Reaction of 6-Amino-1,3-dimethyl-5-nitrosouracil with Thiols

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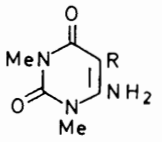
The reactions of 6-amino-1,3-dimethyl-5-nitrosouracil with various thiols lead to condensation as well as oxidation–reduction products. Disulphides, 4,6-dimethyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7-dione, pteridine-2,4-diones, purine-2,6-diones, pyrimidopteridines, and 5,6-diamino-1,3-dimethyluracil were among those isolated. The mechanism of the reaction is discussed.

BASE-CATALYSED condensation between an active methylene group and a nitroso-group attached to an aromatic ring (the Ehrlich–Sachs [1] reaction) was applied by Timmis [2] to 4-amino-5-nitrosopyrimidines in a novel synthesis of pteridines, which has since been thoroughly investigated by others.[3] It has been shown recently [4] that the methylene component need not be highly activated: 4-amino-5-nitrosopyrimidines condense with amine salts to give, depending on the structure of the amine salt, purines or a mixture of purines and pteridines. The condensation of a thiol with 4-amino-5-nitrosopyrimidines is of special interest since it must compete with other reactions of thiols with amino- or nitroso-derivatives. For example, 4-aminopyrimidines are converted into 4-mercaptopyrimidines by heating in alcoholic hydrogen sulphide,[5] in accord with the reported [6] replacement of a 4-amino- by a 4-hydroxy-group in acidic solution, which would be accelerated by an electron-withdrawing 5-nitroso-group.[6] On the other hand, nitroso-compounds are very susceptible to reduction by thiols, giving amines, azo-compounds, and azoxy-derivatives.[7]

[1] P. Ehrlich and F. Sachs, *Ber.*, 1899, **32**, 234.
[2] G. M. Timmis, *Nature*, 1949, **139**, 164.
[3] R. C. Elderfield and A. C. Mehta, in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1967, pp. 49—52; T. S. Osdene in 'Pteridine Chemistry,' eds. W. Pfleiderer and E. C. Taylor, Pergamon, London, 1964, pp. 65—73.
[4] R. D. Youssefyeh and A. Kalmus, *Chem. Comm.*, 1969, 1426.
[5] J. H. Boothe and C. D. Wilson, *J. Amer. Chem. Soc.*, 1946, **68**, 448.
[6] D. J. Brown, 'The Pyrimidines,' Interscience, New York, 1962, pp. 229—232.
[7] E. Gulbaran, *Suomen Kem.* (*B*), 1964, **37**, 229 (*Chem. Abs.*, 1965, **62**, 11,718); H. Wieland and S. Gambarjan, *Ber.*, 1906, **39**, 3036.

Treatment of 6-amino-1,3-dimethyl-5-nitrosouracil (1a) with 2-phenylethanethiol (2a) in ethanol led to a mixture



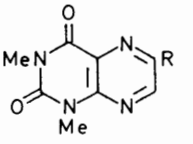
(1) a; R = NO
b; R = NH_2
c; R = N:CHPh

RSH

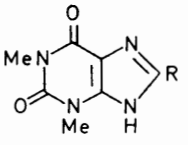
(2) a; R = $CH_2 \cdot CH_2Ph$
b; R = Et
c; R = CH_2Ph

RS·SR

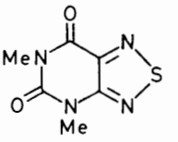
(3) a; R = $CH_2 \cdot CH_2Ph$
b; R = Et
c; R = CH_2Ph



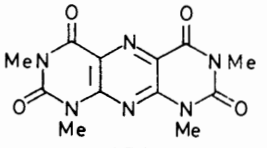
(4) a; R = Ph
b; R = H



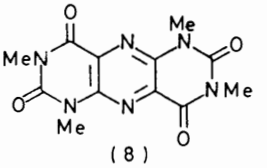
(5) a; R = CH_2Ph
b; R = Me
c; R = Ph



(6)



