SYNTHESIS OF POLYMETHYLENE CHAIN-BRIDGED 6-SUBSTITUTED 8-AZAPURINES AND RELATED COMPOUNDS*

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Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

The synthesis of a series of polymethylene chain-bridged 8-azapurines as potential DNA intercalating agents is described. N,N′-Bis(5-amino-6-chloro-4-pyrimidyl)-1,3-diaminopropane (*III*), N,N′-bis(5-amino-6-chloro-4-pyrimidyl)-1,8-diaminooctane (*IV*), and N,N′-bis(5-amino-6-chloro-4-pyrimidyl)-1,12-diaminododecane (*V*) were synthesized from 5-amino-4,6-dichloropyrimidine (*I*) and 1,3-diaminopropane (*II*, $n = 3$), 1,8-diaminooctane (*II*, $n = 8$), and 1,12-diaminododecane (*II*, $n = 12$), respectively, as the starting materials. 1,3-Bis(6-chloro-9-purinyl)propane (*VI*), 1,8-bis(6-chloro-9-purinyl)octane (*VII*), and 1,12-bis(6-chloro-9-purinyl)dodecane (*VIII*) were prepared by acid-catalyzed reaction of the corresponding pyrimidines *III*—*V* with triethyl orthoformate in N,N-dimethylacetamide. The polymethylene chain-bridged 6-hydroxy-8-azapurines *XII*—*XIV* were obtained via diazotization of the corresponding pyrimidines. The spectral data and other physical properties of the new compounds have been determined.

Because of the established biological activity of compounds such as bis(9-purinyl)-ethane and the ethylenediamine derivatives[1-4], and within the framework of our past and present involvement with systematic studies of new biologically active heterocyclic compounds[5-14], we have become interested in the synthesis of bis-purinyl and the corresponding bis-8-azapurinyl derivatives bridged by polymethylene chains of different length. This represents a follow-up publication on our recent work describing the synthesis of similar compounds bridged by conformationally restricted diphenyl tethers[13].

