Purine Analogues As Potential Chemotherapeutic Agents. III

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Alkylation of 3-phenyl/benzyl-8-mercaptoxanthines and 2-phenyl-8-mercaptoadenine with various alkyl halides under different conditions is studied. The structure of the compounds is confirmed by spectroscopic studies and elemental analyses.

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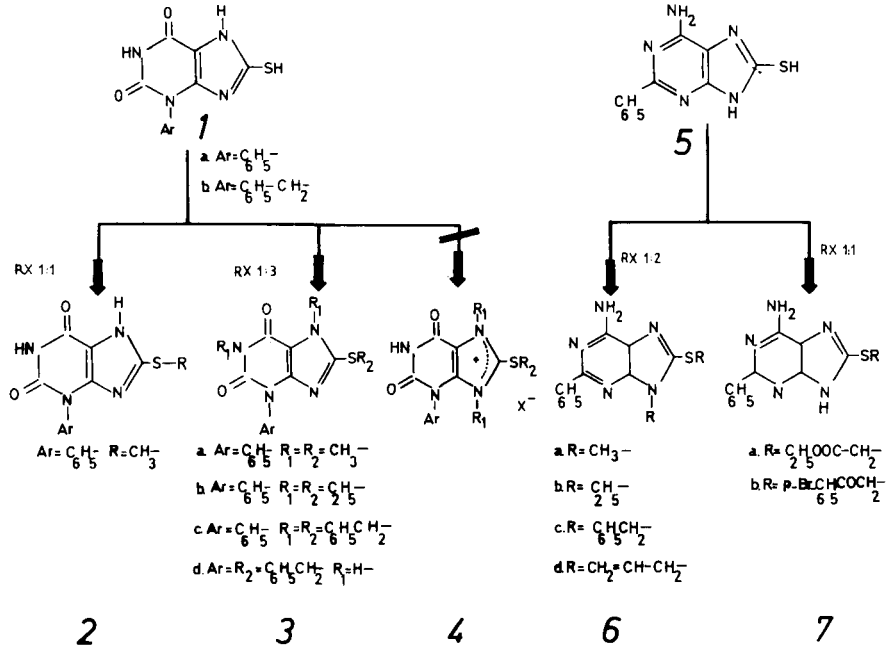
Brown, *et al.*, (2) have recently reported that the activity of the antibiotic phleomycin against *E. coli* is enhanced by the presence of various purines. Among all the purine derivatives screened so far, 2-alkylthiopurines have been found to be the most active analogues whereas 2-alkylaminopurines were active to a lesser extent. An alkyl group at C-8 or C-6 or on an imidazole nitrogen prevents hydroxylation and is always advantageous over halogen and anionic substituents at *p*H 9(3). These compounds have the common characteristic to bind selectively to single stranded DNA (4,5) which is of significance for their mode of action (6,7). It was also noticed that certain 8-alkylthioxanthines posses slight anticancer and central nervous system (CNS) depressant activity in rats and rabbits (8).

The therapeutic importance of these compounds aroused considerable interest to study the alkylation of 8-mercaptoxanthine and adenine derivatives. 3-Phenyl/benzyl-8-mercaptoxanthine and 2-phenyl-8-mercaptoadenine were used as intermediates for alkylation studies and were prepared by fusion of the corresponding 5,6-diaminopyrimidine with thiourea (9). Alkylation of 3-phenyl/benzyl-8-mercaptoxanthine with alkyl halide in an equivalent molar ratio exclusively gave 3-phenyl/benzyl-8-alkylmercaptoxanthine (**2**) whereas in an excess of alkyl halide 1,7-dialkyl-8-alkylmercaptoxanthine (**3**) was formed. The latter compound was also prepared by alkylation of 3-phenyl/benzyl-8-alkylmercaptoxanthine (**2**) and was characterized by elemental analyses and spectroscopic studies. The probability of N-9 alkylation was discarded due to steric hindrance. The formation of the salt (**4**) was excluded since the test for halogen was negative and no molecular peak corresponding to **4** was observed in the mass spectrum.

