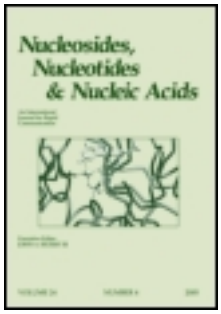


Nucleosides and Nucleotides
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn19

Simplified Analogues of Acyclonucleosides. Synthesis of 6-[N-Alkyl-N-(4-hydroxybutyl)amino]pyrimidine Derivatives

M. Botta [a] , R. Saladino [b] , M. Anzini [a] & F. Corelli [a]

[a] Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Banchi di Sotto 55, 53100, Siena, Italy

[b] Dipartimento di Agrobiologià e Agrochimica, Università della Tuscia, 01100, Viterbo, Italy

Version of record first published: 24 Sep 2006.

To cite this article: M. Botta , R. Saladino , M. Anzini & F. Corelli (1994): Simplified Analogues of Acyclonucleosides. Synthesis of 6-[N-Alkyl-N-(4-hydroxybutyl)amino]pyrimidine Derivatives, Nucleosides and Nucleotides, 13:8, 1769-1777

To link to this article: http://dx.doi.org/10.1080/15257779408009479

NUCLEOSIDES & NUCLEOTIDES, 13(8), 1769-1777 (1994)

SIMPLIFIED ANALOGUES OF ACYCLONUCLEOSIDES. SYNTHESIS OF 6-[N-ALKYL-N-(4-HYDROXYBUTYL)AMINO]PYRIMIDINE DERIVATIVES§

M. Botta, R. Saladino,# M. Anzini and F. Corelli**

Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Banchi di Sotto 55, 53100 Siena, Italy and #Dipartimento di Agrobiologia e Agrochimica, Università della Tuscia, 01100 Viterbo, Italy.

Abstract. *The synthesis of some 6-alkylaminopyrimidine derivatives bearing a 4-hydroxybutyl chain as sugar mimic is described. These new compounds can be regarded as simplified, ring-opened analogues of purine acyclonucleosides.*

The finding that a retrovirus, known as the human immunodeficiency virus (HIV), is the causative agent of the acquired immune deficiency syndrome (AIDS) has been spurring a great deal of searches for new selective anti-HIV agents,[1] leading in particular to the discovery of a myriad of HIV reverse transcriptase (RT) inhibitors. These include a wide array of nucleoside and non-nucleoside compounds, antisense oligonucleotides, and both small and large anionic molecules.[2]

The most well-known and intensively studied HIV RT inhibitors are the nucleoside derivatives.[3] Three representatives of this group, 3'-azido-2',3'-dideoxythymidine (AZT), 2',3'-dideoxyinosine (DDI) and 2',3'-dideoxycytidine (DDC) are the only federally licensed antivirals in U.S.A. for the treatment of AIDS (FIG. 1). However, the demonstrated clinical toxicities of these agents and other members of this class, the emergence of resistance to these agents, and their inability to cure AIDS have propelled the search for different classes of RT inhibitors. Unique among these are 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) and its analogues.[4] Although structurally related to the nucleoside antivirals, HEPT agents exert their anti-HIV-1 activity by interacting with HIV-1 RT at a site that is distinct from the binding site of the anti-HIV-1 nucleosides.[5] In addition, it is remarkable that the RT inhibitory activity of HEPT analogues is associated to the presence of substituents in positions 5 and 6 of the uracil,

§Dedicated to Professor Marino Artico on the occasion of his 60th birthday.

