= 11 800, ϵ_{291} = 6350; IR 1760, 1655, 1585 cm^{-1}; NMR 7.0 (C-1), 6.38 (C-4), 1.18 (C-19), 1.04 (C-18) ppm. Anal. ($C_{24}H_{27}ClO_3$) C, H, O, Cl.

1α-(Acetylthio)-6β,7β:15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (16). A solution of 200 mg (0.55 mmol) of **3** in 4 mL of tetrahydrofuran/methanol (1:1) was stirred with 0.2 mL of water and 0.4 mL of thioacetic acid for 45 min. The reaction mixture was diluted with dichloromethane, washed with water, saturated aqueous $NaHCO_3$, and water, and evaporated in vacuum. The crude product was recrystallized from diisopropyl ether, yielding 230 mg (94.9%) of **16**: mp 212 °C; $[\alpha]^{25}_D$ −141.1°; UV ϵ_{266} = 15 700; IR 1770, 1680, 1665, 1595 cm^{-1}; NMR 6.0 (C-4), 392 (dd, J = 5 and 4 Hz, C-1), 2.34 ($SC(O)CH_3$), 1.26 (C-11), 0.98 (C-18) ppm. Anal. ($C_{26}H_{32}O_4S$) C, H, S.

6β,7β:15β,16β-Dimethylene-1α-(methylthio)-3-oxo-17α-pregn-4-ene-21,17-carbolactone (17). A solution of 750 mg (2.05 mmol) of **3** in 25 mL of tetrahydrofuran was treated with 75 mg of potassium methylate and during 2 h with a constant stream of methyl mercaptan. The reaction mixture was diluted with ether, washed with water, and evaporated under reduced pressure. The crude product was recrystallized from diisopropyl ether, yielding 720 mg (84.8%) of **17**: mp 122.7 °C; $[\alpha]^{25}_D$ −156.4°; UV ϵ_{263} = 14 930; IR 1770, 1665, 1600 cm^{-1}; NMR 6.02 (C-4), 2.06 (SCH_3), 1.21 (C-19), 0.98 (C-18) ppm. Anal. ($C_{25}H_{32}O_3S$) C, H, S.

6β,7β:15β,16β-Dimethylene-1α-mercapto-3-oxo-17α-pregn-4-ene-21,17-carbolactone (18). A solution of 500 mg (1.37 mmol) of **3** in 375 mL of methanol/tetrahydrofuran (2:1) and 0.3 mL of piperidine was treated at room temperature with H_2S for 1.5 h. The reaction mixture was poured into ice water and the resulting precipitate was filtered off and dried. Chromatography on silica gel with dichloromethane/acetone yielded, after recrystallization from diisopropyl ether, 216 mg (39.4%) of **18**: mp 242.2 °C; $[\alpha]^{25}_D$ −136.5°; UV ϵ_{266} = 14 500; IR 2550, 1760, 1660, 1600 cm^{-1}; NMR 6.08 (C-4), 3.37 (m, C-1), 1.22 (C-19), 0.98 (C-18) ppm. Anal. ($C_{24}H_{30}O_3S$) C, H, S.

6β,7β:15β,16β-Dimethylene-1α-methyl-3-oxo-17α-pregn-4-ene-21,17-carbolactone (19). A suspension of 2.2 g (11.5 mmol) of cuprous iodide in 23 mL of ether was treated at 0 °C with 15 mL of a 1.5 M methyllithium solution in ether and the mixture stirred until all the cuprous iodide had dissolved. This solution was treated with a solution of 640 mg (1.75 mmol) of **3** in dimethylformamide/tetrahydrofuran (1:1) and stirred for 3 h at 0 °C. The reaction mixture was diluted with ether, washed with diluted sulfuric acid and water, and evaporated under reduced pressure. Chromatography on silica gel with hexane/acetone yielded, after recrystallization from diisopropyl ether, 64 mg (9.6%) of **19**: mp 252.1 °C; UV ϵ_{267} = 15 050; IR 1770, 1660, 1595 cm^{-1}; NMR 6.02 (C-4), 1.16 (C-19), 0.98 (C-18) ppm. Anal. ($C_{25}H_{30}O_3$) C, H, O.

3-Oxo-1α,2α:6β,7β:15β,16β-trimethylene-17α-pregn-4-ene-21,17-carbolactone (20). A solution of 2.2 g (10 mmol) of trimethylsulfoxonium iodide in 35 mL of dimethyl sulfoxide was stirred with 393 mg (9 mmol) of a 55% suspension of sodium hydride in oil for 1.5 h. This solution was treated with 729 mg (2 mmol) of **3** and stirred for 21 h at room temperature. The reaction mixture was poured into ice water and acidified with sulfuric acid, and the resulting precipitate was filtered and dried. Chromatography on silica gel yielded after, recrystallization from diisopropyl ether/acetone, 540 mg (71.4%) of **20**: mp 261.7 °C; $[\alpha]^{25}_D$ −9.7°; UV ϵ_{259} = 14 800; IR 1770, 1655, 1605 cm^{-1}; NMR 5.85 (C-4), 1.15 (C-19), 1.0 (C-18) ppm. Anal. ($C_{25}H_{30}O_3$) C, H, O.

1α-Cyano-6β,7β:15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (21). A solution of 1 g (2.75 mmol) of **3** in 33 mL of dry tetrahydrofuran was treated with 3 mL of a 1.8 M solution of diethylaluminum cyanide in toluene. After 5 min the reaction mixture was poured in cooled sodium potassium tartrate solution. Extraction with methylene chloride and column chromatography yielded, after recrystallization from diisopropyl ether, 950 mg (88.1%) of **21**: mp 271.4 °C; $[\alpha]^{25}_D$ −147°; UV ϵ_{264} = 17 380; IR 2240, 1760, 1665, 1595 cm^{-1}; NMR 6.16 (C-4), 1.16 (C-19), 0.98 (C-18) ppm. Anal. ($C_{25}H_{29}NO_3$) C, H, N, O.

Registry No. **2**, 67392-87-4; **3**, 74220-07-8; **4**, 95218-05-6; **5**, 95218-06-7; **6**, 95218-07-8; **7**, 95218-08-9; **8**, 95218-09-0; **9**, 95218-10-3; **10**, 95340-87-7; **11**, 95218-11-4; **12**, 95218-12-5; **13**, 95218-13-6; **14**, 95218-14-7; **15**, 95218-15-8; **16**, 95218-16-9; **17**, 95218-17-0; **18**, 95218-18-1; **19**, 95218-19-2; **20**, 95218-20-5; **21**, 95218-21-6; CH_3SO_2Cl, 124-63-0; CH_3COSH, 507-09-5; CH_3SH, 74-93-1; H_2S, 7783-06-4; $LiCH_3$, 917-54-4; $(CH_3)_3SOI$, 1774-47-6; Et_2AlCN, 5804-85-3; aldosterone, 52-39-1.

