A Solution of Structural Ambiguity: *s*-Triazolo[1,5-*a*]- and *s*-Triazolo[4.3-*a*]pyrimidines (1)

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The condensation of 3-amino-5-benzylthio-*s*-triazole (**2**) with acetylacetone in refluxing acetic acid has been reported to have given 3-benzylthio-5,7-dimethyl-*s*-triazolo[4,3-*a*]pyrimidine (**3**). However, it has now been established, with the aid of ^{13}C spectra and a modification of the original synthetic work, that only 2-benzylthio-5,7-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine (**4**) can be obtained by this method of condensation. The erroneously reported, but previously unknown **6** was synthesized and its structure and that of **4** was firmly established by ir, uv, pmr, ^{13}C nmr, tlc and mixed melting point data. The correct structures of 3-mercapto-5,7-dimethyl-*s*-triazolo-[4,3-*a*]pyrimidine (**5**) and 2-mercapto-5,7-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine (**6**) were also established and the facile rearrangement of **5** to **6** was demonstrated.

Isomerization of fused *s*-triazoles by acid, base or heat has been reported in numerous examples (2-11). It was therefore quite surprising to learn of a recent publication (12) describing the synthesis of 3-benzylthio-5,7-dimethyl-*s*-triazolo[4,3-*a*]pyrimidine (3) *via* the condensation of 3(5)-amino-5(3)-benzylthio-*s*-triazole (2) and acetylacetone in refluxing acetic acid since we had earlier reported (13,14) obtaining only 2-benzylthio-5,7-dimethyl-*s*-triazolo[1,5-*a*]-pyrimidine (4) under identical conditions.

The claim to **3** was based upon the reported synthesis of 5,7-dimethyl-3-mercapto-*s*-triazolo[4,3-*a*]pyrimidine (**5**) from the cyclization of 4,6-dimethyl-2-hydrazinopyrimidine (**7**) with carbon disulfide in hot pyridine (15). Alkylation of **5** with benzyl chloride in aqueous alkali was then reported (12) to have given **3**, which was found to be identical in all respects to the product obtained from condensing acetylacetone with **2** in refluxing acetic acid.

Although we suspected that **4** was the correct structure of the product obtained *via* the condensation of **2** in acetic acid, it was not clear as to why **5** would rearrange under the mild alkylation conditions (with benzyl chloride) described by Okabe, *et al.*

The reaction of **7** with carbon disulfide was reexamined. In hot pyridine, one product was obtained (denoted as "the pyridine reaction" product), whereas in refluxing chloroform (denoted as the "chloroform reaction" product), two substances were obtained. One of the materials obtained from the "chloroform reaction" was identical to the sole product of the "pyridine reaction". The reaction of **7** with carbon disulfide in acetonitrile at room temperature afforded a product which had different physical properties (denoted as the "acetonitrile reaction" product) than that obtained from the pyridine reaction, but was identical to one of the products obtained from the chloroform reaction.

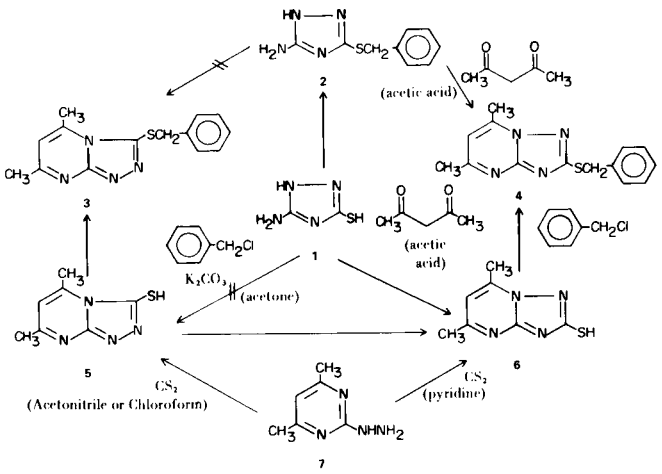
The analyses of the products obtained from the pyridine reaction and the acetonitrile reaction were identical and could be represented by either structure **5** or structure **6** (Figure 1). Alkylation of the product of the "pyridine reaction" with benzyl chloride in anhydrous acetone with anhydrous potassium carbonate gave a substance which analyzed for $C_{14}H_{14}N_4S$. Likewise, benzylation of the product of the "acetonitrile reaction" under the same conditions also gave a product which analyzed for $C_{14}H_{14}N_4S$. The melting point of the product which originated from the "pyridine reaction" (after benzylation) was 133-134°, whereas the melting point of the isomer (from the "acetonitrile reaction") was 134-135°.

