5-Azapurines and the Structures of *sym*-Triazole Intermediates

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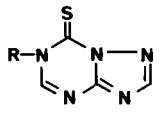
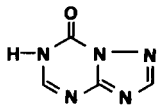
Several isomers are possible when an isocyanate or an isothiocyanate is allowed to react with 3-amino-1,2,4-triazole. It was found that variations in reagents or reaction conditions could be used to produce isomeric derivatives. The effect of substituents on the chemical shifts of adjacent ring protons is described for a number of new triazole derivatives. These data can be used to assign structures to new *sym*-triazole reaction products. Appropriate triazoles were used as intermediates in the synthesis of *s*-triazolo[1,5-*a*]-*s*-triazine (5-azapurine) derivatives. Spectral properties, methods of synthesis, and modes of degradation are described for several new members of this ring system.

Taylor and Hendess (1) have described the synthesis of the 5-aza analogs of adenine and hypoxanthine as potential purine antagonists. Since this initial report, limited attention (2,3) has been devoted to the *s*-triazolo[1,5-*a*]-*s*-triazine (earlier nomenclature used for this ring system was *s*-triazolo[2,3-*a*]-*s*-triazine) (5-azapurine) ring system. Our interest in this system was centered on derivatives of 6-mercapto-5-azapurine (I) by analogy with the well known antitumor drug 6-mercaptopurine.



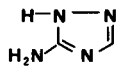
Ia R=H
Ib R=CH_3



II

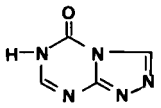
All attempts to convert the known compound (1), 5-azahypoxanthine (II) into Ia were unsuccessful. Thiation reactions, using phosphorus pentasulfide under various conditions, or the two step conversion *via* halogenation, resulted only in the recovery of unchanged starting material. The failure of these routes caused us to turn our efforts toward the preparation of another type of precursor, *i.e.*, *s*-triazole derivatives.

Suitably substituted 1,2,4-triazoles should allow ring closure to the *s*-triazolo[1,5-*a*]-*s*-triazine ring system. When addition reactions (*e.g.* with isocyanates) are carried out with 3-amino-1,2,4-triazole (III), however, four monosubstituted isomers are possible, depending upon whether addition takes place at the amino group or at one of the three different ring nitrogens. This problem was recognized and discussed by Taylor and Hendess (1).



III

While their evidence for the formation of II rather than the possible isomeric product IV was drawn primarily from ultraviolet spectral data, and was well-reasoned, the structural assignment was not completely unambiguous.



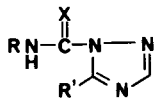
IV

Since the azapurine isomer produced is a function of the structure of triazole used in the final condensation reaction, it was decided that structural studies of appropriate *s*-triazole addition products were needed prior to attempts to synthesize the desired 5-azapurines.

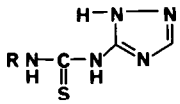
A *sym*-triazole addition reaction, *e.g.* an isocyanate with III, could produce any or all of the isomers, Va-d, X = O. In order to better understand the nature of this type of reaction, a series of derivatives was prepared (see Scheme 1 and Table I).

