m.p. 225–227°. Recrystallization from 60 ml. of 2-methoxyethanol gave 0.9 g. (72%) of product; orange needles; m.p. 230–232°.

Anal. Calcd. for $C_{12}H_{11}N_6Cl_3$ (345.6): C, 41.8; H, 3.2; N, 24.4. Found: C, 41.5; H, 3.7; N, 24.8.

7-Dimethylamino-5-methylmercapto-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine (XVII). A mixture of 0.8 g. (2 mmoles) of 4-amino-6-dimethylamino-2-methylmercapto 5-(2,4,6-trichlorophenylazo)pyrimidine (XV), 2.5 g. of copper sulfate pentahydrate, 7.0 ml. of water, and 14.0 ml. of pyridine was heated at reflux for 4 hr. The solution was then diluted with 50 ml. of water and cooled overnight; yield 0.75 g. (94%); m.p. 214–216°. This was recrystallized from 7 ml. of 2-methoxyethanol; yield: 0.58 g. (72%), m.p. 216–217°.

Anal. Calcd. for $C_{13}H_{11}N_6SCl_3$ (389.6): C, 40.1; H, 2.8; N, 21.6; S, 8.2; Cl, 27.4. Found: C, 39.9; H, 3.1; N, 21.8; S, 8.4; Cl, 27.3.

7-Dimethylamino-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine (XVIII). A mixture of 0.85 g. (2.5 mmoles) of 4-amino-6-dimethylamino-5-(2,4,6-trichlorophenylazo)-pyrimidine (XVI), 2.5 g. of copper sulfate pentahydrate, 7 ml. of water, and 14 ml. of pyridine were heated to reflux for 5 hr. The mixture was diluted with several volumes of water and cooled; yield 0.7 g. (83%); m.p. 262–267°. Recrystallization from 15 ml. of 2-methoxyethanol gave 0.55 g. (65% yield) of product; m.p. 266–268°.

Anal. Calcd. for $C_{12}H_9N_6Cl_3$ (343.6): C, 41.9; H, 2.7; N, 24.5; Cl, 31.0. Found: C, 41.9; H, 2.8; N, 24.8; Cl, 30.6.

Acid hydrolysis of 7-dimethylamino-5-methylmercapto-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine (XVII). A solution of 300 mg. (0.77 mmole) of XVII in 15 ml. of 6*N* hydrochloric acid was heated to reflux for 8 hr. during which time a crystalline solid separated. The solid was collected (yield 60 mg. (23%)), dissolved in 3 ml. of hot 2-methoxyethanol and 2 ml. of hot water added. Cooling gave 35 mg. of 5,7-dihydroxy-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine; m.p. >300°. Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, λ_{max} 317 mμ (ε 7,700); methanol, λ_{max} 280 mμ (ε 10,700); 0.1*N* hydrochloric acid, λ_{max} 281 mμ (ε 11,700).

Anal. Calcd. for $C_{10}H_4N_5O_2Cl_3$ (332.6): C, 36.1; H, 1.2; N, 21.0; Cl, 32.0. Found: C, 36.2; H, 1.5; N, 20.8; Cl, 32.0.

The 6*N* hydrochloric acid filtrate from the reaction was diluted to 70 ml. with water and brought to *p*H 4 with sodium acetate. A crystalline product separated; yield: 160 mg. (57%). This was recrystallized from 5 ml. of 2-methoxyethanol to give 80 mg. of 7-dimethylamino-5-hydroxy-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine; m.p. >300°. Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, λ_{max} 280 mμ (ε 6,800), 334 mμ (ε 9,500); methanol, λ_{max} 287 mμ (ε 16,500), 0.1*N* hydrochloric acid, λ_{max} 299 mμ (ε 12,900).

Anal. Calcd. for $C_{12}H_9N_6OCl_3$ (359.6): C, 40.1; H, 2.5; N, 23.4; Cl, 29.6. Found: C, 39.9; H, 2.8, N, 23.3; Cl, 29.7.

4-Amino-6-dimethylamino-2-methylmercapto-5-phenylazopyrimidine. Aniline (4.7 g., 50 mmoles) was diazotized as described by Bensen *et al.*[6] and the diazonium solution was coupled with 9.2 g. (50 mmoles) of 4-amino-6 dimethylamino-2-methylmercaptopyrimidine dissolved in a solution of 300 ml. of water, 115 ml. of acetic acid, and 52 g. of sodium acetate; yield: 8.1 g. This was recrystallized from 100 ml. of 2-methoxyethanol; yield: 7.2 g. (50%) of an orange product, m.p. 197–198°.

