Synthesis and Anti-Hepatitis B Virus Activity of Some 2,3-Dihydroxyprop-1-yl Unnatural Hetaryls

El Sayed H. El Ashry[a)]*, Adel A.-H. Abdel-Rahman[b)], Nagwa Rashed[a)], and Hanaa A. Rasheed[a)]

[a)] Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

[b)] Chemistry Department, Faculty of Science, Menoufia University, Shebin El Koum, Egypt

Key Words: *Tetraseco-nucleosides; inhibition; cytotoxicity; hepatitis B virus*

Summary

The sodium salts of some hetaryls of the quinoxalin-2-ones **2–4**, phthalazine-1,4-dione **5**, phthalazin-1-one **6**, and pyridazin-6-ones **7** and **8** were alkylated with (±) 2,3-*O*-isopropylidene-1-*O*-(4-toluenesulfonyl)glycerol (**1**) to give the respective *tetraseco*-nucleosides **9–15**. Their deisopropylidenation with 70% acetic acid in water gave the corresponding 2,3-dihydroxyprop-1-yl hetaryls **16–22**. Compounds **16–22** showed varying inhibition activity against Hepatitis B virus (HBV) with low to moderate cytotoxicity, where **18** and **21** showed the highest replication inhibition and low cytotoxicity.

Introduction

Hepatitis B virus (HBV) infection has a great degree of prominence due to the wide prevalence of the disease and the lack of an ideal drug to combat the virus, especially in chronic infections which can lead to cirrhosis of the liver and/or hepatocellular carcinoma. In such carriers vaccination is not an effective therapy and alpha interferon has demonstrated some promise[1–6]. Nucleoside analogues and particularly the unnatural L-configuration have emerged as potential anti-HBV agents with more promising pharmacological and toxicological profiles[3,7–13] than their D-counterparts. Thus, 2′-fluoro-5-methyl-β-L-arabino furanosyluracil (B-L-FMAU) is considered as a clinical candidate for treatment of chronic HBV infections[3,6,14], and is undergoing preclinical toxicology studies[15]. The 2′,3′-dideoxy-β-L-cytidine (β-L-ddc) and its 5-fluoro analogue (β-L-FddC) demonstrated equally potent activity against HBV in vitro, having the same ED_{50} value of 0.01 μM. The unusual group of nucleosides such as L-SddC[(–)-BCH-189] in which the 3′-CH_2 group has been replaced by a hetero-atom[7,16–22] exhibits potent anti-HBV and HIV activity in vitro. The compounds are undergoing clinical trials in patients with AIDS and AIDS related complex. The L-like BCH-189 is more potent than the D-like counterpart [7,10,12].

Considerable effort has been devoted to the synthesis of acyclo-nucleoside analogues which possess potent selective antiherpes activity[23,24]. The *S*-enantiomer of 9-(2,3-dihydroxypropyl)adenine[25] (*S*-DHPA) was found to have inhibitory activity towards a number of DNA and RNA viruses. More recently, the phosphonate derivative 9-(3-hydroxy-2(*S*)-phosphonylmethoxypropyl)adenine (*S*-HPMPA) and its analogues have been found to exhibit potent antiviral effects[26]. Since the trend for anti-HBV activity was similar to that for anti-HIV activity[12], and there is a great demand for the development of novel componds with anti-HBV activity and minimal adverse effects on the host, the present work deals with the synthesis and biological activity of the 2,3-dihydroxypropyl derivatives of some hetaryls.

