Nucleosides CV. Synthesis of the 8-(β-D-ribofuranosyl)pyrazolo[1,5-*a*]-1,3,5-triazine Isosteres of Adenosine and Inosine (1)

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Reaction of ethyl *N*-cyanoformimidate (**3**) and of ethyl *N*-carbethoxyformimidate (**5**) with 3-aminopyrazole (**2**) gave 4-amino- and 4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**4** and **7**), respectively. Reaction of 3-amino-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrazole (**8**) with the same reagents similarly gave the blocked 4-amino-8-ribosyl- and 4-oxo-3*H*-8-ribosyl-pyrazolo[1,5-*a*]-1,3,5-triazine (**9** and **15**), respectively. Deblocking in acid finally afforded the unblocked products **10** (an isostere of adenosine and formycin) and **16** (an isostere of inosine and formycin B). The corresponding derivatives in the α series were made by identical procedures for confirming all structural assignments. Preliminary *in vitro* testing results of **10** are included.

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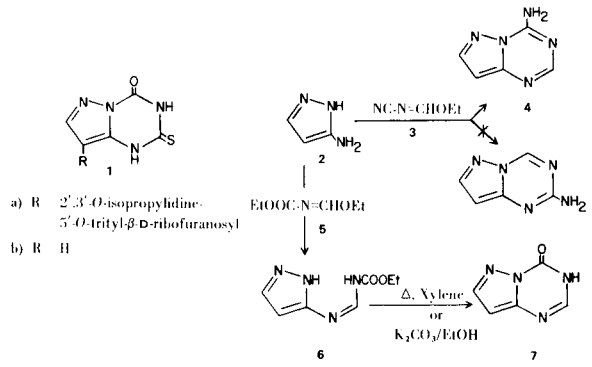
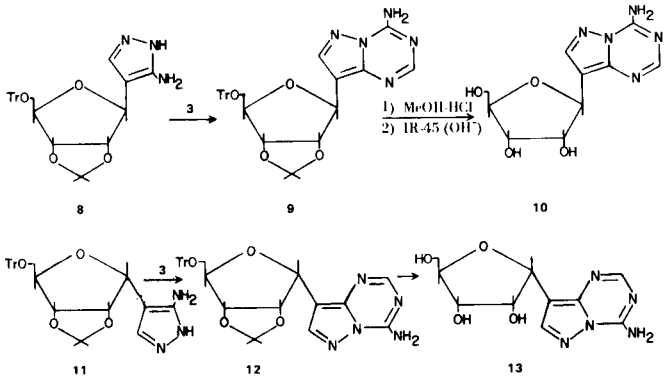
As part of our program concerned with the synthesis and biological testing of *C*-nucleoside analogues of purine nucleosides we have recently reported the synthesis of 8-(β-D-ribofuranosyl)-4-oxo-2-thioxo-1*H*,3*H*-pyrazolo-[1,5-*a*]-1,3,5-triazine (**1a**) (2). We wish to report here the synthesis of the corresponding 4-amino derivative **10** (an isostere of both adenosine and the *C*-nucleoside antibiotic formycin (3)), and of the 4-oxo-3*H* derivative **16** (an isostere of inosine and formycin B (3)). Both **10** and **16** were obtained by reaction of the *C*-ribosylated amino-pyrazole **8** (2) (the synthetic precursor of **1a**) with ethyl *N*-cyano- or ethyl *N*-carbethoxyformimidates, (**3** and **5**), respectively. Utilization of such reagents was suggested by their well-known ability to react with structures incorporating an amidine function to give symmetrical triazine derivatives (4).



In a model experiment, 3-aminopyrazole (**2**) in boiling ethanol reacted smoothly with ethyl *N*-cyanoformimidate to give 4-aminopyrazolo[1,5-*a*]-1,3,5-triazine (**4**) directly in good yield. No trace of the alternate amino derivative that might have been expected to form by a different mode of cyclization could be detected. Proof of structure was obtained by an independent synthesis of **4** consisting of a five step conversion of 4-oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**1b**) according to the reported procedure of J. Kobe, *et al.*, (5). Reaction of **2** with ethyl *N*-carbethoxyformimidate under similar conditions afforded exclusively an intermediate which was characterized as *N*-carbethoxy-*N'*-(3-pyrazolyl)formamidine (**6**). This compound was cyclized to the desired 4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**7**) by either heating in boiling xylene or by treatment with potassium carbonate in ethanol. The same compound was obtained by Raney nickel reduction of **1b** (5).

