Triazoles. III [1]. The Alkylation of 3-*R'*-Thio-5-amino-1,2,4-triazoles

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The alkylation of 3-*R'*-thio-5-amino-1*H*-1,2,4-triazoles **1** or their sodium salt with alkyl and aralkyl halides **2**, respectively, to yield all the four possible monoalkylated derivatives **3, 4, 5** and **6** was studied. The comparison of the spectral data of different type isomers **3, 4, 5** and **6** isolated and their Schiff bases **8, 9** and **10**, respectively, was unequivocal evidence in support of their structure which was then further supported by independent synthesis and ring closure reactions. According to an hplc study the main product of the alkylation is derivative **3**, the by-product is derivative **4**, while derivatives **5** and **6** are formed only in insignificant amounts.

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In the first paper of this series [2] we have reported on the reaction of *N*-cyanocarbonimidodithioic acid esters with different hydrazines to yield 1- and 2-R-3-R'-thio-5-amino-1,2,4-triazoles **3** and **4**, respectively. Based upon the mechanism of the above reaction it became clear that the ratio of products formed would depend on the nature of the R substituents only [2]. As our biological studies required larger quantities of derivatives formed in the above

Table I

Analytical Data

Compound No.	R	R'	Method of Preparation	Isolated Yield (%)	Mp (°C) (crystallized from)	Molecular formula or Reference Mp	Analysis % Calcd./Found C	H	N	S	Hal
3a				42.1	110-111 (EtOAc)	110-111 [2]					
4a	Methyl	Methyl	A	16.5	106-107 (EtOAc)	106-107.5 [2]					
5a				3.1	147-149 (CH_3CN)	$C_4H_6N_4S$ (144.20)	33.31 33.39	5.59 5.72	38.86 38.74	22.24 22.41	
6a				1.8	191-193 (2-PrOH)	$C_4H_6N_4S$ (144.20)	33.31 33.26	5.59 5.65	38.86 38.80	22.24 22.31	
3b				35.5	78-80 (CH:2-PrOH)	$C_6H_{12}N_4S$ (172.25)	41.83 41.90	7.02 7.18	32.53 32.48	18.62 18.52	
4b	1-Propyl	Methyl	A	25.7	121-122 (2-PrOH)	$C_6H_{12}N_4S$ (172.25)	41.83 41.78	7.02 7.15	32.53 32.61	18.62 18.57	
6b				2.0	180-181 (CH_3CN:EtOH)	$C_6H_{12}N_4S$ (172.25)	41.83 41.95	7.02 7.21	32.53 32.71	18.62 18.65	
3c				36.8	58-61 (CH:2-PrOH)	$C_6H_{12}N_4S$ (172.55)	41.83 41.70	7.02 7.12	32.53 32.66	18.62 18.58	
4c	2-Propyl	Methyl	A	17.2	113-114 (2-PrOH)	$C_6H_{12}N_4S$ (172.55)	41.83 41.80	7.02 7.18	32.53 32.50	18.62 18.48	
6c				0.8	173-174 (2-PrOH)	$C_6H_{12}N_4S$ (172.55)	41.83 41.88	7.02 7.25	32.53 32.66	18.62 18.73	
3d				42.2	86-87 (EtOAc)	86-88 [2]					
4d	Allyl	Methyl	A	18.1	120-121 (Bz)	120-122 [2]					
6d				0.6	182-184 (EtOAc)	$C_6H_{10}N_4S$ (170.23)	42.34 42.32	5.92 6.11	32.91 32.77	18.84 18.67	

