Carbocyclic Analogs of Arabinosylpurine Nucleosides

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Abstract □ Carbocyclic analogs of arabinofuranosylguanine (VII) and 2,6-diamino-9-β-arabinofuranosylpurine (VIII) and the corresponding 8-azapurine analogs, 5-amino-7-hydroxy-3-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-ν-triazolo[4,5-*d*]pyrimidine (X) and 5,7-diamino-3-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-ν-triazolo[4,5-*d*]pyrimidine (XI), were prepared. Carbocyclic nucleoside analogs VII and X exhibited significant cytotoxicity against P-388 mouse leukemia cells in culture. *In vitro* testing against herpes simplex type 1 (strain HF) indicated that only VIII exhibited significant antiviral activity.

Keyphrases □ Arabinosylpurine nucleosides—carbocyclic analogs, synthesis and evaluation for antitumor and antiviral activity □ Antitumor activity—carbocyclic analogs of arabinosylpurine nucleosides, synthesis and testing □ Antiviral activity—carbocyclic analogs of arabinosylpurine nucleosides, synthesis and testing

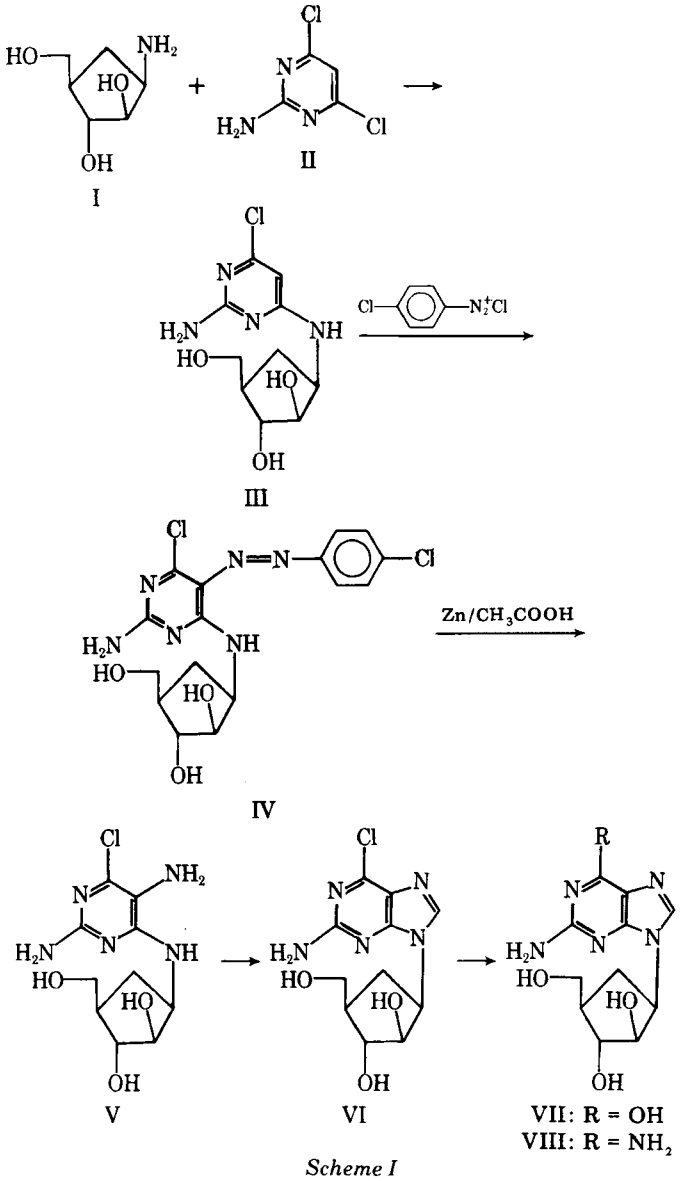
The significant antiviral and antitumor activities exhibited by the adenosine deaminase-resistant carbocyclic analog of arabinofuranosyladenine (1) prompted the synthesis of a variety of carbocyclic arabinosylpurine nucleosides. Recent studies with other antiviral nucleosides suggested that purine derivatives other than adenine should be explored in cases where an adenine nucleoside exhibits antitumor or antiviral properties (2, 3). In the case cited, the antiviral activity of the guanine analog in a series of 9-(2-hydroxyethoxymethyl)purines was two orders of magnitude greater than that of the corresponding adenine analog. In addition, Elion *et al.* (4) demonstrated high antiviral activity with 2,6-diamino-9-β-arabinofuranosylpurine. However, this analog was deaminated rapidly by adenosine deaminase. These results provide an excellent rationale for the synthesis of the guanosine and 2,6-diaminopurine derivatives of carbocyclic arabinosyl nucleosides.

