuranosyl)imidazole-4-carboxamide (6), 5-amino-1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (5), and 5-amino-1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-carbonitrile (8), respectively. Compound 8 was acetylated and then deaminated to give 1-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)imidazole-4-carbonitrile (11). The compounds 8 and 11 were converted into 5-amino-1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-thiocarboxamide (9) and 1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-thiocarboxamide (12), respectively. The synthesis of 1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (13) was achieved for the first time by the treatment of 11 with hydrogen peroxide in the presence of ammonium hydroxide. The compounds were tested for antibacterial, antifungal, and antiviral activity, with 5 and 6 significantly inhibitory to *Staphylococcus aureus*.

A variety of imidazole ribonucleotides are known precursors of de novo purine biosynthetic pathways.[1] The synthesis of imidazole nucleosides and analogs related to these precursors could provide promising chemotherapeutic agents. The imidazole nucleosides and nucleotides reported so far, which exhibit interesting biological properties, include 5-amino-1-β-D-ribofuranosylimidazole-4-thiocarboxamide, 5-amino-1-β-D-ribofuranosylimidazole-4-thiocarboxamide 5'-phosphate, and 5-formamido-1-(2,3,5-tri-*O*-formyl-β-D-ribofuranosyl)imidazole-4-thiocarboxamide. These compounds have shown activity against a variety of animal tumors.[2-4] In most of these instances it has been found that the naturally occurring or modified nucleosides supplied exogenously to the cell require 5'-phosphorylation for activation. However, there are nucleosides[5] such as decoyinine, 4'-methyleneadenosine,[6] and tetrofuranosyl derivatives of adenine,[7] which, although not subject to phosphorylation, are effective inhibitors of cellular growth. It has been suggested that such nucleosides produce these effects through a mechanism different from that of the nucleotide.[8,9] In particular the 5'-deoxy nucleoside derivatives are attractive potential medicinal agents, since such nucleosides because of the impossibility of 5'-phosphorylation cannot be incorporated into host nucleic acids and should therefore be less toxic and more specific in their action. In the present work we describe the synthesis of some 5'-deoxyimidazole nucleosides directly related to those involved in de novo purine biosynthesis.

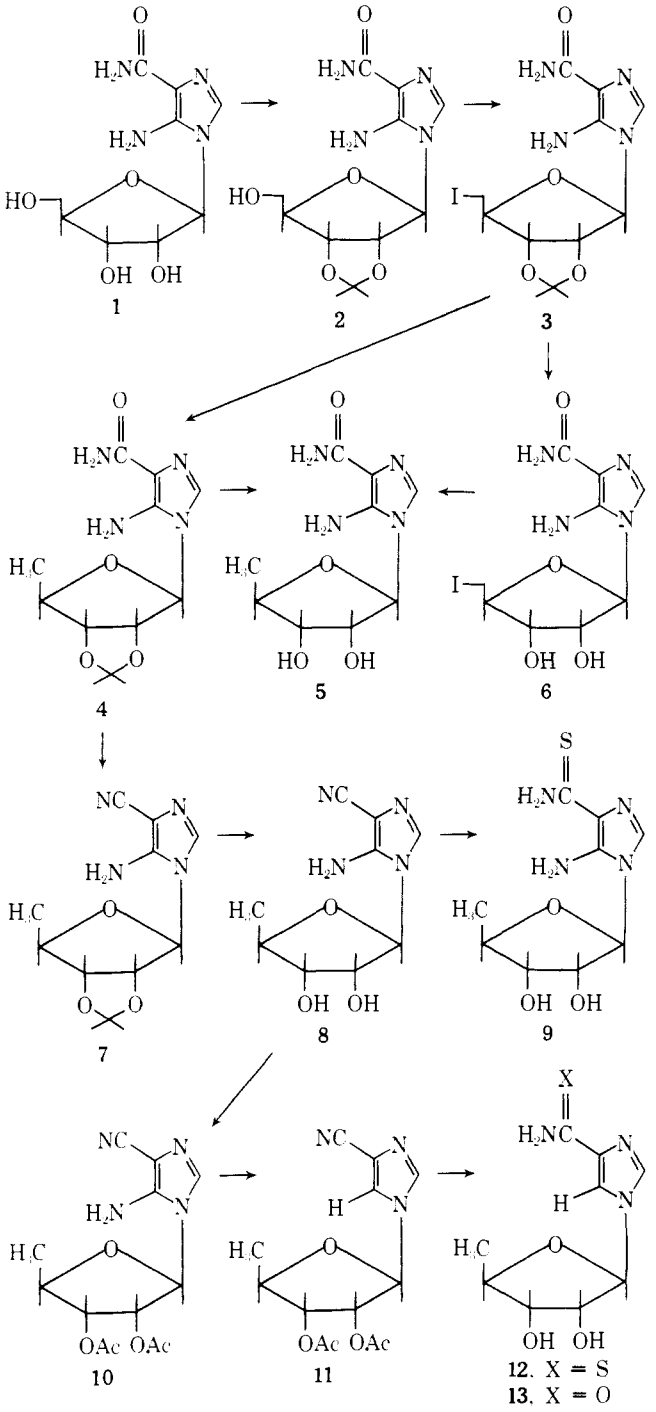
Chemistry. The synthesis of 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (2) from AICA ribonucleoside (1)[10] was achieved by the modification of procedure described in a patent.[11] An excellent procedure for 5'-iodination is described in the literature.[12] In a similar procedure, when we treated 2 with methyltriphenoxyphosphonium iodide (Rydon reagent[13]) in DMF, the desired product 5-amino-1-(5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (3) was indeed formed, but the formation of some side products was also observed, consequently giving a poor yield of compound 3. It seems logical that DMF, being highly polar, might facilitate some side reactions in the molecule, similar to those described in the case of cytidine and purine nucleosides.[12] When DMF was replaced by a less polar solvent, methylene chloride,[14] the pure product 3 was obtained in more than 90% yield.