TABLE I

Addition Products from 1,2,4-Triazole and Isocyanates or Isothiocyanates

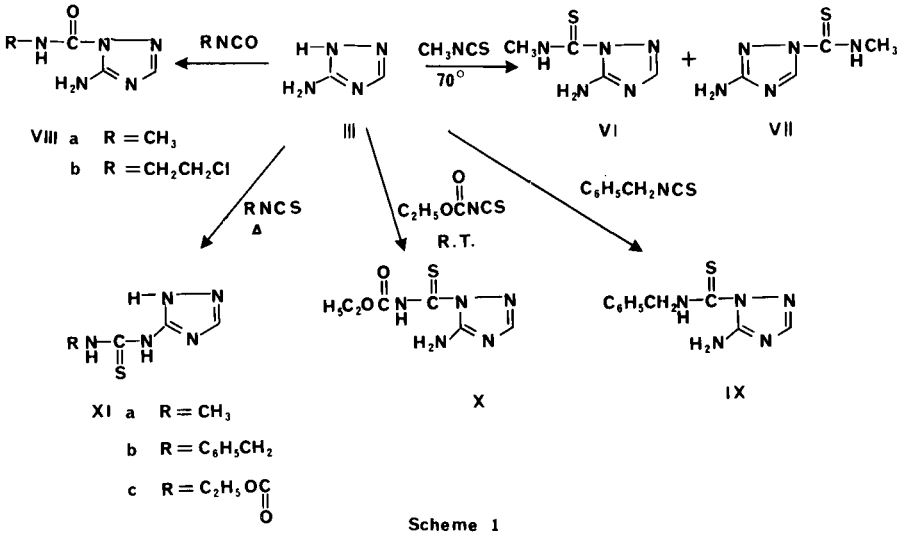


Compound	R′	R	X	M.p., °C	Yield (%)	Reaction Conditions Solvent	Hr.	Calcd., (%) Found, (%) C	H	N	S (Cl)	Ir ν c=o (cm^{-1})	Uv (a) λ max (ε)
XII	H	CH_3	O	126 -141.5	68	Pyridine	20	38.10	4.76	44.44	----	1750, 1720	210 (6300)
								38.19	4.73	44.65	----		
XIII	H	CH_3	S	116 -119	64	Pyridine	5	33.80	4.22	39.44	22.54	----	230 (10800) 285 (7530)
								33.95	4.12	39.70	22.33		
XIV	H	$C_6H_5CH_2$	S	122-123.5	65	Acetone-DMF	1.5	55.02	4.62	25.67	14.69	----	232 (14300) 290 (7900)
								54.85	4.48	25.74	14.33		
XV	H	$ClCH_2CH_2$	O	102 -103.5	76	Acetone-DMF	20	34.39	4.04	32.09	(20.30)	1727	210 (10250)
								34.63	3.95	32.35	(20.34)		
VIIIb	NH_2	$ClCH_2CH_2$	O	129 -130.5	74	Acetone-DMF	6	31.66	4.22	36.94	(18.73)	1725, 1703	208 (5680) 237 (7200)
								31.69	4.33	36.61	(18.60)		

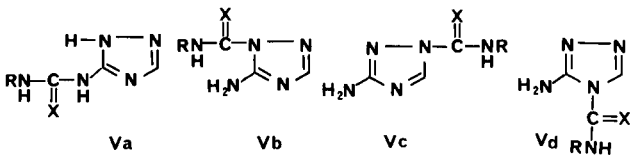


Compound	R	M.p., °C	Yield (%)	Reaction Conditions Solvent	Hr.	Calcd., (%) Found, (%) C	H	N	S	Ir ν c=o (cm^{-1})	Uv (a) λ max (ε)
XIa	CH_3	215-216	82	Pyridine	5	30.57	4.46	44.59	20.39	----	210 (6950) 226 (6850) 259 (18900)
						30.51	4.47	44.82	20.35		
XIb	$C_6H_5CH_2$	228-231	70	Pyridine	20	51.50	4.72	30.04	13.73	----	205 (17800) 228 (13400) 262 (21300)
						51.72	4.96	29.74	13.66		
XIc	C_2H_5OCO	170-174	72	DMF-Acetone	4	33.49	4.19	32.56	14.88	1725	204 (7930) 243 (13000) 278 (14300)
						33.75	4.24	33.38	14.74		

(a) 95% ethanol.



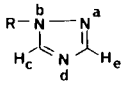
Scheme 1



The addition of a carboxamido or thiocarboxamido group to 1,2,4-triazole (Table II) caused a deshielding of *ca.* 1 ppm of the adjacent ring proton (H_c) while hardly affecting the other ring (H_e) proton. These results are in agreement with the data obtained from the acylation of *s*-triazoles (4,7) and the effect of substituents on H_e (5,6). Substitution of N_d is not indicated in any of the addition products. Unusually high infrared carbonyl stretching frequencies (1725-1750 cm^{-1}) are also observed for the urea derivatives (Table I). An increase in carbonyl frequency upon attachment to the triazole ring has been noted previously (8). Tables III and IV show the nmr data used to assign the structures shown in Scheme 1. Ring (N_b) substitution causes a large deshielding effect on the adjacent amino protons while making only a minor change in H_e (Table III). Substitution on the 3-amino group rather than on a ring nitrogen (Table IV) allows observation of the low field resonance attributable to the ring N-H. This signal occurs as a broad peak at δ 13.60 in *s*-triazole. This is in good agreement with the only other report of this proton (9).

TABLE II

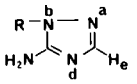
Chemical Shifts for 1-Substituted-1,2,4-Triazoles in DMSO-d_6 (δ Values)



Compound	R	H_c	H_e
XVI	H	8.28	8.28
XVII	H_2NCO	9.08	8.20
XII	CH_3NHCO	9.08	8.22
XV	$Cl(CH_2)_2NHCO$	9.10	8.22
XIII	CH_3NHCS	9.32	8.32
XIV	$C_6H_5CH_2NHCS$	9.33	8.34

TABLE III

Proton Chemical Shifts (DMSO-d_6) for 1-Substituted-5-Amino-1,2,4-Triazoles (δ Values)

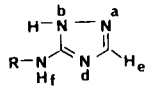


Compound	R	NH_2	H_e
III	H	5.81	7.45
XXIII	H_2NCO	7.16	7.49
VIIIa	CH_3NHCO	7.16	7.50
VIIIb	$Cl(CH_2)_2NHCO$	7.21	7.52
VI	CH_3NHCS	8.16	7.60
IX	$C_6H_5CH_2NHCS$	8.18	7.60

Based on the spectroscopic data and the observed deshielding effect of the thiourea group on all types of adjacent protons (ring N-H, NH_2 and ring C-H), the isomers Va-d should all have characteristically different spectra which should be interpretable. When X = S and

TABLE IV

Chemical Shifts for 3-Substituted Derivatives of 3-Amino-1,2,4-Triazole in DMSO-d_6 (δ Values)

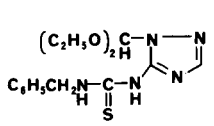


Compound	R	H_b	H_f	H_e
III	H	11.66	5.81	7.45
XIb	$C_6H_5CH_2NHCS$	13.40	10.96	8.36
XIa	CH_3NHCS	13.60	10.78	8.35
XIc	EtOCONHCS	13.67	11.55	8.37
XVIII	Et_2N-C$_6$H$_4$-N=	14.17	----	8.40