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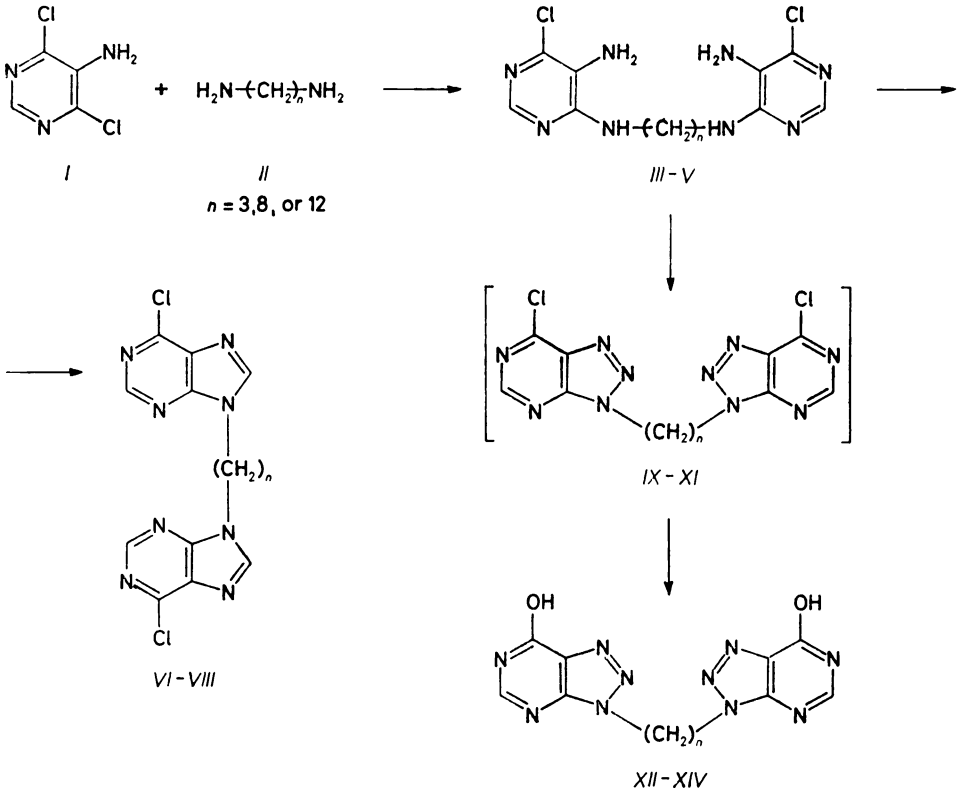
With this goal in mind, the N,N'-bis(4-chloro-5-amino-6-pyrimidyl)-1,3-diaminopropane (*III*), N,N'-bis(4-chloro-5-amino-6-pyrimidyl)-1,8-diaminooctane (*IV*), and N,N'-bis(4-chloro-5-amino-6-pyrimidyl)-1,12-diaminododecane (*V*) were prepared by condensation of 4,6-dichloro-5-aminopyrimidine (*I*) with 1,3-diaminopropane (*II*, $n = 3$), 1,8-diaminooctane (*II*, $n = 8$), and 1,12-diaminododecane (*II*, $n = 12$) in refluxing 1-butanol in the presence of triethylamine by a previously described method[15-17]. The 1,3-bis(6-chloro-9-purinyl)propane (*VI*), 1,8-bis-(6-chloro-9-purinyl)octane (*VII*), and 1,12-bis(6-chloro-9-purinyl)dodecane (*VIII*) were prepared by acid-catalyzed reaction of *III* – *V* with triethyl orthoformate in N,N-dimethylacetamide[15,18,19]. The 1,3-bis(6-hydroxy-8-aza-9-purinyl)propane (*XII*), 1,8-bis(6-hydroxy-8-aza-9-purinyl)octane (*XIII*), and 1,12-bis(6-hydroxy-8-aza-9-purinyl)-dodecane (*XIV*) were obtained through diazotization of *III* – *V*, respectively, with sodium nitrite in aqueous acetic acid. Our attempts to obtain the intermediate



In formulae *III*, *VI*, *IX*, *XII*: $n = 3$; *IV*, *VII*, *X*, *XIII*: $n = 8$; *V*, *VIII*, *XI*, *XIV*: $n = 12$

SCHEME 1

1,3-bis(6-chloro-8-aza-9-purinyl)propane (*IX*), 1,8-bis(6-chloro-8-aza-9-purinyl)octane (*X*), and 1,12-bis(6-chloro-8-aza-9-purinyl)dodecane (*XI*) were unsuccessful when using the common method for the synthesis of 8-azapurines[20,21], even when the reaction had been carried out in aqueous acetic acid as previously described in the successful preparation of 6-chloro-8-azapurine derivatives[22,23]. Instead of the *IX*–*XI*, only 1,3-bis(6-hydroxy-8-aza-9-purinyl)propane (*XII*), 1,8-bis(6-hydroxy-8-aza-9-purinyl)octane (*XIII*), and 1,12-bis(6-hydroxy-8-aza-9-purinyl)dodecane (*XIV*) could be isolated, as evidenced by the UV spectrum, the strong carbonyl absorption band in the IR spectrum, and elemental analysis. The 6-chloro substituent in the 8-azapurinyl ring undergoes nucleophilic displacement much more easily than the corresponding 6-substituent in the purine ring, as described before on several occasions in papers devoted to the preparation of various 8-azapurine derivatives[20–23]. The synthetic steps are shown in Scheme 1.

