[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT NAVAL POWDER FACTORY]

# The Preparation and Reactions of 2-Alkyl-1(or 3)-nitro-2-thiopseudourea. Part I. Reaction with Amines[1]

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The nitration of 2-alkyl-2-thiopseudouronium sulfate and nitrate salts yields the corresponding 2-alkyl-1(or 3)-nitro-2-thiopseudourea. A study was made of the reaction of 2-methyl-1(or 3)-nitro-2-thiopseudourea with amines to produce derivatives of nitroguanidine.

When thiourea is nitrated with sulfuric–nitric acid mixtures, the product formed detonates spontaneously when dry.[2] However, it was found in this investigation that the nitration of S-alkyl thiopseudouronium salts yields stable, water-insoluble products.

A series of 2-alkyl-1(or 3)-nitro-2-thiopseudoureas were formed by either direct reaction of the corresponding sulfate salt with fuming nitric–concentrated sulfuric acid mixture at $-10$ to $+5°$ or adding the nitrate salt to cold concentrated sulfuric acid.

$$\left(\begin{matrix}\mathrm{RSC(=NH)NH_2}\end{matrix}\right)_2\cdot H_2SO_4 \xrightarrow[\text{concd. } H_2SO_4]{\text{fuming } HNO_3} \mathrm{RSC(=NH)NHNO_2} \xleftarrow{\text{concd. } H_2SO_4} \mathrm{RSC(=NH)NH_2\cdot HNO_3}$$

or

$$\mathrm{RSC(=N\text{—}NO_2)NH_2}$$

The method of synthesis and physical constants of the series are summarized in Table I.

$$2RNH_2 + \left(\begin{matrix}\mathrm{CH_3SC(=NH)NH_2}\end{matrix}\right)_2\cdot H_2SO_4 \longrightarrow \left(\begin{matrix}\mathrm{RNHC(=NH)NH_2}\end{matrix}\right)_2\cdot H_2SO_4 + 2CH_3SH \quad (a)$$

$$RNH_2 + \mathrm{CH_3SC(=NH)NHNO_2} \longrightarrow \mathrm{RNHC(=NH)NHNO_2} + CH_3SH \quad (b)$$

reagent dissolving instantly in the amine). Several weakly basic amines required a solvent for the reaction (usually absolute ethanol) and a short period of heating to initiate the reaction.

The ease of preparation, stability of the reagent and wide scope of the reaction, suggest considerable advantages of this procedure for the preparation of substituted nitroguanidine compounds. Heretofore the synthesis of nitroguanidine derivatives was accomplished by: (a) the nitration of alkyl guanidinium salts,[4] (b) the Davis[5] procedure of treating amines with nitroguanidine, and (c) by the method of McKay,[6] treating N-methyl-N-nitroso-N′-nitroguanidine with amines. These methods have been unsuccessful in the preparation of substituted nitroguanidine with secondary linear aliphatic amines other than dimethylamine.[7] Utilizing 2-methyl-1(or 3)-nitro-2-thiopseudourea, the substituted nitroguanidine derivatives of diethylamine and di-*n*-butylamine were prepared in yields of 50.6 and 72.5%, respectively.

Reaction of 2-methyl-1(or 3)-nitro-2-thiopseudourea with other nucleophilic reagents such as alk-

TABLE I

2-ALKYL-1(OR 3)-NITRO-2-THIOPSEUDOUREAS

$\mathrm{RSC(=NH)NHNO_2}$ or $\mathrm{RSC(=N\text{—}NO_2)NH_2}$

| R | M.p.,[c] °C. | Yield,[d] % Method A[a] | Method B[b] | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | 163–164 | 94 | 80 | $C_2H_6N_3O_2S$ | 17.76 | 17.99 | 3.73 | 3.96 | 31.11 | 31.50 |
| $C_2H_5$ | 110–111 | 85 | 78 | $C_3H_7N_3O_2S$ | 24.16 | 23.96 | 4.73 | 4.74 | 28.18 | 28.41 |
| $C_3H_7$ | 98–99 | .. | 80 | $C_4H_9N_3O_2$ | 29.44 | 29.30 | 5.55 | 5.37 | 25.76 | 25.70 |
| $C_4H_9$ | 89.5–90.5 | .. | 80 | $C_5H_{11}N_3O_2S$ | 33.88 | 33.44 | 6.26 | 6.31 | 23.72 | 23.53 |

[a] 2-Alkyl-2-thiopseudouronium sulfate with fuming nitric–concentrated sulfuric acid. [b] 2-Alkyl-2-thiopseudouronium nitrate with concentrated sulfuric acid. [c] Uncorrected melting points. [d] Crude yield.