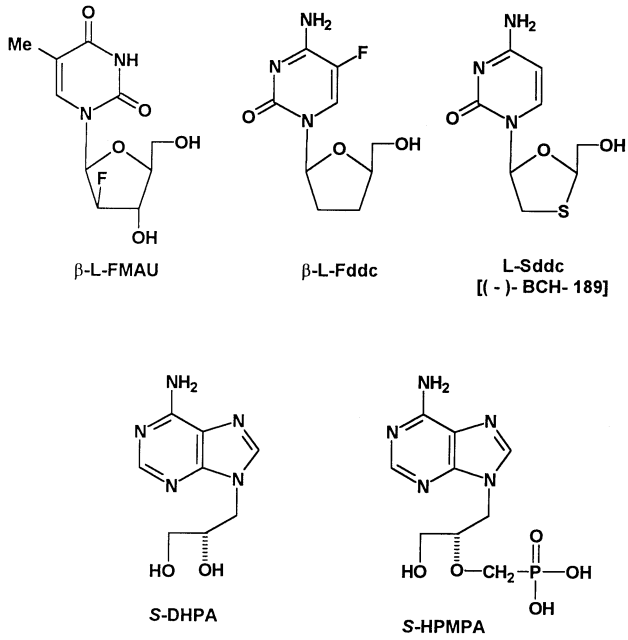


Figure 1

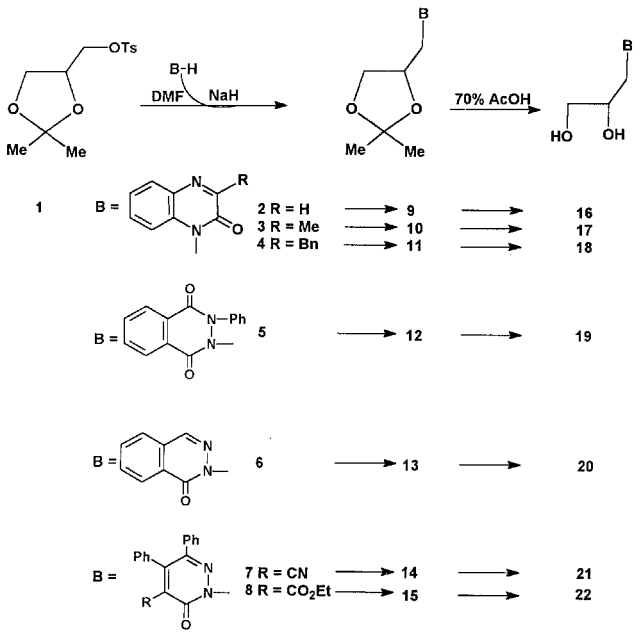
Chemistry

Synthesis of the target nucleosides has been achieved by the nucleophilic displacement of a leaving group on a suitably protected derivative of the propanediol by a suitable hetaryl. Thus, (±)-2,3-*O*-isopropylidene-1-*O*-(4-toluenesulfonyl) glycerol (**1**) was selected as the precursor for their synthesis. It was prepared by 4-toluenesulfonylation of 2,3-*O*-isopropylidene glycerol[27].

The selected bases for this study were of the pyrazine or the pyridazine type and their benzo analogues, which are fragments frequently reported in a wide variety of biologically active compounds. Thus, the conversion of the bases quinoxalinones, phthalazinedione, phthalazinone, and the pyridazinone **2–8** into the respective sodium salts was carried out by heating their solutions in *N*,*N*-dimethylformamide with sodium hydride. Treatment of the aforementioned salts with (±)-2,3-*O*-isopropylidene-1-*O*-(4-toluenesulfonyl)glycerol

 © WILEY-VCH Verlag GmbH, D-69451 Weinheim, 1999 0365-6233/99/0909/0327 $17.50 +.50/0

(**1**) gave the (±)2,3-isopropylidene-dihydroxypropyl derivatives of the quinoxalinones **9–11**, phthalazinedione **12**, phthalazinone **13**, and the pyridazinones **14** and **15** (Scheme 1). Deprotection of the isopropylidene groups was effected with 70% acetic acid in water to give the corresponding (±)-2,3-dihydroxypropyl hetaryls **16–22**, respectively. The isopropylidene derivatives of phthalazinone and some quinoxalinone analogues were not isolated, but converted immediately to the respective 2,3-dihydroxypropyl nucleosides. The structures of the isopropylidene derivatives have been confirmed by analyzing their ^{1}H-NMR spectral data. They showed the presence of two singlets appearing at the high magnetic field in the range 1.26–1.40 and 1.34–1.49 ppm, respectively, corresponding to the two methyl groups of the isopropylidene residue. The difference in their chemical shifts (Δδ) lies in the range 0.08–0.14 ppm, which is in agreement with that required (Δδ > 0.05) for α-terminal isopropylidene derivatives[28]. The higher value of Δδ in such terminal derivatives is due to the interaction of the bulky substituent on the dioxolane ring with only one of the two methyl groups. The deprotected derivatives showed the absence of the signals corresponding to the isopropylidene residue. The presence of signals due to the propyl residue and the hetaryl groups confirmed the successful nucleophilic displacement of the tosyloxy group in **1**.