The structures of these compounds were established on the basis of their analytical and spectral data. For example, a comparison among the three series of synthesized compounds can be made on the basis of IR spectra. The primary and secondary amino groups in compounds *III*–*V* can be identified by the characteristic N—H bond stretching absorptions in the 3 300–3 500 cm^{-1} and 1 660 cm^{-1} regions of the IR spectra. The IR spectra for the compounds *VI*–*VIII* and *XII*–*XIV* follow the expected pattern and no primary and secondary amine absorptions can be seen. In addition, the IR spectra demonstrate that hydroxy groups have replaced the chlorine groups in compounds *XII*–*XIV*, as indicated by the broad hydroxy band at 3 400 cm^{-1} and a strong carbonyl group absorption at 1 700 cm^{-1}. The ^1H NMR spectra of the synthesized compounds show all the peaks corresponding to those expected for the proposed structures.

It is anticipated that the new compounds *III*–*V*, *VI*–*VIII*, and *XII*–*XIV* can be potential bis-intercalating agents.

EXPERIMENTAL

The melting points were determined in capillary tubes heated in a Thomas–Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded in hexadeuteriodimethyl sulfoxide on Varian EM-360 (60 MHz) and IBM NR 200 AF (200 MHz) spectrometers using tetramethylsilane as the internal standard. The chemical shifts are expressed in the δ-scale (ppm) and coupling constants (J) in Hz. UV spectra were obtained in dimethyl sulfoxide on a Perkin–Elmer Lambda 4C spectrophotometer, with a Perkin–Elmer 7700 professional computer (absorption maxima are given in nm). IR spectra were measured in pressed potassium bromide disks on a Perkin–Elmer 580B spectrophotometer with a Perkin–Elmer data station ($\tilde{\nu}$, cm^{-1}; intensity of absorption, s strong, m medium, w weak). The purity of all compounds was checked by thin-layer chromatography (TLC) on silica gel 60 F-254 precoated plates and the spots were located in the UV light or by iodine vapor. Elemental analyses were performed by Desert Analytics, Tucson, AZ. All solvents used were reagent grade except the dimethyl sulfoxide used for spectroscopic measurements (spectrophotometric grade).

N,N′-Bis(4-chloro-5-amino-6-pyrimidyl)-1,3-diaminopropane (*III*)

A mixture of 4,6-dichloro-5-aminopyrimidine (1·1 g, 6·7 mmol), 1,3-diaminopropane (0·24 g, 3·2 mmol), and freshly distilled triethylamine (0·73 g, 7·2 mmol) in 1-butanol (10 ml) was refluxed with stirring for 20 h. The reaction mixture containing a solid material was concentrated on a rotary evaporator and allowed to crystallize at 5°C. The light yellow solid was filtered off and crystallized from ethanol and water (4 : 1). Then it was dried under reduced pressure to give *III* (0·3 g, 25%), m.p. 151—152°C. ^{1}H NMR spectrum: 3·5—3·8 (m, 6 H, $(CH_2)_3$); 5·3—5·6 (m, 4 H, 2 NH_2); 7·25—7·55 (m, 2 H, 2 NH); 8·25 (s, 2 H, 2 Het-H). IR spectrum: 3 420 (m, NH), 3 240 (s, NH_2), 3 030—2 930 (s—m), 1 660 (s, NH_2), 1 590 (s), 1 490 (m), 1 440 (s), 1 370 (s), 1 240 (m), 1 120 (m), 1 080 (m), 910 (m), 850 (m), 770 (m). UV spectrum λ_{max} (log ε): 301·5 (4·17), 269 (4·15). For $C_{11}H_{14}Cl_2N_8.2\,H_2O$ (365·2) calculated: 36·18% C, 4·97% H, 30·68% N; found: 35·93% C, 4·55% H, 30·28% N.

