the absence of a heavy metal salt, they proceed preferentially *via* an SN2 mechanism.

Both **2** and **3** were found to be inactive in the *Lactobacillus leichmannii* assay system[5a] in which **1** shows significant inhibition under the same assay conditions. Preliminary testing of **2** and **3** against the L1210 and Ehrlich ascites cell lines in cultures[13] showed no significant inhibitory activity. It appears that the thioglycoside bonds in **2** and **3** are not cleaved by the cells and that these derivatives as such (as the structurally analogous pseudouridine itself) are inactive in these assay systems. However, **2** may be of future interest in studies relating to pseudouridine.

Experimental Section

Melting points were taken in open capillary tubes on a Mel-temp apparatus and are uncorrected. Nmr spectra were recorded on a Varian Model A-60 spectrophotometer in D_2O with *t*-BuOH as internal standard. Optical rotations were measured in a 1-dm tube using a Perkin-Elmer Model 141 automatic polarimeter at 589 mμ. Evaporations were carried out under reduced pressure on a rotary evaporator at 40° bath temperature. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Anomeric *S*-(2′,3′,5′-Tri-*O*-benzoyl-D-ribofuranosyl)-5-mercaptouracils (5 and 6). To a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (prepared from 10.08 g (20 mmol) of 2,3,5-tri-*O*-benzoyl-1-*O*-acetyl-D-ribofuranose according to Stevens, *et al.*[12b]) in anhydrous DMF (80 ml) was added 5-mercaptouracil[1] (3.16 g, 22 mmol) and Et_3N (3.1 ml, 22 mmol). After the solution was stirred under N_2 atmosphere overnight, H_2O (5 ml) was added, and the solvent was evapoated. The residue was dissolved in $CHCl_3$ and filtered, and the $CHCl_3$ solution was concentrated and applied to a column packed with 300 g of silicic acid in $CHCl_3$. After the elution of some impurities (decomposition products of **4**) with $CHCl_3$, **5** and **6** were eluted, together, with $CHCl_3$–EtOAc (1:3). After pooling and evaporation of the fractions which appeared homogenous by tlc, a mixture of the two anomers was obtained as a solid foam (5.45 g, 46.4%). Heating of this residue in C_6H_6 resulted in rapid dissolution followed by immediate precipitation of **5** as a white powder, 3.74 g, 31.8%, mp 193–196°. Recrystallization from C_6H_6 furnished a sample for analysis, mp 198–199°, $[\alpha]D$ −101.1° (*c* 2.3, $CHCl_3$). *Anal.* ($C_{30}H_{24}N_2O_9S$) C, H, N, S.

The C_6H_6 mother liquor was concentrated to dryness to give **6** as a solid foam (1.05 g, 8.95%). This was purified for analysis by repeated dissolution in C_6H_6 and precipitation with hexane, mp 95–115°, $[\alpha]D$ 111.3° (*c* 0.68, $CHCl_3$). *Anal.* ($C_{30}H_{24}N_2O_9S$) C, H, N, S.

***S*-(β-D-Ribofuranosyl)-5-mercaptouracil (2).** To a suspension of **5** (1.176 g, 2 mmol) in anhydrous MeOH (50 ml) was added $NaOCH_3$, freshly prepared from Na metal (0.092 g, 4 mg-atoms) in MeOH (10 ml), and the resulting solution was stirred for 5 hr. Dowex 50 W × 8 resin, H^+ form (10 ml wet volume in MeOH), was then added. After 10 min the resin was removed by filtration and MeOH concentrated to 15 ml. Crystals deposited on standing at 5°, were collected by filtration, and washed with Et_2O (0.459 g, 83%). After recrystallization from MeOH, the following data were obtained: mp 222–224°; $[\alpha]D$ −142.9° (*c* 0.8, H_2O); nmr (D_2O) anomeric proton δ 5.12 ppm (d, J = 3.8 Hz). *Anal.* ($C_9H_{12}N_2O_6S$) C, H, N, S.