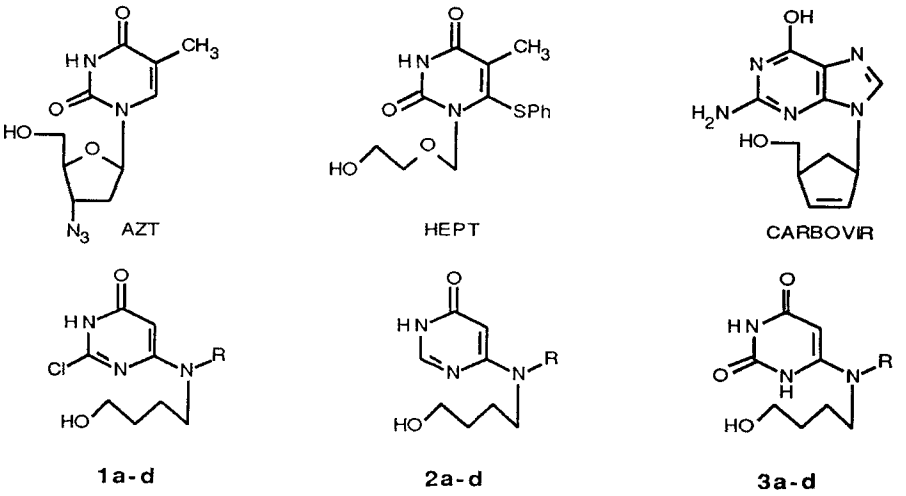


FIG. 1

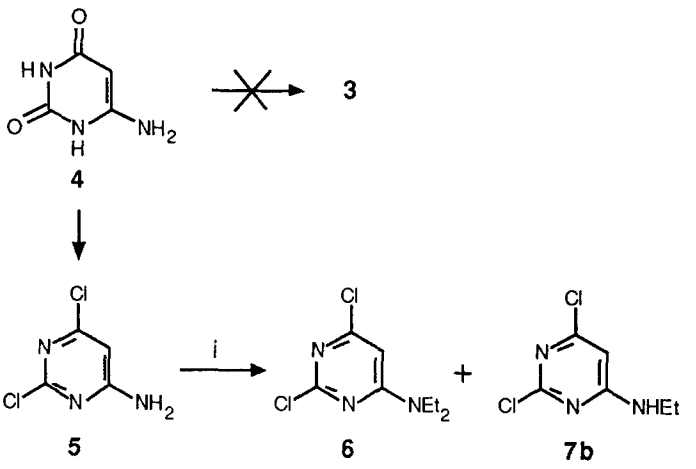
while in position 1 they can also bear chains unable to undergo phosphorylation by thymidine kinase.

Apart from HEPT compounds, little information is available concerning the antiviral properties of 6-substituted pyrimidine derivatives, presumably because the preparation of such compounds is not a trivial task.[6,7]

For several years we have been engaged in the synthesis and biological evaluation of new, usually 6-substituted, pyrimidine derivatives.[8] Here we wish to report the synthesis of some 6-alkylaminopyrimidine derivatives of general formulas **1**, **2**, and **3**, bearing a 4-hydroxybutyl chain as sugar mimic, which can be regarded as simplified, conformationally less rigid analogs of purine acyclonucleosides.

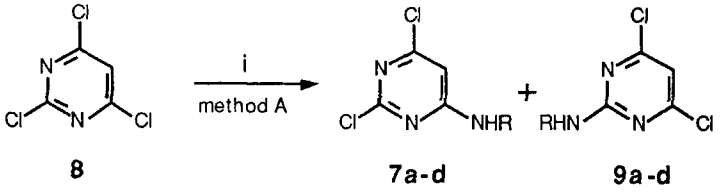
Early attempts to synthesize compounds **3** by direct alkylation of commercially available 6-aminouracil **4** failed, probably because of the poor nucleophilic reactivity and the scarce solubility in the most common solvents of this substrate (Scheme 1). Subsequently we transformed **4** into the dichloro derivative **5**,[9] which was subjected to nitrogen alkylation with ethyl iodide (NaH, DMF) to afford a mixture of compounds **6** and **7b** in the ratio of 2:1. Attempts to obtain the monoalkylated compound **7b** as the main reaction product under different experimental conditions were unsuccessful.

Next we chose as starting material 2,4,6-trichloropyrimidine (**8**) since a patent report claimed the formation of **7** as a single reaction product when **8** was treated with



[a]Key: (i) NaH, EtI, DMF

SCHEME 1[a]