Synthesis and Antiviral Activity of the Carbocyclic Analogues of (*E*)-5-(2-Halovinyl)-2′-deoxyuridines and (*E*)-5-(2-Halovinyl)-2′-deoxycytidines

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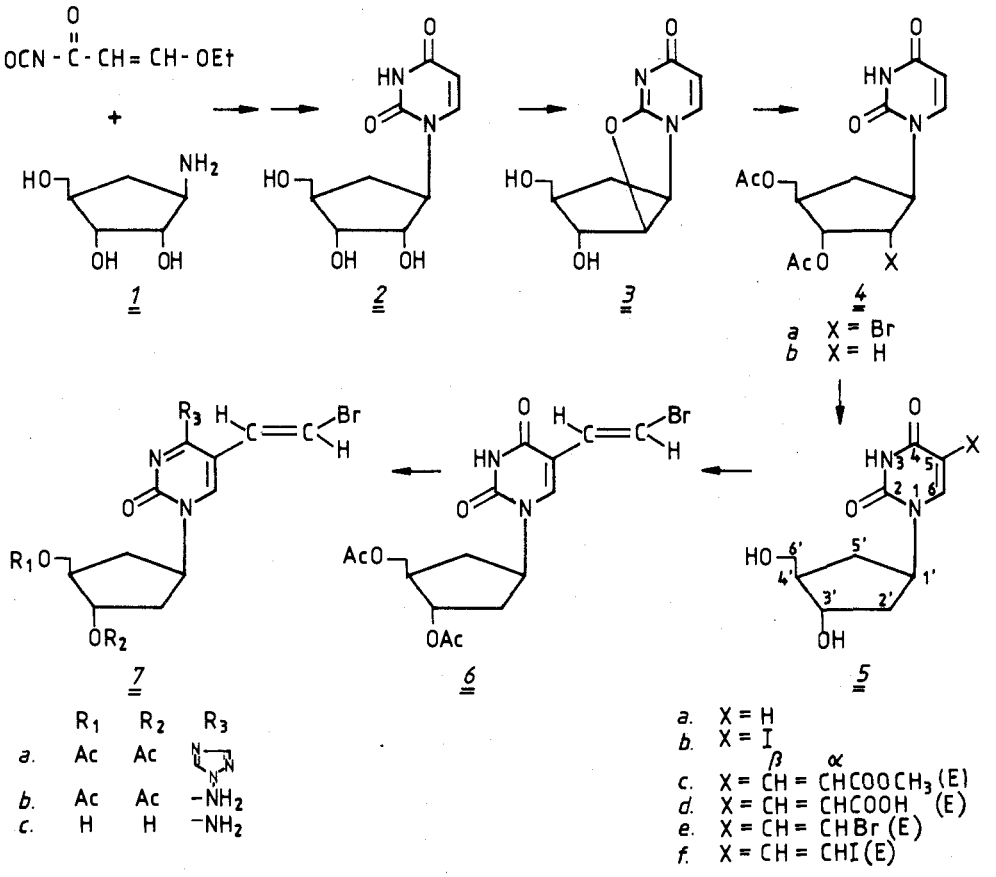
The carbocyclic analogues of the potent and selective antiherpes agents (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU), (*E*)-5-(2-iodovinyl)-2′-deoxyuridine (IVDU), and (*E*)-5-(2-bromovinyl)-2′-deoxycytidine (BVDC) were synthesized by conventional methods with use of carbocyclic 2′-deoxyuridine as starting material. C-BVDU, C-IVDU, and C-BVDC were equally selective, albeit slightly less potent, in their antiherpes action than BVDU, IVDU, and BVDC. Although resistant to degradation by pyrimidine nucleoside phosphorylases, C-BVDU did not prove more effective than BVDU in the systemic (oral, intraperitoneal) or topical treatment of HSV-1 infections in mice.

(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine (BVDU) is a highly potent and selective antiherpes agent,[1] which inhibits herpes simplex virus type 1 (HSV-1),[2] varicella-zoster virus (VZV),[3] pseudorabies virus (suid herpesvirus type 1),[4] infectious bovine rhinotracheitis virus (bovid herpesvirus type 1),[5] and simian varicella virus,[6] at a concentration of 0.001–0.01 μg/mL, while not being toxic for the host cell at concentrations up to 50–100 μg/mL.[1-7] The selectivity of BVDU as an antiherpes agent depends primarily on a specific phosphorylation by the virus-induced 2′-deoxythymidine (dThd) kinase,[8] and its antiviral action would

(1) De Clercq, E.; Descamps, J.; De Somer, P.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2947.
(2) De Clercq, E.; Descamps, J.; Verhelst, G.; Walker, R. T.; Jones, A. S.; Torrence, P. F.; Shugar, D. *J. Infect. Dis.* **1980**, *141*, 563.
(3) Shigeta, S.; Yokota, T.; Iwabuchi, T.; Baba, M.; Konno, K.; Ogata, M.; De Clercq, E. *J. Infect. Dis.* **1983**, *147*, 576.
(4) Reefschläger, J.; Bärwolff, D.; Engelmann, P.; Langen, P.; Rosenthal, H. A. *Antiviral Res.* **1982**, *2*, 41.
(5) Babiuk, L. A.; Acres, S. D.; Misra, V.; Stockdale, P. H. G.; De Clercq, E. *Antimicrob. Agents Chemother.* **1983**, *23*, 715.
(6) Soike, K. F.; Baskin, G.; Cantrell, C.; Gerone, P. *Antiviral Res.* **1984**, *4*, 245.
(7) De Clercq, E. *J. Antimicrob. Chemother.* **1984**, *14* (Suppl. A), 85.