Scheme 1

Biological Activities

Compounds **16–22** were tested for their activity against Hepatitis B virus (HBV) in Hep G_2 2.2.15 cell. The concentrations for the tested compounds were 10 M. Compounds **18** and **21** showed high inhibition activity (Table 1) and low cytotoxicity. Compounds **17**, **19**, and **22** showed high inhibition activity with moderate cytotoxicity, while compounds **16** and **20** showed moderate viral replication inhibition and low cytotoxicity.

Table 1. Inhibition of HBV replication by 10 μM of selected compounds.

Compd.	% Inhibition			Cytotoxicity
	1 Week	2 Weeks	3 Weeks	
16	30.9	30.3	30.1	7.7
17	80.9	80.3	71.3	13.5
18	87.1	83.9	80.5	5.5
19	81.3	80.0	72.1	14.3
20	33.2	31.1	28.9	8.1
21	81.8	79.8	78.3	5.3
22	78.6	77.7	70.5	16.7

Acknowledgments

The authors thank the DANIDA establishment for support of the biological testing and Professor Dr. R. R. Schmidt for making available some spectral measurements performed at Konstanz University.

Experimental Part

Melting points were determined with a Meltemp apparatus 76-mm immersion thermometer and are uncorrected. TLC was performed on Baker flex silica gel 60 F-254 precoated plates. Column chromatography was performed on Merck silica gel (0.040–0.063). ^{1}H-NMR spectra were recorded on Bruker AC 250 and 200 MHz spectrometers, in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in ppm relative to TMS and described as s (singlet), d (doublet), t(triplet), q (quartet), m (multiplet), or bs (broad singlet). Microanalyses were performed by the unit of Microanalysis, Faculty of Science, Cairo University.

*2,3-O-Isopropylidene-1-O-(4-toluenesulfonyl)glycerol (**1**)*

To a stirred ice-cooled solution of glycerol-1,2-acetonide (7.2 g, 0.05 mol) in pyridine (30 ml), 4-toluenesulfonyl chloride (10.4 g, 0.06 mol) was added portionwise. After standing for 16 h, the solution was diluted with ether (30 ml). The resulting mixture was washed successively with 1 N HCl, water and then saturated aqueous $NaHCO_3$. The ether layer was dried over anhydrous Na_2SO_4 and concentrated to give **1** (13.1 g, 84% yield), ref.[22] mp 40 °C, mp 41 °C.

General Procedure
*(±)-2,3-O-Isopropylidene-2,3-dihydroxyprop-1-yl Hetaryls (**9–15**)*

To a stirred solution of the hetaryls (5.0 mmol) in anhydrous DMF (10 ml) was added NaH (60% dispersed in mineral oil, 0.20 g, 5.0 mmol). After complete evolution of hydrogen, the mixture was heated at 100 °C for 1 h, then **1** (1.43 g, 5.0 mmol) was added. The reaction mixture was stirred for 12 h at 100 °C, cooled to room temperature, and filtered. The solvent was evaporated to dryness under reduced pressure and 10 ml of water was added to the residue and the product was extracted with ether (3 × 20 ml). The ether layer was dried and evaporated under reduced pressure to give a dark brown gum which was purified by column chromatography using 1% MeOH/$CHCl_3$.