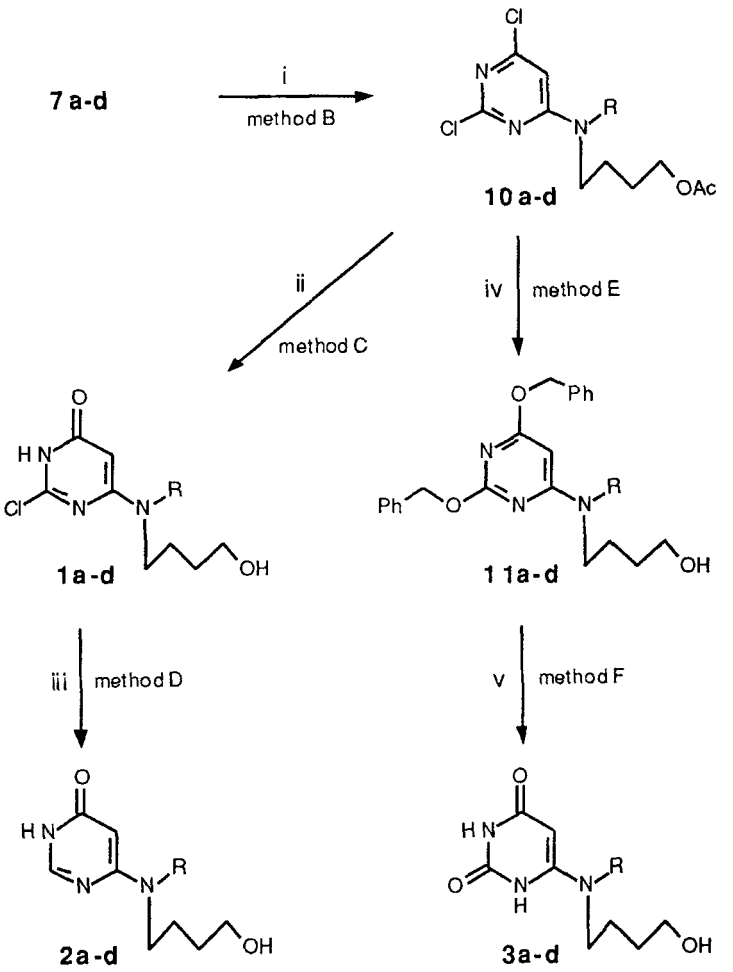


R = Me (a), Et (b), n-Pr (c), n-Bu (d)

[a]Key: (i) RNH_2, EtOH

SCHEME 2[a]

alkyl amines[10] (Scheme 2). In contrast to this result, we always obtained in good yield a mixture of isomers **7** and **9** in about 2.5:1 ratio. The isomers could be separated by column chromatography on silica gel. The first eluted compound **9** showed a ^{1}H-NMR spectrum very similar to that of the isomer **7**, the sole difference being the multiplicity of the signal relative to the protons on the side chain carbon atom linked to the NH group. In the case of **9b-d**, in fact, this signal appears as a very broad singlet, whereas in compounds **7b-d** it appears as a well defined quartet. The structure of **9b** was also chemically confirmed by simply alkylating 2-amino-4,6-dichloropyrimidine with ethyl iodide.



R = Me (a), Et (b), n-Pr (c), n-Bu (d)

[a] (i) $AcO(CH_2)_4I$, NaH, DMF; (ii) 2N HCl, AcOH; (iii) Raney-Ni, H_2O; (iv) BnOH, NaH, dioxane; (v) HCO_2NH_4, Pd/C, MeOH

SCHEME 3[a]

Treatment of derivatives **7a-d** (Scheme 3) with 4-acetoxybutyl iodide (NaH, DMF) gave the intermediates **10a-d**, which were subjected to hydrolysis with 2N hydrochloric acid in refluxing acetic acid to afford the chloropyrimidinones **1a-d**. These compounds could not be transformed into the corresponding uracil derivatives **3a-d** either in acidic or

basic conditions, but were easily dehalogenated to **2a-d** by the action of Raney-Ni in water (120°, 2 h). Compounds **3a-d** were prepared in very good yield via transfer catalytic hydrogenation (ammonium formate, Pd-C) of **11a-d**, that in turn were obtained by substitution of the chlorine atoms of **10a-d** with the sodium salt of benzylic alcohol in refluxing 1,4-dioxane. Under these conditions derivatives **10a-d** underwent concurrent deacetylation.

Chemical and physical data for the new compounds **1-3**, **7**, and **9-11** are reported in TABLE 1.