(7)



(8)

from which 2-phenylethyl disulphide [8] (3a), 6-phenyl-1,3-dimethylpteridine-2,4-dione (4a), 8-benzyl-1,3-dimethylpurine-2,6-dione [4] (5a), 4,6-dimethyl[1,2,5]thiadiazolo-[3,4-*d*]pyrimidine-5,7-dione [9] (6), and the pyrimidopteridine (8) [10] were isolated. In a similar manner, ethyl disulphide (3b), the thiadiazolopyrimidinedione (6), 1,3,8-trimethylpurine-2,6-dione [4] (5b), 1,3-dimethylpteridine-2,4-dione [4] (4b), and the pyrimidopteridine (7) [10] were isolated from the reaction of 6-amino-1,3-dimethyl-5-nitrosouracil (1a) and ethanethiol (13). On the other hand, phenylmethanethiol (2c) and compound (1a) under similar conditions gave dibenzyl disulphide [11] (3c), the thiadiazolopyrimidinedione (6), 5,6-diamino-1,3-dimethyluracil [12] (1b), 1,3-dimethyl-8-phenylpurine-2,6-dione [4] (5c), 6-amino-5-benzylideneamino-1,3-dimethyluracil [13] (1c), and the pyrimidinopteridine (7).

As in the case of amine salts,[4] the products of condensation of thiols with 6-amino-1,3-dimethyl-5-nitrosouracil depend on the structure of the reagent, giving an 8-substituted 1,3-dimethylpurine-2,6-dione or a mixture of this and a 6-substituted 1,3-dimethylpteridine-2,4-dione. Phenylmethanethiol, (2c) having one methylene group to contribute to the condensation gave the expected 8-phenylpurinedione (5c). Ethane- and 2-phenylethane-thiol, however, with an ethylene group to contribute, yielded a mixture of the appropriate purine (5) and pteridine (4).

The disulphides (3) and 5,6-diamino-1,3-dimethyluracil (1b) were probably formed by intramolecular oxidation–reduction involving the thiol and the nitroso-group. The diamine (1b) is known to be very sensitive to oxidation in air.[11] If the reaction mixture was exposed to air, separation and isolation of the components became more difficult.

Isolation of 6-amino-5-benzylideneamino-1,3-dimethyluracil (1c) from the reaction with phenylmethanethiol (2c) may indicate the occurrence of another type of oxidation–reduction process, involving abstraction of the α-proton of the thiol by the nitroso-group to give thiobenzaldehyde and the diamine (1b). Condensation of these products would give the anil (1c), which however could also be formed from the starting nitrosouracil and thiobenzaldehyde through a four-membered ring intermediate. A similar reaction of nitrosobenzene with a variety of >C=X systems (where X is a heteroatom, *e.g.* thioketones) has been reported to give anils.[14]

The thiadiazolopyrimidine (6) is believed to be formed from the nitrosouracil (1a) and hydrogen sulphide, and was indeed formed along with sulphur and the diamine (1b) by treatment of compound (1a) under the same reaction conditions with hydrogen sulphide in ethanol.

The extremely insoluble by-products of the reaction of (1a) with thiols were the pyrimidopteridines (7) and (8). Compound (7) is commonly obtained [10] from reactions involving the diamine (1b), the nitroso-compound (1a), or 6-amino-1,3-dimethyluracil. Its isomer (8) has been isolated from oxidation of 5-aminouracil with potassium ferricyanide.[10b] The intermediates (9)* or (10)† and (11)‡ may be considered as precursors of (7) (see Scheme). Interaction of two molecules of (10) may lead to the isomer (8). The mass spectra of both isomers (7) and

* Aliphatic and atomatic nitroso-compounds evidently are sufficiently nucleophilic to form *N*-substituted hydroxylamines with toluene-*p*-sulphonic acid and hydrogen bromide and chloride (P. W. Robertson, T. R. Hitchings, and G. M. Will, *J. Chem. Soc.*, 1950, 808).