Compound 3 was hydrogenated, at room temperature under pressure, using a commercial 10% palladium-on-carbon catalyst[15] in the presence of sodium acetate to provide 66–70% of 5-amino-1-(5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (4). Removal of the isopropylidene group was achieved in the presence of 88% formic acid. The residue obtained after the evaporation of formic acid was treated with dilute ammonium hydroxide and 5-amino-1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (5) was isolated in crystalline form in 75% yield. The isopropylidene group of 3 was removed in a similiar fashion when it was treated with 88% formic acid to yield the deblocked compound, 5-amino-1-(5-deoxy-5-iodo-β-D-ribofuranosyl)imidazole-4-carboxamide (6). Hydrogenation of 6 in the presence of Raney nickel readily provided 5 in 70% yield.

The dehydration of 4 was conveniently carried out using phosphorus oxychloride and triethylamine in chloroform to give 5-amino-1-(5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carbonitrile (7). Compound 7 was deblocked with formic acid to give 5-amino-1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-carbonitrile (8) in a similar way as described for the synthesis of 5 from the corresponding isopropylidene compound 4. The conversion of 8 into 5-amino-1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-thiocarboxamide (9) was desirable because of the good antitumor activity exhibited by the parent ribonucleoside, 5-amino-1-(β-D-ribofuranosyl)imidazole-4-thiocarboxamide.[2] The synthesis of compound 9 was easily achieved when a methanolic solution of 8 and potassium hydroxide was saturated with hydrogen sulfide and the resulting reaction mixture heated in a bomb.

The acetylation of 8 was achieved in the presence of pyridine and acetic anhydride at 0°. Under these conditions the acetylation of the 5-amino function[16] did not occur and 5-amino-1-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)imidazole-4-carbonitrile (10) was the only product isolated. This compound was needed as the precursor for some diazotization reactions leading to the synthesis of a class of imidazole nucleosides which has yet been unexplored. Our earlier attempts to diazotize AICA ribonucleoside (1) in dilute acid solutions gave only a mixture of highly colored products. The attempts to diazotize 1 in strongly acidic conditions resulted in the facile ring closure to 2-azainosine.[17,18] An obvious approach to circumvent this problem would be the transformation of the carboxamide function into a group like "nitrile" which can no longer participate in this kind of ring closure. As expected, the reductive deamination[19] of 10 was indeed accomplished via diazotiza-

Scheme I



tion using hypophosphorous acid and sodium nitrite. The reaction was carried out at a low temperature (<20°) to avoid the deglycosylation of the nucleoside. The deaminated product, 1-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-imidazole-4-carbonitrile (11) was isolated in pure form by column chromatography. This represents the first successful example of deamination via diazotization in the series.