Compounds **1-3a-d** were tested against conventional DNA (Herpes Simplex type 1, Vaccinia, Polio type 1, Coxsackie B1) and RNA (Vesicular Stomatitis) viruses in plaque-reduction assays in Vero cells according to the procedure of Collins and Bauer,[11] but no activity was found at compound concentration less than 100 μM. Nevertheless, the majority of the test compounds showed cytotoxic effects only at a concentration higher than 1,000 μM. It is interesting to note that derivative **2a** exhibited a selective inhibition of HIV-1 replication in vitro with an ED_{50} of 25 μM.[12]

EXPERIMENTAL

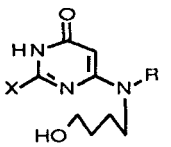
Chemistry. Melting points were determined with a Gallenkamp apparatus and are uncorrected. IR spectra (neat or KBr) were taken on a Perkin-Elmer 398 spectrophotometer. ^{1}H-NMR spectra were recorded at 200 MHz on a Varian XL 200 instrument using tetramethylsilane as the internal standard; chemical shifts are recorded in parts per million (ppm). Mass spectra were measured on a VG 70/250S spectrometer with an electron beam of 70 eV. Column chromatography was carried out on Merck silica gel 60. TLC was performed on silica gel (precoated silica gel plate 60 F_{254}, Merck). Elemental analyses (within ±0.4% of the calculated values) were performed on a Perkin-Elmer 240-C elemental analyzer. Anhydrous sodium sulfate was used to dry organic solutions.

Synthesis. Specific examples presented below illustrate general synthetic methods A-F. In general, samples prepared for physical and biological studies were dried in high vacuum over P_2O_5 for 20 h at temperatures ranging from 25 to 110°, depending on the sample melting point.

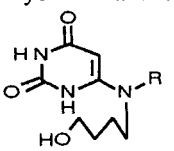
2,6-Dichloro-4-diethylaminopyrimidine 6 and 2,6-dichloro-4-ethylaminopyrimidine 7b.

To a solution of 4-amino-2,6-dichloropyrimidine (1.00 g, 6 mmol) in dry N,N-dimethylformamide (40 ml) 97% sodium hydride (0.26 g, 6.6 mmol) was added. When

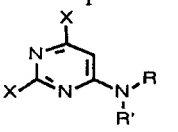
TABLE 1. Chemical and Physical Data for the New Compounds.



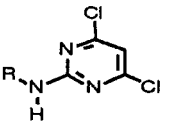
1, 2



3



7, 10, 11



9

Compd	R	R'	X	% yield	mp, °C	formula	MS *m/z* (M^+)
1a	Me	-	Cl	65	oil	$C_9H_{14}ClN_3O_2$	231
1b	Et	-	Cl	50	109-11	$C_{10}H_{16}ClN_3O_2$	245
1c	*n*-Pr	-	Cl	62	151-3	$C_{11}H_{18}ClN_3O_2$	259
1d	*n*-Bu	-	Cl	60	oil	$C_{12}H_{20}ClN_3O_2$	273
2a	Me	-	H	85	oil	$C_9H_{15}N_3O_2$	197
2b	Et	-	H	89	oil	$C_{10}H_{17}N_3O_2$	211
2c	*n*-Pr	-	H	91	oil	$C_{11}H_{19}N_3O_2$	225
2d	*n*-Bu	-	H	86	oil	$C_{12}H_{21}N_3O_2$	239
3a	Me	-	-	93	184-6	$C_9H_{15}N_3O_3$	213
3b	Et	-	-	95	162-4	$C_{10}H_{17}N_3O_3$	227
3c	*n*-Pr	-	-	98	138-40	$C_{11}H_{19}N_3O_3$	241
3d	*n*-Bu	-	-	94	92-4	$C_{12}H_{21}N_3O_3$	255
7a	Me	H	Cl	60	175-7	$C_5H_5Cl_2N_3$	177
7b	Et	H	Cl	68	80-3	$C_6H_7Cl_2N_3$	191
7c	*n*-Pr	H	Cl	70	68-70	$C_7H_9Cl_2N_3$	205
7d	*n*-Bu	H	Cl	64	40-42	$C_8H_{11}Cl_2N_3$	219
9a	Me	-	-	25	85-7	$C_5H_5Cl_2N_3$	177
9b	Et	-	-	28	65-7	$C_6H_7Cl_2N_3$	191
9c	*n*-Pr	-	-	27	38-40	$C_7H_9Cl_2N_3$	205
9d	*n*-Bu	-	-	26	oil	$C_8H_{11}Cl_2N_3$	219
10a	Me	$(CH_2)_4OAc$	Cl	87	oil	$C_{11}H_{15}Cl_2N_3O_2$	291
10b	Et	$(CH_2)_4OAc$	Cl	77	oil	$C_{12}H_{17}Cl_2N_3O_2$	305
10c	*n*-Pr	$(CH_2)_4OAc$	Cl	82	oil	$C_{13}H_{19}Cl_2N_3O_2$	319
10d	*n*-Bu	$(CH_2)_4OAc$	Cl	75	oil	$C_{14}H_{21}Cl_2N_3O_2$	333
11a	Me	$(CH_2)_4OH$	OBn	42	oil	$C_{23}H_{27}N_3O_3$	393
11b	Et	$(CH_2)_4OH$	OBn	35	oil	$C_{24}H_{29}N_3O_3$	407
11c	*n*-Pr	$(CH_2)_4OH$	OBn	53	oil	$C_{25}H_{31}N_3O_3$	421
11d	*n*-Bu	$(CH_2)_4OH$	OBn	62	oil	$C_{26}H_{33}N_3O_3$	435

