C(6)-N(7)-Cyclized Purines [1]

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By reaction of 6-[*N*-(2-hydroxyethyl)-*N*-methyl]aminopurine (**2a**) and of the corresponding 3-hydroxypropyl derivative **2b** with thionyl chloride a bridge to N(1) is formed yielding **5** and **6**, respectively, whereas from 6-[*N*-(4-hydroxybutyl)-*N*-methyl]aminopurine (**2c**) the 4-chlorobutyl compound **4** is obtained, which cyclizes in alkaline medium to the C(6)-N(7) bridged compound **7**. A related cyclization to **11a-11f** is observed when 6-chloropurines are reacted with 3-alkyl-1,3-oxazolidines or 3-methyl-1,3-thiazolidine.

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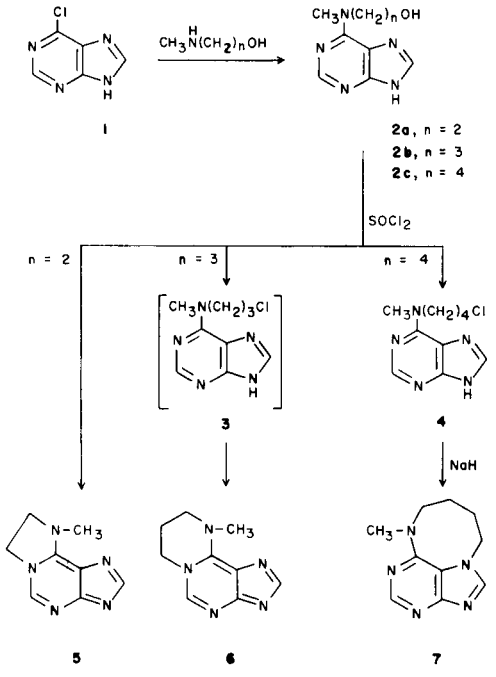
Contrary to the great number of purines known where a bridge between C(6) and N(1) exists [2a-i], only few examples of C(6)-N(7) cyclization have been observed [3-5] or claimed [6]. In order to obtain more insight into the reasons for this observed regioselectivity, the aminoalcohols **2a-2c** have been synthesized and cyclized by reaction with thionyl chloride, which is a common method [2c] to obtain C(6)-N(1) bridges. It was expected that a change in the chain length in **2** would change not only the thermodynamic stability of the new ring formed, but also could influence the regioselectivity of ring formation by kinetic control.

Scheme 1



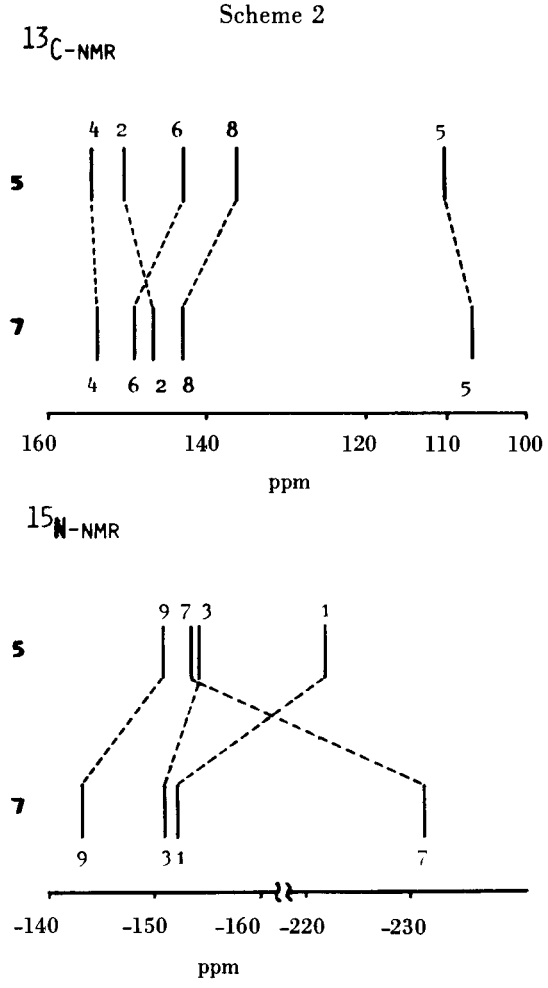
According to the literature [2c] by treatment with thionyl chloride compound **2a** immediately yields **5** (Scheme 1) and no intermediate could be isolated or even detected by tlc. When starting from the next higher homologue **2b** again the site of cyclization has been found to be N(1), but in this case the unstable intermediate **3** is formed first and can be characterized by its nmr spectrum. Yet, on standing or by treatment with base, the bridged product **6** is formed. If the side chain of the starting material is extended for a further methylene group (**2c**), a dramatic change in the cyclization reaction is observed. Now the open chain halide **4** is formed as the main product and only traces of **7** can be detected. Under basic conditions cyclization of **4** to **7** occurs in almost quantitative yield.