N,N′-Bis(4-chloro-5-amino-6-pyrimidyl)-1,8-diaminooctane (*IV*)

A mixture of 4,6-dichloro-5-aminopyrimidine (1·1 g, 6·7 mmol), 1,8-diaminooctane (0·46 g, 3·2 mmol), and freshly distilled triethylamine (0·73 g, 7·2 mmol) in 1-butanol (15 ml) was refluxed with stirring for 24 h. Then the mixture was concentrated on a rotary evaporator at 85°C. The remaining yellow oil solidified when stored at 5°C. The light yellow solid was collected by filtration, washed with anhydrous ether, crystallized from ethanol and water (5 : 1), and dried under reduced pressure to give *IV* (0·47 g, 35%), m.p. 168—170°C. ^{1}H NMR spectrum: 0·9—1·8 (m, 12 H, $(CH_2)_6$); 3·2—3·6 (m, 4 H, 2 × CH_2N); 5·05 (s, 4 H, 2 × NH_2); 6·6—6·9 (m, 2 H, 2 × NH); 7·8 (s, 2 H, 2 × Het-H). IR spectrum: 3 450 (m, NH), 3 370 (s, NH_2), 2 930 to 2 850 (m, CH), 1 660 (s, NH_2), 1 580 (s), 1 510 (m), 1 470 (s), 1 420 (m), 1 340 (m), 1 210 (m), 1 110 (m), 1 050 (m), 920 (m), 850 (m), 730 (m). UV spectrum λ_{max} (log ε): 300 (3·97), 270 (3·96). For $C_{16}H_{24}Cl_2N_8$ (399·3) calculated: 48·12% C, 6·06% H, 28·06% N; found: 48·42% C, 6·31% H, 28·20% N.

N,N′-Bis(4-chloro-5-amino-6-pyrimidyl)-1,12-diaminododecane (*V*)

A mixture of 4,6-dichloro-5-aminopyrimidine (1·1 g, 6·7 mmol), 1·12-diaminododecane (0·64 g, 3·2 mmol) and triethylamine (0·73 g, 7·2 mmol) in 1-butanol (20·5 ml) was refluxed with stirring for 12 h. The reaction mixture was evaporated under reduced pressure and the oily mass was broken up in water. The beige solid which formed was collected by filtration and crystallized from ethanol and water (6 : 1). The solid was dried under reduced pressure to give *V* (0·48 g, 31%), m.p. 170—172°C. ^{1}H NMR spectrum: 1·1—1·6 (m, 16 H, $(CH_2)_8$); 3·1—3·6 (m, 8 H, 2 × CH_2—CH_2—N); 4·85—5·05 (m, 4 H, 2 × NH_2); 6·6—6·8 (m, 2 H, 2 × NH); 7·65 (s, 2 H, 2 × × Het-H). IR spectrum: 3 430 (m, NH), 3 350 (s, NH_2), 3 250 (s, NH_2), 2 930—2 860 (m, CH), 1 660 (m, NH), 1 580 (s), 1 470 (s), 1 420 (s), 1 380 (m), 1 340 (m), 1 300 (m), 1 220 (m), 1 120 (m), 920 (m), 840 (m), 730 (m). UV spectrum λ_{max} (log ε): 300 (4·46), 270 (4·45). For $C_{20}H_{32}Cl_2N_8$ (455·4) calculated: 52·74% C, 7·08% H, 24·60% N; found: 52·76% C, 7·24% H, 24·29% N.

1,3-Bis(6-chloro-9-purinyl)propane (*VI*)

Freshly distilled triethyl orthoformate (2·0 ml, 1·79 g, 12 mmol) was added to a chilled solution (0°C) of N,N′-bis(4-chloro-5-amino-6-pyrimidyl)-1,3-diaminopropane (*III*, 0·2 g, 0·6 mmol) in N,N-dimethylacetamide (2·0 ml). Concentrated hydrochloric acid (35%) (0·1 ml) was added to the cold solution, and the resulting mixture was stirred at room temperature for 18 h. The mixture containing a white solid was filtered, washed with ethanol, and crystallized from dimethyl-