The synthesis of 11 was found even more interesting due to the ability of the nitrile bond to undergo a variety of addition reactions to provide various novel compounds. The two main compounds, 1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-thiocarboxamide (12) and 1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (13), appeared to be significant from a biological standpoint and were synthesized as follows. In a typical experiment a solution of 11 and potassium hydroxide in methanol was saturated with hydrogen sulfide and heated in a bomb. Isolation of the product gave 12 in the crystalline form. The synthesis of 13 was also achieved when an ice-cold suspension of 11 in ammonium hydroxide was treated with 30% hydrogen peroxide (Scheme I).

Table I. Activity MIC,[a] μmol/ml

Compd	*S. aureus*
3	0.16
5	0.02
6	0.01
9	0.16
12	0.4

[a] Activity MIC = minimal inhibitory concentration. Range, 0.4–0.005 μmol/ml.

Biological Evaluation. The 5′-deoxy nucleosides such as **3**, **5**, **6**, **9**, and **12** were inactive when tested in vitro against type 1 herpes, type 13 rhino, and type 3 parainfluenza viruses in KB cells (a continuous cell line derived from a human carcinoma of the nasopharynx).[20] The cytotoxicity data were recorded for **5**, **6**, and **9** by microscopic observation[20] and comparison of the appearance of cell controls and KB cells exposed to compound for a continuous period of 3 days. None of the compounds showed significant toxicity toward KB cells when tested up to a concentration of 1000 μg/ml. These nucleosides were also tested against various microorganisms using broth dilution technique. In vitro inhibitory concentrations for compounds active against *Staphylococcus aureus* are shown in Table I. Of these, compounds **5** and **6** were significantly more active than compounds **3**, **9**, and **12**. The 5′-deoxy nucleosides tested were not active against *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *and Trichophyton mentagrophytes* at concentrations of 0.4 μmol/ml or less.

Experimental Section

The melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo. Where analyses are indicated by only symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical value. The ir spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer (KBr). NMR spectra were determined on a Hitachi Perkin-Elmer Model R-20A spectrometer using DSS as an internal standard. Presence of exchangeable protons and, where indicated by elemental analyses, hydration were confirmed by NMR spectroscopy in absolute Me_2SO-d_6 by exchange with D_2O and reintegration. The uv spectra were recorded on a Cary 15 ultraviolet spectrophotometer. Baker-analyzed silica gel powder (60–200 mesh) was used for column chromatography. The homogeneity of the compounds was checked by thin-layer chromatography using precoated (250-μ) ICN (Life Science Group) Woelm TLC plates (silica gel F-254). Short-wave ultraviolet light (mineralight UVS 11) was used to detect the spots. A Parr apparatus was used for hydrogenation reactions.

5-Amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (2). The reaction was achieved along the lines reported in a patent.[11] Dry hydrogen chloride (9.00 g) was dissolved into a solution of dry acetone (115 ml) and absolute ethanol (138 ml). To this was added AICA ribonucleoside (12.9 g, 50.00 mmol). The reaction mixture was stirred at room temperature for 1 hr and poured into a stirred cold solution of ammonium hydroxide (18 ml) in water (162 ml) (ph 8.0). The reaction mixture was concentrated to a small volume (100 ml). Separated ammonium chloride was removed by filtration, the filtrate was evaporated in vacuo, and the residue was dried at 50° for 2 hr. The dry residue was repeatedly extracted with chloroform. Evaporation of the

chloroform in vacuo gave a foam which was crystallized from ethanol to give **2** (6.5–7.5 g, 45–50%), mp 185–186°. Anal. ($C_{12}H_{18}O_5N_4$) C, H, N.