RESULTS AND DISCUSSION

The synthesis of the carbocyclic purine nucleosides is outlined in Scheme I[1]. Condensation of (±)-4α-amino-2β,3α-dihydroxy-1α-cyclopentanemethanol (I) (1) with 2-amino-4,6-dichloropyrimidine (II) gave the corresponding pyrimidinylamino derivative (III). The 5-(*p*-chlorophenylazo)pyrimidine (IV) was prepared with *p*-chlorobenzenediazonium chloride by the method of Shealy and Clayton (5). Reduction of IV with zinc and acetic acid gave the pyrimidine V, which subsequently was converted to the 9-substituted 2-amino-6-chloropurine (VI) by ring closure with diethoxymethyl acetate and subsequent mild acid hydrolysis. Treatment of VI with 1 *N* HCl under reflux conditions gave carbocyclic arabinosylguanine (VII), while treatment of VI with liquid ammonia gave carbocyclic arabinosyl 2,6-diaminopurine (VIII).

The 8-azapurine analogs were obtained as illustrated in Scheme II. Ring closure of V with sodium nitrite and hydrochloric acid gave an excellent yield of (±)-5-amino-7-chloro-3-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-ν-triazolo[4,5-*d*]pyrimidine (IX). Acid hydrolysis of IX gave the 8-aza analog (X) of carbocyclic arabinosylguanine, whereas treatment of IX with liquid ammonia gave the 8-aza analog (XI) of carbocyclic arabinosyl 2,6-diaminopurine.

The ED_{50} cytotoxicity concentrations of VI–XI in P-388 mouse leukemia cell culture are listed in Table I. Carbocyclic arabinosylguanine



Scheme I

(VII) and 8-aza carbocyclic arabinosylguanine (X) exhibited significant cytotoxicities in this assay. All purine analogs were examined for *in vitro* antiviral activity against herpes simplex virus type 1 (strain HF) by quantitating the inhibition of virus-induced cytopathogenic effects in infected cultures.

The virus was propagated and assayed for infectivity in continuous-

Table I—Inhibitory Concentrations of Carbocyclic Purine Arabinosides for P-388 Leukemia Cells in Culture

Compound	ED_{50}, μM
VI	166.0
VII	4.6
VIII	251.0
IX	33.3
X	6.5
XI	258.0

[1] Structures I–XI depict only one enantiomer of the racemic form that actually was obtained.

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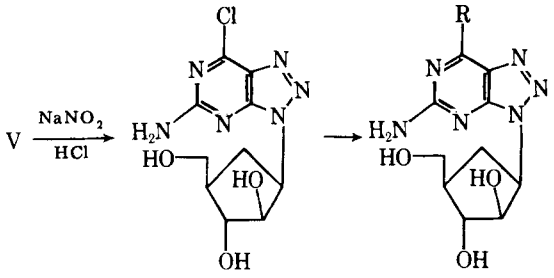

Scheme II

passage, human epidermoid carcinoma of the larynx (H. Ep.-2) cells. Virus ratings were calculated for the activity of each compound using a modification of the method of Ehrlich *et al.* (6) that was described previously (7, 8). Only the carbocyclic arabinosyl 2,6-diaminopurine analog (VIII) exhibited significant antiviral activity with a virus rating of 1.5[2].

EXPERIMENTAL[3]

TLC was performed using 0.25-mm layers of silica gel[4], and column chromatography was performed on silica gel[5]. PMR spectra were taken with a 60-MHz[6] or 100-MHz[7] spectrometer with tetramethylsilane as the internal standard. Melting points were determined in capillaries with a melting-point block[8] and are uncorrected.