† A reverse nitrosation of the intermediate *N*-halogenohydroxylamine has been reported (E. Bamberger and A. Rising, *Ber.*, 1901, **34**, 228).

‡ Phenols are reported to combine at the *ortho*-position with nitroso-compounds with the generation of a new carbon–nitrogen bond and formation of hydroxylamine [A. Silberg, I. Frenkel, and E. Bawer, *Studia Univ. Babes-Bolyai, Ser. Chem.*, 1965, **10**, 31 (*Chem. Abs.*, 1966, **65**, 645)].

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[9] F. F. Blicke and H. C. Godt, jun., *J. Amer. Chem. Soc.*, 1954, **76**, 2798.

[10] (*a*) E. C. Taylor, H. N. Loux, E. A. Falco, and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1955, **77**, 2243; (*b*) M. Ridi, C. Pellerano, and E. Masi, *Ann. Chim.* (*Italy*), 1963, **53**, 1717 (*Chem. Abs.*, 1964, **60**, 10,684).

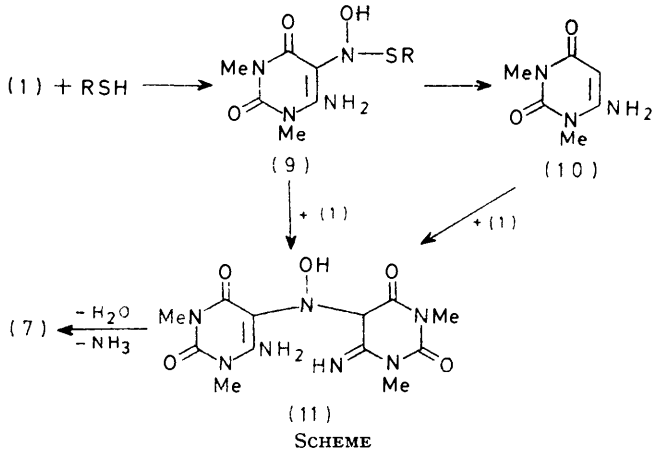
[11] J. A. Smythe, *J. Chem. Soc.*, 1922, 1400.

[12] R. D. Youssefyeh and A. Kalmus, *J. Heterocyclic Chem.*, 1971, **8**, 33.

[13] W. Traube and W. Nitback, *Ber.*, 1906, **39**, 227.

[14] L. Alessandri, *Gazzetta*, 1924, **54**, 426; A. Schonberg and K. H. Brosowki, *Chem. Ber.*, 1959, **92**, 2602; R. D. Youssefyeh and A. Kalmus, *Chem. Comm.*, 1970, 1371.

(8) showed the base peak at *m/e* 304 (M^+) with common fragment ions at *m/e* 276, 248, 219, 192, 134, and 107.



SCHEME

EXPERIMENTAL

M.p.s were determined with a Thomas-Hoover capillary apparatus. Mass spectra were obtained with a Varian MAT CH-5 instrument and n.m.r. spectra with a JEOL C-60 H 60 MHz spectrometer (tetramethylsilane as internal standard). T.l.c. was carried out on plates coated with Kieselgel PF 254 FM (Merck); spots were located with a u.v. lamp. Column chromatography was performed over grade III neutral alumina.