***S*-(α-D-Ribofuranosyl)-5-mercaptouracil (3).** **6** (0.589 g, 1 mmol) was debenzoylated as described above for the deblocking of **4** to give **3** (0.170 g, 61.5%). After recrystallization from MeOH, the following data were obtained: mp 156–160°; $[\alpha]D$ 291.0° (*c* 0.5, H_2O); nmr (D_2O) anomeric proton δ 5.85 ppm (d, J = 5.0 Hz). *Anal.* ($C_9H_{12}N_2O_6S$) C, H, N, S.

Acknowledgment. The authors wish to thank Dr. Alexander Bloch of Roswell Park Memorial Institute, Buffalo, N. Y., for the biological test data.

References

(1) (a) T. J. Bardos, R. R. Herr, and T. Enkoji, *J. Amer. Chem. Soc.*, 77, 960 (1955); (b) R. R. Herr, T. Enkoji, and T. J. Bardos, *ibid.*, 78, 401 (1956).
(2) M. P. Kotick, C. Szantay, and T. J. Bardos, *J. Org. Chem.*, 34, 3806 (1969).
(3) G. Szekeres and T. J. Bardos, *J. Med. Chem.*, 13, 708 (1970).
(4) (a) T. I. Kalman and T. J. Bardos, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 27, 650 (1968); (b) T. I. Kalman and T. J. Bardos, *Mol. Pharmacol.*, 6, 621 (1970).
(5) (a) T. J. Bardos, G. M. Levine, R. R. Herr, and H. L. Gordon, *J. Amer. Chem. Soc.*, 77, 4279 (1955); (b) K. Baranski, T. J. Bardos, A. Bloch, and T. I. Kalman, *Biochem. Pharmacol.*, 18, 347 (1969).
(6) (a) T. J. Bardos, A. Segaloff, and J. L. Ambrus, *Nature (London)*, 183, 612 (1959); (b) T. J. Bardos, J. L. Ambrus, K. Baranski, T. I. Kalman, and C. Ambrus, *Proc. Amer. Ass. Cancer Res.*, 8, 4 (1967).
(7) S. C. Schwartz, T. J. Bardos, G. H. Burgess and E. Klein, *J. Med.*, 1, 174 (1970).
(8) (a) T. J. Bardos and T. I. Kalman, *J. Pharm. Sci.*, 55, 606 (1966); (b) T. I. Kalman and T. J. Bardos, *J. Amer. Chem. Soc.*, 89, 1171 (1967).
(9) M. P. Kotick, T. I. Kalman, and T. J. Bardos, *J. Med. Chem.*, 13, 74 (1970).
(10) I. Goodman, J. R. Fouts, E. Bresnick, R. Menegas, and G. H. Hitchings, *Science*, 130, 450 (1959).
(11) D. A. Shuman, A. Bloch, R. K. Robins, and M. J. Robins, *J. Med. Chem.*, 12, 653 (1969).
(12) (a) J. D. Stevens and H. G. Fletcher, Jr., *J. Org. Chem.*, 33, 1799 (1968); (b) J. D. Stevens, R. K. Ness, and H. G. Fletcher, Jr., *ibid.*, 33, 1806 (1968).
(13) M. Bobek, R. L. Whistler, and A. Bloch, *J. Med. Chem.*, 15, 168 (1972).

1-Glycosyl Derivatives of 5-Aminoimidazole-4-carboxamide†,‡

John A. Montgomery* and H. Jeanette Thomas

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205. *Received May 24, 1972*