*(±)-1-(2,3-O-Isopropylidene-2,3-dihydroxyprop-1-y1) (1H)-Quinoxalin-2-one (**9**)*

Syrup (40% yield). ^{1}H-NMR ($CDCl_3$): δ = 1.26 (s, 3 H, CH_3), 1.34 (s, H, CH_3), 3.84, 4.10 (2 m, 2H, CH_2), 4.27 (m, 1 H, CH), 4.51 (m, 2 H, CH_2), 7.29 (m, 1 H, Ar-H), 7.55 (m, 2 H, Ar-H), 7.85 (d, 1 H, *J* = 9.6 Hz, Ar-H), 8.24 (s, 1 H, Ar-H).

*(±)-1-(2,3-O-Isopropylidene-2,3-dihydroxyprop-1-yl)-3-methyl-(1H)-quinoxalin-2-one (**10**)*

Syrup (45% yield). ^{1}H-NMR ($CDCl_3$): δ = 1.31 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 2.59 (s, 3 H, CH_3), 3.86, 4.13 (2 m, 2 H, CH_2) 4.24 (m, 1 H, CH), 4.54 (m, 2 H, CH_2), 7.33 (m, 1 H, Ar-H), 7.52 (dd, 2H, Ar-H), 7.80 (d, 1 H, *J* = 7.6 Hz, Ar-H).

*(±)-3-(2,3-O-Isopropylidene-2,3-dihydroxyprop-1-yl)-2-phenyl-2,3-dihydrophthalazine-1,4-dione (**12**)*

Syrup (40% yield). ^{1}H-NMR ($CDCl_3$): δ = 1.40 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 3.92 (t, 1 H, *J* = 6.0 Hz, CH_2), 4.16 (t, 1 H, *J* = 6.4 Hz, CH_2), 4.38 (m, 2 H, CH_2), 4.55 (m, 1 H, CH), 7.31 (m, 1 H, Ar-H), 7.45 (m, 2 H, Ar-H), 7.75 (m, 4H, Ar-H), 8.00 (m, 1 H, Ar-H), 8.44 (m, 1 H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ = 25.22 (CH_3), 26.61 (CH_3), 66.28 (CH_2), 67.15 (CH_2), 73.54 (CH), 109.61 (CMe_2), 123.28, 124.19, 125.03, 126.86, 127.40, 128.33, 129.38, 131.97, 132.89, 141.72 (Ar-C), 149.54 (C=O), 158.10 (C=O).

*(±)-5-Cyano-3,4-diphenyl-1-(2,3-O-isopropylidene-2,3-dihydroxyprop-1-yl)(1H)-pyridazin-6-one (**14**)*

Syrup (30% yield). ^{1}H-NMR ($CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 3.95, 4.16 (2 m, 2 H, CH_2), 4.31 (m, 1 H, CH), 4.54 (m, 1 H, CH_2), 7.22 (m, 10 H, Ar-H).

*(±)-5-Carbethoxy-3,4-diphenyl-1-(2,3-O-isopropylidene-2,3-dihydroxyprop-1-yl)-(1H)-pyridazin-6-one (**15**)*

Syrup (38% yield). ^{1}H-NMR ($CDCl_3$): δ = 0.95 (t, 3 H, *J* = 7.1 Hz, CH_3), 1.33 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.95 (m, 2 H, CH_2), 4.11 (m, 2 H, CH_2), 4.28 (m, 1 H, CH), 4.48 (m, 1 H, CH_2), 4.62 (m, 1 H, CH_2), 7.23 (m, 10 H, Ar-H).

General Procedure:
*(±)-2,3-Dihydroxyprop-1-yl Hetaryls (**16–22**)*

The isopropylidenes **9–15** (5.0 mmol) were dissolved in 70% AcOH (5.0 ml). The mixture was heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was coevaporated with H_2O (2 × 3 ml) and ethanol (2 × 3 ml). The residual oil was purified by column chromatography using 3% MeOH/$CHCl_3$.

*(±)-1-(2,3-Dihydroxyprop-1-y1)(1H)-quinoxalin-2-one (**16**)*

Syrup (28% yield). ^{1}H-NMR ($CDCl_3$): δ = 3.68 (m, 3 H, CH_2, OH), 4.19 (m, 3 H, CH, CH_2), 4.45 (brs, 1 H, OH), 7.60 (m, 5 H, Ar-H).– $C_{11}H_{12}N_2O_3$ (220.22) Anal. C,H,N.