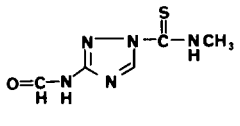
R = CH_3, Va and Vb are compounds XIa and VI respectively. While the analogous isomer related to Vc (VII) was not isolable, its presence (in a 1:2 ratio) in the product of the reaction producing VI was indicated by a highly deshielded (δ = 8.87) aromatic proton and two deuterium oxide exchangeable amino group protons at δ = 6.02. Compound VII could be concentrated as the *N*-formamido derivative (XX) in the reaction mixture by the addition of a condensing agent such as diethoxymethyl acetate which caused a ring closure to a 5-azapurine with VI but not with VII. Isomer Vd was never observed. This compound would be expected to exhibit both amino and aromatic proton deshielding relative to 3-amino-*s*-triazole with approximate values of δ = 8 and 9, respectively. Based on these data we must conclude that the Taylor and Hendess structural assignments (1) for II and XXII are correct.

Since alkylation occurs predominantly at N_b (15), it might be expected that the addition of isocyanate or isothiocyanate would occur at the same position. The actual situation, however, is dependent upon the reactants and reaction conditions (Scheme 1). The reaction of III with methylisocyanate in refluxing pyridine gave VIIIa, a product with ring substitution. However, the reaction of III with methylisothiocyanate under the same reaction conditions furnished the isomeric amino substituted product XIa. The ring substituted isothiocyanate addition product VI, always accompanied by a second ring isomer, VII, was finally prepared by this reaction at low temperature. Selective formation of isomer VI did not occur, in spite of a patent claim to that effect (12). With the benzyl analog, however, compound IX was the sole product. It was observed that when III was reacted with ethoxycarbonyl isothiocyanate (11) in the mixed solvent DMF/acetone at room temperature, a precipitate formed which subsequently dissolved upon reflux, to give XIc in good yield. Upon isolation, the initially formed precipitate was found to be the isomeric compound X.

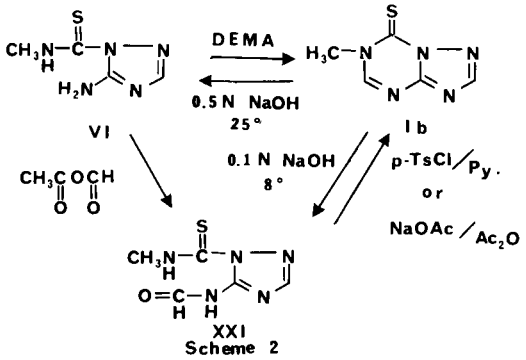
An attempt to prepare the azapurine (Ib) from VI using ethyl orthoformate as a condensing agent was unsuccessful because of the tendency of VI to rearrange to XIa. Prolonged reaction times, even at room temperature, gave XIa rather than the azapurine Ib. In addition, there was no evidence for the formation of a product which was analogous to XIX, a compound produced when XIb was reacted with ethyl orthoformate.



XIX



XX

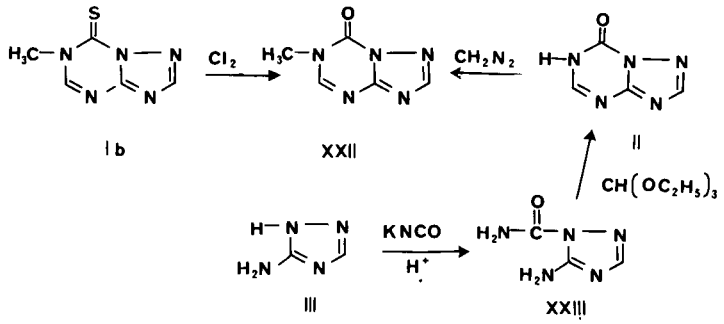


Scheme 2

The use of diethoxymethyl acetate (DEMA) as a condensing agent (2,13,14) enabled us to prepare 1-methyl-6-thio-5-azapurine (Ib) at room temperature in good yield (Scheme 2). The 1,3-disubstituted triazole, XX, was isolated chromatographically from the mother liquor of Ib when VI + VII, the reaction product from III and methylisothiocyanate (Scheme 1), was treated with DEMA. The azapurine Ib was alternatively prepared by the cyclization of compound XXI in either *p*-toluenesulfonyl chloride/pyridine solution or in a sodium acetate/acetic anhydride solution. Compound XXI was prepared by formylation of VI with acetic-formic anhydride. Isomer formation was not observed in this reaction.

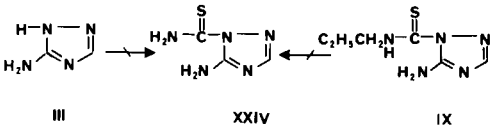
Treatment of the azapurine Ib with 0.5 *N* sodium hydroxide at room temperature furnished VI, while milder hydrolysis with 0.1 *N* sodium hydroxide at 8° gave XXI as the sole product (Scheme 2). Compound Ib was also converted by reaction with chlorine to the known compound 1-methyl-5-azahypoxanthine (XXII) which was prepared from 3-amino-*s*-triazole *via* XXIII and II by the method of Taylor and Hendess (1) (Scheme 3).