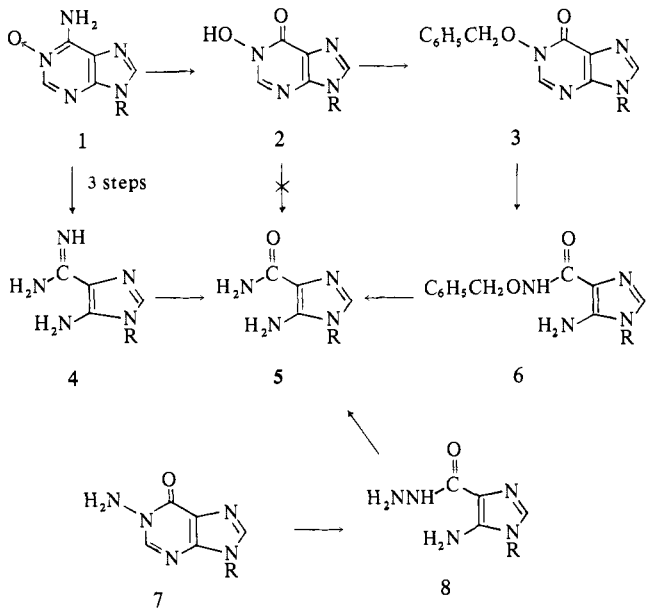
The 5′-phosphate of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide is a key intermediate in the *de novo* biosynthesis of purine ribonucleotides. Formylation of this compound followed by ring closure gives rise to inosinic acid.[1] Various compounds known to interfere with *de novo* purine biosynthesis have shown anticancer activity. It was, therefore, of interest to investigate the synthesis and evaluation of analogs of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (**5b**), since nucleotides themselves cannot penetrate cell membranes. A kinase capable of phosphorylating **5b** has been found in yeast[2] and more recently the biologically active form of pyrazomycin, a closely related nucleoside, has been identified as its 5′-phosphate formed *in vivo*.[3]

A logical approach to the synthesis of imidazole nucleosides pursued by Shaw[4-6] involves the substitution at N-1 of inosine of a removable group that causes base lability of the pyrimidine ring. Shaw used the benzyl,[4] *p*-toluenesulfonyl,[5] and the methoxymethyl[6] groups, but none of these groups appeared to us to be entirely satisfactory. We decided to employ the benzyloxy group, which proved very effective in the synthesis of 5-aminoimidazole-4-carboxamidines.[7] 9-Cyclopentyladenine 1-oxide[7] (**1a**) was deaminated by treatment with sodium nitrite in dilute acetic acid. The resultant 9-cyclopentyl-1-hydroxyhypoxanthine (**2a**) was resistant to aqueous base treatment due, no doubt, to anion formation at the 1-hydroxy position,[8] which prevents attack of the hydroxide ion at C-2 of the purine ring. Benzylation of **2a** with benzyl bromide with DMA gave 1-benzyloxy-9-cyclopentylhypoxanthine (**3a**) as shown by a strong carbonyl doublet centered at 1700 cm^{-1} in its infrared

†This work was supported by funds from the C. F. Kettering Foundation, and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract No. NIH-71-2021.

‡Presented in part at the 19th Southeastern Regional Meeting of the American Chemical Society, Nov 1–2, 1967, Atlanta, Ga., Abstract 74.

spectrum. This compound (**3a**), which cannot form an anion, readily underwent basic ring cleavage and loss of the formyl group from the intermediate formamido compound to give 5-amino-*N*-benzyloxy-1-cyclopentylimidazole-4-carboxamide (**6a**). The benzyloxy group of **6a** was rapidly hydrogenolyzed with Davidson sponge nickel catalyst to give the desired 5-amino-1-cyclopentylimidazole-4-carboxamide (**5a**). This same general procedure was then successfully applied to the synthesis of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (**5b**) and 5-amino-1-β-D-arabinofuranosylimidazole-4-carboxamide (**5d**). The method failed for the preparation of 5-amino-1-(2-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (**5c**), because all attempts to deaminate 2′-deoxyadenosine 1-oxide resulted in cleavage of most of the sugar moiety from the purine of this acid-sensitive nucleoside. 5-Amino-1-(2-deoxy-β-D-ribofuranosyl)-imidazole-4-carboxamide (**5c**) was prepared by aqueous base hydrolysis of the corresponding amidine[7] (**4c**), but the yield was poor and much decomposition was encountered, making the isolation procedure difficult and tedious. This nucleoside is best prepared by amination of 2′-deoxyinosine by the procedure of Broom and Robins[9] to give 1-amino-2′-deoxyinosine. Treatment of this nucleoside with aqueous base opened the pyrimidine ring with loss of the formyl group from the intermediate formamido compound to give 5-amino-1-(2-deoxy-β-D-ribofuranosyl)imidazole-4-carboxylic acid hydrazide (**8c**). The hydrazide was reduced to the amide (**5c**) by means of Raney nickel catalyst. Although not particularly satisfactory for the preparation of **5c**, the base hydrolysis of the amidines **4a**, **4b**, and **4d** proceeded well to give 5-amino-1-cyclopentylimidazole-4-carboxamide (**5a**), 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (**5b**), and 5-amino-1-β-D-arabinofuranosylimidazole-4-carboxamide (**5d**). In addition **5b** was readily prepared in reasonable yield from 1-aminoinosine without isolation of the intermediates, showing that this procedure is the most convenient one for the preparation of 1-glycosyl derivatives of 5-aminoimidazole-4-carboxamide.