*(±)-1-(2,3-Dihydroxyprop-1-y1)-3-methyl-(1H)-quinoxalin-2-one (**17**)*

Syrup (35% yield). ^{1}H-NMR ($CDCl_3$): δ = 2.60 (s, 3 H, CH_3), 3.54 (m, 4 H, CH_2, CH, OH), 4.90 (brs, 1 H, OH), 4.43 (m, 2 H, CH_2), 7.43 (m, 1 H, Ar-H), 7.70 (m, 2 H, Ar-H), 7.80 (d, 1 H, *J* = 8.0 Hz, Ar-H).– $C_{12}H_{14}N_2O_3$(234.25) Anal. C,H,N.

*(±)-3-Benzyl-1-(2,3-dihydroxyprop-1-yl)(1H)-quinoxalin-2-one (**18**)*

Syrup (20% yield). ^{1}H-NMR ($CDCl_3$): δ = 2.42 (s, 2 H, CH_2), 3.62 (m, 3 H, CH_2, OH) 3.94 (m, 2 H, CH_2), 4.32 (brs, 1 H, OH), 4.53 (m, 1 H, CH), 7.28 (m, 5 H, Ar-H), 7.55 (m, 1 H, Ar-H), 7.76 (m, 2 H, Ar-H), 8.02 (m, 1 H, Ar-H).– $C_{18}H_{18}N_2O_3$ (310.34) Anal. C,H,N.

*(±)-3-(2,3-Dihydroxyprop-1-yl)-2-phenyl-2,3-dihydrophthalazine-1,4-dione (**19**)*

Syrup (30% yield). ^{1}H-NMR ($CDCl_3$): δ = 3.71 (m, 4 H, CH_2, 2 OH), 4.11 (m, 1 H, CH), 4.32 (d, 2 H, *J* = 4.0 Hz, CH_2), 7.27 (m, 1 H, Ar-H), 7.39 (t, 2 H, *J* = 8 Hz, Ar-H), 7.66 (m, 4 H, Ar-H), 7.91 (m, 1 H, Ar-H), 8.37 (m, 1 H, Ar-H).– $C_{17}H_{16}N_2O_4$(312.31) Anal. C,H,N.

*(±)-2-(2,3-Dihydroxyprop-1-yl)(2H)-phthalazin-1-one (**20**)*

Syrup (25% yield). ^{1}H-NMR ($CDCl_3$): δ = 3.46 (m, 3 H, OH, CH_2), 4.03 (m, 3 H, CH, CH_2), 4.51 (brs, 1 H, OH), 7.26 (m, 1 H, Ar-H), 7.73 (m, 3 H, Ar-H), 8.34 (m, 1 H, Ar-H).– $C_{11}H_{12}N_2O_3$ (220.22) Anal. C,H,N. .

*(±)-5-Cyano-3,4-diphenyl-1-(2,3-dihydroxyprop-1-yl)(1H)-pyridazin-6-one (**21**)*

Syrup (20% yield). ^{1}H-NMR ($CDCl_3$): δ = 3.68 (m, 4 H, CH_2, 2 OH), 4.33 (m, 2H, CH_2), 4.55 (m, 1 H, CH), 7.26 (m, 10 H, Ar-H).– $C_{20}H_{17}N_3O_3$ (347.36) Anal. C,H,N.

*(±)-5-Carbethoxy-3,4-diphenyl-1-(2,3-dihydroxyprop-1-yl)(1H)-pyridazin-6-one (**22**)*

Syrup (23% yield). ^{1}H-NMR ($CDCl_3$): δ = 0.94 (t, 3 H, *J* = 8.0 Hz, CH_3), 3.69 (m, 2 H, CH_2), 4.07 (m, 4H, CH_2, 2 OH), 4.22 (m, 1 H, CH), 4.45 (m, 2 H, CH_2), 7.11 (m, 5 H, Ar-H), 7.25 (m, 5 H, Ar-H).– $C_{22}H_{22}N_2O_5$ (394.41) Anal. C,H,N.