0022-2623/85/1828-0550$01.50/0

Scheme I[a]



[a] The depicted structures are racemic, only one enantiomeric form is given.

be based upon an inhibition of the viral DNA polymerase by BVDU 5'-triphosphate[9] and/or the incorporation of the latter into viral DNA.[10] From a clinical viewpoint, BVDU offers great promise for the topical and systemic treatment of HSV-1 and VZV infections. It has been applied successfully in the topical treatment of herpetic keratitis[11,12] and the systemic, i.e., oral, treatment of varicella-zoster infections in immunosuppressed patients.[13,14]

Being a dThd analogue, BVDU is an effective substrate for pyrimidine nucleoside phosphorylases, i.e., dThd phosphorylase.[15] This explains why BVDU, upon systemic administration to rats, is cleared within 2–3 h from the plasma, where it is replaced by its inactive metabolite, (*E*)-5-(2-bromovinyl)uracil (BVU).[16] The rapid degradation of BVDU to BVU may obviously affect its therapeutic efficacy, and, therefore, attempts have been undertaken to either inhibit or reverse the phosphorolytic cleavage of BVDU. As demonstrated recently by Desgranges et al.,[16] BVU can be converted again to BVDU if dThd (dUrd or any 5-substituted dThd analogue) is administered shortly after BVDU or BVU.

To protect BVDU from premature degradation by nucleoside phosphorylases, we considered the synthesis of the carbocyclic analogue of BVDU in which the sugar moiety is replaced by a cyclopentane ring (C-BVDU). In addition to C-BVDU, we also prepared the carbocyclic analogues of (*E*)-5-(2-iodovinyl)-2'-deoxyuridine (IVDU) and (*E*)-5-(2-bromovinyl)-2'-deoxycytidine (BVDC). Shealy et al. have previously reported the synthesis of the carbocyclic analogues of 5-fluoro-2'-deoxyuridine (FDU)[17] and 5-iodo-2'-deoxyuridine (IDU).[18] While the carbocyclic analogue of IDU, C-IDU, proved as effective an antiherpes agent as its parent compound,[18] the carbocyclic analogue of FDU, C-FDU, was much less effective as antitumor agent than its parent.[17]

Chemistry. The carbocyclic analogue of 2'-deoxyuridine **5a** was obtained by deoxygenation of the carbocyclic analogue of uridine **2** because the preparation of one of the starting products, i.e., (4-amino-2,3-dihydroxycyclopentyl)methanol[19] (**1**) is more straightforward than that of the monohydroxy derivative.[20] Compound **2** was

(8) Cheng, Y.-C.; Dutschman, G.; De Clercq, E.; Jones, A. S.; Rahim, S. G.; Verhelst, G.; Walker, R. T. *Mol. Pharmacol.* **1981**, *20*, 230.
(9) Allaudeen, H. S.; Kozarich, J. W., Bertino, J. R.; De Clercq, E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2698.
(10) Mancini, W. R.; De Clercq, E.; Prusoff, W. H. *J. Biol. Chem.* **1983**, *258*, 792.
(11) Maudgal, P. C.; Missotten, L.; De Clercq, E.; Descamps, J.; De Meuter, E. *Albrecht von Graefes Arch. Klin. Exp. Ophthalmol.* **1981**, *216*, 261.
(12) Maudgal, P. C.; De Clercq, E.; Missotten, L. *Antiviral Res.* **1984**, *4*, 281.
(13) Wildiers, J.; De Clercq, E. *Eur. J. Cancer Clin. Oncol.* **1984**, *20*, 471.
(14) Benoit, Y.; Laureys, G., Delbeke, M.-J.; De Clercq, E. *Eur. J. Pediatr.* **1985**, *143*, 198.
(15) Desgranges, C.; Razaka, G., Rabaud, M.; Bricaud, H.; Balzarini, J.; De Clercq, E. *Biochem. Pharmacol.* **1983**, *32*, 3583.
(16) Desgranges, C.; Razaka, G.; Drouillet, F.; Bricaud, H.; Herdewijn, P.; De Clercq, E. *Nucleic Acids Res.* **1984**, *12*, 2081. Desgranges, C.; Razaka, G.; Bricaud, H.; De Clercq, E. *Biochem. Pharmacol.* **1985**, *34*, 405.
(17) Shealy, Y. F.; Frye, J. L.; DuBois, N. F.; Shaddix, S. C.; Brockman, R. W. *J. Med. Chem.* **1981**, *24*, 1083.
(18) Shealy, Y. F., O'Dell, C. A.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1983**, *26*, 156.
(19) Cermak, R. C.; Vince, R. *Tetrahedron Lett.* **1981**, *22*, 2331.
(20) Shealy, Y. F.; O'Dell, C. A. *Tetrahedron Lett.* **1969**, 2231.

Table I. Anti-viral Activity of the Carbocyclic Analogues of BVDU, IVDU, IDU, and BVDC

	MIC_{50},[a] μg/mL							
compd	HSV-1 (KOS)	HSV-1 (McIntyre)	HSV-1 (F)	HSV-2 (Lyons)	HSV-2 (G)	vaccinia virus	vesicular stomatitis virus	HSV-1 TK⁻
C-BVDU (**5e**)	0.07	0.04	0.07	7	20	300	>400	>400
C-IVDU (**5f**)	0.07	0.07	0.1	7	2	300	>400	>400
C-IDU (**5b**)	0.2	0.2	0.2	20	40	20	>400	>400
C-BVDC (**7c**)	0.2	0.2	0.1	20	20	>200	>400	>400
BVDU	0.007	0.02	0.01	1	2	7	>400	>10
IVDU	0.007	0.02	0.02	2	2	7	>400	>10
IDU	0.2	0.2	0.2	0.2	0.7	0.2	>400	>400
BVDC[b]	0.07	0.06	0.07	9	7	200	>400	ND

[a] Minimum inhibitory concentration, required to reduce virus-induced cytopathogenicity in primary rabbit kidney cell cultures by 50%. None of the compounds was cytotoxic (based on a microscopically detectable alteration of normal cell morphology) at 400 μg/mL (the highest concentration tested). The origin of the herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) strains has been described previously;[2] HSV-1 TK⁻ represents a dThd kinase deficient mutant of HSV-1 (strain B2006), which was originally supplied by Dr. Y.-C. Cheng (Chapel Hill, NC) and has, in the mean time, been passaged several times in primary rabbit kidney cell cells. [b] The data for BVDC were taken from ref 32. ND, not determined.