(±)-2-Amino-4-*N*-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]amino-6-chloropyrimidine (III)—A mixture of aminoalcohol I [obtained from hydrolysis of 20 mmoles of (±)-4α-acetamido-2β,3α-diacetoxy-1α-cyclopentanemethyl acetate as described in Ref. 1], 2-amino-4,6-dichloropyrimidine (4.92 g, 30 mmoles), and triethylamine (20 ml) in 1-butanol (100 ml) was refluxed under nitrogen gas for 2 days (9). The solvent was removed under reduced pressure, and the residue was dissolved in water (200 ml). The aqueous solution was washed with methylene chloride (2 × 200 ml) to remove excess 2-amino-4,6-dichloropyrimidine. The aqueous solution was stirred briefly with anion-exchange resin[9] (40 ml), evaporated under reduced pressure, and azeotroped with absolute ethanol to dryness.

The liquid residue was dissolved in methanol–methylene chloride (1:4, 20 ml) and refrigerated. A pale-yellow crystalline product was collected by filtration, and recrystallization from methanol–methylene chloride (1:1) gave III as white granules (4.3 g, 78% from the acetamido acetate), mp 189–190°; UV: λ_{max} ($\epsilon \times 10^{-3}$) 310 (9.0), 274 (11.4), 238 (17.0), and 210 (28.0) in 0.1 *N* HCl, 284 (11.5), 239 (13.0), and 210 (30.0) in water, and 284 (11.3) and 236 (13.3) in 0.1 *N* NaOH; IR (KBr): 3500–3200 (NH and OH), 1640 (NH), and 1585 (C=C and C=N) cm^{-1}; PMR (100 MHz, dimethyl sulfoxide-d_6): δ 1.1–2.2 (m, 3H, CH and CH_2), 3.1–3.8, 4.0–5.1 (m, all other protons with water in the solvent), 5.87 (s, 1H, H at pyrimidine C-5), 6.33 (s, 2H, NH_2), and 6.74 (broad s, 1H, NH).

Anal.—Calc. for $C_{10}H_{15}ClN_4O_3$: C, 43.72; H, 5.50; Cl, 12.91; N, 20.40. Found: C, 43.51; H, 5.41; Cl, 12.94; N, 20.24.

(±)-2-Amino-4-*N*-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]amino-5-*p*-chlorophenylazo-6-chloropyrimidine (IV)—A cold (0–5°) solution of *p*-chlorobenzenediazonium chloride was prepared by adding a solution of sodium nitrite (0.65 g, 9.5 mmoles) in water (5 ml) to a solution of *p*-chloroaniline (1.15 g, 9 mmoles) dissolved in 12 *N* HCl (5 ml) and water (15 ml) and cooled in an ice–salt bath (5). The cold solution of *p*-chlorobenzenediazonium chloride was added dropwise to a mixture of III (2.15 g, 7.8 mmoles), sodium acetate trihydrate (17 g), acetic acid (40 ml), and water (40 ml) at room temperature. A yellow precipitate formed immediately, but the reaction mixture was stirred at room temperature overnight. The mixture was cooled in an ice bath; the yellow precipitate was filtered, washed with cold water, and dried.

The solid product was crystallized from methanol to yield yellow crystals (2.5 g, 77.6%, mp 243–246°), which were homogeneous by TLC and were used for the next reaction without further purification. An analytical sample of IV was obtained by recrystallization from methanol, mp 256–258°; UV: λ_{max} ($\epsilon \times 10^{-3}$) 372 (27.6), 266, and 228 (24.0) in 0.1 *N* HCl, 386 (29.8), 278 (11.6), and 226 (17.5) in water, and 386 (30.5) and 267 (13.8) in 0.1 *N* NaOH; IR (KBr): 3450–3100 (OH, NH), 1650 (NH), and 1570 (C=C and C=N) cm^{-1}; PMR (100 MHz, dimethyl sulfoxide-d_6): δ 1.15–2.43 (m, 3H, CH_2 and CH in cyclopentane ring), 3.29–3.92 (m, 5H, 3 CH, OH, and HOD), 4.33–4.72 (m, 2H, CH_2), 4.85 and 5.51 (2d, 2H, 2 OH), and 7.37–7.91 (m, 7H, aromatic, NH_2, and NH).

Anal.—Calc. for $C_{16}H_{18}Cl_2N_6O_3$: C, 46.50; H, 4.39; Cl, 17.16; N, 20.34. Found: C, 46.55; H, 4.38; Cl, 17.42; N, 20.23.