gas evolution ceased, ethyl iodide (0.5 ml, 6 mmol) was rapidly added to the reaction mixture. After stirring at room temperature for 20 min, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated.The residue was treated with chloroform-ethyl acetate (20:1) and filtered. The clear solution was applied to the top of a silica gel column. Elution with the same solvent afforded **6** (0.50 g, 38%) and subsequently **7b** (0.31g, 26%).

Method A Example. 4,6-Dichloro-2-propylaminopyrimidine 9c and 2,6-dichloro-4-propylaminopyrimidine 7c.

A solution of 2,4,6-trichloropyrimidine (3.66 g, 20 mmol) and propylamine (1.48 g, 25 mmol) in dry ethanol (30 ml) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was redissolved in dichloromethane. The solution was washed with saturated sodium carbonate solution, then with brine, and dried. After evaporation of the solvent, the residue was purified by column chromatography (chloroform as eluent) to give **9c** (1.11 g, 27%); ^{1}H-NMR ($CDCl_3$): δ 0.99 (t, 3H); 1.62 (m, 2H); 3.35 (m, 2H); 5.65 (br s, 1H); 6.56 (s, 1H). Further elution with chloroform-ethyl acetate (20:1) afforded **7c** (2.88 g, 70%); ^{1}H-NMR ($CDCl_3$): δ 1.01 (t, 3H); 1.62 (m, 2H); 3.25 (q, 2H); 5.85 (br s, 1H); 6.25 (s, 1H).

Method B Example. 4-[N-(Acetoxybutyl)-N-methylamino]-2,6-dichloropyrimidine 10a.

To a mixture of 97% sodium hydride (0.29 g, 12 mmol) and **7a** (1.78 g, 10 mmol) in dry N,N-dimethylformamide (50 ml) a solution of 85% 4-iodobutyl acetate (2.85 g, 10 mmol) in the same solvent (5 ml) was added dropwise. After stirring at room temperature for 1 h, the mixture was diluted with water and ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue was chromatographed (dichloromethane as eluent) to give **10a** (2.58 g, 87%); ^{1}H-NMR ($CDCl_3$): δ 1.65 (m, 4H); 2.04 (s, 3H); 3.05 (m, 2H); 3.65 (br m, 3H); 4.25 (m, 2H); 6.30 (s, 1H).

Method C Example. 2-Chloro-6-[N-ethyl-N-(4-hydroxybutyl)amino]-4(3H)-pyrimidinone 1b.

A solution of **10b** (0.31 g, 1 mmol), 2N hydrochloric acid (2 ml), and glacial acetic acid (2 ml) was stirred at 120° for 20 h. The mixture was concentrated, diluted with water and neutralized with 25% ammonia solution. Water was removed and the residue was

purified by TLC (chloroform-methanol 7:1) to afford pure **1b** (0.12 g, 50%); ^{1}H-NMR (DMSO-d_6): δ 1.05 (t, 3H); 1.45 (m, 4H); 3.45 (m, 6H); 6.09 (s, 1H); 8.30 (br s, 1H).