prepared, as described previously,[21] by reaction of [(±)-4β-amino-2α,3α-dihydroxy-1β-cyclopentyl]methanol (**1**) with 3-ethoxy-2-propenoyl isocyanate. The (dihydroxycyclopentyl)methanol **1** intermediate was synthesized from cyclopentadiene[19,22] rather than by the much longer norbornadiene route.[23] Treatment of **2** with diphenyl carbonate in hexamethylphosphoramide[24] afforded the carbocyclic analogue of 2,2′-anhydrouridine (**3**) (80%). Opening of the oxide bridge and introduction of a bromine atom at C-2′ was accomplished with acetyl bromide in ethyl acetate–*N*,*N*-dimethylformamide as described by Marumoto et al.[25] This reaction afforded a mixture of the diacetyl derivative **4a** and a triacetyl derivative. These intermediates were not purified but immediately dehalogenated with tributyltin hydride in the presence of azobis(isobutyronitrile)[26] in tetrahydrofuran. Deprotection of **4b** with sodium methoxide in methanol afforded the carbocyclic analogue of 2′-deoxyuridine (**5a**). The physical constants of **5a** are in agreement with those reported for (1α,3β,4α)-(±)-1-[3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione[21] prepared by another reaction scheme. The 2′-deoxy structure was confirmed by comparison of the ^{13}C NMR spectra of **2** and **5a**. The disappearance of the 2′-hydroxyl group causes an upfield shift (6.3 ppm) of the β-carbon atom (C-1′) and a downfield shift (5.0 ppm) of the γ-carbon atom (C-4′) of **5a** relative to **2**. The opposite could be expected for a 3′-deoxy structure. Iodination of **5a** with iodine–nitric acid[27] in dioxane afforded the desired carbocyclic 5-iodo-2′-deoxyuridine (**5b**) in a yield of 98%. The spectroscopic data are in agreement with those reported.[18]

Reaction of **5b** with methyl acrylate in dioxane in the presence of palladium(II) acetate, triphenylphosphine, and triethylamine[28a] afforded the carbocyclic 5-(2-carbomethoxyvinyl)-2′-deoxyuridine (**5c**) in a yield of 80%. Deiodination was observed as a side reaction and 15% of **5a** was recovered. Hydrolysis of the methyl ester was performed in 10% aqueous potassium hydroxide, and **5d** was isolated in a yield of 88%. Treatment of **5d** with *N*-bromosuccinimide[28b] in *N*,*N*-dimethylformamide gave the carbocyclic analogue of (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (**5e**) (C-BVDU). The trans orientation of the bromine atome with respect to the nucleoside residue (*E* isomer) was confirmed by the ^1H NMR spectrum, which showed a coupling constant of 13.6 Hz for the vinylic protons.[29] The 5-iodovinyl congener **5f** (C-IVDU) was obtained by decarboxylative iodination of **5d** with iodine–iodic acid in *N*,*N*-dimethylformamide at 60 °C.[30] C-BVDU (**5e**) was converted into the corresponding cytidine analogue **7c** (C-BVDC) according to the method described by Sung[31] for the conversion of 3′,5′-diprotected-2′-deoxythymidine into 5-methyl-2′-deoxycytidine. By reaction of **6** with 1,2,4-triazole in the presence of *o*-chlorophenyl phosphodichloridate followed by treatment with ammonia, compound **7b** was obtained in 45% yield, some 45% of **6** being recovered. After removal of the acetyl groups with ammonia in methanol, carbocyclic BVDC (**7c**) was obtained.

Biological Results and Discussion

The carbocyclic analogues of BVDU, IVDU, and BVDC (**5e**, **5f**, and **7c**) proved to be potent inhibitors of HSV-1 in primary rabbit kidney cells (Table I) and other cell cultures (data not shown). With an MIC_{50} in the range of 0.04–0.2 μg/mL, they were only slightly less active than their parent compounds. Since C-BVDU, C-IVDU, and C-BVDC were tested as the racemates, somewhat lower MIC_{50} values may be expected for the active enantiomers. C-IDU (**5b**) and IDU were both active at an MIC_{50} of 0.2 μg/mL, which confirms the findings of Shealy et al.[18] The antiviral activity spectrum of C-BVDU, C-IVDU, and C-BVDC was remarkably similar to that of BVDU, IVDU, and BVDC, in that they were (i) inhibitory to HSV-2 only at a concentration 100-fold higher than that required to inhibit HSV-1, (ii) virtually inactive against vaccinia virus, and (iii) not inhibitory toward dThd kinase-deficient (TK⁻) HSV-1 and vesicular stomatitis virus (an RNA virus) (Table I). Also, C-BVDU proved highly active against VZV

(21) Shealy, Y. F.; O'Dell, C. A. *J. Heterocycl. Chem.* **1976**, *13*, 1015.
(22) Jagt, J. C.; van Leusen, A. M. *J. Org. Chem.* **1974**, *39*, 564.
(23) Shealy, J. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 3075.
(24) Verheyden, J. P. H.; Wagner, D.; Moffatt, J. G. *J. Org. Chem.* **1971**, *36*, 250.
(25) Marumoto, R.; Honjo, M. *Chem. Pharm. Bull.* **1974**, *22*, 128.
(26) Holy, A. In "Nucleic Acid Chemistry"; Townsend, L. B., Tipson, R. S., Eds.; Wiley Interscience: New York, 1978; Part 1, p 347.
(27) Michelson, A. M. In "Synthetic Procedures in Nucleic Acid Chemistry"; Zorbach, W., Tipson, R., Eds.; Wiley Interscience: New York, 1968; Vol. 1, p 491.
(28) (a) Colla, L.; Busson, R.; De Clercq, E.; Vanderhaeghe, H. *Eur. J. Med. Chem.* **1982**, *17*, 569. (b) Jones, A. S.; Verhelst, G.; Walker, R. T. *Tetrahedron Lett.* **1979**, *45*, 4415.
(29) Jones, A. S.; Rahim, S. G.; Walker, R. T.; De Clercq, E. *J. Med. Chem.* **1981**, *24*, 759.
(30) Maudgal, P. C.; Verbruggen, A. M.; De Clercq, E.; Busson, R.; Bernaerts, R.; De Roo, M.; Ameye, C.; Missotten, L. *Invest. Ophthalmol.*, in press.
(31) Sung, W. L. *J. Chem. Soc., Chem. Commun.* **1981**, 1089; *J. Org. Chem.* **1982**, *47*, 3623.

Table II. Inhibitory Effects of the Carbocyclic Analogues of BVDU, IVDU, and IDU on the Proliferation of Tumor Cells

compd	MIC_{50},[a] μg/mL: murine leukemia L1210 (wild type)	murine leukemia L1210 (TK^-)	human lympho-blast Raji	Novikoff rat hepatoma
C-BVDU (**5e**)	>200	>200	>200	>200
C-IVDU (**5f**)	>200	>200	>200	>200
C-IDU (**5b**)	>200	>200	>200	22.8
BVDU	30.6	12.3	48.4	ND
IVDU	16.3	5.1	21.1	4.6
IDU	35.6	>500	4.7	5.5

[a] Minimum inhibitory concentration, required to inhibit the proliferation of the cells during their linear growth phase by 50%. Cell growth was monitored as described previously.[33] ND, not determined.