Reactions of 6-Amino-1,3-dimethyl-5-nitrosouracil.—(a) *With ethanethiol.* A mixture of the nitrosouracil, ethanethiol (1.5 cm³), and absolute ethanol (1.5 cm³) was heated in a sealed tube at 120 °C for 16 h. It was then evaporated to dryness and the residue was chromatographed over alumina (100 g). Elution with light petroleum gave first diethyl disulphide [15] (3b), δ (CCl_4) 1.28 (6 H, t, CH_3) and 2.63 (4 H, q, CH_2), and then the thiadiazolopyrimidine (6) [9] (122 mg), m.p. 147—149° (from ether–light petroleum) (lit.,[9] m.p. 149—151°), δ($CDCl_3$) 3.52 (3 H, s, NMe) and 3.75 (3 H, s, NMe), *m/e* 198 (M^+), 170 ($M-CO$), 141 ($M-CH_3NCO$), 114 (141—HCN), 113 (141—CO), and 86 (114—CO) (Found: C, 36.25; H, 3.5; N, 28.4; S, 15.65. Calc. for $C_6H_6N_4O_2S$: C, 36.1; H, 3.2; N, 28.3; S, 16.2%). Elution with 20% ether–light petroleum gave 1,3-dimethylpteridine-2,4-dione [4] (4b) (6 mg), m.p. 198—200° (lit.,[4] 200°), δ ($CDCl_3$) 3.51 (3 H, s, NMe), 3.69 (3 H, s, NMe), and 8.54 (2 H, 2- and 7-H). Elution with 5% methanol–dichloromethane gave 1,3,8-trimethylpurine-2,6-dione [4] (5b) (141 mg), m.p. 324—327° (lit.,[4] 325°), δ ($CDCl_3$) 2.60 (3 H, s, CH_3), 3.48 (3 H, s, NMe), and 3.62 (3 H, s, NMe), *m/e* 194 (M^+), 166 ($M-CO$), 137 ($M-CH_3NCO$), 109 (137—CO), and 68 (109—CH_3CN).

(b) *With phenylmethanethiol.* A mixture of the nitrosouracil, phenylmethanethiol (2 cm³), and ethanol (2 cm³) was heated in a sealed tube at 90 °C for 8 h. It was then evaporated to dryness and extracted with 50% ether–dichloromethane. The insoluble fraction was extracted a few times with methanol. The residue was extracted with dichloromethane. The insoluble substance was 1,3-dimethyl-8-phenylpurine-2,6-dione [13] (5c) (12 mg), m.p. 320°, δ ($CF_3{\cdot}CO_2H$) 3.65 (3 H, s, NMe), 3.89 (3 H, s, NMe), and 8.82 (5 H, aromatic). The dichloromethane solution was evaporated to give the pyrimidopteridine (7),[10] (56 mg) m.p. 360° from dichloromethane (lit.,[10] 403°). The methanolic solution contained 5,6-diamino-1,3-dimethyluracil,[12] (185 mg), m.p. 203—210° (from methanol) (lit.,[12] 209°), δ [$(CD_3)_2SO$] 3.14 (3 H, s, NMe) and 3.28 (3 H, s, NMe), *m/e* 170 (M^+), 142 ($M-CO$), 113 ($M-CH_3NCO$), 85 (113—CO), and 31 (58—HCN). The ether–dichloromethane solution was concentrated and the products separated by t.l.c. to give dibenzyl disulphide,[11] R_F 0.82 (ether), δ ($CDCl_3$) 3.60 (2 H, s, CH_2) and 7.26 (5 H, s, aromatic); the thiadiazolopyrimidine (6)[9] (174 mg), R_F 0.58 (ether); and 6-amino-5-benzylidineamino-1,3-dimethyluracil [13] (1c) (242 mg), m.p. 225—228° (from methanol–ether), R_F 0.32 (ether), δ [$(CD_3)_2SO$] 3.23 (3 H, s, NMe), 3.44 (3 H, s, NMe), 7.45 and 7.92 (5 H, m, aromatic), and 9.62 (1 H, s, CH), *m/e* 258 (M^+), 201 ($M-CH_3NCO$), 181 ($M-C_6H_5-CN$), 98 (201—C_6H_5—CN), 124 (181—CH_3NCO), 127 (155—CO), and 98 (155—CH_3NCO). (Found: C, 60.3; H, 5.7; N, 22.05. Calc. for $C_{13}H_{14}N_4O_2$: C, 60.5; H, 5.45; N, 2.17%).