5-Amino-1-(5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (3). Rydon reagent[13] (20 g, 44.00 mmol) was added in nitrogen atmosphere to a suspension of **2** (6.0 g, 20 mmol) in methylene chloride (400 ml). The resulting suspension cleared up immediately. Stirring was continued at room temperature for 20 hr. Methanol (1 ml) was added to decompose the excess of Rydon reagent. The reaction solution was washed with sodium thiosulfate (10%, 200 ml) and then with water. The methylene chloride layer was dried ($MgSO_4$) and concentrated in vacuo. The crystalline product **3** separated out and was collected by filtration. Additional crystallization occurred when some ethyl ether was added to the mother liquor: total yield 7.2 g (90%). An analytical sample was obtained by recrystallization from ethanol or chloroform–hexane: mp 166–167° (slow dec above 170°); $\lambda_{max}^{pH\ 1}$ 265 nm (ε 11460) and 247 (sh) (10030); $\lambda_{max}^{pH\ 11}$ 264 nm (ε 13610); NMR (Me_2SO-d_6) δ 6.8 [s (br), 2, $CONH_2$] and 5.9–6.1 ppm [d (br), 3, J = 3 Hz, NH_2 and $C_1'H$ (superimposed)]; NMR (Me_2SO-d_6–D_2O) δ 7.51 (s, 1, C_2H), 5.88 (d, 1, J = 2 Hz, $C_1'H$), and 3.32 ppm (d, 2, J = 7 Hz, $C_5'H_2$). Anal. ($C_{12}H_{17}N_4O_4I$) C, H, N.

5-Amino-1-(5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide (4). Compound **3** (6.5 g, 16.00 mmol) was dissolved in hot ethanol (200 ml) and added to a suspension of anhydrous sodium acetate (1.6 g) and 10% Pd/C catalyst (1.76 g) in ethanol (100 ml). The mixture was hydrogenated at 48 psi at room temperature for 2 hr. The insoluble material and the catalyst were removed by filtration and the catalyst was washed with hot ethanol. The filtrate and the washings were collected and the solvent was evaporated in vacuo. A solution of the residue in ethyl acetate (400 ml) was washed with 10% sodium bicarbonate solution and then with water. The ethyl acetate portion was dried ($MgSO_4$) and evaporated in vacuo. The residue was crystallized from ethanol to give 3.3 g (75%) of the pure product **4**: mp 152–153°; $\lambda_{max}^{pH\ 1}$ 265 nm (ε 6860) and 245 (sh) (5700); $\lambda_{max}^{pH\ 11}$ 265 nm (ε 8110); NMR (Me_2SO-d_6) δ 1.2 ppm (d, 3, J = 7 Hz, $C_5'H_3$). Anal. ($C_{12}H_{18}N_4O_4$) C, H, N.

General Procedure A. Removal of 2',3'-*O*-Isopropylidene Blocking Groups. A solution of isopropylidene-blocked compound (2.00 mmol) in formic acid (88%, 10 ml) was stirred for 2 hr at room temperature and then at 0° overnight. Solvent was evaporated in vacuo at 30°, and the traces of formic acid were removed by repeated addition of water and evaporation in vacuo. Finally, the residue was dissolved in a solution of methanol (8 ml) and ammonium hydroxide (1 ml) and stirred for 10–15 min. The solvent was evaporated and the crystalline residue thus obtained was recrystallized from water.

5-Amino-1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (5). Method A. The product **5** was obtained from **4** as described in general procedure A in 75% yield; mp 207–208°; $\lambda_{max}^{pH\ 1}$ 266 nm (ε 10580) and 244 (sh) (8970); $\lambda_{max}^{pH\ 11}$ 265 (12710); NMR (Me_2SO-d_6) δ 6.81 [s (br), 2, $CONH_2$] and 5.81 ppm (s, 2, NH_2); NMR (Me_2SO-d_6–D_2O) δ 7.38 (s, 1, C_2H), 5.45 (d, 1, J = 5 Hz, $C_1'H$), and 1.27 ppm (d, 3, J = 5 Hz, $C_5'H_3$). Anal. ($C_9H_{14}N_4O_4$) C, H, N.