(MIC_{50} = 0.02–0.04 μg/mL).[38] All carbocyclic analogues, including C-IDU, discriminated between HSV-1 and HSV-2 and may therefore be equally useful as BVDU[1,7] as markers for the identification of type 1 and type 2 strains in clinical HSV isolates.

The fact that C-BVDU, C-IVDU, and C-BVDC were virtually inactive against vaccinia virus points to their selectivity as antiherpes agents. This selectivity is also apparent from a comparison of the MIC_{50} values for HSV-1 (Table I) with the MIC_{50} values for tumor cell growth (Table II). For C-BVDU and C-IVDU, the ratios of MIC_{50} for cell growth to MIC_{50} for HSV-1 were greater than 2000–5000. For BVDU and IVDU, these ratios were in the range of 600–7000 and 250–3000, respectively. Thus, C-BVDU and C-IVDU were at least as selective in their antiherpes activity as their 2'-deoxyuridine counterparts.

The mechanism of action of C-BVDU and C-IVDU is the subject of further study. Considering the similarity in the activity spectrum of the carbocyclic analogues and their parent compounds, it is likely that they share a common mode of antiviral action. Our preliminary data indicate that C-BVDU and C-IVDU act equally well as substrates for the HSV-1 encoded dThd kinase as do BVDU and IVDU. Thus, the carbocyclic nucleosides may be activated (phosphorylated) by the viral dThd kinase in infected cells just as the ribose counterparts, i.e., IVDU,[34] are known to be. This dependence on a specific phosphorylation by the viral dThd kinase would also explain why the carbocyclic analogues are inactive against dThd kinase deficient variants of HSV-1 (Table I).

C-BVDU was further compared with BVDU for their efficacy in two experimental model HSV-1 infections in which BVDU has been found effective previously,[35,36] viz., NMRI mice infected intraperitoneally with HSV-1 (KOS) (Table III) and hairless mice infected intracutaneously with HSV-1 (KOS) (Table IV). It was reasoned that, if BVDU were to loose part of its antiviral potentials due to premature degradation to BVU, C-BVDU, which is not degraded in vivo to BVU by pyrimidine nucleoside phosphorylases,[37] may be more efficacious than BVDU. As shown in Tables III and IV, this did not prove to be the case. In both animal models, BVDU achieved a better protection against HSV-1 infection than C-BVDU, irrespective of the route by which the compounds were administered (perorally, intraperitoneally, or topically). The poor performance of C-BVDU in vivo contrasts sharply with its high potency against HSV-1 in vitro. The reason(s) for this discrepancy is not immediately clear. It may be related to pharmacokinetic problems characteristic of carbocyclic nucleosides.

Table III. Effect of Systemic Treatment with the Carbocyclic Analogue of BVDU on the Survival Rate of NMRI Mice Infected Intraperitoneally with HSV-1 (KOS)

treatment regimen[a]: route	compd	survival rate (at 20th day postinfection)
peroral	C-BVDU (**5e**)	0/10
	BVDU	7/10
	Control	0/20
intraperitoneal	C-BVDU (**5e**)	3/10
	BVDU	6/10
	Control	0/20

[a] The compounds were administered at 100 mg/kg per day from day 0 until day 4 postinfection. For intraperitoneal administration, C-BVDU was dissolved at 1 mg/mL in physiological saline containing 10% propylene glycol; it was administered twice a day in a volume of 0.5 mL. For peroral administration, C-BVDU was suspended at 2 mg/mL in water and given by gavage once a day in a volume of 0.5 mL. Virus inoculum: 10^3PFU/0.2 mL per mouse. For further details on the efficacy of BVDU in this model infection, see ref 35.

Table IV. Effect of Topical Treatment with the Carbocyclic Analogue of BVDU on the Survival Rate of Hairless (hr/hr) Mice Infected Intracutaneously with HSV-1 (KOS)

treatment regimen[a]: compd	concn, %	survival rate (at 20th day postinfection)
C-BVDU (**5e**)	3	2/5
	1	0/5
	0.3	0/5
BVDU	3	10/10
	1	10/10
	0.3	9/10
control		0/15

[a] The compounds were applied topically at the indicated concentrations four times a day for 5 days, starting immediately after virus infection. The vehical consisted of 5% azone (1-dodecylazacycloheptan-2-one) in Me_2SO (dimethyl sulfoxide). Virus inoculum: $10^{4.7}$ PFU/0.05 mL per mouse. For further details on the efficacy of BVDU in this model infection, see ref 36.

Experimental Section

General Procedures. Melting points were determined in capillary tubes with a Büchi–Tottoli apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 257 spectrophotometer on samples in potassium bromide disks at 1.5%. Ultraviolet spectra were recorded with a Beckman UV 5230 spectrophotometer. Mass spectra were determined with an AEI MS-12 apparatus. Only the peak due to the molecular ion M^+ is listed. The ^1H NMR and ^{13}C NMR spectra were determined with a JEOL FX 90Q spectrometer, operating at 89.55 MHz for proton and at 22.50 MHz for carbon-13 spectra, with tetramethylsilane as internal standard (s = singlet, d = doublet, m = multiplet). Precoated Merck silica gel F254 plates were used for TLC and the spots were examined with UV light and iodine vapors. Column chromatography was performed on Merck silica gel (0.063–0.200 nm). Anhydrous solvents were obtained as follows: tetrahydrofuran was obtained by distillation after reflux overnight with lithium aluminum hydride; pyridine was refluxed overnight in *p*-toluenesulfonyl chloride, distilled, refluxed over-

(32) De Clercq, E.; Balzarini, J.; Descamps, J.; Huang, G.-F.; Torrence, P. F.; Bergstrom, D. E.; Jones, A. S.; Serafinowski, P.; Verhelst, G.; Walker, R. T. *Mol. Pharmacol.* **1982**, *21*, 217.
(33) De Clercq, E.; Balzarini, J.; Torrence, P. F.; Mertes, M. P.; Schmidt, C. L.; Shugar, D.; Barr, P. J.; Jones, A. S.; Verhelst, G.; Walker, R. T. *Mol. Pharmacol.* **1981**, *19*, 321.
(34) Descamps, J.; De Clercq, E. *J. Biol. Chem.* **1981**, *256*, 5973.
(35) De Clercq, E.; Zhang, Z.-X.; Sim, I. S. *Antimicrob. Agents Chemother.* **1982**, *22*, 421.
(36) De Clercq, E. *Antimicrob. Agents Chemother.* **1984**, *26*, 155.
(37) Desgranges, C.; Razaka, G.; Bricaud, H.; Herdewijn, P.; De Clercq, E., unpublished data, 1984.
(38) Shigeta, S.; De Clercq, E., personal communication, 1984.

night in potassium hydroxide, and distilled again; ethyl acetate was stored for 2 days in anhydrous sodium sulfate and anhydrous potassium carbonate, filtered, and distilled; methanol was dried by distillation after it has been refluxed overnight with magnesium–iodine; water was removed from *N,N*-dimethylformamide by distillation with benzene followed by distillation in vacuo. All solvents were stored on 4-Å molecular sieves.