The preparation of XXIV, the thio analog of XXIII,



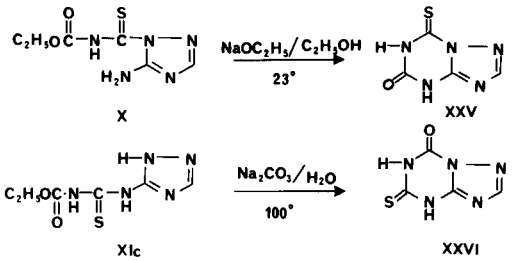
Scheme 3

which would serve as the precursor to Ia has not thus far been successful. The condensation of 3-amino-*s*-triazole (III) with either potassium thiocyanate or nickel isothiocyanate (16), or the debenzylation of IX using either palladium or palladium hydroxide on charcoal (10) have yielded only starting material or intractable products (Scheme 4).



Scheme 4

The isolation of the two isomeric triazole derivatives X and XIc enabled us to prepare the isomeric azapurines XXV and XXVI as shown in Scheme 5.



Scheme 5

The three new azapurines Ib, XXV and XXVI as well as the two previously prepared 5-azahypoxanthine derivatives, II and XXII, were characterized by analyses and mass spectral data. They were shown to be homogeneous by thin layer chromatographic analysis.

While the nmr spectra of Ib and XXII were readily interpretable, a peculiarity was noted in the spectra of XXV and XXVI. Only one of the two N-H proton signals was observed. A similar situation was observed with the N-H proton of 5-azahypoxanthine, II. When the purine analogs of II and XXVI, *i.e.*, hypoxanthine and 2-thioxanthine, were examined under the same nmr conditions, they, also, had one N-H proton signal missing. While the reason for the unobservable protons is not known at present, it may be due to a nitrogen quadrupolar effect (17) or to the presence of a trace of water which exchanges protons with the heterocyclic N-H at such a rate that the signal is not observable. This is still under investigation. Methylation of II with diazomethane (Scheme 3) gave XXII, a compound with a completely interpretable nmr spectrum. Additional evidence for azapurine structures are found in the previously discussed hydrolysis reactions (Scheme 2) and the uv spectra which were earlier (1) analyzed in detail for II and XXII.

In addition to being the expected reaction products based on the intermediates used, the infrared spectral data from the isomeric 5-azathioxanthine derivatives (XXV and XXVI) are consistent with the structure-frequency relationships noted earlier for the triazoles (Table I). Compound XXVI, which has a carbonyl group adjacent to the ring nitrogen of the triazole system, has two high frequency (1780, 1750 cm^{-1}) carbonyl absorption bands. Compound XXV, however, with a carbonyl group in the 2-position of the 5-azapurine ring, has a lowered absorption (1737 and 1711 cm^{-1}).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured with Perkin-Elmer 621 and 137 spectrometers as nujol mulls. Ultraviolet spectra were determined on a Cary Model 15 spectrometer, in 95% ethanol, unless otherwise stated. Nmr spectra were recorded on a Varian HA-100D spectrometer and chemical shifts are given in ppm from tetramethylsilane. Nmr spectra were determined as approximately 5% solutions in DMSO-d_6 unless otherwise stated. Elemental analyses were carried out by Dr. W. C. Alford, NIAMD, NIH. Mass spectra were determined by Mr. W. R. Landis, NIAMD, NIH, on a Hitachi/Perkin-Elmer RMU-7 instrument.

Preparation of *s*-Triazole-1-carboxamides (General Procedure).

To a solution of 3-amino-*s*-triazole or *s*-triazole in (a) dry pyridine or (b) a mixture of dry dimethylformamide and dry acetone was added an equimolar amount of alkylisocyanate in the solvent used. The reaction mixture was refluxed for 1.5 to 20

hours and the solvent removed under vacuum. The residues were generally solids which were triturated with ether and/or ethylacetate, and collected by filtration to give crude products. Recrystallization from 95% ethanol gave analytically pure crystals. The yields, reaction conditions, and physical data for these compounds are shown in Table I.

3-(3-Substituted thioureido)-*s*-triazoles (General Procedure).

Thioureas were prepared by same general procedure as for the above ureas, using suitable alkylisothiocyanates. Reaction conditions, yields, and physical data are shown in Table I.

5-Amino-*N*-methylthio-1*H*-1,2,4-triazole-1-carboxamide (VI).

Method A.

To a solution of 3-amino-*s*-triazole (8.4 g., 0.1 mole) in 30 ml. of dry DMF below 25°, was added 7.3 g. (0.1 mole) of methylisothiocyanate. The solution was then heated at 70° for 15 hours and evaporated *in vacuo* at 45°. The resulting solid was triturated (ether) and filtered to give 10.6 g. (64%) of solid which appeared to be a mixture of 5-amino-*N*-methylthio-1*H*-1,2,4-triazole-1-carboxamide (VI) and 3-amino-*N*-methylthio-1*H*-1,2,4-triazole-1-carboxamide (VII) with a ratio of 67% to 33%, respectively, from the nmr spectrum. Nmr signals assigned to 5-amino isomer; 9.98 δ (1, broad, -NH-), 8.16 (2, s, NH_2), 7.60 (1, s, C_3H), 3.04 (3, d, J = 4 Hz, CH_3); signals assigned to 3-amino isomer; 9.73 (1, broad, -NH-), 8.87 (1, s, C_5H), 6.02 (2, s, NH_2), 3.04 (3, d, J = 4 Hz, CH_3).