formamide and water (1 : 10) giving *VI* (0·13 g, 66%), m.p. 243—245°C. ^{1}H NMR spectrum: 3·5—3·7 (m, 2 H, CH_2); 4·4 (t, 4 H, J = 7·0, 2 × CH_2N); 8·7 (s, 2 H, 2 × N=CH—N); 8·75(s, 2 H, 2 × Het-H). IR spectrum: 3 140—2 990 (m—w, CH), 1 590 (s), 1 560 (s), 1 500 (s), 1 450 (s), 1 400 (s), 1 340 (s), 1 220 (s), 1 190 (m), 1 150 (s), 940 (s), 860 (s), 790 (m), 640 (s). UV spectrum λ_{max} (log ε): 266 (4·04). For $C_{13}H_{10}Cl_2N_8.\frac{1}{2}H_2O$ (358·2) calculated: 43·59% C, 3·09% H, 31·28% N; found: 43·59% C, 2·68% H, 30·98% N.

1,8-Bis(6-chloro-9-purinyl)octane (*VII*)

Freshly distilled triethyl orthoformate (1·7 ml, 1·5 g, 10 mmol) was added to a chilled solution (0°C) of N,N′-bis(4-chloro-5-amino-6-pyrimidyl)-1,8-diaminooctane (*IV*, 0·2 g, 0·5 mmol) in N,N-dimethylacetamide (1·7 ml). Concentrated hydrochloric acid (0·1 ml) was added to the cold solution and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was evaporated under reduced pressure at 25°C and the yellow solid was crystallized from ethanol and water (4 : 1) and dried under reduced pressure to give *VII* (0·09 g, 43%), m.p. 126—128°C. ^{1}H NMR spectrum: 1·2—1·4 (m, 4 H, $(CH_2)_2$); 3·4—3·8 (m, 8 H, $(CH_2)_4$); 4·55 (t, 4 H, J = 7·0, 2 × CH_2N); 8·7 (s, 2 H, 2 × N=CH—N); 8·75 (s, 2 H, 2 × Het-H). IR spectrum: 2 950—2 860 (m—w, CH), 1 590 (s), 1 550 (s), 1 500 (s), 1 470 (m), 1 440 (s), 1 400 (m), 1 330 (s), 1 230 (s), 1 190 (s), 1 100 (s), 940 (s), 650 (s). UV spectrum λ_{max} (log ε): 266·4 (4·16). For $C_{18}H_{20}$·.Cl_2N_8 (419·3): 51·56% C, 4·81% H, 26·72% N; found: 51·67% C, 4·77% H, 26·41% N.

1,12-Bis(6-chloro-9-purinyl)dodecane (*VIII*)

Freshly distilled triethyl orthoformate (1·5 ml, 1·3 g, 9 mmol) was added to a solution of N,N′--bis(4-chloro-5-amino-6-pyrimidyl)-1,12-diaminododecane (*V*, 0·2 g, 0·44 mmol) in N,N-di, methylacetamide (1·5 ml). Concentrated hydrochloric acid (0·075 ml) was added to the solution and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was evaporated under reduced pressure and the oily mass was broken up in ether. The beige solid was collected by filtration and dried under reduced pressure to give *VIII* (0·17 g, 81%), m.p. 88—92°C. ^{1}H NMR spectrum: 1·0—1·4 (m, 12 H, $(CH_2)_6$); 1·7—2·0 (m, 4 H, 2 × CH_2); 3·4 to 3·7 (m, 4 H, 2 × CH_2); 4·35 (t, 4 H, J = 7·0, 2 × CH_2N); 8·75 (s, 2 H, 2 × N=CH—N); 8·8 (s, 2 H, 2 × Het-H). IR spectrum: 3 070—2 860 (m—s), 1 590 (s), 1 560 (s), 1 500 (s), 1 440 (m), 1 400 (m), 1 340 (s), 1 260 (m), 1 220 (m), 1 190 (m), 1 150 (m), 940 (s), 860 (m), 640 (s). UV spectrum λ_{max} (log ε): 266·4 (4·16). For $C_{22}H_{28}Cl_2N_8$ (475·4): 55·58% C, 5·94% H, 23·57% N; found: 55·51% C, 6·02% H, 23·24% N.