(±)-1-[(1α,3β,4α)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (5a). A mixture of 2.904 g (12 mmol) of **2**, 3.424 g (16 mmol) of diphenyl carbonate, and 0.084 g (1 mmol) of sodium bicarbonate in hexamethylphosphoramide was heated at 150 °C for 30 min. The mixture was cooled, diluted with water (180 mL), and washed with $CHCl_3$ (3 × 120 mL), and the insoluble materials were filtered off. The filtrate was evaporated and the residue was purified by silica gel column chromatography (EtOAc–MeOH, 6:4), yielding 2.150 g (9.6 mmol, 80%) of **3**. To a stirred suspension of **3** (2.150 g, 9.6 mmol) in a mixture of anhydrous DMF (11 mL) and anhydrous ethyl acetate (55 mL) was added 2.43 mL (3.69 g, 30 mmol) of acetyl bromide. The mixture was refluxed for 1 h, cooled to room temperature, and evaporated under reduced pressure. The residue was partitioned between water (150 mL) and ethyl acetate (150 mL). The organic phase was washed with water (2 × 100 mL), dried (Na_2SO_4), and evaporated. The residue was dissolved in anhydrous tetrahydrofuran (150 mL), tributyltin hydride (9.31 g, 32 mmol) and azobis(isobutyronitrile) (40 mg) were added, and the reaction mixture was refluxed for 45 min. After removal of the solvent, the oily residue was washed twice with petroleum ether (bp 40–60 °C) and purified by chromatography on a silica gel column with $CHCl_3$–MeOH (97.5;2.5) as eluent to yield **4b** (2.60 mg, 8.39 mmol, 87.5% starting from **2**) as a white powder.

Removal of the acetyl protecting groups was performed with 0.1 N sodium methoxide in MeOH (40 mL) overnight at room temperature. The mixture was neutralized with Dowex 50 X-8 (H^+), the ion-exchange resin was filtered off and washed with methanol, and the filtrate and washings were combined and evaporated to dryness. Crystallization from EtOH–Et_2O yielded 1.84 g (8.14 mmol, 97%) of **5a** with mp 158–160 °C and spectral properties identical with those described by Shealy et al.:[21] R_f 0.48 (EtOAc–MeOH, 1:1); MS, *m/e* 226 (M^+); UV λ_{max} 269 nm (0.1 N HCl), 266 (0.1 N NaOH); IR (1700–1200-cm^{-1} region) 1675, 1620, 1460, 1435, 1370, 1350, 1320, 1290, 1265, 1220, 1210 cm^{-1}; ^1H NMR (CD_3OD) δ 1.38–1.70 and 1.95–2.47 (overlapping m, 2 × CH_2 and C*H*CH_2OH), 3.67 (m, CH_2OH), 4.16 (m, C*H*OH), 5.05 (m, CHN), 5.69 (d, *J* = 8.0 Hz, H-5), 7.67 (d, *J* = 8.0 Hz, H-6); ^{13}C NMR (CD_3OD) 33.5 (C-5′), 40.0 (C-2′), 50.3 (C-4′), 56.3 (C-1′), 64.3 (C-6′), 73.7 (C-3′), 102.6 (C-5), 144.0 (C-6), 152.8 (C-2), 166.2 (C-4) ppm.

(±)-1-[(1α,3β,4α)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (5b). A mixture of **5a** (1.81 g, 8 mmol) and iodine (4.06, 16 mmol) in 80 mL of dioxane, containing 10.67 mL 0.75 N nitric acid, was stirred at 100 °C for 1 h, cooled to room temperature, and evaporated under reduced pressure. The residue was flushed three times with EtOH and three times with $CHCl_3$. The yellow solid was purified by crystallization from EtOH, yielding 2.69 g (7.64 mmol, 95.5%) of the title compound as a white crystalline product (mp 196–198 °C). An additional amount of **5b** (70 mg, 0.2 mmol, 2.5%) can be obtained from the mother liquid by column chromatography on silica gel (mobile phase EtOAc–MeOH, 8:2). The spectroscopic data (MS, IR, ^1H NMR, UV) were identical with those reported by Shealy et al.[18] R_f 0.45 (EtOAc–MeOH, 8:2), ^{13}C NMR (CD_3OD) 33.4 (C-5′), 40.1 (C-2′), 50.1 (C-4′), 57.2 (C-1′), 64.1 (C-6′), 68.1 (C-5), 73.6 (C-3′), 148.9 (C-6), 152.6 (C-2), 163.0 (C-4) ppm.

(±)-1-[(1α,3β,4α)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-[(*E*)-2-carbomethoxyvinyl]-2,4(1*H*,3*H*)-pyrimidinedione (5c). A suspension of **5b** (2.74 g, 7.78 mmol) and methyl acrylate (1.4 mL, 15.6 mmol) in dioxane (50 mL) was added to a solution of palladium(II) acetate (112.3 mg, 0.5 mmol), triphenylphosphine (262 mg, 1 mmol), and triethylamine (1.75 mL, 12.5 mmol) in dioxane (125 mL), which had been heated at 85 °C for 15 min. The reaction mixture was heated for 3 h at 85 °C, filtered, cooled, and evaporated after addition of 10 g of Celite. The remaining solid was applied to a silica gel column (50 g) using first EtOAc as eluent, followed by EtOAc–MeOH (9:1). Fractions containing the same product were combined and concentrated to yield 1.93 g (6.23 mmol, 80%) of the title compound **5c**: R_f 0.49 (EtOAc–MeOH, 8:2); mp 190 °C (MeOH–EtOAc); MS, *m/e* 310 (M^+); UV λ_{max} 308 nm (0.1 N HCl), 308 and 275 (0.2 N, NaOH); ^1H NMR (CD_3COCD_3) δ 6.94 (d, *J* = 16.3 Hz, vinylic H), 7.40 (d, *J* = 16.3 Hz, vinylic H), 8.19 (s, H-6); ^{13}C NMR (CD_3COCD_3) 33.5 (C-5′), 40.4 (C-2′), 50.2 (C-4′), 51.4 (OMe), 55.9 (C-1′), 64.4 (C-6′), 73.6 (C-3′), 109.8 (C-5), 117.8 (C-α), 138.6 (C-β), 146.4 (C-6), 150.7 (C-2), 162.1 (C-4), 168.2 (COOR) ppm. Some 0.264 g (1.17 mmol, 15%) of **5a**, R_f 0.32 (EtOAc–MeOH, 8:2), was obtained from the subsequent fractions.