Repeated recrystallization from 95% ethanol, methanol and ethylacetate gave almost homogeneous 5-amino-*N*-methylthio-1*H*-1,2,4-triazole-1-carboxamide, m.p. 152-154°, contaminated with less than 5% of isomer. Ir and nmr spectra were superimposable with those of 5-amino derivative which was prepared by method B, the degradation of 6-methyl-*s*-triazolo[1,5-*a*]-*s*-triazine-7(6*H*)-thione (Ib).

Anal. Calcd. for $C_4H_7N_5S$: C, 30.57; H, 4.46; N, 44.59; S, 20.38. Found: C, 30.76; H, 4.52; N, 44.30; S, 20.42.

Method B.

A solution of 6-methyl-1,2,4-triazolo[1,5-*a*]-*s*-triazine-7(6*H*)-thione (Ib) (0.2 g., 1.2 mmoles) in 10 ml. of 0.5 *N* sodium hydroxide solution was allowed to stand at room temperature (23°) for 60 minutes and then cooled to 0° and neutralized to *p*H 7 with 1 *N* hydrochloric acid. The solid which separated was filtered to give 0.17 g. (91%) of white solid which was recrystallized from 95% ethanol to give white crystals, m.p. 161-162°, λ max 222 nm (9,050), 259 (14,700).

5-Amino-1-methylaminocarbonyl-1*H*-1,2,4-triazole (VIIIa).

This compound was prepared by refluxing a suspension of 3-amino-1,2,4-triazole (4.2 g., 0.05 mole) with methylisocyanate (2.8 ml., 0.05 mole) in dry pyridine for 9 hours in 78% yield. Recrystallization from ethanol gave white crystals, m.p. 188-190° (lit. (1) 191-193°); ν max 1710, 1650 cm^{-1}; λ max 205 nm (11,400), 236 (14,700).

Anal. Calcd. for $C_4H_7N_5O$: C, 34.04; H, 4.96; N, 49.65. Found: C, 33.80; H, 4.92; N, 49.70.

5-Amino-*N*-benzylthio-1*H*-1,2,4-triazole-1-carboxamide (IX).

To a 0° solution of 8.4 g. (0.1 mole) of 3-amino-*s*-triazole in 40 ml. of dry dimethylformamide was added 14.9 g. (0.1 mole) of benzylisothiocyanate in 10 ml. of dry acetone. The reaction mixture was stirred at room temperature overnight and evaporated *in vacuo* below 35°. The resulting white solid was triturated with ether and collected by filtration to give 10 g. of product. The filtrate was concentrated and worked up as previously described to give 5 g. of second crop, (total yield 15 g., 65%). Recrystallization from 95% ethanol gave fine needles, m.p. 155.5-156.5°; λ max 218 nm (sh. 15,000), 267 (17,500); nmr 10.50 δ (1, broad -NH-), 8.18 (2, s, NH_2), 7.60 (1, s, C_3H), 7.30 (5, s, aromatic), 4.82 (2, d, J = 5.5 Hz, $PhCH_2$).

Anal. Calcd. for $C_{10}H_{11}N_5S$: C, 51.50; H, 4.72; N, 30.04; S, 13.73. Found: C, 51.78; H, 4.63; N, 30.39; S, 13.34.

5-Amino-1-ethoxycarbonylaminothiocarbonyl-1,2,4-triazole (X).

To a solution of 3-amino-1,2,4-triazole (2.52 g., 0.03 mole) was added 3.54 ml. (0.03 mole) of ethoxycarbonyl isothiocyanate at 20-22°. After 15 minutes stirring, the precipitated solid was collected by filtration to give 1.41 g. (27%) of a light yellow powder. The crude powder (810 mg., 3.76 mmoles) was dissolved in 5% aqueous sodium carbonate (400 mg., 4 mmoles) at < 10°. The insoluble impurities were filtered and the filtrate acidified with 1*N* hydrochloric acid at < 10°. The fine solid which precipitated was collected by filtration using a Millipore® filter, washed with cold water and dried *in vacuo* at 40° overnight to give 630 mg. (78% purification yield) of slightly yellowish solid, m.p. 117-118.5°; ν max 1770 cm^{-1}; λ max 258 nm (11,100), nmr (pyridine d-5) 9.39 δ (3, broad, NH_2 and CONHCS), 7.79 (1, s, C_3H), 4.22 (2, q, J = 7 Hz, $-CH_2$-Me), 1.14 (3, t, J = 7 Hz, $-CH_3$).

Anal. Calcd. for $C_6H_9N_5O_2S$: C, 33.49; H, 4.19; N, 32.56; S, 14.88. Found: C, 33.59; H, 4.23; N, 32.40; S, 14.87.

1*H*-1,2,4-Triazole-1-carboxamide (XVII).