A mechanistic interpretation for this directional change is suggested which follows from a consideration of the geometric factors for ring closure to N(1) or N(7), respectively. Clearly the geometry of the ring formed is greatly determined by the rather rigid purine skeleton. The N(1)-C(6)-N^6 bond angle is considerably smaller than the C(6)-C(5)-N(7) angle [7]. Therefore, in a consideration of the discrimination between N(1) and N(7) as site of ring closure of **2a** (five membered ring *versus* six membered ring) the well known rules for ring formation under kinetic or thermodynamic control (*e.g.* [8]) and for the alkylation of the purine system [9] can only be applied with reservation. Probably the N(1)-C(6)-N^6 angle is more favorable for a five membered ring than the C(6)-C(5)-N(7) angle for a six membered one. Similar geometric factors seem to be responsible for the formation of **6** when starting from **2b**. Yet, if the cyclizing chain is elongated for a further methylene group in case of starting material **2c** cyclization to N(7) is favored since for this larger ring the C(6)-C(5)-N(7) bond angle seems to be of advantage. Moreover the cyclization of **4** to **7** is performed in alkaline medium under which conditions N(7) and N(9) are the preferred sites of alkylation [9].

For structural assignment mainly compounds **5** and **7** have been chosen for spectroscopic investigations. The ^{1}H-nmr spectra are quite similar except for the signals of the purine protons where in **7** H-2 [10] and H-8 coincide and appear at lower field than in **5** where also two signals are observed. As this effect depends on solvent and concentration, in this case the diagnostic importance of ^{1}H-nmr is rather limited. However, the differences in the ^{13}C-nmr spectra are much more significant (Scheme 2). For the

spectral assignment literature data for related compounds, mainly alkylated purines, have been used [2c,11,12]. In addition to the information obtained by chemical shift differences, the site of cyclization can easily be deduced from the non-decoupled spectra. C-5 appears as a singlet in **7** and as a doublet in **5** (long-range coupling with H-8), C-4 as a doublet in **7** (coupling with H-8) [13] and as a triplet in **5** (coupling with H-2 and H-8).