A sample (0.45 g.) was recrystallized from 80 ml. of ethanol; yield: 0.25 g., m.p. 198–199°.

Anal. Calcd. for $C_{13}H_{16}N_6S$ (288): C, 54.2; H, 5.7; N, 29.2; S, 11.1. Found: C, 53.8; H, 5.6; N, 29.0; S, 11.0.

7-Dimethylamino-5-methylmercapto-2-phenyl-2H-v-triazolo(d)pyrimidine. A solution of 6.5 g. (22.6 mmoles) of 4-amino-6-dimethylamino-2-methylmercapto-5-phenylazopyrimidine, 16.7 g. of copper sulfate pentahydrate, 64 ml. of pyridine, and 34 ml. of water was heated at reflux for 2.5 hr. and cooled; yield of product 6.3 g. (98%); m.p. 193–194°; mixed melting point with starting material 165–180°.

A sample (0.5 g.) was recrystallized from 80 ml. of ethanol; yield of light yellow crystalline product 0.4 g.; m.p. 194–195°.

Anal. Calcd. for $C_{13}H_{14}N_6S$ (286): C, 54.6; H, 4.9; N, 29.4. Found: C, 54.4; H, 5.9; N, 29.7.

Acknowledgment. The authors are indebted to Mr. Louis Brancone and staff for the microanalytical data and to Mr. William Fulmor and Mr. George Morton for the spectral data.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY]

Potential Purine Antagonists. XXIII. Synthesis of Some 7-Substituted Amino-v-triazolo(d)pyrimidines[1]

RONALD WEISS, ROLAND K. ROBINS, AND C. WAYNE NOELL

Received November 11, 1959

The preparation of certain 7-alkylamino-v-triazolo(d)pyrimidines from 7-methylthio-v-triazolo(d)pyrimidine (XIV) has been accomplished. Some 7-alkylthio-5-amino-v-triazolo(d)pyrimidines have been synthesized by ring closure of the corresponding 6-alkylthio-2,4,5-triaminopyrimidines with nitrous acid. 5-Amino-7-methoxy-v-triazolo(d)pyrimidine has been prepared.

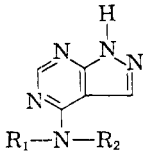
The antitumor activity of 5-amino-7-hydroxy-v-triazolo(d)pyrimidine[2] (8-azaguanine) and 6-amino-4-hydroxypyrazolo(3,4-d)pyrimidine[3] strongly suggested the possibility that antitumor activity similar to that exhibited by the 4-substituted-

(1) Supported by research grant CY-4008 from the National Cancer Institute of the National Institutes of Health, Public Health Service. Presented before the Division of Medicinal Chemistry at the 136th Meeting of the American Chemical Society, September 18, 1959, Atlantic City, N. J.

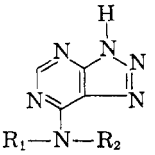
(2) G. W. Kidder, V. C. Dewey, R. E. Parks, and G. L. Woodside, *Cancer Research*, 11, 204 (1949).

(3) H. E. Skipper, R. K. Robins, J. R. Thomson, C. C. Cheng, R. W. Brockman, and F. M. Schabel, Jr., *Cancer Research*, 17, 583 (1957).

aminopyrazolo(3,4-d)pyrimidines (I)[3] might also be found with isomeric derivatives of 7-substituted-amino-v-triazolo(d)pyrimidine (II).



I



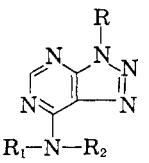
II

The synthesis of compounds of type II has now been accomplished in several steps from 4-amino-6-chloro-5-nitropyrimidine (III).[4]

Treatment of 4-amino-6-chloro-5-nitropyrimidine with a dialkylamine resulted in the preparation of the corresponding 4-amino-6-dialkylamino-5-nitropyrimidine (IV) which was reduced with hydrogen in the presence of Raney nickel to the corresponding 6-dialkylamino-4,5-diaminopyrimidine (V). Cyclization of V with nitrous acid gave the desired 7-dialkylamino-v-triazolo(d)pyrimidine (VI). The 7-dialkylamino-v-triazolo(d)pyrimidines (VI) prepared in this manner are listed as the first three compounds in Table I. The cyclization of 4,5-diamino-6-methylaminopyrimidine (VII)[5] with nitrous acid could theoretically give rise to either 7-methylamino-v-triazolo(d)pyrimidine (VIII) or 7-amino-3-methyl-v-triazolo(d)pyrimidine (IX).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 7-ALKYLAMINO-V-TRIAZOLO(d)PYRIMIDINES