(±)-1-[(1α,3β,4α)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-[(*E*)-2-bromovinyl]-2,4(1*H*,3*H*)-pyrimidinedione (5e). A solution of 1.92 g (6.2 mmol) in **5c** in 25 mL of 1.8 N potassium hydroxide was kept overnight at room temperature. The clear solution was cooled (4 °C) and acidified with concentrated HCl to pH 2. The precipitate was collected by filtration, washed with H_2O, and dried in vacuo over P_2O_5, yielding 1.43 g of **5d**. A second crop of **5d** (0.257 g) was obtained by concentrating the filtrate and washings. The two portions were combined and dissolved in MeOH. The solution was filtered and concentrated to a small volume and the resulting solid was separated by filtration and dried in vacuo: yield 1.62 g (5.47 mmol, 88%) of **5d**; R_f 0.45 (EtOAc–MeOH–HOAc, 8:1:1). The carbocyclic 5-(2-carboxyvinyl)-2′-deoxyuridine (1.62 g), obtained in this reaction, was dissolved in 30 mL of DMF and 1.64 g of solid potassium bicarbonate was added with stirring. A solution of 0.98 g (5.5 mmol) of *N*-bromosuccinimide in 10 mL of DMF was added dropwise over a period of 10 min. The mixture was further stirred at room temperature for 90 min, filtered, and evaporated at reduced pressure. The oily residue was taken up in H_2O and evaporated again (2×), leaving a white solid, which was collected by filtration and washed with MeOH. Further concentration of the mother liquor gave a second fraction of **5e**. Recrystallization of the combined fractions from MeOH yielded 1.255 g (3.79 mmol, 69.3%) of **5e**: mp 185 °C dec; UV (MeOH) λ_{max} 299 nm (ε 13 840), 252 (16 280), λ_{min} 272 nm (ε 8208); MS, *m/e* 330 (M^+); IR (1700–1200-cm^{-1} region) 1690, 1675, 1595, 1470, 1430, 1365, 1295, 1280 cm^{-1}; ^1H NMR (CD_3OD) δ 1.42–2.4 (overlapping multiplets, 2 × CH_2 and C*H*CH_2OH), 3.65 (m, CH_2OH), 4.15 (m, C*H*OH), 5.02 (m, CHN), 6.80 (d, *J* = 13.6 Hz, vinylic H), 7.34 (d, *J* = 13.6 Hz, vinylic H), 7.75 (s, H-6); ^{13}C NMR (CD_3OD) 33.5 (C-5′), 40.3 (C-2′), 50.3 (C-4′), 56.7 (C-1′), 64.3 (C-6′), 73.7 (C-3′), 108.7 (C-α), 112.3 (C-5), 130.3 (C-β), 142.1 (C-6) ppm. The purity was verified by HPLC analysis (zorbax C_8/MeOH–H_2O–phosphate buffer, 1 M, pH 7.0, 35:60:1). Anal. ($C_{12}H_{15}N_2O_4Br$) C, H, N.

(±)-1-[(1α,3β,4α)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-5-[(*E*)-2-iodovinyl]-2,4(1*H*,3*H*)-pyrimidinedione (5f). A mixture of **5d** (0.1 g, 0.34 mmol), potassium bicarbonate (0.26 g, 2.6 mmol), iodine (0.173 g, 0.68 mmol), and iodic acid (0.06 g, 0.34 mmol) in 5 mL of DMF was heated at 60 °C for 2 h. The reaction mixture was evaporated at reduced pressure and coevaporated several times with EtOH, and the residue was crystallized from MeOH–H_2O to yield 0.084 g (0.22 mmol, 65%) of **5f**: R_f 0.47 (EtOAc–MeOH, 8:2); MS, *m/e* 378 (M^+); UV (MeOH) λ_{max} 302 nm (ε 14 800), 256 (16 218), λ_{min} 277 nm (ε 9000); ^1H NMR (CD_3OD) δ 1.42–2.5 (overlapping multiplets, 2 × CH_2 and C*H*CH_2OH), 3.68 (m, CH_2OH), 4.20 (m, C*H*OH), 5.07 (m, CHN), 7.13 (d, *J* = 14.8 Hz, vinylic H), 7.40 (d, *J* = 14.8 Hz, vinylic H), 7.80 (s, H-6); ^{13}C NMR (CD_3OD) 33.5 (C-5′), 40.2 (C-2′), 50.3 (C-4′), 56.6 (C-1′), 64.3 (C-6′), 73.7 (C-3′), 78.6 (C-α), 113.8 (C-5), 137.6 (C-β), 142.1 (C-6) ppm. Anal. ($C_{12}H_{15}N_2O_4I$) C, H, N.

(±)-1-[(1α,3β,4α)-3-Hydroxy-4-(hydroxymethyl)cyclopentyl]-4-amino-5-[(*E*)-2-bromovinyl]-2(1*H*)-pyrimidinone (7c). A solution of **5e** (0.199 g, 0.6 mmol) in 4 mL of pyridine and 0.57 mL (6 mmol) of acetic anhydride was kept at room temperature for 5 h. Methanol (1 mL) was added and the reaction mixture was stirred for 20 min. Evaporation of the reaction mixture and coevaporation several times with toluene afforded **6** (R_f 0.65, $CHCl_3$–MeOH, 95:5) in near-quantitative yield. Only traces of a triacetyl derivative could be detected.

o-Chlorophenyl phosphodichloridate (0.246 g, 0.165 mL, 1 mmol) was added to a solution of **6** (0.6 mmol) and 0.138 g of 1,2,4-triazole (2 mmol) in 5 mL of anhydrous pyridine and the mixture was stirred at room temperature for 4 days. Then 2 mL of ammonia (25%) was added and the mixture was stirred for 1 h. After removal of solvent in vacuo, the residue was purified

by column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to give **7b** (0.112 g, 45%), while 0.112 g (45%) of **6** was recovered.