A mixture of the anil (1c) (37 mg) and dry iron(III) chloride (37 mg) in absolute ethanol (4 cm³) was heated to 100 °C. A colour change from green to dark yellow was observed. The mixture was filtered and evaporated to dryness, and the residue washed well with water to give 1,3-dimethyl-8-phenylpurine-2,6-dione [13] (5c), m.p. >320°.

(c) *With 2-phenylethanethiol.* A mixture of the nitrosouracil (1 g), the thiol (2a) (2 cm³), and ethanol (2 cm³) was heated in a sealed tube at 100 °C for 16 h. It was then evaporated to dryness and the residue chromatographed over alumina (100 g). Elution with light petroleum gave the disulphide (3a), δ (CCl_4) 2.86 and 7.09 (ratio 4 : 5, 2 CH_2 and 5 aromatic H), *m/e* 274 (M^+), 136 ($M-C_6H_5CH_2SH$), 105 ($C_6H_5CH_2CH_2$), 104 (105—H), 91 (136—CH_3), and 77 (105—$CH_2{:}CH_2$). Elution with 50% ether–light petroleum gave the thiadiazolopyrimidine (6) [9] (162 mg). Elution with ether gave 1,3-dimethyl-8-phenylpteridine-2,4-dione [4] (4a), (46 mg), δ ($CDCl_3$) 3.56 (3 H, s, NMe), 3.74 (3 H, s, NMe), 7.48 and 8.08 (5 H, m, aromatic), and 9.02 (1 H, s, 7-H), *m/e* 268 (M^+), 240 ($M-CO$), 239 ($M-CH_2NH$), 211 ($M-CH_3NCO$), 183 (240—CH_3NCO), 156 (183—HCN), and 211 (239—CO). Elution with 20% ether–dichloromethane gave 8-benzyl-1,3-dimethylpurine-2,6-dione [4] (5a) (186 mg), m.p. 287—289°, δ [$(CD_3)_2SO$] 3.21 (3 H, s, NMe), 3.38 (3 H, s, NMe), 4.03 (2 H, s, CH_2), and 7.25 (3 H, s, aromatic), *m/e* 270 (M^+), 242 ($M-CO$), 213 ($M-CH_3NCO$), 186 (213—HCN), 185 (213—CO), 158 (185—HCN), 69 (185—C_6H_5-CH_2CN), and 117 ($C_6H_5CH_2CN$). Elution with dichloromethane gave the pyrimidopteridine (8)[10] (148 mg), m.p. 362—364° (from dichloromethane–methanol) (lit.,[10] 358—360°), δ ($CF_3{\cdot}CO_2H$) 3.65 (s, NMe) and 3.88 (s, NMe), *m/e* 304 (M^+) (Found: C, 47.6; H, 4.05; N, 27.4. Calc. for $C_{12}H_{12}N_6O_4$: C, 47.35; H, 3.95; N, 27.6%.)

(d) *With hydrogen sulphide.* A mixture of the nitrosouracil (200 mg), hydrogen sulphide gas, and ethanol (3 ml) was heated in a sealed tube at 85 °C for 16 h. It was then evaporated to dryness and the residue extracted with 50% ether–dichloromethane. The fraction not soluble in this medium was filtered off and crystallized from methanol. The fraction insoluble in methanol was sulphur. The fraction soluble in methanol was recrystallized from methanol to give the diamine (1b), m.p. 204—210°. The ether dichloromethane solution was evaporated to dryness and the residue crystallized from ether to give the thiadiazolopyrimidine (6) [9], m.p. 145—148° (lit.,[9] 149—151°).

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[15] I. F. Trotter and H. W. Thompson, *J. Chem. Soc.*, 1946, 481.