The 2-alkyl-1(or 3)-nitro-2-thiopseudoureas were found to react with amines in a manner similar to the thiopseudouronium salts (Rathke procedure)[3] except that nitroguanidine derivatives were formed instead of guanidinium salts.

A study was then made of the reaction of 2-methyl-1(or 3)-nitro-2-thiopseudourea with various types of amines which are listed in Tables II and III. The majority of the reactions were carried out at room temperature without a solvent (the

(1) Publication approved by the Bureau of Ordnance, Navy Department.

(2) (a) J. E. Reynolds, *J. Chem. Soc.*, **22**, 6 (1869); (b) A. E. Dixon, *ibid.*, **111**, 62 (1917).

(3) (a) B. Rathke, *Ber.*, **17**, 297 (1884); (b) W. Schoeller and H. Schotte, German Patent 455,682 (June 23, 1931); (c) M. Heyn, British Patent 272,686 (June 18, 1926); (d) E. Schutte, *Z. physiol. Chem.*, **279**, 52 (1943); (e) M. Heyn, U. S. Patent 1,672,092 (June 25, 1928); (f) W. Schoeller and H. Schotte, U. S. Patent 1,805,889 (May 19, 1931).

(4) T. L. Davis and R. C. Elderfield, THIS JOURNAL, **55**, 731 (1933).

(5) (a) T. L. Davis and A. J. Abrams, *Proc. Am. Acad. Arts Sci.*, **61**, 437 (1926); (b) T. L. Davis and R. C. Elderfield, THIS JOURNAL, **55**, 731 (1933).

(6) (a) A. F. McKay and G. F Wright, *ibid.*, **69**, 3028 (1947); (b) A. F. McKay, *ibid.*, **71**, 1968 (1949); (c) A. F. McKay, *Chem. Revs.*, **51**, 316 (1952).

(7) A. F. McKay and G. F Wright, THIS JOURNAL, **69**, 3028 (1947).

TABLE II

1-SUBSTITUTED-3-NITROGUANIDINES

| Product | Yield, %[a] | M.p., °C.[b] | Recryst.[c] solv. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| 1-Methyl-[d] | 95 | 160.5–161 | | | | | | | | |
| 1-Propyl-[d] | 71 | 98–98.5 | | | | | | | | |
| 1-Butyl-[d] | 90 | 84–85 | | | | | | | | |
| 1-*t*-Butyl- | 70 | 199–201 | B | $C_5H_{12}N_4O_2$ | 37.48 | 37.56 | 7.55 | 7.56 | 34.98 | 35.20 |
| 1-(2-Ethylhexyl)- | 95 | 88–89 | A | $C_9H_{20}N_4O_2$ | 49.98 | 49.90 | 9.32 | 9.30 | 25.92 | 26.00 |
| 1-Cyclohexyl-[d] | 79 | 197–198 | | | | | | | | |
| 1-(2-Hydroxyethyl)-[d] | 77 | 118 | | | | | | | | |
| 1-Methyl-1-(2-hydroxyethyl)- | 70 | 100–101 | D | $C_4H_{10}N_4O_3$ | 29.63 | 29.52 | 6.22 | 6.10 | 34.56 | 35.00 |
| 1-(3-Methoxypropyl)- | 73 | 93–94 | C | $C_5H_{12}N_4O_3$ | 34.08 | 33.84 | 6.86 | 7.09 | 31.81 | 32.00 |
| 1-(3-Isopropoxypropyl)- | 80 | 91.5–92.5 | C | $C_7H_{16}N_4O_3$ | 41.16 | 40.98 | 7.89 | 7.65 | 27.43 | 27.60 |
| 1-(3-Isopropylaminopropyl)- | 75 | 118–120 | C | $C_7H_{17}N_5O_2$ | 41.36 | 41.30 | 8.43 | 8.21 | 34.46 | 34.60 |
| 1-(3-Dimethylaminopropyl)- | 77 | 102.5–103.5 | A | $C_6H_{15}N_5O_2$ | 38.08 | 38.17 | 7.99 | 7.73 | 37.02 | 37.00 |
| 1-(3-Diethylaminopropyl)-[d] | 90 | 133–135 | | | | | | | | |
| 1,1-Diethyl- | 50 | 92–94 | A | $C_5H_{12}N_4O_2$ | 37.48 | 37.50 | 7.55 | 7.50 | 34.98 | 35.00 |
| 1,1-Di-*n*-butyl- | 72 | 74–75 | D | $C_9H_{20}N_4O_2$ | 49.98 | 49.81 | 9.32 | 9.35 | 25.92 | 26.08 |
| 1-Benzyl-[d] | 70 | 181–182 | | | | | | | | |
| 1-β-Phenylethyl-[d] | 89 | 162–163 | | | | | | | | |
| 1-(*m*-Tolyl)-[d] | 65 | 126–127 | | | | | | | | |
| 1-Piperidyl-[d] | 73 | 155.5–156.5 | | | | | | | | |
| 1-(2-Pyridyl)-[d] | 55 | 228–229 | | | | | | | | |
| 1-Morpholinyl-[d] | 80 | 186–188 | | | | | | | | |
| 1-Pyrrolidyl- | 77 | 188–190 | D | $C_5H_{10}N_5O_2$ | 37.87 | 38.13 | 6.37 | 6.29 | 35.43 | 35.23 |
| 1-(2-Furfuryl)- | 80 | 138–139 | A | $C_6H_8N_4O_3$ | 39.13 | 39.20 | 4.38 | 4.40 | 30.43 | 30.54 |
| 1-Amino-[d,e] | 75 | 188–190 | | | | | | | | |
| 1-Anilino-[d] | 59 | 170–172 | | | | | | | | |