a, R = cyclopentyl
b, R = β-D-ribofuranosyl
c, R = 2-deoxy-β-D-ribofuranosyl
d, R = β-D-arabinofuranosyl

Biologic Evaluations. 9-Cyclopentyl-1-hydroxyhypoxanthine (**2a**), 1-benzyloxy-9-cyclopentylhypoxanthine (**3b**), 9-β-D-arabinofuranosyl-1-hydroxyhypoxanthine (**2d**), and the imidazolecarboxamides **5a–d** were not cytotoxic to H.Ep.-2 cells at 100 μg/ml, the highest level tested. 5-Amino-1-cyclopentylimidazole-4-carboxamide (**5a**) was toxic to mice at 80 mg/kg (day 2 only) and inactive against leukemia L1210 at 40 mg/kg. 5-Amino-1-β-D-arabinofuranosylimidazole-4-carboxamide (**5d**) was nontoxic and inactive against L1210 at 400 mg/kg (day 1 only), the highest level tested.

Experimental Section

Except where noted, melting points were determined with a Kofler Heizbank and are corrected. The uv spectra were determined in aqueous solution with a Cary Model 14. Ir spectra were determined in pressed KBr disks with a Perkin-Elmer Model 621. All compounds were found to be chromatographically homogeneous by tlc on plates of silica gel H (Brinkmann). The spots were detected by uv light after spraying with Ultraphor (WT, highly conc) and by charring after spraying with $(NH_4)_2SO_4$ soln.

9-Cyclopentyl-1-hydroxyhypoxanthine (2a). To a solution of 9-cyclopentyladenine 1-oxide[7] (482 mg, 2.23 mmoles) in 55 ml of 29% HOAc was added 1.54 g of $NaNO_2$. After standing 4 days at room temperature, the solution was evaporated to dryness *in vacuo*. A solution of the residue in 25 ml of water was extracted with four 50-ml portions of $CHCl_3$, and the $CHCl_3$ extract was dried over $MgSO_4$ before evaporation to dryness. The resulting orange glass was recrystallized from ethanol (charcoal); yield 181 mg (37%), mp 228–229°. The analytical sample was obtained in the same manner from a previous run: mp 229–230°; λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, 253 (8.80), pH 7 and 0.1 *N* NaOH, 228 (32.2), 256 (6.43), 292 nm (3.58). *Anal.* ($C_{10}H_{12}N_4O_2$) C, H, N.

1-Benzyloxy-9-cyclopentylhypoxanthine (3a). To a solution of 9-cyclopentylhypoxanthine 1-oxide (220 mg, 1.0 mmole) in 20 ml of DMA containing K_2CO_3 (132 mg, 1.0 mmole) was added benzyl bromide (171 mg, 1.0 mmole), and the resulting mixture was stirred 15 hr at 70° before it was filtered and evaporated to dryness *in vacuo*. The residue crystallized from ethanol containing a small amount of H_2O: yield 752 mg (81%): mp 198°; λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, pH 7, 0.1 *N* NaOH 253 nm (9.70). *Anal.* ($C_{17}H_{18}N_4O_2$) C, H, N. A second, larger run gave 1.49 g (94%).