This compound was prepared in 62% yield by the general method of Taylor, and Hendess (1). Recrystallization from tetrahydrofuran gave white crystals, m.p. 130-138°; ν max 1750 cm^{-1} λ max 207 nm (6,170); nmr 8.20 δ (1, s, C_3H), 9.08 (1, s, C_5H), 8.11 (2, s, NH_2).

Anal. Calcd. for $C_3H_4N_4O$: C, 32.14; H, 3.57; N, 50.00. Found: C, 32.24; H, 3.74; N, 50.27.

3-[(*p*-(Diethylamino)phenyl)]azo-1,2,4-triazole (XVIII).

To a cold solution of 3-amino-1,2,4-triazole (2.1 g., 0.025 mole) in 2 ml. of concentrated hydrochloric acid and 10 ml. of water was added 1.75 g., (0.025 mole) of sodium nitrite in 5 ml. of water during a 20 minute period while keeping the temperature < 2°. After another 10 minutes stirring, 4.2 g. (0.028 mole) of diethylaniline in a small amount of ethanol was added. A deep red solution resulted. The orange solid which precipitated was filtered and recrystallized from 30% aqueous ethanol to give 2.2 g. (36%) of tan crystals, m.p. 189-195°; ν max 1600 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}N_6$: C, 59.02; H, 6.56; N, 34.43. Found: C, 58.98; H, 6.38; N, 34.35.

1-Benzyl-3-(1-formyl-1*H*-1,2,4-triazol-5-yl)-2-thiourea Diethyl Acetal (XIX).

A suspension of 1-benzyl-2-thio-3-*s*-triazol-3-yl-urea (XIb) (1.0 g., 4.3 mmoles) in freshly distilled ethylorthoformate (50 ml.) was heated to 150°. All the solid went into solution. The clear solution was heated at 100-110° for 20 hours and then evaporated *in vacuo* to give an oily residue which solidified upon scratching. Trituration with ether and filtration gave 1.18 g. (82%) of product which was recrystallized from ethylacetate to give crystals, m.p. 125-128°; λ max 229 nm (17,200), 262 (29,100); nmr 11.05 δ (1, s, proton on nitrogen attached to triazole ring), 10.15 (1, t, BzNH), 8.59 (1, s, C_3H), 7.31 (5, s, aromatic), 6.29 (1, s, $CH(OEt)_2$), 4.89 (2, d, J = 5 Hz, $PhCH_2$), 3.70 (4, q, J = 7.0 Hz, CH_2O), 1.12 (6, t, J = 7.0 Hz, CH_3).

Anal. Calcd. for $C_{15}H_{21}N_5O_2S$: C, 53.73; H, 6.27; N, 20.89;

S, 9.55. Found: C, 53.59; H, 6.52; N, 21.12; S, 9.64.

6-Methyl-1,2,4-triazolo[1,5-*a*]-1,3,5-triazine-7(6*H*)thione (Ib).

Method A.

The recrystallized addition product (8.35 g., 0.053 mole) of 3-amino-1,2,4-triazole with methyl isothiocyanate (mixture of VI and VII with ratio of 72:28) was suspended in 60 ml. of diethoxymethyl acetate at room temperature. The resulting clear solution was stirred for 20 hours. Precipitated solid was filtered to give 5.6 g. of solid and filtrate *A*. The solid was recrystallized from hot water to give rhombic crystals, m.p. 233-236°; ir, no absorption band > 1600 cm^{-1}; λ max 292 nm (15,300), 235 (11,500); λ max (0.1 *N* hydrochloric acid), 290 nm (15,400), 233 (7,990); nmr 8.85 δ (1, s, C_5H), 8.52 (1, s, C_2H), 3.84 (3, s, CH_3); M^+ m/e 167, R_f, 0.56 (silica gel 1B-F, 95% ethanol-ethyl acetate, 3:7).

Anal. Calcd. for $C_5H_5N_5S$: C, 35.92; H, 3.01; N, 41.89; S, 19.17. Found: C, 36.05; H, 3.06; N, 41.63; S, 19.03.

The Isolation of 3-Formamido-*N*-methylthio-1*H*-1,2,4-triazole-1-carboxamide (XX).

The filtrate *A* was concentrated *in vacuo* below 30° to give 3.8 g. of crude solid which was chromatographed on silica gel using benzene as elution solvent. Concentration of a first fraction gave 1.1 g. of white solid which was recrystallized from methanol to give fine needles of compound (XX), m.p. 159.5-161.5°; ν max 1700 cm^{-1}; λ max 258 nm (ε, 11,700), 297 (10,100); nmr 10.71 δ (2, broad, -CONH- and -CS-NH-), 9.16 (1, s, C_5H), 8.98 (1, broad, -CHO), 3.12 (3, s, CH_3).

Anal. Calcd. for $C_5H_7N_5OS$: C, 32.43; H, 3.78; N, 37.84; S, 17.30. Found: C, 32.65; H, 3.97; N, 37.47; S, 17.28.

Method B.