1,3-Bis(6-hydroxy-8-aza-9-purinyl)propane (*XII*)

A solution of sodium nitrite (0·018 g, 0·26 mmol) in water (0·26 ml) was added dropwise to a cold (0—5°C) solution of N,N′-bis(4-chloro-5-amino-6-pyrimidyl)-1,3-diaminopropane (*III*, 0·035 g, 0·105 mmol) in N,N-dimethylacetamide (0·3 ml) and acetic acid (0·28 ml). The mixture was stirred for 1 h at 0°C and for 14 h at room temperature. The yellowish-white solid was collected by filtration, washed with ethanol and crystallized from ethanol and dimethylformamide (5 : 1) to give *XII* (0·020 g, 66%), m.p. 295—300°C (dec.). ^{1}H NMR spectrum: 3·4—3·7 (m, 2 H, CH_2); 4·85 (t, 4 H, J = 7·0, 2 × CH_2N); 8·8 (s, 2 H, 2 × Het-H). IR spectrum: 3 440 (m, OH), 3 170—2 850 (s—m), 1 700 (s, C=O), 1 590 (s), 1 560 (s), 1 440 (s), 1 400 (m), 1 360 (s), 1 180 (s), 1 150 (s), 1 080 (s), 960 (m), 870 (s), 800 (s), 700 (s), 610 (s). UV spectrum λ_{max} (log ε): 268 (4·25). For $C_{11}H_{10}N_{10}O_2$ (314·3) calculated: 42·04% C, 3·21% H, 44·57% N; found: 42·02% C, 3·23% H, 44·67% N.

1,8-Bis(6-hydroxy-8-aza-9-purinyl)octane (*XIII*)

A solution of sodium nitrite (0·069 g, 1 mmol) in water (1 ml) was added dropwise to a cold solution (0—5°C) of N,N′-bis(4-chloro-5-amino-6-pyrimidyl)-1,8-diaminooctane (*IV*, 0·2 g, 0·5 mmol) in N,N-dimethylacetamide (3·8 ml) and acetic acid (1·6 ml). The mixture was stirred for 1 h at 0°C and for 15 h at room temperature. The mixture which contained a solid material, was concentrated under reduced pressure at 25°C. The white solid was collected by filtration and crystallized from ethanol and water (4 : 1) to give *XIII* (0·12 g, 63·2%), m.p. 211—214°C. ^{1}H NMR spectrum: 1·2—1·4 (m, 8 H, $(CH_2)_4$); 1·7—2·1 (m, 4 H, 2 × CH_2); 3·1—3·7 (m, 2 H, 2 × OH); 4·4—4·6 (t, 4 H, $J = 7·0$, 2 × CH_2N); 8·25 ppm (s, 2 H, 2 × Het-H). IR spectrum: 3 440 (m, OH), 3 170—2 850 (m), 1 700 (s, C=O), 1 590 (s), 1 560 (s), 1 460 (m), 1 360 (s), 1 270 (s), 1 170 (m), 1 060 (m), 800 (m). UV spectrum λ_{max} (log ε): 266 (4·12). For $C_{16}H_{20}N_{10}O_2$ (384·3) calculated: 50·00% C, 5·25% H, 36·43% N; found: 49·56% C, 5·13% H, 36·27% N.