Treatment of the 4-ribosyl-3-aminopyrazole (**8**) with ethyl *N*-cyanoformimidate in benzene afforded exclusively the 8-ribosyl-4-aminopyrazolo-triazine (**9**) as an amorphous solid in good yield. Brief treatment with methanolic hydrogen chloride finally gave the free *C*-nucleoside **10** in crystalline form. A similar procedure has afforded **12** and **13** from the corresponding α-aminopyrazolo derivative **11**. The uv spectra of **9**, **10**, **12** and **13** are similar to that of model compound **4**. Assignment of the β configuration to **9** and **10** and of the α configuration to **12** and **13** is

based on a comparison of the pmr spectra of these compounds. Thus, the chemical shift of H-1′ for the α-anomers occurs at lower field than that for the corresponding β-anomer (6). This relationship has been utilized successfully for the structural determination of other *C*-nucleosides synthesized in our laboratory (2,7).



The mild conditions described for simultaneous detritylation and deisopropylidenation of **9** and **12** (see Experimental) to their respective deblocked derivatives **10** and **13** are critical to the retention of anomeric purity since interconversion of **10** and **13** occurs slowly under prolonged acid treatment. Pmr studies on a sample of α derivative **13** in DMSO-d_6 in the presence of deuterium chloride have shown that it is slowly converted to a mixture of **10** and **13** (**10**:**13** ~ 4:1). Comparable results were obtained when a mixture of **9** and **12** (**9**:**12** ~ 2:3) was unblocked by prolonged treatment (~ 3 days) with methanolic hydrogen chloride to afford an equilibrium mixture of **10** and **13** with the β derivative **10** again predominating over its α isomer **13** by a ratio of 4:1. The two products could be readily separated by silica gel chromatography using chloroform/methanol (4:1) as the eluant.

Treatment of **8** with ethyl *N*-carbethoxyformimidate (**5**) in ethanol gave intermediate **14** which, without isolation, was cyclized by treatment with potassium carbonate followed by neutralization to the desired 8-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**15**). Deblocking by brief treatment with methanolic hydrogen chloride afforded the free *C*-nucleoside **16** as the pure β derivative. A similar sequence, when applied to the α-aminopyrazole **11**, provided the open-chain intermediate **17** which cyclized to the blocked pyrazolo[1,5-*a*]-1,3,5-triazine derivative **18**. Final acid treatment (methanolic hydrogen chloride) gave the pure α-*C*-nucleoside **19**. Proof for the structures and anomeric identities of **15**, **16**, **18** and **19** was obtained by the same criteria utilized in the case of the corresponding amino derivatives. Again, the β derivative **16** and α derivative **19** were found to be susceptible to epimerization at C-1′ upon prolonged treatment with acid to give a mixture in which the β anomer predominates by a ratio of at least 2:1.

Preliminary *in vitro* testing (8) indicates that compound **10** has moderate inhibitory activity against mouse leukemia L1210 (ID_{50} = 0.1 μg./ml.), L5178Y (ID_{50} = 1 μg./ml.) and P815 (ID_{50} = 0.3 μg./ml.) and is more active than formycin in all systems tested. The α isomer **13** is much less active than **10**.

Further investigation of all compounds is in progress.

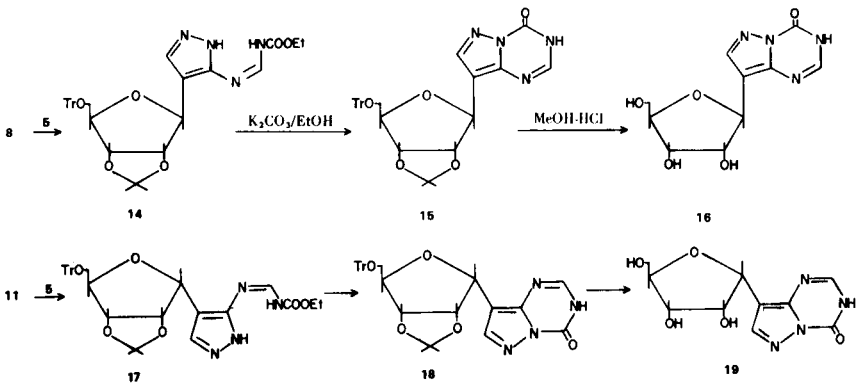
EXPERIMENTAL

General.