A solution of 0.110 g (0.266 mmol) of **7b** in methanol, saturated with ammonia at 0 °C, was kept overnight at room temperature. The clear solution was evaporated to dryness and **7c** was crystallized from MeOH–EtOAc (0.081 g, 0.245 mmol, 92%): mp 202 °C dec; MS, *m/e* 329; UV λ_{max} 304 nm and 245 (at pH 1), 292 and 251 (at pH 13), λ_{min} 276 nm (at pH 1), 282 (at pH 13); IR (1700–1200-cm^{-1} region) 1670, 1620, 1480, 1410, 1350, 1320, 1300, 1255, 1205 cm^{-1}; ^1H NMR (CD_3OD) δ 1.54–2.47 (overlapping multiplets, 2 × CH_2 and $CHCH_2OH$), 3.67 (m, CH_2OH), 4.2 (m, $CHOH$), 5.1 (m, CHN), 6.78 (d, J = 13.04 Hz, vinylic H), 7.00 (d, J = 13.04 Hz, vinylic H), 7.8 (s, H-6); ^{13}C NMR (CD_3OD) 33.9 (C-5′), 40.7 (C-2′), 50.5 (C-5′), 57.7 (C-1′), 64.3 (C-6′), 73.8 (C-3′), 106.4 (C-5), 108.8 (C-α), 129.1 (C-β), 141.7 (C-6) ppm. Anal. ($C_{12}H_{16}N_3O_3Br$) C, H, N.

Biological Evaluation. The methods used for measuring the inhibitory effects of the compounds on virus-induced cytopathogenicity[2] and cell proliferation[33] and for evaluating their efficacy in the treatment of herpes virus infections in animal models, i.e., mice infected intraperitoneally[35] or intracutaneously[36] with HSV-1 (KOS), have all been described previously.

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Registry No. **2**, 59967-83-8; **3**, 69975-22-0; **4b**, 95313-01-2; **5a**, 62102-28-7; **5b**, 83967-03-7; **5c**, 95344-18-6; **5d**, 91739-45-6; **5e**, 91661-22-2; **5f**, 91661-25-5; **6**, 95313-02-3; **7b**, 95313-03-4; **7c**, 95313-04-5; methyl acrylate, 96-33-3.

Synthesis and Central Dopaminergic Effects of *N*-(4,6-Dimethyl-2-pyridinyl)benzamides

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N-(4,6-Dimethyl-2-pyridinyl)benzamides **1–24** and the corresponding tertiary derivatives **29–33** were synthesized and studied for possible dopamine-inhibitory properties by testing their effect on motility of naive and reserpinized mice. Unlike the orthopramides, they failed to show any antidopaminergic properties, but some of the secondary derivatives showed instead effects of postsynaptic dopaminergic agonism. The latter compounds were subsequently studied for their effects on apomorphine reversal of reserpine-induced alkinesia and on cerebral HVA levels in rats. Contraversive circling induced by compound **11** in 6-hydroxydopamine-lesioned mice suggests that a direct mechanism was involved.

Benzamide derivatives constitute a class of drugs with diverse pharmacological activities. Some of these molecules now in clinical use have a neuroleptic effect which is somewhat different from that shown by butyrophenones or phenothiazines.[1] In addition to antipsychotic activity, some drugs, such as metoclopramide or sulpiride, have antivomitive[2] and gastric stimulant effects.[3]

It has been shown that some benzamide molecules with a 2-aminopyridine structure exhibit antiinflammatory[4,5] or antiulcerogenic and sedative properties.[6] Our work on the synthesis and antiinflammatory effects of *N*-(4,6-dimethyl-2-pyridinyl)phthalimide derivatives[7] prompted us to synthesize the secondary *N*-(4,6-dimethyl-2-pyridinyl)benzamides **1–24** and the tertiary derivatives **29–33**. Their structural similarity with orthopramides led us to investigate their possible effect on central dopaminergic systems. When these molecules exhibited major effects in tests on the motility of naive or reserpinized mice, additional pharmacological properties were investigated (**1**, **5**, **9**, **11**, and **12**).

Chemistry. The reaction of benzoic acids with amines in the presence of dicyclohexylcarbodiimide constitutes a mild and general procedure for the conversion of 3- and 4-aminopyridines into their benzamides; however, it cannot be used in the case of 2-aminopyridines, even when there is an excess of acid.[8] As acylation of the free amino group in 2-aminopyridine by acid chlorides proceeds readily,[5,6,8] secondary benzamides **1–3** and **9–24** were prepared by this method (Scheme I, method A). No simultaneous hydrogenation of the nitrogen heterocycle was observed when reducing 3- and 4-nitrobenzamides **2** and **3** (method B). Acetylation of the resulting primary amines **4** and **5** with acetyl chloride proceeded without concomitant formation of diamides (method A_1). Salicylamide **8** was obtained by aminolysis of phenyl salicylate (method C).

The normal method of preparing benzamides **29–33** is via N-alkylation of the corresponding secondary benzamides, especially since simultaneous quaternization of heterocyclic nitrogen was a priori excluded in the present case.[9] Nevertheless, methylation trials of benzamide **1**, in the presence of the systems K_2CO_3/acetone, NaH/DMF, CH_3ONa/CH_3OH, and even of KOH/DMSO at 60 °C,[10] were unsuccessful. Although the triflate ion constitutes a more reactive leaving group than the halogen in methyl

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(1) Costall, B.; Naylor, R. J. *Eur. J. Pharmacol.* **1976**, *35*, 161.
(2) Justin-Besancon, L.; Laville, C. *C. R. Seances Soc. Biol. Ses Fil.* **1964**, *158*, 723.
(3) Fontaine, J.; Reuse, J. *Arch. Int. Pharmacodyn.* **1978**, *235*, 51.
(4) Buzas, A.; Canal, F.; Egnell, C.; Freon, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1966**, *262*, 658.
(5) Dorsey, W. S.; Easterly, W. D. *J. Pharm. Sci.* **1971**, *60*, 1723.
(6) Moffett, R. B.; Robert, A.; Skaletsky, L. L. *J. Med. Chem.* **1971**, *14*, 963.
(7) Floc'H, R. Ph.D. Pharmaceutical Sciences, Nantes, 1979.
(8) Moragues, J.; Melone, G.; Villaverde, C. *Quim. Ind. (Madrid)* **1971**, *17*, 104.
(9) Walker, G. N.; Doore, M. A.; Weaver, B. N. *J. Org. Chem.* **1961**, *26*, 2740.
(10) Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.

0022-2623/85/1828-0555$01.50/0