1,12-Bis(6-hydroxy-8-aza-9-purinyl)dodecane (*XIV*)

A solution of sodium nitrite (0·060 g, 0·88 mmol) in water (0·5 ml) was added dropwise to a cold (0—5°C) solution of N,N′-bis(4-chloro-5-amino-6-pyrimidyl)-1,12-diaminododecane (*V*, 0·2 g, 0·44 mmol) in N,N-dimethylacetamide (10 ml) and acetic acid (1·4 ml). The mixture was stirred for 1 h at 0°C and for 24 h at room temperature. The reaction mixture was then evaporated under reduced pressure at 30°C and the beige solid was collected, filtered off, crystallized from ethanol and water (3 : 1), and dried under reduced pressure to yield *XIV* (0·10 g, 52%), m.p. 199—203°C. ^{1}H NMR spectrum: 1·1—1·4 (m, 12 H, $(CH_2)_6$); 1·7—2·05 (m, 4 H, 2 × CH_2); 3·4—3·7 (m, 4 H, 2 × CH_2); 4·85 (t, 4 H, $J = 7·0$, 2 × CH_2N); 8·8 (s, 2 H, 2 × Het-H). IR spectrum: 3 450 (m, OH), 3 180—2 850 (m), 1 700 (s, C=O), 1 600 (m), 1 560 (m), 1 360 (m), 1 280 (m), 1 180 (w), 1 060 (w), 800 (m). UV spectrum λ_{max} (log ε): 268 (4·13). For $C_{20}H_{28}N_{10}O_2$ (440·5) calculated: 54·53% C, 6·41% H, 31·80% N; found: 54·45% C, 6·35% H, 31·39% N.

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REFERENCES

1. Lister J. H.: J. Chem. Soc. *1960*, 3394.
2. Lettre H., Ballweg H.: Naturwissenschaften *45*, 364 (1958).
3. Lister J. H.: J. Chem. Soc. *1963*, 2228.
4. Rose F. L.: J. Chem. Soc. *1954*, 4116.
5. Gut J., Morávek J., Párkányi C., Prystaš M., Škoda J., Šorm F.: Collect. Czech. Chem. Commun. *24*, 3154 (1959).
6. Škoda J., Čihák A., Gut J., Prystaš M., Pískala A., Párkányi C., Šorm F.: Collect. Czech. Chem. Commun. *27*, 1736 (1962).
7. Párkányi C.: Chem. Listy *56*, 652 (1962).
8. Párkányi C., Šorm F.: Collect. Czech. Chem. Commun. *28*, 2491 (1963).
9. Párkányi C., Cho N. S., Yoo G. S.: J. Organomet. Chem. *342*, 1 (1988).
10. Párkányi C., Yuan H. L., Cho N. S., Jaw J.-H. J., Woodhouse T. E., Aung T. L.: J. Heterocycl. Chem. *26*, 1339 (1989).
11. Cho N. S., Song K. Y., Párkányi C.: J. Heterocycl. Chem. *26*, 1807 (1989).
12. Párkányi C., Yuan H. L.: J. Heterocycl. Chem. *27*, 1409 (1990).

13. Párkányi C., Yuan H. L., Tsai M.-K. M.: J. Heterocycl. Chem. *28*, 465 (1991).
14. Cho N. S., Shon H. I., Párkányi C.: J. Heterocycl. Chem., in press.
15. Schaeffer H. J., Vogel D., Vince R.: J. Med. Chem. *8*, 502 (1965).
16. Schaeffer H. J., Bhargava P. S.: Biochemistry *4*, 71 (1965).
17. Colla L., Busson R., De Clercq E., Vanderhaeghe H.: Eur. J. Med. Chem. *17*, 569 (1982).
18. Shealy Y. F., O'Dell C. A., Shannon W. M., Arnett G.: J. Med. Chem. *27*, 1416 (1984).
19. Shealy Y. F., O'Dell C. A., Arnett G.: J. Med. Chem. *30*, 1090 (1987).
20. Ballweg H.: Justus Liebigs Ann. Chem. *657*, 141 (1962).
21. Shealy Y. F., Struck R. F., Clayton J. D., Montgomery J. A.: J. Org. Chem. *26*, 4433 (1961).
22. Temple C. jr, McKee R. L., Montgomery J. A.: J. Org. Chem. *27*, 1671 (1962).
23. Albert A.: J. Chem. Soc. C, *1969*, 152.