(±)-2,5-Diamino-4-*N*-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]amino-6-chloropyrimidine (V)—A mixture of IV (2.5 g, 6.1 mmoles), zinc dust (200 mesh, 4 g), and acetic acid (2 ml) in ethanol (100 ml) and water (100 ml) was refluxed under nitrogen until the yellow color of IV disappeared (5 hr) (5). Excess zinc was removed by filtration, and the solvent was evaporated under reduced pressure. The brown residue was dissolved in water (150 ml), and the aqueous solution was washed with methylene chloride to remove *p*-chloroaniline. After removal of water under reduced pressure, the residue was dissolved in ethanol–ethyl acetate and the solution was refrigerated overnight.

Filtration and dryness gave a crude brown product[10] (1.545 g, mp 213–215°). Repeated crystallization (three times) from water-ethanol (1:4) gave V as a slightly pink powder, mp 236–238°; UV: λ_{max} ($\epsilon \times 10^{-3}$) 298 (7.9) and 234 (18.9) in 0.1 *N* HCl, 302 (9.3), 242, 226, and 202 (19.1) in water, and 302 (9.0) and 244 in 0.1 *N* NaOH; IR (KBr): 3400–3200 (NH and OH), 1650, 1615, 1575, 1505, and 1470 cm^{-1}; PMR (100 MHz, dimethyl sulfoxide-d_6): δ 0.82–2.17 (m, 3H, CH_2 and CH in cyclopentane ring), 3.1–3.8 and 4.0–4.82 (m, other protons with HOD), 5.40 (broad s, 2H, NH_2), and 5.87 (d, 1H, NH).

Anal.—Calc. for $C_{10}H_{16}ClN_5O_3$: C, 41.45; H, 5.57; Cl, 12.24; N, 24.17. Found: C, 41.64; H, 5.68; Cl, 12.05; N, 24.39.

(±)-2-Amino-6-chloro-9-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]purine (VI)—Compound V (200 mg, 0.7 mmole) in diethoxymethyl acetate (20 ml) was stirred at room temperature for 1 hr, and the clear solution was heated at 80° for 24 hr with stirring. The solvent was removed under reduced pressure, and the oil residue was dissolved in 0.5 *N* HCl (10 ml) and stirred at room temperature for 30 min. The reaction solution was neutralized with anion-exchange resin[9] (pH 7–8), and the water was evaporated and azeotroped with absolute ethanol. The residue was purified by passing it through a silica gel column with methanol–methylene chloride (3:17) as the eluent.

Evaporation of the solvent of the corresponding fraction left 145 mg (69%) of a pink solid, mp 208–209°, which was homogeneous by TLC. Recrystallization from methanol–methylene chloride gave the analytically pure VI as a pink powder, mp 209–210°; UV: λ_{max} ($\epsilon \times 10^{-3}$) 312 (7.0), 242, and 218 (29.2) in 0.1 *N* HCl, 306 (8.2), 246, and 222 (28.2) in water, and 306 (8.1) and 246 in 0.1 *N* NaOH; IR (KBr): 3490, 3350 (br), 3220, 1658 (NH), 1610, 1565 (C=C and C=N), and 1035 (C–O) cm^{-1}; PMR (100 MHz, dimethyl sulfoxide-d_6): δ 1.65–2.35 (m, 3H, CH_2 and CH in cyclopentane ring), 3.11–4.01, 4.41–5.31 (CH_2O, 2 CHO, CHN, 3 OH, and HOD in dimethyl sulfoxide-d_6), 6.86 (s, 2H, NH_2), and 8.12 (s, 1H, H at purine C-8).

Anal.—Calc. for $C_{11}H_{14}ClN_5O_3$: C, 44.08; H, 4.71; Cl, 11.83; N, 23.37. Found: C, 44.24; H, 4.78; Cl, 11.93; N, 23.50.

(±)-9-[2α,3β-Dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]guanine (VII)—A solution of VI (146 mg, 0.49 mmole) in 1 *N* HCl (10 ml) was refluxed for 5 hr, and then the water was evaporated and azeotroped with absolute ethanol. The liquid residue was dissolved in a small amount of water, and the solution was neutralized (pH 6–7) with 6 *N* NaOH. The white precipitate formed immediately, but the solution was refrigerated for 1 hr. The solid product was collected by filtration and washed with cold water to yield 130 mg (94.3%) of a white powder, mp 290–293°.