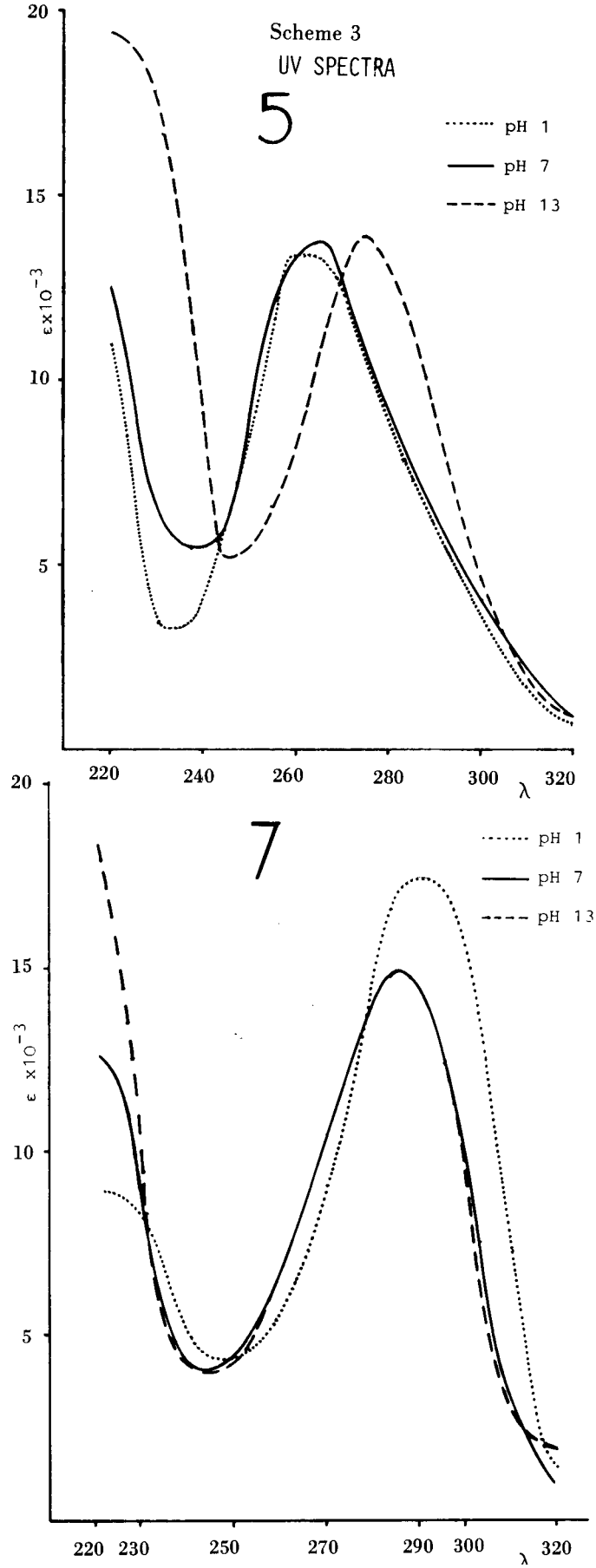
Scheme 2



Due to the good solubility of these two compounds, ^{15}N-nmr spectra could be obtained using the experimental method reported by Roberts [14]. Although measuring was complicated by the rather unfavorable NOE of the nitrogens in the purine ring system, acceptable spectra could be recorded within a few hours (Scheme 2). As expected, the spectra for **5** and **7** are quite different, but the limited number of reported ^{15}N-nmr spectra of purines [14] (due to the low solubility of many purine derivatives) does not allow an unambigous assignment of the signals.

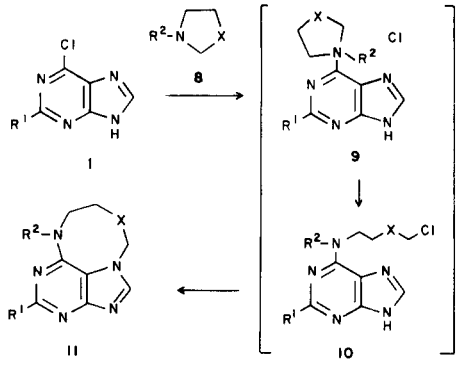
Useful structural information is also obtained from the uv spectra (Scheme 3). Among all dialkylated purines investigated [15] only the 6,7-isomer shows a pronounced hyperchromic and bathochromic shift of the spectrum in acid as compared to neutral conditions.

Scheme 3



A similar cyclization as in Scheme 1 is observed when *N*-alkyl-1,3-oxazolidines are reacted with 6-chloropurines, which was studied in pursuing the investigations on the use of cyclic aldehyde derivatives as alkylating agents [16-18] (Scheme 4). In this case compounds **11a-11e** are obtained *via* intermediates **9** and **10**. When starting from 1-methyl-1,3-thiazolidine cyclization to **11f** occurs.

Scheme 4



I, 8-11	R^1	R^2	X
a	H	CH_3	O
b	Cl	CH_3	O
c	H	CH_3CH_2	O
d	H	$CH_3(CH_2)_3$	O
e	H	$CH_2{=}CHCH_2$	O
f	H	CH_3	S

Recently a comparable ring opening reaction has been published where similar intermediates have been isolated [19].

EXPERIMENTAL

Melting points were determined on a Tottoli melting point apparatus and are uncorrected. Ultraviolet spectra were determined on a Beckman DB spectrometer, ^{1}H-nmr spectra were measured on a Bruker WH 90 spectrometer, and ^{13}C and ^{15}N-nmr on a Varian XL 200 spectrometer. Column chromatography was performed on silica gel 60, Merck. Elemental analyses were performed by Institut für Organische Chemie, Universität Graz.

6-[*N*-(2-Hydroxyethyl)-*N*-methyl]aminopurine (**2a**) [2c].

Following the described synthesis of this compound [2c], with slight modification, a mixture of 5 g (32 mmoles) of 6-chloropurine and 9.6 g (0.13 moles) of 2-(methylamino)ethanol in 100 ml of 1-butanol was heated under reflux for 3 hours. After removal of the solvents *in vacuo*, the residue was recrystallized from water to yield 5.15 g (82%) of **2a**.