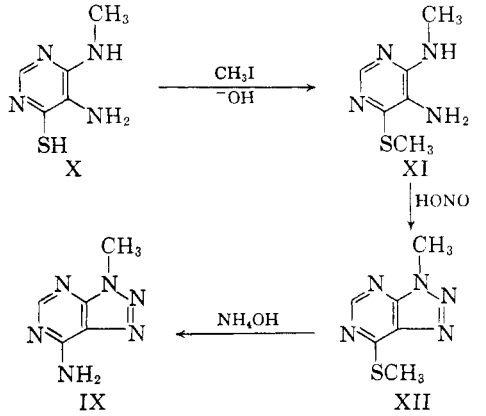


			pH 1		pH 11	
			λ max,		λmax,	
R	R_1	R_2	mμ	ε	mμ	ε
H	CH_3	CH_3	287	15,300	294	32,400
H	C_2H_5	C_2H_5	287	11,400	294	16,600
H	n-C_3H_7	n-C_3H_7	290	10,800	295	15,900
CH_3	H	H	263	12,900	277	12,400
CH_3	H	CH_3	270	12,800	288	12,700
CH_3	C_2H_5	C_2H_5	278	19,200	298	17,500
C_2H_5	H	C_2H_5	271	11,600	289	11,600

Ring closure of 4,5-diamino-6-methylaminopyrimidine (VII) with nitrous acid gave exclusively 7-amino-3-methyl-v-triazolo(d)pyrimidine (IX).

The structure of IX was established by independent synthesis from 3-methyl-7-methylthio-v-triazolo(d)pyrimidine (XII) and hot aqueous ammonia. The preparation of XII was accomplished in two steps from 5-amino-4-methylamino-6-pyrimidinethiol.[6]

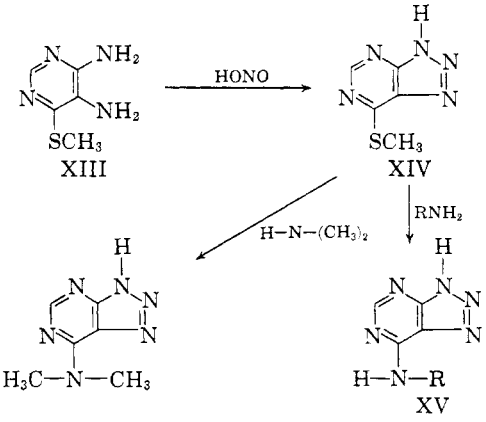
The ease of nucleophilic displacement of the methylthio group of 3-methyl-7-methylthio-v-triazolo(d)pyrimidine (XII) suggested that this might be a useful method of preparing a number of desired 7-alkylamino-v-triazolo(d)pyrimidines unsubstituted at position 3.



The synthesis of 7-methylthio-v-triazolo(d)pyrimidine (XIV) was accomplished in good yield from 4,5-diamino-6-methylthiopyrimidine (XIII)[7] and nitrous acid.

Treatment of XIV with various primary amines in refluxing aqueous solution gave the desired 7-alkylamino-v-triazolo(d)pyrimidines XV listed in Table II.

The replacement of the methylthio group has similarly been accomplished in the purine series to give 6-substituted-aminopurines.[8,9] Substitution of



the 2-methylthio group by amines has similarly been reported for 6-hydroxy-2-methylthiopurine.[10]

(4) S. M. Greenberg, L. O. Ross, and R. K. Robins, *J. Org. Chem.*, **24**, 1314 (1959).

(5) W. Daly and B. E. Christensen, *J. Org. Chem.*, **21**, 177 (1956).

(6) R. K. Robins and H. H. Lin, *J. Am. Chem. Soc.*, **79**, 490 (1957).

(7) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 3832 (1954).

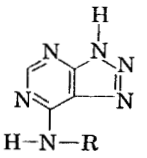
(8) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

(9) J. A. Montgomery, L. B. Holum, and T. P. Johnston, *J. Am. Chem. Soc.*, **81**, 3963 (1959).

(10) G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 217 (1956).