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The pmr spectra were obtained on a Jeol PS-100 spectrometer with TMS as internal standard. Ultraviolet absorption data were determined with a Cary recording spectrophotometer, Model 15. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Thin layer chromatography (tlc) was performed on microscope slides coated with Merck silica gel GF_{254} and substances were visualized either by uv absorption, iodine vapor, or by spraying with 20% ethanolic sulfuric acid and charring. Column chromatography was done using Woelm silica gel (70-230 mesh).

4-Aminopyrazolo[1,5-*a*]-1,3,5-triazine (**4**).

A solution of 3-aminopyrazole (**2**) (420 mg., 5 mmoles) in methanol (10 ml.) was slowly added to a warm solution of ethyl



N-cyanoformimidate (**3**) (4a) (2 g., 20 mmoles) in methanol (30 ml.). The solution was then heated to reflux for 11 hours and evaporated to dryness *in vacuo*. The residue was crystallized from methanol to give 420 mg. of **4** (78%), m.p. 204-205° (lit. (5) 204-205°); pmr (DMSO-d_6): δ 6.44 (d, 1, $J_{7,8}$ = 2.2 Hz, H-8), 8.08 (s, 1, H-2), 8.15 (d, 1, H-7), 8.40 and 8.64 (2 broad s, 2, NH_2); uv: λ max (*p*H = 7) 279 nm (ε, 6,370); λ min (*p*H = 7) 242 (ε, 1,020); λ max (*p*H = 1) 260 (ε, 4,000) and 296 (ε, 2,390); λ min (*p*H = 1) 256 (ε, 3,980) and 279 (ε, 2,220).

Anal. Calcd. for $C_5H_5N_5$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.43; H, 3.76; N, 51.90.

4-Amino-8-(β-D-ribofuranosyl)pyrazolo[1,5-*a*]-1,3,5-triazine (**10**).

A solution of **8** (2) (1 g., 2 mmoles) in benzene (10 ml.) was slowly added to a warm solution of ethyl *N*-cyanoformimidate **3** (800 mg., 8 mmoles) in benzene (8 ml.). The mixture was heated to reflux for 5 hours and evaporated to dryness *in vacuo* to afford a syrupy product which was washed with warm water to remove excess **3**. After decantation, the residue was dissolved in chloroform and dried with anhydrous sodium sulfate. Evaporation of the chloroform solution gave a syrupy product which was shown to contain >90% of **9** by tlc. Silica gel column chromatography with ethyl acetate/petroleum ether (30-60°) (4:1) as the eluant afforded pure **9** as an amorphous solid (670 mg., 61%); pmr (deuteriochloroform): δ 1.38 and 1.62 (2 s, 6, CMe_2), 3.21-3.26 (m, 2, H-5′ and H-5″), 4.33 (m, 1, H-4′), 4.78 (dd, 1, $J_{3',2'}$ = 5.5 Hz, $J_{3',4'}$ = 3.4 Hz, H-3′), 5.11-5.26 (m, 2, H-1′ and H-2′), 6.74 (broad s, 2, NH_2), 7.18-7.49 (m, 15, trityl), 8.06 and 8.14 (2 s, 2, H-2 and H-7).