Biological Activity Studies

Maintenance media (RPMI/Glutamax, 93%; Pencilin + Streptomycin, 1%; Gentamycin, 1%; Fetal/Calf serum, 5% and Geneticin 4 ml/100 ml media) were added to the cell culture (Hep) G_2 2.2.15 together with the tested compounds (concentration = 10 μM). The supernatant media were collected after one, two, and three weeks for the tested compounds and the controls (Hep G_2 2.2.15 cells without added compds). The DNA replication was estimated by PCR (polymerase chain reduction) technique which was carried out in three steps: extraction of DNA from supernatant, amplification of DNA by using thermal cycler and finally detection by DIG-ELISA technique. The percent inhibition was calculated by the relation

$$\% \text{ Inhibition} = \left(\frac{\text{Inhibition of compd}}{\text{Inhibition of control}} - 1\right) \times 100$$

The percentage cytotoxicity could be estimated by the relation between the number of the living and dead cells after three weeks counted by the hemocytometer.

References

[1] S. B. Pai, S.-H. Liu, Y.-L. Zhu, C.K. Chu, Y. C. Cheng, *Antimicrob. Agents Chemother*. **1996**, *40*, 380–386.

[2] J. M. Chirgwin, A. F. Przybla, R. J. Mac Donald, W. J. Rutter, *Biochemistry* **1979**, *18*, 5294.

[3] C. K. Chu, T. W. Ma, K. Shanmuganathan, C. Wang, Y. Xiang, S. B. Pai, G.-Q. Yao, J.-P. Sommadossi, Y.-C. Cheng, *Antimicrob. Agents Chemother*. **1995**, *39*, 979–981.

[4] J. M. Colcacino, S. K. Malcolm, S. R. Jaskunas, *Antimicrob. Agents Chemother*. **1994**, *38*, 1997–2002.

[5] B. A. Larder, B. Chesebro, D. D. Richman, *Antimicrob. Agents Chemother*. **1990**, *34*, 436–441.

[6] W. B. Parker, Y.-C. Cheng, *J. NIH Res.* **1994**, *6*, 57–61.

[7] J. W. Beach, L. S. Jeong, A. J. Alves, D. Pohl, H. O. Kim, C.-N. Chang, S.-L. Doong, R. F. Schinazi, Y.-C. Cheng, C. K. Chu, *J. Org. Chem.* **1992**, *57*, 2217–2219.

[8] L. D. Condreay, R. W. Jansen, T. F. Powdrill, L. C. Johnson, D. W. Selleseth, M. T. Paff, S. M, Daluge, G. R. Painter, P. A. Furman, M. N. Ellis, D. R. Averett, *Antimicrob. Agents Chemother*. **1994**, *38*, 616–619.

[9] S.-L. Doong, C.-H. Tsai, R. F. Shinazi, D. C. Liotta, Y.-C. Cheng, *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 8495–8499.

[10] P. A. Furman, M. Davis, D. C. Liotta, M. Paff, L. W. Frick, D. J. Nelson, R. E. Dornsife, J. A. Warster, L. J. wilson, J. A. Fyfe, J. V. Tuttle, W. H. Miller, L. Condreay, D. R. Averett, R. F. Shinazi, G. R. Painter, *Antimicrob. Agents Chemother*. **1992**, *36*, 2686–2692.

[11] G. Gosselin, R. F. Schinazi, J.-P. Sommadossi, C. Mathe, M.-C. Bergogne, A.-M. Aubertin, A. Kirn and J.-L. Imbach, *Antimicrob. Agents Chemother*. **1994**, *38*, 1292.

[12] H. O. Kim, K. Shanmuganathan, A. J. Alves, L. S. Jeong, J. W. Beach, R. F. Shinazi, C.-N. Chang, Y.-C. Cheng, C. K. Chu, *Tetrahedron Lett.* **1992**, *33*, 6899–6902.