TABLE II

PREPARATION OF 7-ALKYLAMINO-v-TRIAZOLO(d)-PYRIMIDINES FROM 7-METHYLTHIO-v-TRIAZOLO(d)PYRIMIDINE



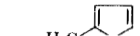
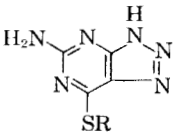
R	M.P.	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	Yield, %	Recrystallization Solvent	pH 1 λmax, mμ	pH 1 ε	pH 11 λmax, mμ	pH 11 ε
CH_3	>300	40.0	40.1	4.0	4.3	56.0	56.3	95.0	Water	270	22,300	285	15,200
C_2H_5	260–262	43.8	44.1	4.9	5.1	51.2	51.4	98.0	Water	270	16,600	285	18,700
t-C_4H_9	248–250	49.9	50.2	6.3	6.7	43.8	44.2	49.6	Ethanol	274	16,400	288	20,700
n-C_4H_9	223–225	50.0	50.5	6.3	6.0	43.8	44.2	61.0	Ethanol	273	14,700	297	17,500
	255–257	49.8	50.1	4.1	4.1	38.7	39.1	53.8	Ethyl acetate	278	17,300	284	12,700

TABLE III

SOME 7-ALKYLTHIO-5-AMINO-v-TRIAZOLO(d)PYRIMIDINES

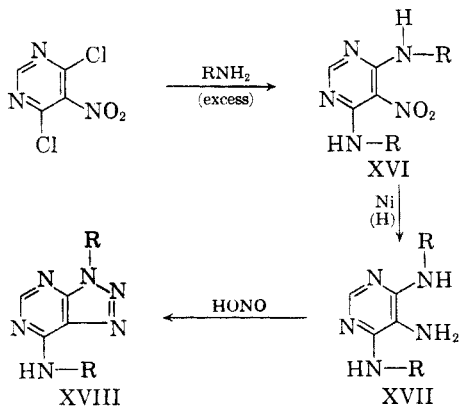


R	M.P.	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	Yield, %	Recrystallization Solvent	pH 1 λmax, mμ	pH 1 ε	pH 11 λmax, mμ	pH 11 ε
CH_3	282–284 dec.	33.0	33.4	3.3	3.5	46.2	46.5	78.7	Water-methanol	298	19,100	321	10,700
C_2H_5	206–208	36.7	36.3	4.1	4.0	42.9	42.7	95.5	Water-ethanol	301	20,100	265 320	10,000 11,000
n-C_3H_7	200–202	40.0	40.4	4.8	5.1	40.0	40.2	87.5	Ethyl acetate	304	20,400	265 324	9,600 11,400
n-C_4H_9	195–197	42.8	43.3	5.4	5.6	37.5	37.8	71.5	Water-ethanol	303	32,800	265 324	9,900 15,200
$CH_3CH_2{=}CH_2$	231–233	40.4	40.9	3.8	4.0	40.4	40.7	90.5	Ethyl acetate	304	18,300	266 323	13,000 11,400
p-$ClCH_2C_6H_4$	242–244 dec.	45.2	45.7	3.1	2.8	28.7	29.0	33.8	Water-ethanol	307	12,400	265 323 267	9,600 23,500 22,100

However, in each instance of replacement of the methylthio group by an amine reported in the purines, temperatures of 130° to 160° were employed. These conditions require sealed tubes or pressure reaction vessels. It is quite significant that the presence of an additional nitrogen atom at position 8 of the purine ring lowers the electron density in the pyrimidine ring to the extent that nucleophilic displacement of the methylthio group by amines can be effected without recourse to sealed tube procedures.

The preparation of 7-dimethylamino-v-triazolo-(d)pyrimidine was likewise accomplished from XIV and aqueous methylamine.

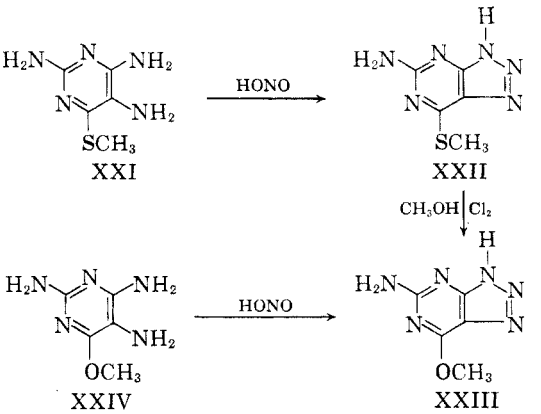
The preparation of 3-ethyl-7-ethylamino-v-triazolo(d)pyrimidine (XVIII R=C_2H_5) and 3-methyl-7-methylamino-v-triazolo(d)pyrimidine (XVIII R=CH_3) was accomplished according to reaction scheme I.



REACTION SCHEME I

Because of the antitumor activity of 6-benzylthiopurine,[11] 6-benzylthio-4,5-diaminopyrimidine (XIX)[12] was cyclized with nitrous acid to give 7-benzylthio-v-triazolo(d)pyrimidine(XX).