TABLE III

BIS-(3-NITROGUANIDINO)-ALKANES

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1,2-Bis-(3-nitroguanidino)-ethane[d] | 76 | 248–250 | | | | | | | | |
| 1,6-Bis-(3-nitroguanidino)-hexane | 60 | 237–239 | D | $C_8H_{18}N_8O_4$ | 33.10 | 33.15 | 6.25 | 6.30 | 38.61 | 38.72 |
| Bis-(3-nitroguanidinopropyl)-amine | 80 | 121–122 | A | $C_8H_{19}N_9O_4$ | 31.47 | 31.68 | 6.27 | 6.55 | 41.30 | 41.54 |

[a] These yields represent those of crude products. [b] All melting points are uncorrected. [c] Recrystallization solvents: A, ethanol; B, methanol; C, ethanol–water; D, acetone–methanol. [d] Compounds previously reported, ref. 6c. [e] The nitroguanylhydrazones of 2-ethylbutyraldehyde and 1-ethylhexaldehyde were prepared by the procedure of W. F. Whitmore, THIS JOURNAL, **57**, 706 (1935). Nitroguanylhydrazone of 2-ethylbutyraldehyde, m.p. 138–140°. *Anal.* Calcd. for $C_7H_{15}N_5O_2$: C, 41.78; H, 7.51; N, 34.81. Found: C, 41.61; H, 7.57; N, 34.76. Nitroguanylhydrazone of 2-ethylhexaldehyde, m.p. 125.5–126.5°. *Anal.* Calcd. for $C_9H_{19}N_5O_2$: C, 47.14; H, 8.36; N, 30.55. Found: C, 47.33; H, 8.23; N, 30.63.

oxide and phthalimido ions are currently being investigated.

## Experimental

**2-Methyl-1(or 3)-nitro-2-thiopseudourea.** By **Method A.**—2-Methyl-2-thiopseudouronium sulfate (20.0 g., 0.0718 mole) was added portionwise over a period of ten minutes to a nitrating mixture consisting of 20 cc. of 98% nitric acid and 60 cc. of 95% sulfuric acid. The nitration was carried out at −10° for half the reacting substance, the remaining portion was added at 0° to +5°. The contents were cooled to 0° then poured in two portions into 850 g. of ice. The precipitate was filtered through a glass fritted funnel and washed with 150 cc. of water, then air-dried. The yield of crude product (m.p. 154–158°) was 18.4 g. or 94.8%. Two crystallizations from a mixture of ethanol and water (1:2) gave white crystals melting at 163–164°, $n^{25}D$ 1.486, $d^{25}_4$ 1.93.