The similarity, however, ended at this point. The ir, uv and pmr spectra (see Table I) of the two compounds were sufficiently different to describe them as isomers of each other, namely **3** and **4**. Thin layer chromatography revealed values of R_f 0.40 for the product from the "pyridine reaction" and R_f 0.54 for the product from the "acetonitrile reaction" (benzylthio derivatives).

Positive identification and structure assignment of

products **3** and **4** were achieved *via* carbon-13 (^{13}C) NMR spectroscopy. The pertinent ^{13}C chemical shifts are summarized in Table II. The bridgehead carbon atoms (C_{4a}) in both **3** and **4** were readily assigned on their appearance as singlets in the spin-coupled spectra. On the other hand, the C_6 carbon atoms exhibit the usual large C-H couplings.

Figure 1



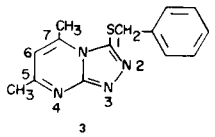
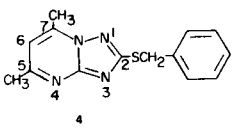
The assignment of the remaining ^{13}C signals were based on the proton splitting pattern in the spin-coupled spectra and also by off-resonance decoupling techniques. The C_5 and C_7 carbons were further differentiated by their characteristic chemical shifts in relation to model compounds (17).

The carbon atoms which are of particular interest in this study are the C_1 atom of **3** and the C_2 atom of **4**. One major difference between these carbons is that the C_2 atom of **4** is bonded to two adjacent ring nitrogens while the C_1 atom of **3** is bonded to a ring nitrogen and a bridgehead nitrogen. For nitrogen heterocyclic systems, the carbons bonded to nitrogen atoms are known to be appreciably deshielded relative to benzene while β carbons are shielded (17). Nitrogen atoms at bridgehead positions, however, have little deshielding effect on the adjacent carbon atoms due to the significant delocalization of the lone pair of electrons (18,19). These considerations, together with the chemical shift comparison with related compounds (17), suggested that the C_2 carbon in the triazolo[1,5-*a*]system should occur considerably further downfield compared to the C_1 carbon in the triazolo[4,3-*a*]-system. We have observed a chemical shift of 140.5 ppm for the C_1 atom of **3** and 164.1 ppm for the C_2 atom of **4**. The reported chemical shifts in Table II are therefore consistent with the proposed structures given in Figure 1 and structures of **3** and of **4** were unambiguously assigned by this procedure.

Since **4** was obtained by alkylation (with benzyl chloride) of the product obtained from **7** and carbon disulfide in pyridine, the intermediate must have been **6** and not **5**, as previously reported (12,15). The previously unknown

Table I

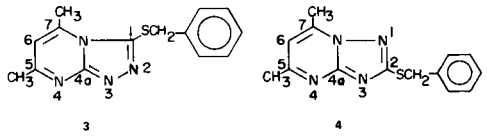
Physical Data for Compounds **3** and **4**

	M.p., °C	Mixed (a) m.p.	Tlc (b) Rf	Uv (c) in nm	Pmr (d) in ppm (δ) C_5	C_7	$-CH_2-S$	C_6	Phenyl
					s, 2.55 (3)	s, 2.71 (3)	s, 4.03 (2)	s, 6.4 (1)	s, 7.3 (5)
	134-135		0.54	232 (ϵ 2.7x10^4) 280 (ϵ 3.5x10^3)					
		109-113		304 (ϵ 7.0x10^2)					
					C_5	C_7	$-CH_2-S$	C_6	Phenyl
	133-134	109-113	0.40	233 (ϵ 3.1x10^4) 290 (ϵ 7.5x10^3)	s, 2.6 (6)	s, 2.7 (3)	s, 4.55 (2)	s, 6.7 (1)	m, 7.3 (5)

(a) Mixed m.p. of isomers **3** and **4**. (b) Thin layer chromatography on Woelm silica gel plates, solvent system methanol/chloroform (1:10). (c) Run in methanol. (d) Run in deuteriochloroform with 1% TMS as internal standard.