Method D Example. 6-[N-Ethyl-N-(4-hydroxybutyl)amino]-4(3H)-pyrimidinone 2b.

A mixture of **1b** (0.25 g, 1 mmol), water (10 ml) and one drop of methanol was treated with Raney-Ni at 120° for 2 h. The mixture was filtered and evaporated to give pure **2b** (0.19 g, 89%); ^{1}H-NMR (CD_3OD): δ 1.50 (m, 4H); 3.00 (s, 3H); 3.30-4.10 (m, 7H); 5.80 (d, 1H); 7.45 (d, 1H). MS *m/z* 211 (M^+).

Method E Example. 2,6-Dibenzyloxy-4-[N-(hydroxybutyl)-N-methylamino]pyrimidine 11a.

A mixture of **10a** (0.29 g, 1 mmol), benzyl alcohol (0.97 g, 9 mmol), 97% sodium hydride (0.16 g, 6.5 mmol), and dry 1,4-dioxane (10 ml) was refluxed for 3 h. After cooling, the reaction was quenched by adding water and ethyl acetate. The organic layer was washed with brine, dried, and evaporated. The residue was purified by column chromatography (hexanes-ethyl acetate 9:1 to 3:2) to give **11a** (0.16 g, 42%); ^{1}H-NMR ($CDCl_3$): δ 1.60 (m, 4H); 2.95 (s, 3H); 3.45 (m, 2H); 3.65 (m, 2H); 5.35-5.45 (m, 4H), 7.30 (m, 10H).

Method F Example. 6-[N-Butyl-N-(4-hydroxybutyl)amino]uracil 3d.

To a solution of **11d** (0.87 g, 2 mmol) in dry methanol (10 ml) ammonium formate (1.26 g, 20 mmol) and 10% palladium on charcoal (0.25 g) were added. After stirring for 3 h at reflux temperature the mixture was filtered and the solution was evaporated to afford pure **3d** (0.48 g, 94%); ^{1}H-NMR (CD_3OD): δ 0.95 (t, 3H); 1.28 (m, 2H); 1.65 (m, 6H); 3.30 (m, 4H); 3.60 (t, 2H).

Acknowledgements. We wish to thank Italian MURST and Mediolanum Farmaceutici for financial support.

REFERENCES

1. De Clercq, E. *Adv. Drug Res.* **1988**, *17*, 1.
2. Mohan, P. *Pharm. Res.* **1992**, *9*, 703.

3. De Clercq, E.; Van Aerschot, A.; Herdewijn, P.; Baba, M.; Pauwels, R.; Balzarini, J. *Nucleosides Nucleotides* **1989**, *8*, 659.
4. Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Nitta, I.; Baba, M.; Shigeta, S.; Walker, R.T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem.* **1992**, *35*, 4713 and references cited therein.
5. Baba, M.; De Clercq, E.; Tanaka, H.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Umezu, K.; Nakashima, H.; Mori, S.; Shigeta, S.; Walker, R.T.; Miyasaka, T. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2356.
6. Botta, M.; Cavalieri, M.; Ceci, D.; De Angelis, F.; Finizia, G.; Nicoletti, R. *Tetrahedron* **1984**, *40*, 3313.
7. Tanaka, H.; Baba, M.; Hayakawa, H.; Sakamaki, T.; Miyasaka, T.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Shigeta, S.; Walker, R.T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1991**, *34*, 349.
8. Botta, M.; Saladino, R.; Nicoletti, R. *Heterocycles* **1992**, *34*, 729 and references cited therein.
9. Bretschneider, H.; Kloetzer, W.; Spiteller, G. *Monatsh. Chem.* **1961**, *92*, 128.
10. Schneider, R. Ger. Offen. 2,006,145, **1970** (Chem. Abstr. **74**:22877w).
11. Collins, P.; Bauer, D.J. *N.Y. Acad. Sci.* **1977**, *284*, 49.
12. Biological studies were performed by Professor Paolo La Colla and coworkers, University of Cagliari, Italy, and will be published elsewhere.

Received 11/8/93
Accepted 2/15/94