Compounds **2b** and **2c** were prepared in the same way from 6-chloropurine and the corresponding aminoalcohols, physical constants and spectral data for each are given below.

6-[*N*-(3-Hydroxypropyl)-*N*-methyl]aminopurine (**2b**).

The product was recrystallized from ethanol/water to yield 4.97 g (75%) of **2b**, mp 178°; nmr (DMSO-d_6): δ 1.8 (m, $CH_2CH_2CH_2$, 2H), 3.4 (s, NCH_3, 3H), 3.5 (t, NCH_2, J = 7 Hz, 2H), 4.1 (t, OCH_2, J = 7 Hz, 2H), 8.1 (s, H-8, 1H), 8.2 (s, H-2, 1H).

Anal. Calcd. for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.79. Found: C, 52.09; H, 6.34; N, 33.70.

6-[*N*-(4-Hydroxybutyl)-*N*-methyl]aminopurine (**2c**).

The product was recrystallized from ethanol/water to yield 6.37 g (90%) of **2c**, mp 162°; nmr (DMSO-d_6): δ 1.3-1.8 (m, $CH_2CH_2CH_2CH_2$, 4H), 3.4 (s, NCH_3, 3H), 3.5 (t, NCH_2, J = 7 Hz, 2H), 4.1 (t, OCH_2, J = 7 Hz, 2H), 4.5 (broad, OH, 1H), 8.1 (s, H-8, 1H), 8.2 (s, H-2, 1H).

Anal. Calcd. for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.65. Found: C, 54.37; H, 6.79; N, 31.43.

9-Methyl-8,9-dihydro-7*H*-imidazo[2,1-*i*]purine (**5**).

Following the described synthesis of this compound [2c], with slight modification, 0.5 g (2.6 mmoles) of **2a** were stirred in 15 ml of thionyl chloride at room temperature for 3 hours. The suspension was evaporated under reduced pressure, dissolved in 5 ml of water and brought to *p*H 10 with 2*N* sodium hydroxide. After removal of the water *in vacuo*, **5** was recrystallized from dimethylformamide to yield 420 mg (92%), mp 339°; uv (water): *p*H 1 λ max 263 nm (13,590), *p*H 7 λ max 265 nm (13,760), *p*H 13 λ max 274 nm (13,940); nmr (DMSO-d_6): δ 3.1 (s, NCH_3, 3H), 3.8 (t, NCH_2, J = 7 Hz, 2H), 4.2 (t, NCH_2, J = 7 Hz, 2H), 7.7 (s, H-8, 1H), 7.9 (s, H-2, 1H); ^{13}C-nmr (200 MHz, deuterium oxide): δ 29.5 (NCH_3), 42.9 and 46.0 (CH_2CH_2), 110.1 (C-5), 136.0 (C-8), 142.7 (C-6), 150.5 (C-2), 154.3 (C-4); ^{15}N-nmr (deuterium oxide, ppm downfield from nitromethane): −298.5 (N-6), −221.9 (N-1), −154.8 (N-3), −153.8 (N-7), −150.9 (N-9).

Anal. Calcd. for $C_8H_9N_5$: C, 54.85; H, 5.18; N, 39.97. Found: C, 54.91; H, 5.19; N, 39.97.

10-Methyl-7,8,9,10-tetrahydropyrimido[2,1-*i*]purine (**6**).

A suspension of 2 g (9.7 mmoles) of **2b** in 10 ml of thionyl chloride was stirred at room temperature for 3 hours. The excess of thionyl chloride was removed *in vacuo*, the residue treated with 5 ml of water, and neutralized with 2*N* sodium hydroxide. After filtration from byproducts (mainly **3** [20]) and evaporation of the solvents, the residue was extracted twice with 20 ml of boiling dimethylformamide. The solution was concentrated to 5 ml, and **6** was precipitated by the addition of acetone. After recrystallization from dimethylformamide/acetone, 890 mg (49%) of **6** were obtained, mp >300°; nmr (DMSO-d_6): δ 2.2 (m, $CH_2CH_2CH_2$, 2H), 3.6 (t, NCH_2, J = 7 Hz, 2H), 3.9 (s, NCH_3, 3H), 4.3 (t, NCH_2, J = 7 Hz, 2H), 8.45 (s, H-8, 1H), 8.55 (s, H-2, 1H).

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.17; H, 5.88; N, 36.89.