5-Amino-*N*-benzyloxy-1-cyclopentylimidazole-4-carboxamide (6a). A solution of 1-benzyloxy-9-cyclopentylhypoxanthine (1.40 g, 4.53 mmoles) in 18.5 ml of 1.0 *N* NaOH and 150 ml of EtOH was refluxed for 2 hr before it was neutralized with 1.0 *N* HCl and evaporated to dryness *in vacuo*. An aqueous solution (15 ml) of the residue was extracted three times with $CHCl_3$ (50 ml), and the combined extracts were evaporated to dryness. The residue crystallized from ethanol: yield 827 mg (61%); mp 200°; λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, 245 (7.23), 275 (11.2), pH 7, 272 (13.9), 0.1 *N* NaOH, 250 nm (10.5). *Anal.* ($C_{16}H_{20}N_4O_2$) C, H, N.

5-Amino-1-cyclopentylimidazole-4-carboxamide (5a). A. A solution of 5-amino-*N*-benzyloxy-1-cyclopentylimidazole-4-carboxamide (827 mg, 2.76 mmoles) in 700 ml of ethanol was hydrogenated for 0.5 hr at room temperature and atmospheric pressure using Davidson sponge nickel catalyst (*ca.* 250 mg). The catalyst was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol: yield 450 mg (84%), mp 228° (subl); λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, 243 (7.46), 268 (10.4), pH 7 and 0.1 *N* NaOH, 267 nm (12.4). *Anal.* ($C_9H_{14}N_4O$) C, H, N.

B. A solution of 5-amino-1-cyclopentylimidazole-4-carboxamidine[7] (230 mg, 1.0 mmole) in 10 ml of 0.2 *N* NaOH was refluxed for 5 hr. The crystals that precipitated on cooling were recrystallized from EtOH, yield 118 mg (61%). This material was identical in all respects with the material prepared as described in A above.

5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide[10] (5b). A. A solution of 1-hydroxyinosine[8] (828 mg, 2.92 mmoles) and benzyl bromide (498 mg, 2.92 mmoles) in 60 ml of DMA containing K_2CO_3 (403 mg) was heated at 70° for 16 hr before it was evaporated to dryness *in vacuo*. A solution of the residue (3b) in 100 ml of EtOH containing 12.3 ml of 1.0 *N* NaOH was refluxed for 2 hr before it was neutralized and then evaporated to dryness. A solution of the residue (9b) in EtOH was filtered to remove salt before it was evaporated to a glass. A solution of the glass in 1:1 MeOH–H_2O (100 ml) was hydrogenated for 0.5 hr at room temperature and atmospheric pressure with Davidson sponge nickel catalyst (*ca.* 200 mg). The catalyst was removed by filtration, washed with water, and the combined filtrate and washings evaporated to dryness. The residue was crystallized from water: yield 389 mg (52%); mp 218° (lit.[10] 213–214°); λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, 245 (8.7), 267 (10.3), pH 7 and 0.1 *N* NaOH, 267 nm (12.6) [lit.[10] pH 7, 267 (12.8)].

B. 1-Benzyloxyadenosine[7] (4.54 g, 10.0 mmoles) was converted to 5-amino-1-β-D-ribofuranosyl-4-carboxamidine by the published procedure.[7] A solution of the crude amidine (4b) in 100 ml of 0.1 *N* NaOH was refluxed for 2 hr before it was neutralized with HOAc, filtered, and treated with picric acid (2.29 g) in 50 ml of H_2O. The crystalline picrate was collected by filtration and converted back to the free base by treatment with Dowex 1-X8 (CO_3^{2-}) resin. The product was recrystallized from water, yield 452 mg (18% from 1-benzyloxyadenosine). This material was essentially identical with that prepared by method A described above.

C. A solution of 1-aminoinosine[9] (283 mg, 1.0 mmole) in 50 ml of 0.2 *N* NaOH was refluxed for 1 hr to give 8b before 1 g of Raney nickel catalyst was added and refluxing continued for an additional hr. The catalyst was removed by filtration, and the solution neutralized with HOAc and concentrated to *ca.* 10 ml before the addition of picric acid (1.0 mmole). The picrate was collected by filtration and converted back to the free base by treatment with Dowex 1-X8 (CO_3^{2-}). Concentration of the solution to about 2 ml caused the product to crystallize from solution, yield 95 mg (37%). It was essentially identical with that prepared by procedures A and B described above.