Interest in the antitumor activity of several 6-alkylthio-2-aminopurines[11,13] suggested the preparation of some related 7-alkylthio-5-amino-v-triazolo(d)pyrimidines. The simplest compound of this type, 5-amino-7-methylthio-v-triazolo(d)-pyrimidine (XXII) was prepared from 6-methylthio-2,4,5-triaminopyrimidine (XXI)[14] and nitrous acid. A number of additional 7-alkylthio-5-amino-v-triazolo(d)pyrimidines were prepared by ring closure of the corresponding 6-alkylthio-2-amino-4,5-diaminopyrimidines.[14] (See reaction scheme II.) These compounds are listed in Table III.



REACTION SCHEME II

Attempts to prepare 5-amino-7-chloro-v-triazolo-(d)pyrimidine from XXII with chlorine in methanol gave instead 5-amino-7-methoxy-v-triazolo-(d)pyrimidine XXIII. This reaction was unexpected, as 2-amino-6-methylthiopurine under similar conditions gives 2-amino-6-chloropurine.[14] That XXIII was indeed 5-amino-7-methoxy-v-triazolo-(d)pyrimidine was established by ring closure of 6-methoxy-2,4,5-triaminopyrimidine (XXIV)[15] with nitrous acid to yield XXIII identical to the product obtained from 5-amino-7-methylthio-v-triazolo(d)-pyrimidine (XXII).

EXPERIMENTAL[16]

Preparation of 4-amino-5-nitro-6-ni-n-propylaminopyrimidine (IV). To 85 ml. of *p*-dioxane, containing 6 g. of 4-amino-6-chloro-5-nitropyrimidine,[4] was added 6.7 g. of di-*n*-propylamine. The mixture was stirred for 30 min., cooled, and then poured onto 100 g. of ice water. The precipitate which formed was filtered and washed with water. The dried crude product was recrystallized from absolute ethanol to yield 7 g. of crystalline needles, m.p. 115–117°.

Anal. Calcd. for $C_{10}H_{17}N_5O_2$: C, 50.2; H, 7.1; N, 29.3. Found: C, 49.9; H, 7.4; N, 29.6.

4,5-Diamino-6-di-n-propylaminopyrimidine (V). Five grams of 4-amino-6-di-*n*-propylamino-5-nitropyrimidine was dissolved in 150 ml. of methanol, and the solution was shaken with Raney nickel catalyst at a hydrogen pressure of approximately 40 p.s.i. for 1 hr. The solution was boiled with charcoal and filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude product was recrystallized from ethyl acetate to yield 3.7 g. of light-green needles, m.p. 108–110°.

Anal. Calcd. for $C_{10}H_{19}N_5$: C, 57.4; H, 9.1; N, 33.5. Found: C, 57.1; H, 9.1; N, 33.2.

7-Di-n-propylamino-v-triazolo(d)pyrimidine (VI). One gram of 4,5-diamino-6-di-*n*-propylaminopyrimidine was dissolved in 30 ml. of water containing 10 ml. of glacial acetic acid. To this cold solution was added, with stirring, a solution of 0.6 g. of sodium nitrite in 10 ml. of water. A precipitate formed almost immediately. The product was filtered and washed with water to yield 0.7 g. of compound. A small portion was recrystallized from petroleum ether to give a melting point of 104–106°.

(11) H. E. Skipper, J. A. Montgomery, J. R. Thomson, and F. M. Schabel, Jr., *Cancer Research*, **19**, 425 (1959).

(12) G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 2858 (1956).

(13) D. A. Clarke, G. B. Elion, G. H. Hitchings, and C. C. Stock, *Cancer Research*, **18**, 445 (1958).

(14) G. D. Daves, Jr., C. W. Noell, R. K. Robins, H. C. Koppel, and A. G. Beaman, "Potential Purine Antagonists. XXII. . . . ," *J. Am. Chem. Soc.* (in press).

(15) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Am. Chem. Soc.*, **73**, 2869 (1951).

(16) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus, unless otherwise stated.

Anal. Calcd. for $C_{10}H_{16}N_6$: C, 54.6; H, 7.3; N, 38.2. Found: C, 54.8; H, 7.4; N, 38.6.

7-Diethylamino-v-triazolo(d)pyrimidine (VI). Preparation of this compound by the cyclization of 4,5-diamino-6-diethylaminopyrimidine[17] with nitrous acid was carried out in a manner identical to that employed for the preparation of 7-di-*n*-propylamino-v-triazolo(d)pyrimidine previously described. The product was recrystallized from water to give white crystals, m.p. 188–190°.