6-[*N*-(4-Chloro-*n*-butyl)-*N*-methyl]aminopurine (**4**).

A suspension of 2 g (9 mmoles) of **2c** in 10 ml of thionyl chloride was stirred for 4 hours at room temperature. After removal of the excess thionyl chloride *in vacuo*, the residue was dissolved in 5 ml of water and neutralized with 10% sodium carbonate solution. Compound **4** was filtered off and recrystallized from water to yield 1.73 g (80%) of **4**, mp 161°; nmr (DMSO-d_6): δ 1.8 (m, $CH_2CH_2CH_2CH_2$, 4H), 3.4 (s, NCH_3, 3H), 3.7 (t, NCH_2, J = 7 Hz, 2H), 4.1 (broad, CH_2Cl, 2H), 8.1 (s, H-8, 1H), 8.2 (s, H-2, 1H).

Anal. Calcd. for $C_{10}H_{14}ClN_5$: C, 50.11; H, 5.89; N, 29.22. Found: C, 49.83; H, 5.84; N, 29.00.

8-Methyl-5,6,7,8-tetrahydro-4*H*-[1,4]diazocino[1,2,3-*g*,*h*]purine (**7**).

To a solution of 2 g (8.35 mmoles) of **4** in 20 ml of dimethylformamide were added under stirring 220 mg (9.17 mmoles) of sodium hydride. The mixture was stirred at room temperature until no more starting material could be detected by tlc (about 2 hours). After filtration and removal of the solvent *in vacuo*, the residue was recrystallized from 2-propanol to yield 1.65 g (97%) of **7**, mp 175°; uv (water): *p*H 1 λ max 290 nm (17,700), *p*H 7 λ max 285 nm (15,000), *p*H 13 λ max 285 nm (14,700); nmr (DMSO-d_6): δ 1.9 (m, $CH_2CH_2CH_2CH_2$, 4H), 3.2 (s, NCH_3, 3H), 3.5 (t, NCH_2, J = 7 Hz, 2H), 4.4 (t, NCH_2, J = 7 Hz, 2H), 8.3 (s, H-8 and H-2, 2H); ^{13}C-nmr (200 MHz, deuterium oxide): δ 19.6 and 21.8 ($CH_2CH_2CH_2CH_2$), 32.8 (NCH_3), 44.0 and 46.7 (2 NCH_2), 107.0 (C-5), 142.8 (C-8), 146.6 (C-2), 148.9 (C-6), 154.0 (C-4); ^{15}N-nmr (deuterium oxide, ppm downfield from nitromethane): −294.0 (N-6), −232.3 (N-7), −152.0 (N-1), −150.7 (N-3), −143.0 (N-9).

Anal. Calcd. for $C_{10}H_{13}N_5$: C, 59.10; H, 6.45; N, 34.46. Found: C, 59.20; H, 6.53; N, 34.64.

8-Methyl-7,8-dihydro-6*H*-[1,3,6]oxdiazocino[3,4,5-*g*,*h*]purine (**11a**).

A solution of 5 g (33 mmoles) of 6-chloropurine in 200 ml of dimethylacetamide at 110° was treated with 8.8 g (0.1 mole) of 3-methyl-1,3-oxazolidine [18] under vigorous stirring. After stirring at this temperature for 30 minutes, the solvents were removed *in vacuo* and the resulting oil was chromatographed with chloroform/methanol 9/1 as eluant. After recrystallization from 2-propanol/ether, 4.0 g (60%) of **11a** were obtained, mp 199°; uv (methanol): λ max 284.5 nm (12,600); nmr (DMSO-d_6): δ 3.2 (s, NCH_3, 3H), 3.8 (t, NCH_2, J = 4 Hz, 2H), 3.85 (t, CH_2CH_2O, J = 4 Hz, 2H), 5.8 (s, NCH_2O, 2H), 8.35 (s, H-8, 1H), 8.4 (s, H-2, 1H); ^{13}C-nmr (90 MHz, DMSO-d_6): δ 36.7 (NCH_3), 50.4 (NCH_2), 68.1 (OCH_2), 76.2 (NCH_2O), 111.0 (C-5), 144.5 (C-8), 151.2 (C-2), 152.7 (C-6), 160.5 (C-4).

Anal. Calcd. for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.47; H, 5.49; N, 34.14.

8-Methyl-10-chloro-7,8-dihydro-6*H*-[1,3,6]oxdiazocino[3,4,5-*g*,*h*]purine (**11b**).

