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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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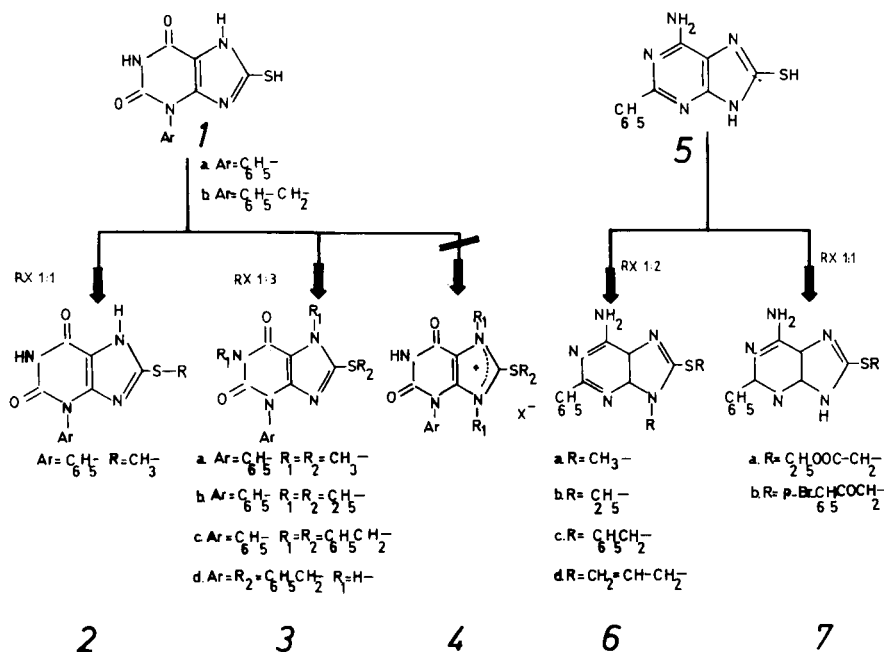
Brown, *et al.*, (2) have recently reported that the activity of the antibiotic phleomycin against *E. coli* is enhanced by the presence of various purines. Among all the purine derivatives screened so far, 2-alkylthiopurines have been found to be the most active analogues whereas 2-alkylaminopurines 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 pH 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 possess 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 mmole) 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 pH 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 mmole) 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 preceding 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 mmole) 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 $C_{33}H_{26}N_4O_2S$: 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) and 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 preceding 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-allyl-adenine (**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 $C_{16}H_{18}N_5O_2S$: 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 $C_{13}H_{14}BrN_5OS$: C, 51.8; H, 3.18; N, 15.9. Found: C, 51.62; H, 3.43; N, 15.55.

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