2-Methyl-1(or 3)-nitro-2-thiopseudourea (1.8 g., 0.0133 mole) was heated together with 50 cc. of acetic anhydride in 20 cc. of pyridine on a steam-bath for five hours. The solution was concentrated *in vacuo* to *ca.* 10 cc. On cooling, 1.5 g. (64.1% yield) of white crystals separated out. The melting point of the acetyl derivative 98–101° was raised to 105–106° by two crystallizations from acetone.

*Anal.* Calcd. for $C_4H_7N_3O_3S$: C, 27.11; H, 3.98; N, 23.73. Found: C, 27.44; H, 4.05; N, 23.83.

**Method B.**—2-Methyl-2-thiopseudouronium nitrate (1 g., 0.0065 mole) was added portionwise over a period of five minutes to 4 cc. of 95% sulfuric acid at 0–5°. The clear reaction mixture was added with stirring to 10 g. of ice. The precipitate was filtered off and washed with 15 cc. of ice-water; yield 0.7 g. (80%). The purified product melted at 163–164° alone and admixed with an authentic sample of 2-methyl-1(or 3)-nitro-2-thiopseudourea.

**2-Butyl-2-thiopseudouronium Nitrate.**—2-Butyl-2-thiopseudouronium iodide was prepared by the procedure of Urquhart.[8] 2-Butyl-2-thiopseudouronium iodide (18.2 g., 0.07 mole) dissolved in 100 cc. of water was mixed with 12.0 g. (0.07 mole) of silver nitrate in 200 cc. of water. The contents were heated on a steam-bath for 30 minutes, then allowed to stand overnight at room temperature. The precipitate of silver iodide was filtered and washed with 100 cc. of water. The filtrate was evaporated on a steam-bath to *ca.* 15 cc., which on cooling deposited 10.9 g. (80%) of white crystals. The melting point of 62–63° was raised to 63–64° by one crystallization from chloroform.

*Anal.* Calcd. for $C_5H_{13}N_3O_3S$: C, 30.76; H, 6.71; N, 21.53. Found: C, 30.67; H, 6.88; N, 21.61.

The nitrate salts of 2-ethyl- and 2-propyl-2-thiopseudourea were prepared in an analogous manner as described above.

2-Ethyl-2-thiopseudouronium nitrate, m.p. 53–54°. *Anal.* Calcd. for $C_3H_9N_3O_3S$: C, 21.56; H, 5.43; N, 25.14. Found: C, 21.62; H, 5.53; N, 25.00.

2-Propyl-2-thiopseudouronium nitrate, m.p. 74–76°. *Anal.* Calcd. for $C_4H_{11}N_3O_3S$: C, 26.52; H, 6.12; N, 23.19. Found: C, 26.30; H, 6.15; N, 23.00.

**1-(3-Isopropoxypropyl)-3-nitroguanidine.**—Five grams (0.036 mole) of 2-methyl-1(or 3)-nitro-2-thiopseudourea was added to 4.7 g. (0.04 mole) of 3-isopropoxypropylamine

(8) J. M. Urquhart, *Org. Syntheses*, **21**, 36 (1941).

(American Cyanamid). The reagent dissolved in the amine with the immediate evolution of methyl mercaptan. The reaction mixture was allowed to stand at room temperature for two hours. A mixture of 100 cc. of ethanol and water (1:1) was added to the pasty mass. The precipitate (5.9 g., 80.3% yield) was recovered by filtration. The melting point of 87–90° was raised to 91.5–92.5° by one crystallization from a mixture of ethanol and water (1:1).

**1-(*t*-Butyl)-3-nitroguanidine.**—*t*-Butylamine (7.3 g., 0.1 mole), 10.8 g. (0.08 mole) of 2-methyl-1(or 3)-nitro-2-thiopseudourea and 25 cc. of absolute ethanol were heated on a water-bath at 45° for six minutes. The contents on standing overnight at room temperature deposited 8.9 g. (70.0%) of white crystals. The melting point of 192–196° was raised to 199–201° by one crystallization from methanol.

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# Monomer Synthesis. X.[1] The Preparation and Polymerization of 4-Vinylpyrimidine and 2-N,N-Dimethylamino-4-vinylpyrimidine

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Convenient syntheses of 4-vinylpyrimidine and 2-N,N-dimethylamino-4-vinylpyrimidine are described. These are the first simple vinylpyrimidines reported in the literature. The general reaction consists of the conversion of the appropriate methylpyrimidine to the β-hydroxyethyl derivative followed by dehydration over solid potassium hydroxide. A number of derivatives of the two vinylpyrimidines are reported. Polymers have been prepared by radical catalysis and characterized. The vinylpyrimidines are inactive against sarcoma 180.