Table II

^{13}C Nmr Chemical Shifts of the Ring Carbons



3 4

Compound	Chemical shift, ppm (a)					
	C_1	C_2	C_{4a}	C_5	C_6	C_7
3	144.2	---	155.8	164.7	111.5	140.5
4	---	164.1	155.5	166.8	103.4	145.6

(a) Chemical shifts were measured from deuteriochloroform then converted to the tetramethylsilane (TMS) scale using the relationship $\delta_{TMS} = \delta_{CDCl_3} + 77.2$ ppm.

but erroneously described **3** must then have been obtained from **5**, which was the product of **7** and carbon disulfide in acetonitrile. The unexpected formation of **6** from **7** in pyridine was due to either the basicity of the solvent or a thermal rearrangement, since acetonitrile is equally as polar a solvent as the former.

In order to substantiate the rearrangement of the triazolo[4,3-*a*]- system to the triazolo[1,5-*a*]- system, **5** was heated in pyridine and was thus converted into **6** in quatitative yield. The rearrangement of **5** to **6** also occurred in dilute sodium hydroxide solution indicating that even if **5** had been prepared, benzylation in the presence of aqueous alkali could not possibly have given **3**.

The most likely explanation for this facile rearrangement in aqueous solution appears to be the opening of the pyrimidine ring (Figure 2) near the bridgehead in **3** to yield the proposed triazole intermediate **8**. Recyclization of **8** would yield **4**. It seems unlikely that the triazole ring opens since the pyrazole ring remains intact in a similar rearrangement (19) involving 3-cyano-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine.

The mechanism for the thermal, non-aqueous rearrangement of **3** to **4** (or **5** to **6**) in pyridine probably proceeds along similar lines described by Sirikawa (4) for certain

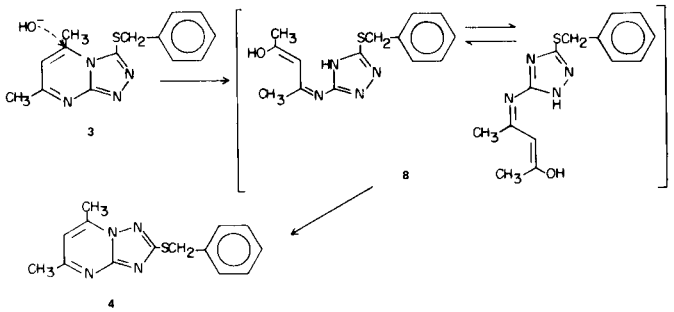


Figure 2

triazolopurines and covered in a review by Mosby (6). The present work clarifies the ambiguity regarding the reported (12,13,14) structures of **3** and **4**, and also establishes the fact that substituted triazolo[4,3-*a*]- systems may easily rearrange to triazolo[1,4-*a*]- systems under a variety of mild reaction conditions. This type of rearrangement may have been overlooked in recent work involving fused triazoles (20-22).

Acknowledgment.

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EXPERIMENTAL

All uv spectra were taken in methanol and recorded on a Cary 15 spectrometer. The ir of the compounds were taken in potassium bromide discs and recorded on a Perkin-Elmer 257 instrument. Pmr spectra were determined in the solvents listed in Table I and in the Experimental Section and were recorded on a 60 MHz Hitachi Perkin-Elmer R20A spectrometer. Carbon-13 (^{13}C) nmr spectra of 20% deuteriochloroform solutions were obtained on a Bruker HX-90 nmr spectrometer operating at 22-62 MHz in the Fourier Transform mode at a probe temperature of 35°. All analyses were performed by Galbraith Laboratories of Knoxville, Tennessee. Physical data not included in this section appear in either Table I or Table II.

3-Mercapto-5,7-dimethyl-*s*-triazolo[4,3-*a*]pyrimidine (**5**) (Acetonitrile Reaction).

To a hot solution of 2-hydrazino-4,6-dimethylpyrimidine (23) (**7**) (2.0 g., 14.5 mmoles) in acetonitrile (100 ml.) was added carbon disulfide (5 ml.). The yellow mixture was stirred at room temperature overnight. The resulting crystals were collected and washed with acetonitrile, yield 2.1 g. (81.7%), m.p. 246-247° dec. The material was sufficiently pure for analysis; uv (methanol) in nm: 245 (ϵ, 1.4×10^4), 285 (ϵ, 2×10^3); pmr (d_6-DMSO) in ppm (δ): s, 2.45 (3); s, 3.5 (3); s, 6.6 (1).