There are several sites for alkylation in 2-phenyl-8-mercaptoadenine (**5**) but preferential positions are 8-SH and N-9 (10). The possibility of alkylation at N-7, N-1 and N-3 was omitted due to steric factors and mild conditions. We too were able to isolate and characterize 2-phenyl-8-alkylmercapto-9-alkyladenine (**6**). Reactions of 2-phenyl-8-

scheme 1



mercaptoadenine with ethylchloroacetate and *p*, ω-dibromoacetophenone in an equimolar ratio separately in dimethylformamide (DMF) and potassium carbonate exclusively gave the corresponding 8-substituted mercaptoadenines (**7a,b**). The structure of the compounds was confirmed by spectroscopic studies and elemental analyses.

EXPERIMENTAL

Melting points were determined on a Tottoli apparatus and are uncorrected. Mass spectra were recorded on a Jeol JMS-01SG apparatus operating at 70 eV ionization energy.

3-Phenyl-8-mercaptoxanthine (**1a**).

1-Phenyl-5,6-diaminouracil (1.0 g, 4.6 mmoles) and thiourea (3.0 g) were fused at 210° in an oil bath for one hour and cooled. The fused material was dissolved in 1 *N* aqueous sodium hydroxide, filtered and acidified with dilute sulphuric acid *p*H 3. The precipitate thus obtained was filtered, washed several times with water and finally crystallized from a DMF-ethanol mixture, 46%, (literature (9)), mp 300-302° dec; ms: m/e 260.

Anal. Calcd. for $C_{11}H_8N_4O_2S$: C, 50.77; H, 3.10; N, 21.53. Found: C, 50.82; H, 3.20; N, 21.42.

3-Benzyl-8-mercaptoxanthine (**1b**).

A mixture of 1-benzyl-5,6-diaminouracil hydrochloride (1.3 g, 4.85 mmoles) and thiourea (3.4 g) was fused for one hour in an oil bath at 200°. The title compound was isolated as described in the preceeding experiment. The crude product was crystallized from a DMF-water mixture, 70%, mp 270-271° dec; ms: m/e 274.

Anal. Calcd. for $C_{12}H_{10}N_4O_2S$: C, 52.55; H, 3.65; N, 20.44. Found: C, 52.71; H, 3.8; N, 20.13.

2-Phenyl-8-mercaptoadenine (**5**).

2-Phenyl-4,5,6-triaminopyrimidine hydrochloride (1.0 g, 4.2 mmoles) and thiourea (3.0 g) were fused at 185° for one hour in an oil bath. The reaction mixture was dissolved in alkali and the compound was precipitated by acidification. The crude product was crystallized from ethanol, 60%, mp 300-301°; ms: m/e 243.

*Anal.*Calcd. for $C_{11}H_9N_5S$: C, 54.32; H, 3.70; N, 28.81. Found: C, 54.55; H, 3.8; N, 28.65.

3-Phenyl-8-methylmercaptoxanthine (**2**).

This compound was prepared by stirring an equimolar mixture of **1a** and methyl iodide with anhydrous potassium carbonate in DMF for 3 hours. The solid obtained after acidification with acetic acid was filtered, washed with water and dried (literature (9)); mp 300-302°; ms: m/e 274.

Anal. Calcd. for $C_{12}H_{10}O_2N_4S$: C, 52.54; H, 3.68; N, 20.42. Found: C, 52.31; H, 3.60; N, 20.34.

3-Phenyl-1,7-dimethyl-8-methylmercaptoxanthine (**3a**).

A solution of **1a** (0.2 g, 0.77 mmole) in DMF (3 ml) was stirred with potassium carbonate (0.31 g) and methyl iodide (0.32 g) for 3 hours. The precipitate obtained after addition of water was filtered off, washed with water and crystallized from ethanol, 60%, mp 206-208°; ms: m/e 302.