Method B. Raney nickel (wet, 500 mg) was added to a solution of **6** (180 mg, 0.500 mmol) in water (10 ml), and the mixture was hydrogenated at 40 psi for 2 hr. Catalyst was removed by filtration and the solvent evaporated. The residue thus obtained was crystallized from water to give 80 mg (70%) of **5**, mp 206–207°. This nucleoside was identical (uv, TLC, and mixture melting point) with **5** prepared by method A.

5-Amino-1-(5-deoxy-5-iodo-β-D-ribofuranosyl)imidazole-4-carboxamide (6) Deblocking of **3**, as described in general procedure A, gave **6** in 75% yield: mp 168–169° dec; $\lambda_{max}^{pH\ 1}$ 265 nm (ε 11200) and 247 (sh) (10020); $\lambda_{max}^{pH\ 11}$ 264 nm (ε 13440); NMR (Me_2SO-d_6–D_2O) δ 7.45 (s, 1, C_2H), 5.53 (d, 1, J = 6 Hz, $C_1'H$), and 3.4–3.6 ppm (m, 3, $C_4'H$, $C_5'H_2$). Anal. ($C_9H_{13}N_4O_4I$) C, H, N.

5-Amino-1-(5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carbonitrile (7). Compound **4** (2.12 g, 7.50 mmol) was dissolved in chloroform (25 ml). The solution was cooled to 0° and triethylamine (8 ml) was added, followed by the dropwise addition of $POCl_3$ (1.0 ml) at 0°. After complete addition, the reaction mixture was stirred at room temperature for 1 hr and diluted by the addition of chloroform (200 ml). This was washed with a 10% solution of sodium bicarbonate followed by water, and the organic layer was dried ($MgSO_4$). Evaporation of the solvent in vacuo left a residue which was crystallized from ethanol: yield 1.6 g (80%); mp 153–154°; $\lambda_{max}^{pH\ 1}$ 238 nm (ε 11580); $\lambda_{max}^{pH\ 11}$ 244 nm (ε 12720); ir 2210 cm^{-1} (–C≡N). Anal. ($C_{12}H_{16}N_4O_3$) C, H, N.

5-Amino-1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-carbonitrile (8). Compound **8** was obtained from **7** as described in general procedure A: yield 94%; mp 205–206° dec; $\lambda_{max}^{pH\ 1}$ 237 nm (ε 11930); $\lambda_{max}^{pH\ 11}$ 243 nm (ε 13770); ir 2180 cm^{-1} (–C≡N); NMR (Me_2SO-d_6) δ 6.25 ppm (s, 2, NH_2); NMR (Me_2SO-d_6–D_2O) δ 7.45 [s (br), 1, C_2H], 5.47 (d, 1, J = 6 Hz, $C_1'H$), and 1.32 ppm (d, 3, J = 6 Hz, $C_5'H_3$). Anal. ($C_9H_{12}N_4O_3$) C, H, N.

General Procedure B. Conversion of a Carbonitrile Compound into the Corresponding Thiocarboxamide. The carbonitrile compound (1.00 mmol) was dissolved in methanol (20 ml) with powdered KOH (224 mg, 4.00 mmol). Hydrogen sulfide gas was passed through the reaction mixture at 0° until the solution was saturated. This reaction mixture was heated in a bomb at 100° for 4 hr. Solvent was evaporated in vacuo and the residue dissolved in water (ca. 4 ml). The pH was adjusted to 5 by the addition of dilute acetic acid. The corresponding crystalline thiocarboxamide compound precipitated and was recrystallized from water: yield 70–80%.

5-Amino-1-(5-deoxy-β-D-ribofuranosyl)imidazole-4-thiocarboxamide (9). This compound was isolated from **8** as described in general procedure B: mp 205°; $\lambda_{max}^{pH\ 1}$ 324 nm (ε 16410) and 276 (9510); $\lambda_{max}^{pH\ 11}$ 325 nm (ε 16920) and 269 (10230). Anal. ($C_9H_{14}N_4O_3S$) C, H, N.