Anal. Calcd. for $C_8H_{12}N_6$: C, 50.0; H, 6.3; N, 43.7. Found: C, 50.0; H, 6.6; N, 43.4.

7-Methylthio-v-triazolo(d)pyrimidine (XIV). Two grams of 4,5-diamino-6-methylthiopyrimidine[7] was added to 110 ml. of water, containing 0.9 ml. of sulfuric acid. The mixture was filtered and cooled. To this solution was added, with stirring, 1 g. of sodium nitrite in 10 ml. of water. The product was filtered and washed with petroleum ether to give 1.5 g. of product which was recrystallized from water to give white needles, m.p. 203–205°.

Anal. Calcd. for $C_5H_5N_5S$: C, 35.9; H, 2.9; N, 41.8. Found: C, 35.7; H, 2.7; N, 41.5.

7-Benzylthio-v-triazolo(d)pyrimidine (XX). One gram of 6-benzylthio-4,5-diaminopyrimidine[12] was dissolved in 35 ml. of water, containing 7 ml. of hydrochloric acid. A solution containing 0.7 g. of sodium nitrite in 10 ml. of water was added slowly with stirring. The product was filtered and washed with petroleum ether to yield 1 g. Recrystallization from water yielded white crystals, m.p. 164–166°.

Anal. Calcd. for $C_{11}H_9N_5S$: C, 54.4; H, 3.7; N, 28.9. Found: C, 54.4; H, 3.7; N, 29.3.

Preparation of 7-alkylamino-v-triazolo(d)pyrimidines (see Table II). *Example A. 7-Furfurylamino-v-triazolo(d)pyrimidine.* Seven grams of 7-methylthio-v-triazolo(d)pyrimidine (XIV) was placed in a solution of 100 ml. of water to which had been previously added 8 g. of furfurylamine. This mixture was then refluxed for 4 hr. The solution was evaporated to dryness under reduced pressure using a steam bath as the source of heat. The crude product was collected and reprecipitated from dilute ammonium hydroxide with glacial acetic acid to give 4.9 g. of compound. Recrystallization from ethyl acetate yielded white crystals, m.p. 255–257°.

Anal. Calcd. for $C_9H_8N_6O$: C, 49.8; H, 4.1; N, 38.7. Found: C, 50.1; H, 4.1; N, 39.1.

Example B. 7-Dimethylamino-v-triazolo(d)pyrimidine (II). *Method (1).* 7-Methylthio-v-triazolo(d)pyrimidine (2.0 g.) was placed in a solution of 50 ml. of water containing 40 ml. of dimethylamine (40% in water). This was then refluxed for 3 hr. The solution was then evaporated to dryness under reduced pressure using a steam bath as a source of heat, and the product was recrystallized from ethyl acetate to give 1.7 g., m.p. 288–290°.

Method (2). One gram of 4,5-diamino-6-dimethylaminopyrimidine[15] was dissolved in 50 ml. of water containing 10 ml. of glacial acetic acid. To this cold solution was added, with stirring, a solution of 0.6 g. of sodium nitrite in 10 ml. of water. A precipitate formed almost immediately. The product was filtered and washed with water to yield 0.8 g. A small portion was recrystallized from ethyl acetate to yield white crystals, m.p. 288–290°. This product was identical with that prepared by method (1) as judged by mixed melting points and ultraviolet spectra at *p*H 1 and *p*H 11.

Anal. Calcd. for $C_6H_8N_6$: C, 43.8; H, 4.9; N, 51.2. Found: C, 43.9; H, 5.1; N, 51.5.

3-Methyl-7-methylamino-v-triazolo(d)pyrimidine (XVIII). Two grams of 5-amino-4,6-*bis*(methylamino)pyrimidine[6] was added to 50 ml. of water, and the solution was adjusted to *p*H 5 with acetic acid. To this cold solution was added 1 g. of sodium nitrite in 10 ml. of water. A precipitate formed almost immediately. The crude product was recrystallized from absolute ethanol to yield white crystals, m.p. 233–235°.

Anal. Calcd. for $C_6H_8N_6$: C, 43.9; H, 4.9; N, 51.2. Found: C, 44.1; H, 5.0; N, 50.8.