To a solution of 5-formamido-*N*-methylthio-1*H*-1,2,4-triazole-1-carboxamide (XXI) (0.5 g., 2.7 mmoles) in 8 ml. of dry pyridine was added portionwise, *p*-toluenesulfonyl chloride (0.5 g., 2.4 mmoles), and the reaction mixture was refluxed overnight. After evaporation of the solvent *in vacuo*, the yellow-brown oily residue was treated with water and extracted with chloroform. The chloroform extract was dried over calcium chloride, filtered and evaporated to give a residue which, when triturated with 95% ethanol, gave a solid (30 mg., 7%). Recrystallization from hot water afforded rhombic crystals, m.p. 233-234.5°, identical with the material obtained above.

Method C.

A mixture of 5-formamido-*N*-methylthio-1*H*-1,2,4-triazole-1-carboxamide (XXI) (0.5 g., 2.7 mmoles) in 15 ml. of acetic anhydride was heated to 60° to give a complete solution. Anhydrous sodium acetate (0.3 g., 3.7 mmoles) was added and the reaction mixture was stirred for 5 hours at 55°. After removal of acetic anhydride *in vacuo*, the solid residue was washed with ether and then water. The crude material was filtered to give 70 mg. (17%) of product. Recrystallization from hot water gave crystals which were identical with the materials obtained above, m.p. 233-235.5°.

5-Formamido-*N*-methylthio-1*H*-1,2,4-triazole-1-carboxamide (XXI).

Method A.

Acetic-formic anhydride was prepared by heating acetic anhydride (2.04 ml., 0.02 mole) and 97% formic acid (0.86 ml., 0.02 mole) at 53-55° for 2 hours. 5-Amino-*N*-methylthio-1*H*-*s*-triazole-1-carboxamide (VI) (1.57 g., 0.01 mole) was added portionwise to this solution at 25°. An exothermic reaction was observed. Dry ether (30 ml.) was added and reaction mixture was stirred for 70 hours. The product which separated was filtered and washed with ether to give 1.15 g. (61%) of a white solid, which was recrystallized from methanol to give fine needles, m.p. is not definite; λ max 257 nm (10,400), 288 (9,900); ν max 1700 cm^{-1}; nmr 11.35 δ (1, broad, Me-NH-), 10.55 (1, broad, -CONH-), 9.05 (1, broad, CHO), 8.00 (1, s, C_3H), 3.08 (3, s, CH_3).

Anal. Calcd. for $C_5H_7N_5OS$: C, 32.43; H, 3.78; N, 37.84. Found: C, 32.33; H, 3.62; N, 37.56.

Method B.

A solution of 6-methyl-*s*-triazolo[1,5-*a*]-*s*-triazine-7(6*H*)thione (Ib) (0.2 g., 1.2 mmoles) in 50 ml. of 0.1 *N* sodium hydroxide was stirred at 8° for 10 minutes and then neutralized with 1 *N* hydrochloric acid (*ca.* 6 ml.). The product which separated was filtered to give 140 mg. (63%) of white solid. Recrystallization from methanol gave fine needles, which do not have a definite melting point. These crystals were identical with the material prepared by Method A, as determined by comparison of ir, uv, and nmr spectra.

Anal. Calcd. for $C_5H_7N_5OS$: C, 32.43; H, 3.78; N, 37.84; S, 17.30. Found: C, 32.29; H, 3.80; N, 37.83; S, 16.89.

6-Methyl-*s*-triazolo[1,5-*a*]-*s*-triazine-7(6*H*)one (XXII).

Method A.

1,2,4-Triazolo[1,5-*a*]-1,3,5-triazine (II) (2.7 g., 0.02 mole) was methylated with an etheral solution of diazomethane (from 10.8 g. of Diazald®) by the procedure of Taylor (1) to give 2.3 g. (78%) of product which was recrystallized from 95% ethanol to give white crystals, m.p. 221-223° dec. (lit. (1), 220-222° dec.); ν max 1750 cm^{-1}; λ max 257 nm (7,150); nmr 8.58 δ (1, s, C_5H), 8.37 (1, s, C_2H), 3.54 (3, s, CH_3); M^+ m/e 151; R_f 0.45 (silica gel 1B-F, 95% ethanol-ethyl acetate, 3:7).

Anal. Calcd. for $C_5H_5N_5O$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.79; H, 3.21; N, 46.38.

Method B.

Chlorine gas was passed through a suspension of 6-methyl-*s*-triazolo[1,5-*a*]-*s*-triazine-7(6*H*)thione (Ib) (0.3 g., 1.8 mmoles) in 50 ml. of absolute ethanol for 1 hour, while the temperature was kept below 33°. The clear solution was allowed to stand overnight at room temperature. The resulting precipitate was filtered to give 10 mg. of solid, m.p. 220-223° dec., which was not depressed by mixing with crystals prepared by Method A. The ir spectrum is superimposable with that of the product from Method A. Evaporation of the filtrate gave an oily residue from which another 20 mg. (total yield 11%) of product was obtained.

5-Amino-1-aminocarbonyl-1*H*-1,2,4-triazole (XXIII).

This compound was prepared according to the method of Taylor and Hendess (1) in 73% yield.

1,2,4-Triazolo[1,5-*a*]-1,3,5-triazine-7(6*H*)one (II).