Anal. Calcd. for $C_{14}H_{14}N_4O_2S$: C, 55.63; H, 4.63; N, 18.54. Found: C, 55.72; H, 4.44; N, 18.38.

3-Phenyl-1,7-diethyl-8-ethylmercaptoxanthine (**3b**).

Ethyl iodide (0.36 g) was added gradually to a mixture of **1a** (0.2 g, 0.77 mmole) and potassium carbonate (0.31 g) in DMF. The mixture was stirred for 3 hours at ambient temperature and the resulting precipitate was filtered off, washed with water and dried, 40%, mp 159-161°; ms: m/e 344.

Anal. Calcd. for $C_{17}H_{20}N_4O_2S$: C, 59.30; H, 5.81 N, 16.28. Found: C, 59.21; H, 5.63; N, 16.52.

3-Phenyl-1,7-dibenzyl-8-benzylmercaptoxanthine (**3c**).

This compound was prepared by stirring a mixture of **1a** (0.2 g, 0.77 mmole), benzyl chloride (0.28 g) and potassium carbonate (0.31 g) in DMF (3 ml) and isolated as described earlier. The crude product was crystallized from a DMF-water mixture, 50%, mp 191-193°; ms: m/e 530 (M^+), 439 (M^+-$CH_2C_6H_5$); 348 (439-$CH_2C_6H_5$); 304 (348-CS); 278 (304-CN); 252 (278-CN); 175 (252-C_6H_5); 161 (252-$CH_2C_6H_5$).

Anal. Calcd. for $C_{32}H_{26}N_4O_2S$: C, 72.45; H, 4.91; N, 10.57. Found: C, 72.66; H, 5.20; N, 10.82.

3-Benzyl-8-benzylmercaptoxanthine (**3d**).

3-Benzyl-8-mercaptoxanthine (0.2 g, 0.73 mmole) was dissolved in DMF and stirred with potassium carbonate (0.1 g) and benzyl chloride (0.09 g) for 3 hours. The precipitate thus obtained was filtered off and washed with water. The dried crude product was crystallized from a DMF-water mixture, 77%, mp 134-136°; ms: m/e 364 (M^+); 321 (M^+-NHCO); 273 (364-$CH_2C_6H_5$); 299 (273-CS).

Anal. Calcd. for $C_{19}H_{16}N_4O_2S$: C, 62.64; H, 4.4; N, 15.38. Found: C, 62.48; H, 4.3; N, 15.62.

2-Phenyl-8-methylmercapto-9-methyladenine (**6a**).

To a solution of **5** (0.2 g, 0.82 mmole) in DMF (3 ml), potassium carbonate (0.22 g) amd methyl iodide (0.32 g) were added and the resulting mixture was stirred for 3 hours. The white precipitate thus obtained was filtered off, washed with water and finally crystallized from ethanol, 70%, mp 212-213°; ms: m/e 271 (M^+); 256 (M^+-CH_3); 215 (256-CH_3NC); 209 (256-SCH_3).

Anal. Calcd. for $C_{13}H_{13}N_5S$: C, 57.56; H, 4.80; N, 25.83. Found: C, 57.72; H, 4.64; N, 25.75.

2-Phenyl-8-ethylmercapto-9-ethyladenine (**6b**).

This compound was prepared by reaction of **5** (0.2 g, 0.82 mmole) ethyl iodide in the presence of potassium carbonate in DMF as described in the preceeding experiment, 45%, mp 179-181°; ms: m/e 292 (M^+); 284 (M^+-CH_3); 270 (M^+-C_2H_5); 256 (270-NH_2); 222 (M^+-C_6H_5).

Anal. Calcd. for $C_{15}H_{17}N_5S$: C, 60.20; H, 5.69; N, 23.41. Found: C, 60.50; H, 5.81; N, 23.62.