Recrystallization from water gave VII as a white powder, mp 292–294°; UV: λ_{max} ($\epsilon \times 10^{-3}$) 227 (sh) and 252 (14.1) in 0.1 *N* HCl, 270 (sh) and 251 (13.5) in water, and 267 (12.0) and 254 (sh) in 0.1 *N* NaOH; IR (KBr): 3470, 3320, 3210, 2940–2500 (br), 1735 (C=O), 1630, and 1610 cm^{-1}; PMR (100 MHz, dimethyl sulfoxide-d_6): δ 1.6–2.3 (m, 3H, CH_2 and CH in cyclopentane ring), 3.31 (s, OH and HOD), 3.4–3.9 (m, 4H, CHO, CHN, and

[2] Virus rating (VR) is a weighted measurement of antiviral activity based on the *in vitro* inhibition of virus-induced cytopathogenic effects and the cytotoxicity exhibited by the drug as described in Ref. 6. A VR of >1.0 indicates definite (+) antiviral activity, and a VR of <0.5 indicates no (−) apparent antiviral activity.

[3] Elemental analyses were performed by M-H-W Laboratories, Phoenix, Ariz.

[4] Merck 60 F-254.

[5] Merck 60.

[6] Varian A-60D and T-60.

[7] Varian XL-100.

[8] Mel-Temp apparatus.

[9] Amberlite IRA-400 (OH^-).

[10] The crude brown products usually were contaminated with zinc acetate dihydrate (mp 237°) so that yields were variable.

CH_2O), 4.56–5.20 (m, 4H, 3 OH and CHO), 6.38 (s, 2H, NH_2), and 7.68 (s, 1H, H at purine C-8).

Anal.—Calc. for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.74; H, 5.42; N, 24.89.

(±)-2-Amino-9-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (VIII)—The chloropurine VI (390 mg, 1.3 mmoles) was stirred in excess liquid ammonia in a steel bomb at 75° for 42 hr. The bomb was cooled in a dry ice bath, and the reaction mixture was transferred to a beaker using methanol. The ammonia was allowed to evaporate at room temperature, and evaporation of methanol left a white powder.

Crystallization from water gave VIII as pink crystals (323 mg, 83.3%), mp 266–268°; UV: λ_{max} ($\epsilon \times 10^{-3}$) 290 (11.0), 251 (12.7), and 216 (27.0) in 0.1 *N* HCl, 280 (10.5), 254 (8.7), and 214 (273) in water, and 279 (11.5) and 254 (9.4) in 0.1 *N* NaOH; IR (KBr): 3470, 3410, 3330, 3210, 3130, 2900–2500 (br), 1670, 1630, and 1600 (NH, C=C and C=N) cm^{-1}; PMR (100 MHz, dimethyl sulfoxide-d_6): δ 1.71–2.31 (m, 3H, CH_2 and CH in cyclopentane ring), 3.27–3.91 (m, 8H, CHO, CNH, CH_2O, and H_2O), 4.57–5.33 (m, 4H, 3 OH and CHO), 5.77 (s, 2H, NH_2), 6.63 (s, 2H, NH_2), and 7.71 (s, 1H, H at purine C-8).

Anal.—Calc. for $C_{11}H_{16}N_6O_3 \cdot H_2O$: C, 44.28; H, 6.08; N, 28.18. Found: C, 44.04; H, 6.12; N, 28.56.

(±)-5-Amino-7-chloro-3-[2α,3β-dihydroxy-4α-(hydroxymethyl)-cyclopent-1α-yl]-ν-triazolo[4,5-*d*]pyrimidine (IX)—A solution of V (180 mg, 0.62 mmole) in 1 *N* HCl (1.3 ml) and water (4 ml) was cooled in an ice–salt bath, and sodium nitrite (45 mg, 0.65 mmole) was added with stirring. After 5 min (the solution was frozen), the ice–salt bath was removed and the solution was stirred at room temperature for 1 hr. The reaction solution was neutralized with sodium bicarbonate (109 mg, 1.3 mmoles) and then evaporated to dryness by azeotroping with absolute ethanol. The remainder was passed through a silica gel column with methanol–methylene chloride (1:4) as the eluent and gave a solid product (152 mg, 82%), mp 209–210°.