3-Ethyl-7-ethylamino-v-triazolo(d)pyrimidine (XVIII). Ten grams of 4,6-dichloro-5-nitropyrimidine[18] was dissolved in 200 ml. of ethyl alcohol. To this solution, which was constantly stirred, was added slowly 12 g. of ethylamine. The mixture was then boiled with charcoal and filtered, and the filtrate was evaporated to dryness under reduced pressure. A yellowish residue remained. The crude 4,6-bis(ethylamino)-pyrimidine was dissolved in 150 ml. of methanol, and the solution was shaken with Raney nickel catalyst at a hydrogen pressure of approximately 40 p.s.i. for 1 hr. The solution was boiled with charcoal and filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude 5-amino-4,6-bis(ethylamino)pyrimidine was added directly to 25 ml. of water containing 5 ml. of acetic acid. To this cold solution was added 3 g. of sodium nitrite in 10 ml. of water. A precipitate formed almost immediately. The crude product was recrystallized from ethanol to give a crystalline substance, m.p. 104–106°.

Anal. Calcd. for $C_8H_{12}N_6$:C, 50.0; H, 6.8; N, 43.7. Found: C, 50.1; H, 6.2; N, 44.0.

7-Diethylamino-3-methyl-v-triazolo(d)pyrimidine. Ten grams of 4-chloro-6-methylamino-5-nitropyrimidine[6] was dissolved in 120 ml. of 1,4-dioxane. To this solution was slowly added 8.3 g. of diethylamine, and then the solution was heated and refluxed for 1 hr. The solution was then evaporated to dryness under reduced pressure. A dark brown, oily residue remained. The crude material was dissolved in 150 ml. of methanol, and the solution was shaken with Raney nickel catalyst at a hydrogen pressure of approximately 40 p.s.i. for 1 hr. The solution was boiled with charcoal and filtered, and the filtrate was evaporated to dryness under reduced pressure. A dark brown residue remained. The crude material was dissolved in 50 ml. of water containing 7 ml. of acetic acid. To this cold solution was added, with stirring, 4 g. of sodium nitrite in 10 ml. of water. Stirring was continued for an additional hour. The product was filtered and washed with petroleum ether. A small portion of this compound was recrystallized from heptane to give a melting point of 87–89°.

Anal. Calcd. for $C_9N_6H_{13}$: C, 52.4; H, 6.8; N, 40.8. Found: C, 53.0; H, 6.7; N, 41.2.

3-Methyl-7-methylthio-v-triazolo(d)pyrimidine (XII). Five grams of 5-amino-4-methylamino-6-pyrimidinethiol[6] was dissolved in 50 ml. of 1*N* potassium hydroxide. The solution was stirred, and 2.5 ml. of methyl iodide was added. Stirring was continued for an additional 30 min. The product was filtered and washed with petroleum ether. The crude 5-amino-4-methylamino-6-methylthiopyrimidine was not purified but added directly to 150 ml. of water containing 5 ml. of sulfuric acid. The solution was cooled to 10°, and 4 g. of sodium nitrite in 10 ml. of water was added with stirring. After an additional 10 min. of stirring, the *p*H was adjusted to *p*H 8–9, cooled, and filtered to yield 2.8 g. of product. Recrystallization from water yielded white crystals, m.p. 122–124°.

Anal. Calcd. for $C_6H_7N_5S$: C, 39.7; H, 3.9; N, 38.7. Found: C, 40.1; H, 4.2; N, 38.7.

7-Amino-3-methyl-v-triazolo(d)pyrimidine (IX). *Method (1).* One gram of 4,5-diamino-6-methylaminopyrimidine sulfate was dissolved in 75 ml. of water and cooled to 10°. Sodium nitrite (0.5 g.) in 10 ml. of water was added dropwise with stirring. The mixture was then allowed to stir for an additional 30 min. at room temperature. At the end of this time the *p*H was adjusted to 8. The product was filtered and washed with a small amount of cold water to yield 0.5 g. A small portion was recrystallized from absolute ethanol to give a melting point of 313–315°.

Anal. Calcd. for $C_5H_6N_6$: C, 40.0; H, 4.0; N, 56.0. Found: C, 40.4; H, 4.4; N, 56.0.

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(18) W. R. Boon, W. C. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 99 (1951).

Method (2). One gram of 3-methyl-7-methylthio-v-triazolo(d)pyrimidine was placed in 75 ml. of ammonium hydroxide, and the solution was refluxed for 2 hr. The mixture was then cooled to yield 0.8 g. of product which was found to be identical to that produced by method (1) as judged by mixed melting point behavior.

Preparation of 7-alkylthio-5-amino-v-triazolo(d)pyrimidines. (See Table III). Example A. *5-Amino-7-methylthio-v-triazolo(d)pyrimidine* (XXII). Ten grams of 6-methyl-2,4,5-triaminopyrimidine[14] was added to 30 ml. of acetic acid and 100 ml. of water. The solution was stirred, and 6 g. of sodium nitrite, in 24 ml. of water, was added dropwise over a period of approximately 20 min. The mixture was then allowed to stir an additional 30 min., and the precipitate was filtered and washed with water to give 3.4 g. of product. A small portion was recrystallized from a water-methanol solution to give a melting point of 282–284° dec.