It was of interest to prepare vinylpyrimidines in order to study their polymerization and the properties of their polymers. In particular the effect of a vinyl monomer, which would give a polymer of related structure to a portion of a polynucleic acid, on abnormal cell mitosis was of interest. Many of the most promising compounds tested against sarcoma 180 with the exception of nitrogen mustards contain a pyrimidine or triazine ring. Rather few synthetic polymeric materials have been screened, this being largely due to their insolubility. It is unlikely that a polymer containing carbon–carbon chains would diffuse through the cell wall although polyesters and polyamides would probably be susceptible to enzymatic hydrolysis. It was hoped that the relatively water-soluble vinylpyrimidines would diffuse through the cell wall and polymerize within the cell due to the probable one-electron transfer, oxidation–reduction process within the cell. Association of this polymer with the chromosome would then be realized. Up to now, this type of approach has received no attention. This paper will describe the synthesis of 4-vinylpyrimidine and 2-N,N-dimethylamino-4-vinylpyrimidine and their effect on sarcoma 180. In addition, their polymerization with a radical catalyst is reported.

No simple vinylpyrimidines have previously been recorded. Price and Zomlefer[3] reported the attempted preparation of 4-hydroxy-6-methyl-2-vinylpyrimidine by reaction of β-hydroxyethylacetamidine and acetoacetic ester. When this product was heated in decalin, dehydration occurred but only polymeric material was obtained. Recently several styryl derivatives have been reported.[4] 4-(β-Phenylvinyl)-pyrimidine was prepared from 4-methylpyrimidine and benzaldehyde.[5] Ross found that 6-methyluracil would not condense to give the styryl derivative but that a 5-nitro group activated the methyl group and the styryl derivative was obtained. The *p*-dimethylamino and the *p*-nitro derivatives also have been prepared.[6]

The synthesis shown was used to prepare 2-N,N-dimethylamino-4-vinylpyrimidine.

Compound I also has been reported by Russell, Elion and Hitchings[7] by reaction of 2-ethylmercapto-4-hydroxy-6-methylpyrimidine with an ethanolic solution of dimethylamine in a sealed tube at 130°. Reduction of the chloro compound with palladium-on-charcoal and magnesium oxide was more satisfactory than chemical methods. The Mannich base VI was obtained from II as indicated. This compound is stable in refluxing 20, 40 and 65% aqueous sodium hydroxide, 15% ethanolic sodium hydroxide and 15% potassium *t*-butoxide. Graham, *et al.*,[8] have reported the only known case of formation of a Mannich base on a methylpyrimidine from 4-acetyl-5-methyl-2-phenylpyrimidine. They suggest that reaction occurs on the acetyl methyl group.

The conversion of II to give III and IV was carried out with paraformaldehyde and an excess of methylpyrimidine at 160° for 3.5 hours in a sealed tube. Compound II was always recovered and could be conveniently recycled without further purification. When the reaction tube was heated at 160° for 24 hours, a third product was isolated also, an analysis and molecular weight of which indicated a dimer. Attempts to condense II with IV with sodium ethoxide or by employing the sealed tube conditions of the condensation reaction with formaldehyde were unsuccessful. The picrate of the

(1) This is the tenth in a series of articles concerned with the synthesis of monomers and their polymerization; for the ninth paper in this series, see C. G. Overberger and Irving C. Kogon, THIS JOURNAL, **76**, 1065 (1954).

(2) Public Health Research Fellow 1951–1953. This paper comprises a portion of a thesis presented by Mr. Irving C. Kogon in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

(3) C. C. Price and J. Zomlefer, *J. Org. Chem.*, **14**, 210 (1949).

(4) D. M. Brown and G. A. R. Kon, *J. Chem. Soc.*, 2147 (1948).

(5) W. C. J. Ross, *ibid.*, 1128 (1948).

(6) D. M. Brown and W. C. J. Ross, *ibid.*, 1715 (1948).

(7) P. B. Russell, G. B. Elion and G. H. Hitchings, THIS JOURNAL, **71**, 474 (1949).

(8) B. Graham, A. M. Griffith, C. S. Pease and B. F. Christensen, *ibid.*, **67**, 1294 (1945).