Recrystallization from methanol gave IX as a white powder, mp 210° dec.; UV: λ_{max} ($\epsilon \times 10^{-3}$) 314 (7.5) and 223 (27.0) in 0.1 *N* HCl, 314 (7.5) and 223 (22.9) in water, and 276 (12.4) in 0.1 *N* NaOH; IR (KBr): 3360, 3320, 3200 (OH and NH), 2960, 2920, 1640 (NH), 1600, 1570, 1510 (C=C and C=N), and 1110 (C—O) cm^{-1}; PMR (100 MHz, dimethyl sulfoxide-d_6): δ 1.80–2.46 (m, 3H, CH and CH_2 in cyclopentane ring), 3.40–4.14 (m, 4H, CHO, CHN, and CH_2O), 4.54–5.14 (m, 4H, CHO and 3 OH), and 7.56 (s, 2H, NH_2).

Anal.—Calc. for $C_{10}H_{13}ClN_6O_3$: C, 39.93; H, 4.35; Cl, 11.79; N, 27.95. Found: C, 39.66; H, 4.31; Cl, 11.79; N, 28.03.

(±)-5-Amino-7-hydroxy-3-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-ν-triazolo[4,5-*d*]pyrimidine (X)—A solution of IX (139 mg, 0.46 mmole) in 10 ml of 1 *N* HCl was refluxed for 5 hr, and the solvent was removed under reduced pressure and azeotroped with absolute ethanol. The solid residue was dissolved in a small amount of water, and the aqueous solution was refrigerated. Filtration afforded a fine crystalline product (pale brown, 80 mg, 62%), mp 210–215°.

Recrystallization from water gave X as pale-brown fine crystals, mp 215–217° (shrinking) and 275–277° dec.; UV: λ_{max} ($\epsilon \times 10^{-3}$) 270 (sh) and 252 (15.2) in 0.1 *N* HCl, 270 (sh), 252 (13.5), and 202 (24.0) in water, and 277 (13.0) in 0.1 *N* NaOH; IR (KBr): 3480, 3400, 3360, 3300, 3200 (OH and NH), 2940, 2880, 2800, 2740, 1700 (C=O), 1640, 1590, 1530 (C=C and C=N), and 1035 (C—O) cm^{-1}; PMR (100 MHz, dimethyl sulfoxide-d_6): δ 1.70–2.44 (m, 3H, CH and CH_2 in cyclopentane ring), 3.34 (s, OH and HOD), 3.40–4.10 (m, 4H, CHO, CHN, and CH_2O), 4.46–5.00 (m, 4H, 3 OH and CHO), and 6.80 (s, 2H, NH_2).

Anal.—Calc. for $C_{10}H_{14}N_6O_4$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.21; H, 5.07; N, 29.52.

(±)-5,7-Diamino-3-[2α,3β-dihydroxy - 4α - (hydroxymethyl)cyclopent-1α-yl]-ν-triazolo[4,5-*d*]pyrimidine (XI)—The chloro compound IX (202 mg, 0.67 mmole) was shaken with excess liquid ammonia in a steel bomb at room temperature for 2 days. Evaporation of ammonia left a solid residue, which was dissolved in hot water (10 ml). Refrigeration of the aqueous solution yielded a solid product (147 mg, 75.6%), mp 245–247°.

Recrystallization from water afforded XI as a white powder, mp 260–262°; UV: λ_{max} ($\epsilon \times 10^{-3}$) 282 (9.2), 252 (13.0), and 211 (32.8) in 0.1 *N* HCl, 283 (11.7), 250 (sh), and 222 (27.2) in water, and 283 (12.6) and 254 (sh) in 0.1 *N* NaOH; IR (KBr): 3500, 3400, 3320, 3140 (OH and NH), 2940, 2880, 1675 (NH), 1610, 1490 (C=C and C=N), and 1050 (C—O) cm^{-1}; PMR (100 MHz, dimethyl sulfoxide-d_6): δ 1.76–2.40 (m, 3H, CH_2 in cyclopentane ring), 3.40–4.12 (m, 4H, CHO, CNH, and CH_2O), 4.50–5.04 (m, 4H, 3 OH and CHO), 6.28 (s, 2H, NH_2), and 7.46 (s, 2H, NH_2).

Anal.—Calc. for $C_{10}H_{15}N_7O_3 \cdot 1/2H_2O$: C, 41.37; H, 5.56; N, 33.78. Found: C, 41.62; H, 5.56; N, 33.63.

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