5-Amino-1-(5-deoxy-2,3-di-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (10). To a stirred cold suspension of compound **8** (448 mg, 2.00 mmol) in dry pyridine (10 ml) was added acetic anhydride (1 ml). The reaction mixture was stirred at 5 ± 5° for 3 hr. Ice-cold water (10 ml) was added to the reaction mixture. After 5 min, the solvent was evaporated in vacuo at 30°. The residue dissolved in $CHCl_3$ was washed with water, 10% sodium bicarbonate, and water, successively. The organic layer was dried ($MgSO_4$) and solvent evaporated in vacuo. The residue was crystallized from ethanol to give 465 mg (76%) of the pure product **10**: mp 129–130°; $\lambda_{max}^{pH\ 1}$ 240 nm (ε 12430); $\lambda_{max}^{pH\ 11}$ 244 nm (ε 12870); NMR (Me_2SO-d_6) δ 6.41 ppm (s, 2, NH_2); (Me_2SO-d_6–D_2O) δ 7.57 (s, 1, C_2H), 5.81 (d, 1, J = 5 Hz, $C_1'H$), 2.1 (d, 6, J = 2.5 Hz, $C_2'OCOCH_3$, $C_3'OCOCH_3$), and 1.4 ppm (d, 3, J = 7 Hz, $C_5'H_3$). Anal. ($C_{13}H_{16}N_4O_5$) C, H, N.

1-(5-Deoxy-2,3-di-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (11). Compound **10** (308 mg, 1.00 mmol) was stirred in cold (−25°) hypophosphorous acid (50%, 20 ml). To this was slowly added a solution of sodium nitrite (210 mg, 3.00 mmol) in water (1 ml). The stirring was continued at −20 to −25° for 3 hr. The reaction mixture was then adjusted to pH 6 by careful addition of cold ammonium hydroxide, keeping the temperature below −20°. The resulting mixture was extracted with ethyl acetate (2 × 100 ml). The combined ethyl acetate layers were washed with water and dried ($MgSO_4$). Evaporation of the solvent gave crude syrup which was chromatographed on a silica gel column packed in chloroform. Elution with chloroform–ethyl acetate (75:25) gave the product **11** in the form of a syrup (145 mg, 50%) which was crystallized from MeOH: mp 109–110°; $\lambda_{max}^{pH\ 1}$ 218 nm (ε 11000); $\lambda_{max}^{pH\ 11}$ 226 nm (ε 7600); ir 2205 cm^{-1} (–C≡N); NMR (Me_2SO-d_6) δ 8.25 and 8.53 [s (pair), 2, C_2H and C_5H], 6.07 (d, 1, J = 5 Hz, $C_1'H$), and 1.44 ppm (d, 3, J = 6.5 Hz, C_3H). Anal. ($C_{13}H_{15}N_3O_5$) C, H, N.

1-(5-Deoxy-β-D-ribofuranosyl)imidazole-4-thiocarboxamide (12). Compound **12** was obtained from **11** as described in general procedure B: mp 198–199°; $\lambda_{max}^{pH\ 1}$ 298 nm (ε 9500) and 248 (8920); $\lambda_{max}^{pH\ 11}$ 301 nm (ε 11100) and 254 (12300). Anal. ($C_9H_{13}N_3O_3S$) C, H, N.

1-(5-Deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (13). Hydrogen peroxide (30%, 0.2 ml) was added to the stirred ice-cold suspension of **11** (146 mg, 0.500 mmol) in ammonium hydroxide (2 ml). The solution, which became clear after ca. 10 min, was stirred at 0° overnight. Solvent was evaporated in vacuo. The residue was dissolved in water (2 × 2 ml) and evaporated in vacuo. The final residue on trituration with acetone provided a crystalline compound, which was recrystallized from methanol–water to yield 170 mg (75%) of **13**: mp 187–188° dec; $\lambda_{max}^{pH\ 1}$ 214 nm (ε 12100); $\lambda_{max}^{pH\ 11}$ 235 nm (ε 9430). Anal. ($C_9H_{13}N_3O_4$) C, H, N.