Anal. Calcd. for $C_5H_6N_6S$: C, 33.0; H, 3.3; N, 46.2. Found: C, 33.3; H 3.5; N, 46.5.

Example B. 5-Amino-7-(p-chlorobenzylthio)-v-triazolo(d)-pyrimidine. Ten grams of 6-*p*-chlorobenzylthio-2,4,5-triaminopyrimidine[14] was added to 50 ml. of acetic acid and 150 ml. of water. Ten grams of sodium nitrite, in 40 ml. of water, was then added dropwise over a period of approximately 20 min. The mixture was then allowed to stir an additional hour. The crude product was collected and reprecipitated from dilute potassium hydroxide by glacial acetic acid to give 3.5 g. of product. A small portion was recrystallized from a water-ethanol solution for analysis, m.p. 242–244° dec.

Anal. Calcd. for $C_{11}H_9N_6S$: C, 45.2; H, 3.1; N, 28.7. Found: C, 45.7; H, 2.8; N, 29.0.

5-Amino-7-methoxy-v-triazolo(d)pyrimidine (XXIII). *Method (1).* Five grams of 5-amino-7-methylthio-v-triazolo-(d) pyrimidine was added to 50 ml. of methanol, and chlorine gas was allowed to bubble through the solution for approximately 20 min. with no external cooling. The product was filtered and washed with water. Recrystallization from water yielded a white crystalline substance, m.p. >300°.

Anal. Calcd. for $C_5H_6N_6O$: C, 36.2; H, 3.6; N, 50.6. Found: C, 36.5; H, 4.1; N, 50.2.

Method (2). To 1 g. of 6-methoxy-2,4,5-triaminopyrimidine sulfate,[15] in 40 ml. of water, was added, with stirring, 0.75 g. of sodium nitrite. The product was filtered and washed with a small amount of cold water to yield 0.7 g., m.p. >300°. An analytical sample was prepared by recrystallization from water. This product was identical with that prepared by method (1), as judged by identical ultraviolet and infrared absorption spectra. At *p*H 11, 5-amino-7-methoxy-v-triazolo(d)pyrimidine exhibits absorption maxima λ max. 291, mμ, ε 7,300; at *p*H 1, λ max. 283 mμ, ε 12,800, and λ max. 236 mμ, ε 8,800.

Anal. Calcd. for $C_5H_6N_6O$: C, 36.2; H, 3.6; N, 50.6. Found: C, 35.8; H, 3.5; N, 50.2.

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Reaction of 4-Arylthiosemicarbazides with Some α-Keto Acids and Synthesis of Some Substituted 3-Thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines[1a]

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4-Arylthiosemicarbazides were treated with glyoxylic, pyruvic, and benzoylformic acids to form derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines *via* the corresponding intermediate thiosemicarbazones. The thione-thiol tautomerism of these substances is discussed.

It is well known that with thiosemicarbazones of α-keto acids ring closure can occur with the formation of derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (II) and these were reviewed recently.[1b] Besides the above-mentioned method of preparation they were prepared also from thiosemicarbazide and oximes of α-keto esters.[2,3] All these derivatives represent mainly 6-substituted derivatives. Known are also 2-substituted derivatives, formulated as 2-alkyl-3-mercapto-5-oxo-2,5-dihydro-1,2,4-triazines, which can be in turn prepared from 2-alkylthiosemicarbazides and α-keto acids.[4–7] Of 4-substituted derivatives only some alkyl derivatives are known[3,8,9] and the cyclization failed in the case of the benzyl derivative.[9] It was therefore desirable to study the cyclization of products, obtained from condensation of 4-substituted thiosemicarbazides with α-keto acids, and the tautomerism associated with these compounds.

The cyclization of thiosemicarbazones could be achieved by refluxing an ethanolic solution, except in the case of 4-arylthiosemicarbazones of glyoxylic acid. The use of an alkaline solution was therefore attempted as it is known that the cyclization of 2-alkylthiosemicarbazones of phenylpyruvic acid proceeds with great facility in dilute sodium hydroxide solution.[7] Such cyclization failed with 4-arylthiosemicarbazones of pyruvic acid and the compounds could be recovered unchanged, but in the case of some 4-arylthiosemicarbazones of glyoxylic acid the molecules were split into the corresponding *N*-arylthioureas (III).

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