[13] T. S. Lin, M. Z. Luo, S. B. Pai, G. E. Dutschuman, Y.-C. Cheng, *J. Med. Chem.* **1994**, *37*, 798–803.

[14] T. W. Ma, S. B. Pai, Y. L. Zhu, J. S. Lin, K. Shanmuganathan, J. Du, C. G. Wang, H. Kim, M. G. Newton, Y.-C. Cheng, C. K. Chu, *J.Med. Chem.* **1996**, *39*, 2835–2843.

[15] T. W. Ma, J. S. Lin, M. G. Newton, Y.-C. Cheng, C. K. Chu, *J. Med. Chem.* **1997**, *40*, 2750–2754.

[16] C. K. Chu, J. W. Beach, L. S. Jeong, B. G. Choi, F. L. Comer, A. J. Alves, R. F. Schinazi, J. Org. Chem., **1991**, *56*, 6503–6505.

[17] L. S. Jeong, A. J. Alves, S. W. Carrigan, H. O. Kim, J. W. Beach, C. K. Chu, *Tetrahedron Lett.* **1992**, *33*, 595–598.

[18] J. A. V. Coates, N. S. Cammack, H. J. Jenkinson, I. M. Mutton, B. A. Pearson, R. Storer, J. M. Cameron, C. R. Penn, *Antimicrob. Agents Chemother.* **1992**, *36*, 202–205.

[19] D. W. Norbeck, S. Spanton, S. Broder, H. Mitsuya, *Tetrahedron Lett.* **1989**, *30*, 6263–6266.

[20] C. K. Chu, S. K. Ahn, H. O. Kim, J. W. Beach, A. J. Alves, L. S. Jeong, Q. Islam, P. Van Roey, R. F. Schinazi, *Tetrabedron Lett.* **1991**, *32*, 3791–3794.

[21] H. O. Kim, S. K. Ahn, A. J. Alves, J. W. Beach, L. S. Jeong, B. G. Choi, P. Van Roey, R. F. Shinazi, C. K. Chu, *J. Med. Chem.* **1992**, *35*, 1987–1995.

[22] K. L. Grove, X. Guo, S.-H. Liu, Z. Gao, C. K. Chu, Y.-C. Cheng, *Cancer Res.* **1995**, *55*, 3008–3011.

[23] E. S. H. El Ashry, Y. El kilany, *Adv. Heterocycl. Chem.* **1996**, *67*, 391–438; E. S. H. El Ashry, Y. El kilany, *Adv. Heterocycl. Chem.* **1997**, *68*, 1–88; E. S. H. El Ashry, Y. El kilany, *Adv. Heterocycl. Chem.* **1998**, *69*, 129–215; C. K. Chu, S. J. Cutler, *J. Heterocycl. Chem.* **1986**, *23*, 289–319; R. J. Remy, J. A. Secrist, III, *Nucleosides Nucleotides* **1985**, *4*, 411–427.

[24] M. MacCoss, R. L. Tolman, W. T. Ashton, A. F. Wagner, J. Hannah, A. K. Field, J. D. Karkas, J. I. Germershausen, *Chem. Scr.* **1986**, *26*, 113–121; M. Yokoyama, S. Watanabe, *Yuki Gosei Kagaku Kyokaishi* **1989**, *47*, 694–706 [CA **1990**, *11*, 98984C]; J. Balzarini, E. De Clercq, *Pharmacochem. Libr.* **1990**, *14*, 175–194; C. K. Chu, D. C. Baker, *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*, Plenum Press, New York, **1993**; E. De Clercq, *1nt. J. Immunopharmacol.* **1991**, *13*, 91–98.

[25] E. De Clercq, P. F. Torrence, *J. Carbohydr. Nucleosides Nucleotides* **1978**, *5*, 187–224; A. Holy, *Collect. Czech. Chem. Commun.* **1975**, *40*, 187–214; E. De Clercq, A. Holy, *J. Med. Chem.* **1979**, *22*, 510–513.