5-Amino-1-(2-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (5c). A. A solution of 2′-deoxyinosine (630 mg, 2.5 mmoles) and hydroxylamine-*O*-sulfonic acid (425 mg, 3.75 mmoles) in 12.5 ml of 0.6 *N* NaOH was allowed to stand at 4° for 3 days to give 7c before 2 ml of 2 *N* NaOH was added and the resulting solution refluxed for 2 hr to give 8c. Raney nickel catalyst (W. R. Grace & Co.) (500 mg) was then added, and the solution was refluxed for another hr. The catalyst was removed by filtration and washed with water, and the combined filtrate and washings were neutralized with acetic acid before the addition of picric acid (2.5 mmoles). The resulting picrate was collected by filtration and converted back to the free base by treatment with Dowex 1-X8 (CO_3^{2-}) resin. The cream-colored glass that resulted was recrystallized from MeOH: yield 109 mg (18%); mp 174–176° (Mel-Temp); λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, 245 (8.87), 268 (10.4), pH 7 and 0.1 *N* NaOH, 267 nm (12.6). *Anal.* ($C_9H_{14}N_4O_4$) C, H, N.

B. A solution of 5-amino-1-(2-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamidine[7] (595 mg, 2.46 mmoles) in 10.5 ml of 0.24 *N* NaOH was refluxed for 2 hr, filtered, and treated with picric acid (563 mg) in MeOH (20 ml). The resulting picrate was treated with Dowex 1-X8 (CO_3^{2-}) to regenerate the free base which was further purified by chromatography on a silica gel G plate developed twice with 3:1 $CHCl_3$–MeOH. The product was eluted with methanol, yield 84 mg (14%). This material was essentially the same as that prepared by method A described above.

9-β-D-Arabinofuranosyl-1-hydroxyhypoxanthine (2d). To a solution of 9-β-D-arabinofuranosyladenine 1-oxide[11] (687 mg, 2.43 mmoles) in 25 ml of 29% HOAc was added $NaNO_2$ (1.68 g, 24.3 mmoles). After 4 days at room temperature, the solution was extracted twice with 400 ml of ether before evaporation to dryness several times with additions of water. The crude product was purified by water elution from a Dowex 50W-X4 (100–200 mesh) column (3.2 × 25 cm). The yield was 304 mg (44%). A small sample was recrystallized from water: mp 147°; λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, 251 (9.15), pH 7 and 0.1 *N* NaOH, 227 (31.2), 256 (6.58), 291 nm (3.62). *Anal.* ($C_{10}H_{12}N_4O_6$) C, H, N.

9-β-D-Arabinofuranosyl-1-benzyloxyhypoxanthine (3d). A solution of 9-β-D-arabinofuranosyl-1-hydroxyhypoxanthine (774 mg, 2.7 mmoles) and benzyl bromide (465 mg, 2.7 mmoles) in 60 ml of DMA containing K_2CO_3 (376 mg, 2.7 mmoles) was heated at 70° for 16 hr. After filtration, the reaction mixture was evaporated to dryness *in vacuo*. A solution of the residue in acetonitrile was filtered before it was evaporated to a light orange syrup (1.0 g) that crystallized on standing. A small portion of this material was recrystallized from 50% EtOH: mp 241°; λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl and pH 7, 251 nm (9.35). *Anal.* ($C_{17}H_{18}N_4O_6$) C, H, N.