Anal. Calcd. for $C_7H_8N_4S$: C, 46.66; H, 4.48; N, 31.10.

Found: C, 46.68; H, 4.38; N, 30.98.

2-Mercapto-5,7-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine (**6**) (Pyridine Reaction).

This compound was prepared from **7** in the same manner as reported by Williams (15) and again by Okabe *et al.* (12) in 77% yield, m.p. 253-254° dec. The ir and pmr spectra of **6** differed from **5**, as described in the text and in Table I; uv (methanol) in nm: 240 (ϵ 2.6×10^4), 335 (ϵ 6×10^3); pmr (d_6-DMSO) in ppm (δ): s, 2.6 (3); s, 2.7 (3); s, 7.3 (1).

Mixture of **5** and **6** (Chloroform Reaction).

A solution of 2.0 g. (14.5 mmoles) of **7** in 100 ml. of chloroform was refluxed for 10 hours. Upon cooling the solution, a solid separated and was filtered and dried. Analysis of this material by thin layer chromatography (methanol/chloroform, 1:10 on silica gel) indicated that it was a mixture compound of *ca.* equal quantities of **5** and **6** plus a small amount of unreacted **7**.

3-Benzylthio-5,7-dimethyl-*s*-triazolo[4,3-*a*]pyrimidine (**3**).

A mixture of 3-mercapto-5,7-dimethyl-*s*-triazolo[4,3-*a*]pyrimidine (**5**) (1.6 g., 9 mmoles), benzylchloride (1.20 g., 9.5 mmoles) and anhydrous potassium carbonate (0.7 g.) in dry acetone (50 ml.) was stirred at room temperature overnight. After filtering the mixture, the filtrate was concentrated *in vacuo* and the solid residue was collected and washed with ether. Recrystallization from ethyl acetate gave colorless needles, yield 1.95 g. (80%) m.p. 134-135°.

Anal. Calcd. for $C_{14}H_{14}N_4S$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.32; H, 5.30; N, 20.70.

A mixed melting point (see Table I) showed a m.p. depression of 109-113° when this material was mixed with an authentic sample of **4**.

2-Mercapto-5,7-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine (**6**).

The title compound was prepared in a manner identical to that reported by Okabe, *et al.* (12) m.p. 255-256.5° dec.

2-Benzylthio-5,7-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine (**4**).

The title compound was prepared in the same manner as reported by Okabe, *et al.* (12) *via* both condensation of acetylacetone with **2** (12) in acetic acid and by alkylation of **6** with benzyl chloride in aqueous sodium hydroxide, m.p. 133-134°.

Rearrangement of **5** to **6** in Pyridine.

A mixture of 3-mercapto-5,7-dimethyl-*s*-triazolo[4,3-*a*]pyrimidine (**5**) (1 g.) in pyridine (15 ml.) was heated on the steam bath for 2 hours. The pale yellow solution was diluted with water (30 ml.) and concentrated *in vacuo* to 15 ml. After cooling the mixture the pale yellow needles which separated were collected and washed with water. Recrystallization from water gave colorless needles, yield 0.3 g., m.p. 255-256°. The ir, uv and pmr of the product confirmed the structure as being identical with **6**. There was no mixed m.p. depression observed with the product and an authentic sample of **6**.

Rearrangement of **5** to **6** in Dilute Alkali.

A solution of 0.4 g. of **5** in 1% aqueous sodium hydroxide was heated for 2 hours at reflux. The solution was allowed to cool to room temperature and was then acidified with hydrochloric acid to yield colorless needles, m.p. 255-256 dec., identified by ir and uv spectra as **6**.

A similar procedure using 10% aqueous sodium hydroxide at 25°, followed by acidification also confirmed the rearrangement of **5** to **6** in dilute alkali.

Rearrangement of **5** to **6** in Dilute Acid (Acetic).

A solution of 0.5 g. of **5** in 20 ml. of acetic acid was refluxed for 1 hour. Upon cooling, the product separated and was washed with water and dried *in vacuo* at 50°. The product had m.p. 255-256° dec., and was shown by ir and uv to be identical to **6**.

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