[26] E. De Clercq, A. Holy, I. Rosenberg, T. Sakuma, J. Balzarini, P. C. Maudgal, *Nature (London)* **1986**, *323*, 464–468; A. Holy, I. Rosenberg, *Collect. Czech. Chem. Commun.* **1987**, *52*, 2775–2791; R. R. Webb II, J. C. Martin, *Tetrahedron Lett.* **1987**, *28*, 4963–4964; L. Naesens, J. Balzarini, E. De Clercq, *Rev. Med. Virol.*, **1994**, *4*, 147–159; E. De Clercq, T. Sakuma, M. Baba, R. Pauwels, J. Balzarini, I. Rosenberg, A. Holy, *Antiviral Res.* **1987**, *8*, 261–272.

[27] J. J. Baldwin, A. W. Raab, K. Mensler, B. H. Arison, D. E. Mc Clure, *J. Org. Chem.* **1978**, *43*, 4876–4878.

[28] E. S. H. El Ashry, *Eur. Carbohydr. Symp.* Darmstadt Germany **1987**, C-35; E. S. H. El Ashry, *J. Chem. Soc. Chem. Commun.* **1986**, 1024–1026.

Received: April 15, 1999 [FP385]

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 1999 – Printed in the Federal Republic of Germany

Alle Rechte, insbesondere die der Übersetzung in fremde Sprachen, vorbehalten. Kein Teil dieser Zeitschrift darf ohne schriftliche Genehmigung des Verlages in irgendeiner Form – durch Fotokopie, Mikrofilm oder irgendein anderes Verfahren – reproduziert oder in eine von Maschinen, insbesondere von Datenverarbeitungsmaschinen verwendbare Sprache übertragen oder übersetzt werden.– All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers.– Von einzelnen Beiträgen oder Teilen von ihnen dürfen nur einzelne Vervielfältigungsstücke für den persönlichen und sonstigen eigenen Gebrauch hergestellt werden. Die Weitergabe von Vervielfältigungen, gleichgültig zu welchem Zweck sie hergestellt werden, ist eine Urheberrechtsverletzung. Der Inhalt dieses Heftes wurde sorgfältig erarbeitet. Dennoch übernehmen Autoren, Herausgeber, Redaktion und Verlag für die Richtigkeit von Angaben, Hinweisen und Ratschlägen sowie für eventuelle Druckfehler keine Haftung. This journal was carefully produced in all its parts. Nevertheless, authors, editors and publishers do not warrant the information contained therein to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.– Die Wiedergabe von Gerbrauchsnamen, Handelsnamen,Warenbezeichnungen u. dgl. in dieser Zeitschrift berechtigt nicht zu der Annahme, daß solche Namen ohne weiteres von jedermann benutzt werden dürfen. Es handelt sich häufig um gesetzlich eingetragene Warenzeichen, auch wenn sie in dieser Zeitschrift nicht als solche gekennzeichnet sind. Druck und Buchbinder: Druck Partner Rübelmann GmbH, D-69502 Hemsbach.– Unverlangt zur Rezension eingehende Bücher werden nicht zurückgesandt.

For USA and Canada: Archiv der Pharmazie (ISSN 0365-6233) is published monthly.– Printed in the Federal Republic of Germany.
US Postmaster: Periodicals postage paid at Jamaica, NY 11431. Air freight and mailing in the USA by Publications Expediting Services Inc., 200 Meacham Ave., Elmont NY 11003. Send address changes to: "Archiv der Pharmazie", c/o Publications Expediting Services Inc., 200 Meacham Ave., Elmont NY 11003
Valid for users in the USA: The appearance of the code at the bottom of the first page of an article in this journal (serial) indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that copier pay the stated per copy fee throught the Copyright Clearance Center, Inc., for copying beyond that permitted by Sections 107 for 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective work, or for resale. For copying from back volumes of this journal see »Permissions to Photo-Copy: Publisher's Fee List« of the CCC.

Printed on chlorine- and acid-free paper/Gedruckt auf säurefreiem und chlorfrei gebleichtem Papier