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Studies on 1-Substituted 4-(1,2-Diphenylethyl)piperazine Derivatives and Their Analgesic Activities. 1[1]

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The preparation and analgesic activities of a series of the entitled compounds (**5–22**) and the optical isomers of the 1-cyclohexyl derivative **5** are described. Reactions of *N,N*-bis(2-chloroethyl)-1,2-diphenylethylamine (**3**) with ammonia and primary amines gave *N*-(1,2-diphenylethyl)piperazine (**4**) and N^1-substituted derivatives (**5–20, 22**), respectively. The alkylation of **4** afforded **12–21**. Compounds **5–18** and **22** were also obtained by the reactions of 1,2-diphenylethylamine (**23**) and N-substituted 2,2′-dichlorodiethylamine. Racemate **5** was resolved with (+)- or (−)-2′-nitrotartranilic acid into its optical isomers [(+)-**5** and (−)-**5**], and the absolute configuration of (+)-**5** was determined to be *S* configuration by the synthesis and optical rotatory dispersion measurements. The most active members in this series of compounds were **5–7**, which were approximately as potent as (−)-morphine. In the case of **5**, the more potent enantiomer (*S*)-(+)-**5** has the opposite configuration to that of (−)-*N,N*-dimethyl-1,2-diphenylethylamine (Spa) or (−)-morphine with respect to the (C-9) asymmetric center and belongs to a new series of compounds having potent analgesic activity.

It is well known that certain derivatives of 10,11-dihydrodibenzo[*b,f*]thiepine having a piperazinyl group at position 10 exhibit a number of interesting effects on the central nervous system.[2] Among them perathiepine [10-(4-methylpiperazinyl)-10,11-dihydrodibenzo[*b,f*]thiepine] (**1**)[2] has been used clinically as a major tranquilizer. After considering structural modifications of **1**, it appeared that an investigation of derivatives of 1-piperazinyl-1,2-diphenylethane, which were derived from **1** by opening the central seven-membered ring with the loss of the sulfur atom, might lead to compounds with useful pharmaceutical properties.

On the other hand, Fujimura et al.[3] reported syntheses of 1,2-diphenylethylamine derivatives, and they found that (−)-*N,N*-dimethyl-1,2-diphenylethylamine (Spa) was about one-tenth as potent as (−)-morphine. Since 1-piperazinyl-1,2-diphenylethane derivatives bear a close structural resemblance to Spa, they might be also interesting as analgesics.

In order to investigate the activities on the central nervous system and analgesic activities, we have synthesized a number of 1-substituted 4-(1,2-diphenylethyl)piperazine derivatives[4] and found that some of these compounds were highly active as analgesics in animal tests.[5]

Chemistry. 1-Substituted 4-(1,2-diphenylethyl)piperazine derivatives were prepared by several procedures as shown in Scheme I. *N,N*-Bis(2-hydroxyethyl)-1,2-diphenylethylamine (**2**), which was prepared according to the method of Goodson et al.,[6] was chlorinated with thionyl chloride to give *N,N*-bis(2-chloroethyl)-1,2-diphenylethylamine (**3**) hydrochloride. Reactions of **3** with primary amines gave several 1-substituted 4-(1,2-diphenylethyl)piperazine derivatives (**5–20** and **22**). The catalytic hydrogenolysis of 1-benzyl-4-(1,2-diphenylethyl)piperazine (**22**) on palladium/carbon gave the debenzylated compound, *N*-(1,2-diphenylethyl)piperazine (**4**). Although the reaction of **3** and ammonia also gave **4**, the yield was very poor.

The alkylation of **4** afforded 1-substituted 4-(1,2-diphenylethyl)piperazine derivatives (**12–21**). Compounds **5–18** and **22** were also obtained by the reactions of 1,2-diphenylethylamine (**23**) and N-substituted 2,2′-dichlorodiethylamine.[8] Synthesized compounds are summarized in Table I.

It is well known that steric factors are important in analgesics. In most potent analgesics which have an asymmetric center, analgesic activity largely resides in one member of each enantiomorphic pair. The difference in potency between enantiomorphs is very likely due to the asymmetric topography of the receptor.[9,20]

Since 1-substituted 4-(1,2-diphenylethyl)piperazine has an asymmetric carbon, the 1-cyclohexyl derivative **5**, which showed a strong analgesic activity,[5] was resolved into its optical isomers and the absolute configuration of each enantiomorph was determined to assess the structure–activi-