5-Amino-1-β-D-arabinofuranosylimidazole-4-carboxamide (5d). A. A solution of crude 9-β-D-arabinofuranosyl-1-benzyloxyhypoxanthine (938 mg, 2.5 mmoles) in 86 ml of EtOH and 10.6 ml of 1.0 *N* NaOH and enough H_2O to give a clear solution was refluxed for 3 hr before it was neutralized with 1.0 *N* HCl and then evaporated to dryness. The residue was dissolved in 150 ml of EtOH, and the solution filtered to remove salt before evaporation to an orange syrup, which was dissolved in 70 ml of 50% EtOH. Hydrogenolysis was carried out for 18 hr at room temperature and atmospheric pressure in the presence of *ca.* 200 mg of Raney nickel catalyst, which was then removed by filtration and washed with water. The combined filtrate and washings were evaporated to dryness *in vacuo* to give a residue which crystallized from methanol: yield 180 mg (28%); mp 191°; λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, 245 (8.90), 267 (9.98), pH 7 and 0.1 *N* NaOH, 267 nm (12.3). *Anal.* ($C_9H_{14}N_4O_5$) C, H, N.

B. A solution of 5-amino-1-β-D-arabinofuranosylimidazole-4-carboxamidine[7] (224 mg, 0.87 mmole) in 10 ml of 0.1 *N* NaOH was refluxed for 1 hr before it was neutralized with HOAc and treated with picric acid (0.87 mmole). The picrate, which was collected by filtration, was converted back to the free base by treatment with Dowex 1-X8 (CO_3^{2-}) resin. The free base was recrystallized from methanol, yield 122 mg (55%). This material was essentially identical with that prepared by procedure A described above.

Acknowledgment. The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute for the spectral and microanalytical data reported, to Dr. L. J. Wilkoff for the cytotoxicity determinations, and Dr. W. R. Laster, Jr., for the leukemia L1210 testing.

References

(1) J. M. Buchanan, "The Nucleic Acids," Vol. 3, E. Chargoff and J. N. Davidson, Ed., Academic Press, New York, N. Y., 1960, p 303.
(2) H. T. Huang, *Biochemistry*, **4**, 58 (1965).
(3) M. J. Sweeney, G. E. Gutowski, G. A. Poore, and R. L. Hamill, *Proc. Amer. Ass. Cancer Res.*, 13, 108 (1972).
(4) E. Shaw, *J. Amer. Chem. Soc.*, **80**, 3899 (1958).
(5) E. Shaw, *ibid.*, **81**, 6021 (1959).
(6) E. Shaw, *ibid.*, 83, 4770 (1961).
(7) J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, **15**, 182 (1972).
(8) J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.*, 31, 966 (1966).
(9) A. D. Broom and R. K. Robins, *ibid.*, **34**, 1025 (1969).
(10) G. R. Greenberg and E. L. Spilman, *J. Biol. Chem.*, **219**, 411 (1956).
(11) E. J. Reist, D. F. Calkins, and L. Goodman, *J. Med. Chem.*, **10**, 130 (1967).

Effects of Some Substituted Phenanthrenes on the Central Nervous System†

Adolph P. Roszkowski,* Margery E. Schuler, and Peter H. Nelson

Institutes of Clinical Medicine and Organic Chemistry, Syntex Research, Palo Alto, California 94304. *Received May 24, 1972*

A variety of substituted phenanthrenes were prepared by Mosettig and van de Kamp,[1] Fieser,[2] Mosettig and Burger,[3] and others and found by Eddy[4-8] to produce a variety of pharmacological effects when given orally to cats. Central nervous depression and analgesia were prominent effects seen with some compounds. 3-Substituted carboxylic acids were very active.

Such findings prompted us to synthesize a number of phenanthrenes monosubstituted in the 2, 3, and 9 positions and evaluate these for various central nervous system effects. Central nervous depressant, analgetic, and anticonvulsant properties were found among a number of agents in mice.

Synthesis. The novel phenanthrene compounds described herein were obtained by the reactions shown in Scheme I. The unstable ylide methoxymethylenetriphenylphosphorane was allowed to react with the various acetylphenanthrenes to give the cis-trans enol ether mixture a. Acid hydrolysis generated the aldehydes b in good yield, and oxidation or reduction of the latter compounds gave respectively the corresponding carboxylic acids c and the

†This is Publication No. 396 from the Institute of Organic Chemistry.