2-Phenyl-8-benzylmercapto-9-benzyladenine (**6c**).

Compound **5** (0.2 g, 0.82 mmole) in DMF (3 ml) was stirred with potassium carbonate (0.22 g) and benzyl chloride (0.18 g) for 3 hours and the crude product was isolated as described earlier. The compound was crystallized from an acetic acid-water mixture, 60%, mp 208-210°; ms: m/e 423.

Anal. Calcd. for $C_{25}H_{21}N_5S$: C, 70.92; H, 4.96; N, 16.55. Found: C, 71.2; H, 4.85; N, 16.32.

2-Phenyl-8-allylmercapto-9-allyladenine (**6d**).

Stirring a mixture of **5** (0.2 g, 0.82 mmole) and potassium carbonate (0.22 g) in DMF (3 ml) with allyl bromide (0.18 g) for 3.5 hours afforded the title compound, 40%, mp 144-145°; ms: m/e 323 (M^+); 307 (M^+-NH_2); 281 (307-CN).

Anal. Calcd. for $C_{17}H_{17}N_5S$: C, 63.16; H, 5.26; N, 21.67. Found: C, 63.45; H, 5.6; N, 21.32.

2-Phenyl-8-ethoxycarbonylmethylmercaptoadenine (**7a**).

An equimolar mixture of **5** (0.2 g, 0.82 mmole), ethyl chloroacetate (0.1 g) and potassium carbonate in 3 ml of DMF was stirred for 5 hours and the desired product was isolated in the usual manner, 50%, mp 218-219; ms: m/e 329.

Anal. Calcd. for $C_{15}H_{15}N_5O_2S$: C, 54.71; H, 4.56; N, 21.28. Found: C, 54.82; H, 4.71; N, 21.56.

2-Phenyl-8-*p*-bromobenzoylmethylmercaptoadenine (**7b**).

A mixture of **5** (0.2 g, 0.82 mmole), *p*,ω-dibromoacetophenone (0.24 g) and potassium carbonate (0.22 g) in DMF afforded the title compound which was crystallized from acetic acid, 60%, mp 247-248°; ms: m/e 440.

Anal. Calcd. for $C_{19}H_{14}BrN_5OS$: C, 51.8; H, 3.18; N, 15.9. Found: C, 51.62; H, 3.43; N, 15.55.

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REFERENCES AND NOTES

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(2a) D. J. Brown, A. M. Angyal and G. W. Grigg, *J. Chem. Soc., Perkin Trans. I,* 1819 (1972).

(2b) R. J. Badger and D. J. Brown, *ibid.*, 152 (1974).

(3) K. Bhushan, D. J. Brown, J. H. Lister, L. G. Stephanson and F. Yoneda, *Aust. J. Chem.*, **28**, 2553 (1975).

(4) G. W. Grigg, *Mol. Gen. Genetics,* **107**, 162 (1970).

(5) G. W. Grigg, M. J. Edwards and D. J. Brown, *J. Bacteriol.*, **107**, 599 (1971).

(6) G. W. Grigg, *Mol. Gen. Genetics,* **104**, 1 (1969).

(7) P. Pietsch, *J. Cell Biol.*, **31**, 86A (1966).

(8) A. J. Dietz, Jr. and R. M. Burgison, *J. Med. Chem.*, **9**, 500 (1966).

(9) T. Kishikawa and H. Yuki, *Chem. Pharm. Bull.*, **12**, 1365 (1966).

(10a) J. H. Montgomery and H. J. Thomas, *J. Org. Chem.*, **30**, 3235 (1965); *J. Heterocyclic Chem.*, **1**, 115 (1964).

(10b) U. Reichman, F. Bergman, Dov. Lichtenberg and Z. Neiman, *J. Chem. Soc., Perkin Trans. I,* 793 (1973).