To a solution of **9** (410 mg., 0.75 mmoles) in methanol (5 ml.) was slowly added 5 ml. of a 10% solution of hydrogen chloride in methanol. The reaction mixture was then immediately evaporated to dryness *in vacuo* at <30°. After trituration with ether and decantation, the residue was dissolved in methanol (10 ml.) and treated with Amberlite IR-45 resin (OH^-) until neutral. Filtration and evaporation to dryness afforded the crude product which crystallized from methanol to give 159 mg. of **10** (80%), m.p. 210-212°; pmr (DMSO-d_6): δ 3.54 (m, 2, H-5′ and H-5″), 3.80 (m, 1, H-4′), 3.98 (dd, 1, $J_{3',4'}$ = 3.6 Hz, $J_{3',2'}$ = 5.2 Hz, H-3′), 4.20 (dd, 1, $J_{2',1'}$ = 7.0 Hz, H-2′), 4.83 (d, 1, $J_{1',2'}$ = 7.0 Hz, H-1′), 8.06 and 8.19 (2 s, 2, H-2 and H-7), 8.48 (broad s, 2, NH_2); uv: λ max (*p*H = 7) 273 nm (ε, 8,950), λ min (*p*H = 7) 236 (ε, 1,540); λ max (*p*H = 1) 255 (ε, 5,750), shoulder 290 (3,840); λ min (*p*H = 1) 245 (ε, 5,470).

Anal. Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 45.02; H, 4.82; N, 26.18.

4-Amino-8-(α-D-ribofuranosyl)pyrazolo[1,5-*a*]-1,3,5-triazine (**13**).

A solution of **11** (400 mg., 0.8 mmoles) in benzene (4 ml.) was treated with **3** (320 mg., 3.2 mmoles) in benzene (3.2 ml.) as described above to give 314 mg. (71%) of **12** as a syrup after final purification by silica gel column chromatography with ethyl acetate/petroleum ether (30-60°) (4:1) as the eluant; pmr (deuteriochloroform): δ 1.32 and 1.58 (2 s, 6, CMe_2), 3.25-3.31 (m, 2, H-5′ and H-5″), 4.38 (m, 1, H-4′), 4.79 (broad s, 2, H-3′ and H-2′), 5.55 (broad s, 1, H-1′), 6.93 (broad s, 2, NH_2), 7.26-7.54 (m, 15, trityl), 8.15 and 8.30 (2 s, 2, H-2 and H-7).

Using the same procedure described for the preparation of **10**, **12** (150 mg. in 2 ml. of methanol) was deblocked with a 10% solution of hydrogen chloride in methanol (1.5 ml.) to give a 75% yield (58 mg.) of **13**. Crystallization from ethanol afforded an analytical sample of the monohydrate, m.p. 142-146° dec.; pmr (DMSO-d_6): δ 3.34 (water of hydration), 3.45 (dd, 1, $J_{5',4'}$ = 4.9 Hz, $J_{5',5''}$ = 11.9 Hz, H-5′), 3.63 (dd, 1, $J_{5'',4'}$ = 2.5 Hz, H-5″), 3.86 (m, 1, H-4′), 3.95 (m, 1, H-2′), 4.16 (dd, 1, $J_{3',4'}$ = 7.7 Hz, $J_{3',2'}$ = 4.3 Hz, H-3′), 5.21 (d, 1, $J_{1',2'}$ = 3.1 Hz, H-1′), 8.04 and 8.17 (2 s, 2, H-2 and H-7), 8.39 and 8.41 (2 broad s, 2, NH_2); uv: λ max (*p*H = 7) 272 nm, λ min (*p*H = 7) 235; λ max (*p*H = 1) 255 and 290, λ min (*p*H = 1) 247 and 272.

Anal. Calcd. for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.01; H, 5.34; N, 24.37.

N-Carbethoxy-*N*′-(3-pyrazolyl)formamidine (**6**).

3-Aminopyrazole (83 mg., 1 mmole) was dissolved in 2.5 ml. of ethanol and the solution was heated to reflux. Ethyl *N*-carbethoxyformimidate (**5**) (4e) (290 mg., 2 mmoles) was then added dropwise. The mixture was refluxed for another 4 hours. After evaporation of the solution *in vacuo*, the residue was thoroughly washed with petroleum ether (30-60°) and filtered to afford, after drying 166 mg. of **6** (91%), m.p. 140-141° after recrystallization from ethyl acetate/petroleum ether; pmr (DMSO-d_6): δ 1.24 (t, 3, CH_3), 4.17 (q, 2, CH_2), 6.08 (d, 1, $J_{4,5}$ = 2.2 Hz, H-4), 7.54 (d, 1, H-5), 8.56 (s, 1, N-C*H* = N), 11.04 (broad s, 1, NH).