This compound was prepared in 75% yield by the method of Taylor and Hendess (1) by condensing 5-amino-1-(aminocarbonyl)-1,2,4-triazole (XXIII) with triethyl orthoformate. Recrystallization from water gave white crystals, m.p. 246° dec. (lit. 244° dec); ν max 1790, 1770 cm^{-1}; λ max (0.1 *N* sodium hydroxide) 244 nm (sh.) (6,600), 257 (7,100); nmr (trifluoroacetic acid) 8.82, 8.86 δ (two one proton singlets, C_2H and C_5H); M^+ m/e 137; R_f 0.18 (silica gel 1B-F, 95% ethanol-ethyl acetate, 3:7).

7-Thio-1,2,4-triazolo[1,5-*a*]-1,3,5-triazine-5,7(4*H*,6*H*)dione (XXV).

A solution of 5-amino-1-ethoxycarbonylaminothiocarbonyl-1*H*-triazole (X) (200 mg., 0.93 mmole) in alcoholic sodium ethoxide [prepared by dissolving 120 mg. (0.052 mole) of sodium metal in 20 ml. of absolute ethanol] was stirred at room temperature for 2 hours. The precipitated sodium salt was collected, dissolved in 10 ml. of water and acidified with 1 *N* hydrochloric acid. The resulting precipitate was filtered and dried to give 120 mg. (76%) of white solid which was recrystallized from hot water. The recrystallized compound appeared to be a hemihydrate, m.p. $> 350°$; ν max 1737 cm^{-1}; λ max 245 (sh., 4,700), 275 (sh., 9,400), 291 (12,400); λ max (0.1 *N* sodium hydroxide) 237 (11,200), 275 (13,900), 282 (13,900); nmr 12.8 δ (1, very broad NH), 8.10 (1, s, C_2H); M^+ m/e 169; R_f 0.25 (silica gel 1B-F, 95% ethanol-ethyl acetate, 3:7).

Anal. Calcd. for $C_4H_3N_5OS \cdot 0.5H_2O$: C, 26.98; H, 2.27; N, 39.34; S, 17.90. Found: C, 26.84; H, 2.24; N, 39.14; S, 17.44.

5-Thio-*s*-triazolo[1,5-*a*]-*s*-triazine-5,7(4*H*,6*H*)dione (XXVI).

1-Ethoxycarbonyl-2-thio-3-triazol-3-yl-urea (XIc) (1.29 g., 0.006 mole) was refluxed with sodium carbonate (0.32 g., 0.03 mole) in 10 ml. of water for 20 minutes. After cooling, the solution was acidified with concentrated hydrochloric acid solution. The product which separated was filtered to give 800 mg. (79%) of white solid. Recrystallization from hot water gave analytically pure crystals, m.p. $> 350°$; ν max 1780, 1750 cm^{-1}; λ max 212 (7,220), 295 (16,800); λ max (0.1 *N* sodium hydroxide) 239 nm (15,900), 280 (17,200); nmr 8.13 δ (1, s, C_2H), 13.0 (1, s, NH), M^+ m/e 169; R_f 0.37 (silica gel 1B-F, 95% ethanol-ethyl acetate, 3:7).

Anal. Calcd. for $C_4H_3N_5OS \cdot H_2O$: C, 25.65; H, 2.69; N, 37.40; S, 17.10. Found: C, 25.98; H, 2.72; N, 37.43; S, 17.19.

REFERENCES

(1) E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.*, 87, 1980 (1965).

(2) J. Kobe, B. Stanovnik, and M. Fišler, *Tetrahedron*, 26, 3357 (1970).

(3) G. Cipens, R. Bokaldares and V. Grinsteins, U.S.S.R. Patent 213,888 (1968).

(4) K. T. Potts and T. H. Crawford, *J. Org. Chem.*, 27, 2631 (1962).

(5) W. Freiberg, C.-F. Kröger, and R. Radeglia, *Tetrahedron Letters*, 2109 (1967).

(6) G. B. Barlin and T. J. Batterham, *J. Chem. Soc.* (B), 516 (1967).

(7) M. D. Coburn, E. D. Loughran, and L. C. Smith, *J. Heterocyclic Chem.*, 7, 1149 (1970).

(8a) H. A. Staab, W. Otting, and A. Ueberle, *Z. Elektrochem.*, **61**, 1000 (1957); (b) W. Otting, *Chem. Ber.*, **89**, 1940 (1956).

(9) L. T. Creagh and P. Truitt, *J. Org. Chem.*, 33, 2956 (1968).

(10) R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.*, 83, 4798 (1961).

(11) A. E. Dixon and J. Taylor, *J. Chem. Soc.*, **93**, 684 (1908).

(12) British Patent, 919,458 (1963).

(13) H. W. Post and E. R. Erickson, *J. Org. Chem.*, 2, 261 (1938).

(14) C. Temple, R. L. McKee and J. A. Montgomery, *ibid.*, 28, 2257 (1963).

(15a) M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 141 (1954); (b) C. Ainsworth and R. G. Jones, *J. Am. Chem. Soc.*, 77, 621 (1955).

(16) R. G. Neville and J. J. McGee, *Can. J. Chem.*, 41, 2123 (1963).

(17) J. W. Emsley, J. Feeney and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy", Vol. 2, Pergamon, N. Y., 1966, 1037.