A solution of 0.63 g (3.3 mmoles) of 2,6-dichloropurine in 20 ml of dimethylacetamide at 110° was treated with 0.9 g (10 mmoles) of 3-methyl-1,3-oxazolidine under vigorous stirring. After stirring for 1 hour at this temperature, the solvents were removed *in vacuo* and the residue recrystallized from ethanol to yield 450 mg (57%) of **11b**, mp 212°; uv (methanol): λ max 287 nm (13,400); nmr (DMSO-d_6): δ 3.25 (s, NCH_3, 3H), 3.8 (t, NCH_2, J = 4 Hz, 2H), 3.85 (t, OCH_2, J = 4 Hz, 2H), 5.9 (s, NCH_2O, 2H), 8.4 (s, H-8, 1H); ^{13}C-nmr (90 MHz, DMSO-d_6): δ 36.8 (NCH_3), 50.5 (NCH_2), 68.0 (OCH_2), 76.3 (NCH_2O), 110.1 (C-5), 145.4 (C-8), 152.0 (C-2), 153.5 (C-6), 162.3 (C-4).

Anal. Calcd. for $C_9H_{10}ClN_5O$: C, 45.11; H, 4.21; N, 29.35. Found: C, 44.90; H, 4.19; N, 29.17.

8-Ethyl-7,8-dihydro-6*H*-[1,3,6]oxdiazocino[3,4,5-*g*,*h*]purine (**11c**).

The compound was prepared as described for **11a**, from 2 g (13 mmoles) of 6-chloropurine and 4.04 g (40 mmoles) of 3-ethyl-1,3-oxazolidine [18] and a reaction time of 6 hours. Recrystallization from 2-propanol/ether afforded 400 mg (14%) of **11c**, mp 188°; nmr (DMSO-d_6): δ 1.2 (t, CH_3CH_2N, J = 7 Hz, 3H), 3.5-4.0 (m, $CH_2NH_2CH_2$, 6H), 5.8 (s, NCH_2O, 2H), 8.3 (s, H-2 and H-8, 2H).

Anal. Calcd. for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.81; H, 5.90; N, 31.89.

8-*n*-Butyl-7,8-dihydro-6*H*-[1,3,6]oxdiazocino[3,4,5-*g*,*h*]purine (**11d**).

The compound was prepared in the same way as described for **11c** from 2 g (13 mmoles) of 6-chloropurine and 5.16 g (40 mmoles) of 3-*n*-butyl-1,3-oxazolidine [18] to yield 350 mg (11%) of **11d**, mp 148°; nmr (DMSO-d_6): δ 0.9 (t, CH_3, J = 7 Hz, 3H), 1.0-1.8 (m, $CH_3CH_2CH_2$, 4H), 3.6-4.0 (m, $CH_2NCH_2CH_2$, 6H), 5.8 (s, NCH_2O, 2H), 8.3 (s, H-2 and H-8).

Anal. Calcd. for $C_{12}H_{17}N_5O$: C, 58.28; H, 6.93; N, 28.32. Found: C, 58.16; H, 6.93; N, 28.24.

8-Allyl-7,8-dihydro-6*H*-[1,3,6]oxdiazocino[3,4,5-*g*,*h*]purine (**11e**).

The compound was prepared in the same way as described for **11c**, from 2 g (13 mmoles) of 6-chloropurine and 4.52 g (40 mmoles) of 3-allyl-1,3-oxazolidine [18] to yield 400 mg (13%) of **11e**, mp 153°; nmr (DMSO-d_6): δ 3.6-4.0 (m, NCH_2CH_2O, 4H), 4.4 (d, $CH_2CH{=}CH_2$, 2H), 5.1 (s) and 5.25 (d, J = 4.5 Hz, $CH_2{=}CH$, 2H), 5.8 (s, NCH_2O, 2H), 5.8-6.2 (m, $CH_2CH{=}CH_2$, 1H), 8.3 (s, H-2 and H-8, 2H).

Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 56.98; H, 5.59; N, 30.13.

8-Methyl-7,8-dihydro-6*H*-[1,3,6]thiadiazocino[3,4,5-*g*,*h*]purine (**11f**).