Anal. Calcd. for $C_7H_9N_4O_2$: C, 46.15; H, 5.53; N, 30.75. Found: C, 46.18; H, 5.48; N, 30.86.

4-Oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**7**).

Method A.

Compound **6** (364 mg., 2 mmoles) was dissolved in 100 ml. of xylene and refluxed for 20 hours. The solution was then concentrated to 5 ml. The precipitate was filtered off and washed with ether. Recrystallization from methanol afforded 219 mg. of **7** (80.5%), m.p. 256-257° dec.; 263-265° dec. from ethyl acetate (Lit. (5) 267-268° from ethyl acetate); pmr (DMSO-d_6): δ 6.54 (d, 1, $J_{7,8}$ = 2.0 Hz, H-8), 8.02 (s, 1, H-2), 8.06 (d, 1, H-7); uv: λ max (*p*H = 7) 263 nm (ε, 7,400), λ min (*p*H = 7) 229 (ε, 1,700); λ max (*p*H = 1) 258 (ε, 6,920), λ min (*p*H = 1) 231 (ε, 2,310); λ max (*p*H = 13) 266 (ε, 7,740); λ min (*p*H = 13) 227 (ε, 750).

Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.16. Found: C, 44.18; H, 2.98; N, 41.17.

Method B.

Intermediate **6** (166 mg., 0.91 mmole) was dissolved in 3 ml. of ethanol and to the solution was added potassium carbonate (138 mg., 1 mmole). The mixture was refluxed for 4 hours. A precipitate was formed while the reaction proceeded. The mixture was then evaporated to dryness and a solution of the residue in water was passed through a short column of Dowex-50 (H^+) resin. After evaporation of the eluate, the residue crystallized from ethanol to afford compound **7**, 96 mg. (77%).

4-Oxo-3*H*-8-(β-D-ribofuranosyl)pyrazolo[1,5-*a*]-1,3,5-triazine (**16**).

Aminopyrazole **8** (2 g., 4 mmoles) was dissolved in 20 ml. of ethanol and the solution was brought to boiling. *N*-Carbethoxyformimidate **5** (1.5 g., 10.3 mmoles) was then added dropwise and heating was continued for 4 hours. The solution was evaporated to give a syrupy residue which was repeatedly washed with petroleum ether, redissolved in a minimum amount of ethanol and poured into 200 ml. of petroleum ether with rapid stirring to precipitate crude intermediate **14**. More of this compound could be obtained by evaporating all washings almost to dryness. The precipitate which formed was then collected, washed with a small amount of petroleum ether and combined with previously isolated material. The crude **14** was dried *in vacuo* and dissolved in 10 ml. of dry ethanol. The solution was heated to reflux and potassium carbonate (552 mg., 4 mmoles) was added slowly. Heating was

continued for 5 hours. The undissolved potassium carbonate was filtered off. After evaporation of the filtrate *in vacuo*, the residue was dissolved in methanol, treated briefly with Amberlite IRC-50 (H^+), filtered and evaporated to dryness. The residue dissolved in minimum amount of chloroform was then chromatographed on a silica gel column (2 x 15 cm) with chloroform/methanol (10:1). Evaporation of the proper fractions afforded 1.5 g. of **15** as a syrup; pmr (deuteriochloroform): δ 1.37 and 1.61 (2 s, 6, CMe_2), 3.22-3.27 (m, 2, H-5′ and H-5″), 4.32-4.35 (m, 1, H-4′), 4.74 (dd, 1, $J_{2',3'}$ = 6.5 Hz, $J_{3',4'}$ = 3.0 Hz, H-3′), 4.98-5.21 (m, 2, H-1′ and H-2′), 7.19-7.48 (m, 15, trityl), 8.00 and 8.09 (2 s, 2, H-2 and H-7), 11.23 (broad s, 1, NH).