The compound was prepared in the same way as described for **11a** from 600 mg (3.88 mmoles) of 6-chloropurine and 1.1 g (10.66 mmoles) of 3-methyl-1,3-thiazolidine [21] and a reaction time of 2 hours to obtain 200 mg (23%) of **11f**, mp 201°; nmr (DMSO-d_6): δ 3.0 (t, NCH_2, J = 5 Hz, 2H), 3.2 (s, NCH_3, 3H), 3.8 (t, SCH_2, J = 5 Hz, 2H), 5.5 (s, NCH_2S, 2H), 8.3 (s, H-2 and H-8, 2H).

Anal. Calcd. for $C_9H_{11}N_5S$: C, 48.85; H, 5.01; N, 31.65. Found: C, 48.52; H, 4.94; N, 31.45.

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REFERENCES AND NOTES

[1] Presented in part at the Eighth International Congress of Heterocyclic Chemistry, Graz, 1981.

[2a] N. J. Leonard and R. A. Swaringen, *J. Org. Chem.*, **34**, 3814 (1969) and references cited therein; [b] G. B. Chheda, S. P. Dutta, A. Mittelman and L. Baczynskyj, *Tetrahedron Letters*, 433 (1974); [c] M. Dryefus, G. Dodin, O. Bensaude and J. E. Dubois, *J. Am. Chem. Soc.*, **99**, 7027 (1977); [d] C. Ivancsics and E. Zbiral, *Monatsh. Chem.*, **106**, 417 (1975) and references cited therein; [e] I. L. Doerr and R. E. Willette, *J. Org. Chem.*, **38**, 3878 (1978); [f] R. N. Prasad and K. Tietje, *Nucl. Acid. Chem.*, **2**, 701 (1978); [g] K. Kayasuga-Mikado, T. Hashimoto, T. Negishi, K. Negishi and H. Hayatsu, *Chem. Pharm. Bull.*, **28**, 932 (1980); [h] R. S. Hosmane and N. J. Leonard, *J. Org. Chem.*, **46**, 1457 (1981) and references cited therein; [i] I. A. Mikhailopulo and E. N. Kalinichenko, *Nucleic Acid Symp. Ser.*, **9**, 57 (1981).

[3] Y. Mizuno, Y. Watanabe, K. Ikeda and J. A. McCloskey, *Heterocycles*, **2**, 439 (1974).

[4] Y. Mizuno, Y. Watanabe, K. Ikeda and J. A. McCloskey, *Chem. Pharm. Bull.*, **23**, 1411 (1975).

[5] K. Doyama, F. Hama, Y. Sakata and S. Misumi, *Tetrahedron Letters*, 4101 (1981).

[6] C. Temple, Jr. and J. A. Montgomery, *J. Org. Chem.*, **31**, 1417 (1966).

[7] J. H. Lister, *Adv. Heterocyclic Chem.*, **24**, 215 (1979).

[8] E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, 1962, p 198.

[9] M. Miyaki and B. Shimizu, *Chem. Pharm. Bull.*, **18**, 1446 (1970).

[10] The numbering corresponds to the numbering in the purine series throughout the whole paper.

[11] M.-T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica and L. B. Townsend, *J. Am. Chem. Soc.*, **97**, 4627 (1975).

[12] M.-T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica and L. B. Townsend, *ibid.*, **97**, 4636 (1975).

[13] A. A. Akhrem, I. A. Mikhailopulo and A. F. Abramov, *Org. Magn. Reson.*, **12**, 247 (1979).

[14] V. Markowski, G. R. Sullivan and J. D. Roberts, *J. Am. Chem. Soc.*, **99**, 714 (1977).

[15] N. J. Leonard, K. L. Carraway and J. P. Helgeson, *J. Heterocyclic Chem.*, **2**, 291 (1965).

[16] H. Griengl, W. Hayden, E. Schindler and E. Wanek, *Arch. Pharm.*, **316**, 146 (1983).

[17] H. Griengl, W. Hayden, W. Kalchauer and E. Wanek, *ibid.*, in press.

[18] H. Griengl, A. Bleikolm, W. Grubbauer and H. Söllradl, *Ann. Chem.*, 392 (1979) and references cited therein.

[19] H. Miki and F. Kasahara, *Chem. Pharm. Bull.*, **30**, 3471 (1982).

[20] As **3** decomposed on drying, the nmr spectrum obtained is not very satisfactory, but a CH_2Cl signal was found at 4.2 ppm.

[21] K. Schimmelschmidt, H. Hoffmann and E. Mundlos, *Chem. Ber.*, **96**, 38 (1963).