Without further purification, this compound (**15**) was unblocked by dissolving in 3 ml. of 10% methanolic hydrogen chloride, followed by immediate evaporation *in vacuo* at < 30°. The residue, after being washed with ether 2 x 5 ml., was redissolved in methanol and treated with Amberlite IR 45 (OH^-) to neutrality. The compound was finally purified on a 2 x 20 cm cellulose column previously washed with 1-butanol. The compound was eluted with acetone/1-butanol/water (8:1:1). The appropriate fractions were evaporated to give 387 mg. (36% from **8**) of compound **16**, which was crystallized from ethanol, m.p. 227-228° dec., pmr (DMSO-d_6): δ 3.50 (m, 2, H-5′ and H-5″), 3.77 (m, 1, H-4′), 3.95 (dd, 1, $J_{3',4'}$ = 3.6 Hz, $J_{3',2'}$ = 5.2 Hz, H-3′), 4.10 (dd, 1, $J_{2',1'}$ = 6.4 Hz, H-2′), 4.79 (d, 1, H-1′), 8.03 and 8.13 (2 s, 2, H-2 and H-7); uv: λ max (*p*H = 7) 269 nm (ε, 9,740); λ min (*p*H = 7) 231 (ε, 1,590); λ max (*p*H = 1) 262 (ε, 9,080); λ min (*p*H = 1) 233 (ε, 3,100); λ max (*p*H = 13) 269 (ε = 10,280); λ min (*p*H = 13) 231 (ε, 1,870).

Anal. Calcd. for $C_{10}H_{12}O_5N_4$: C, 44.78; H, 4.51; N, 20.89. Found: C, 44.44; H, 4.58; N, 20.68.

4-Oxo-3*H*-8-(α-D-ribofuranosyl)pyrazolo[1,5-*a*]-1,3,5-triazine (**19**).

Aminopyrazole **11** (500 mg., 1 mmole) in 10 ml. of ethanol was treated with *N*-carbethoxyformimidate **5** (290 mg., 2 mmoles) to form intermediate **17** which, without isolation, was cyclized to **18** (600 mg., 100%) as described above for the corresponding β-isomer; pmr (deuteriochloroform): δ 1.32 and 1.56 (2 s, 6, CMe_2), 3.30 (m, 2, H-5′ and H-5″), 4.35 (m, 1, H-4′), 4.70-4.76 (m, 2, H-2′ and H-3′), 5.50 (d, 1, $J_{1',2'}$ = 2.7 Hz, H-1′), 7.24-7.42 (m, 15, trityl), 7.90 and 8.19 (2 s, 2, H-2 and H-7).

All of **18** obtained above was deblocked by dropwise addition of 2 ml. of 10% methanolic hydrogen chloride to a solution of the compound in 1 ml. of methanol. The mixture was evaporated immediately *in vacuo* (< 30°) and co-evaporated with another 2 ml. of methanol. After being washed with ether (2 x 5 ml.), the residue was dissolved in methanol and treated with Amberlite IR-45 (OH^-) to neutrality. After filtration and evaporation of the solution, crude **19** obtained was purified by preparative tlc on cellulose using 1-butanol/ethanol/water (5:1:4, upper layer) to give 100 mg. (37%) of **19**. Crystallization from ethanol afforded the analytical sample m.p. 176-181°; pmr (DMSO-d_6): δ 3.54 (m, 2, H-5′ and H-5″), 3.75-3.96 (m, 2, H-2′ and H-4′), 4.14 (dd, 1, $J_{3',4'}$ = 7.6 Hz, $J_{3',2'}$ = 4.2 Hz, H-3′), 5.13 (d, 1, $J_{1',2'}$ = 3.4 Hz, H-1′), 7.98 and 8.06 (2 s, 2, H-2 and H-7); uv: λ max (*p*H = 7) 268 nm; λ min (*p*H = 7) 237; λ max (*p*H = 1) 260 nm; λ min (*p*H = 1) 234.

Anal. Calcd. for $C_{10}H_{12}N_4O_5 \cdot H_2O$: C, 41.98; H, 4.93; N, 19.57. Found: C, 41.98; H, 4.52; N, 19.55.

REFERENCES AND NOTES

(1) This investigation was supported in part by funds from the National Institutes of Health, U. S. Public Health Service (Grant No. CA 18856, 17085, 08748) and by the Hearst Fund.

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