Table I, continued

Analytical Data

Compound No.	R	R'	Method of Preparation	Isolated Yield (%)	Mp (°C) (crystallized from)	Molecular formula or Reference Mp	Analysis % Calcd./Found C	H	N	S	Hal
3e				41.0	140-141 (EtOAc)	140-141 [2]					
4e				18.0	92-93 (Bz)	92-93 [2]					
5e	Benzyl	Methyl	A	2.6	174-176 (EtOH)	$C_{10}H_{12}N_4S$ (220.29)	54.52 54.46	5.49 5.63	25.44 25.38	14.56 14.71	
6e				0.4	184-185 (2-PrOH)	$C_{10}H_{12}N_4S$ (220.29)	54.52 54.65	5.49 5.70	25.44 25.41	14.56 14.53	
3f				34.2	128-130 (EtOAc)	$C_{10}H_{11}FN_4S$ (238.29)	50.40 50.32	4.65 4.70	23.51 23.48	13.46 13.32	7.97 8.11
4f	2-Fluoro-benzyl	Methyl	A	17.2	89-91 (EtOAc)	$C_{10}H_{11}FN_4S$ (238.29)	50.40 50.45	4.65 4.83	23.51 23.42	13.46 13.50	7.97 7.90
3g				42.5	128-129 (Bz)	128-129 [2]					
4g	4-Chloro-benzyl	Methyl	A	17.5	137-138 (Bz)	137-138 [2]					
5g				2.5	235-236 (MeOH)	$C_{10}H_{11}ClN_4S$ (254.74)	47.15 47.03	4.35 4.54	22.00 22.11	12.59 12.48	13.92 13.88
6g				0.5	196-198 (2-PrOH)	$C_{10}H_{11}ClN_4S$ (254.74)	47.15 47.34	4.35 4.48	22.00 22.07	12.59 12.65	13.92 13.71
3h				34.4	147-148 (2-PrOH)	$C_{11}H_{12}N_4O_2S$ (264.30)	49.98 49.87	4.58 4.77	21.20 20.98	12.13 12.28	
4h	(3,4-Methylenedioxybenzyl)	Methyl	A	12.1	141-142 (2-PrOH)	$C_{11}H_{12}N_4O_2S$ (264.30)	49.98 49.67	4.58 4.69	21.20 20.95	12.13 12.07	
5h				1.9	176-179 (EtOAc)	$C_{11}H_{12}N_4O_2S$ (264.30)	49.98 49.82	4.58 4.61	21.20 21.08	12.13 12.27	
6h				0.5	206-208 (2-PrOH)	$C_{11}H_{12}N_4O_2S$ (264.30)	49.98 50.11	4.58 4.73	21.20 21.04	12.13 12.08	
3i				23.0	138-140 (2-PrOH)	$C_{14}H_{20}N_4OS$ (292.40)	57.50 57.40	6.89 6.98	19.16 19.24	10.97 11.13	
4i	3-(2,6-Dimethylphenoxypropyl)	Methyl	A	10.1	80-82 (CH:2-PrOH)	$C_{14}H_{20}N_4OS$ (292.40)	57.50 57.58	6.89 7.10	19.16 19.02	10.97 10.76	
3j				19.3	110-111 (EtOAc)	110-111 [2]					
4j	2-(2,6-Dichlorophenoxy)ethyl	Methyl	A	6.1	93-94 (EtOAc)	93-95 [2]					
5j				0.8	207-209 (CH_3CN)	$C_{11}H_{12}Cl_2N_4OS$ (319.22)	41.39 41.45	3.79 3.92	17.55 17.48	10.05 10.08	22.21 22.26
6j				0.5	187-189 (2-PrOH)	$C_{11}H_{12}Cl_2N_4OS$ (319.22)	41.39 41.28	3.79 3.88	17.55 17.36	10.05 10.11	22.21 22.00
3k				20.1	158-160 (EtOAc)	$C_{18}H_{20}N_4OS$ (340.44)	63.50 63.30	5.92 6.11	16.46 16.38	9.42 9.45	
4k	3-(4-Phenylphenoxy)propyl	Methyl	A	5.7	118-120 (EtOAc)	$C_{18}H_{20}N_4OS$ (340.44)	63.50 63.62	5.92 6.21	16.46 16.22	9.42 9.38	
3l				15.2	109-111 (EtOAc)	$C_{15}H_{20}N_4O_2S$ (320.41)	56.26 56.10	6.29 6.35	17.49 17.33	10.01 9.89	
4l	3-[4-(1-Ketopropyl)phenoxy]propyl	Methyl	A	8.6	122-124 (EtOAc)	$C_{15}H_{20}N_4O_2S$ (320.41)	56.26 56.22	6.29 6.42	17.49 17.35	10.01 10.09	

reactions as minor components we tried to find other methods for their preparation.

Such a method could be the direct alkylation of the 3-R'-thio-5-amino-1*H*-1,2,4-triazole derivatives **1** or their sodium salt with the corresponding alkyl or aralkyl halides **2** in the presence of triethylamine catalyst or following the alkylation method reported in the literature [3]. In these reactions all of the four monoalkylated derivatives **3**, **4**, **5** and **6** were formed (Scheme 1) which were separated and their spectral data compared (Table I).

Table I, continued

Analytical Data

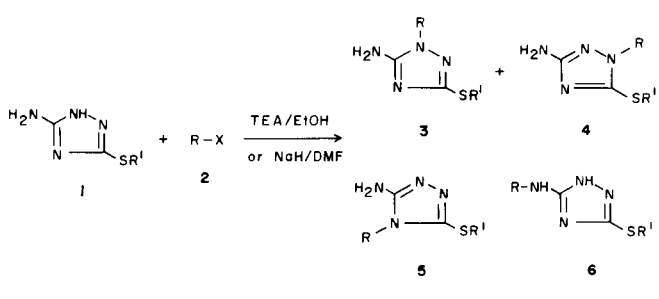
Compound No.	R	R'	Method of Preparation	Isolated Yield (%)	Mp (°C) (crystallized from)	Molecular formula or Reference Mp	Analysis % Calcd./Found C	H	N	S	Hal
3m	Cyano-methyl	Methyl	A	40.2	151-152 (EtOAc)	$C_5H_7N_5S$ (169.21)	35.49 / 35.44	4.17 / 4.35	41.39 / 41.20	18.95 / 18.82	
4m				12.1	162-163 (CH_3CN)	$C_5H_7N_5S$ (169.21)	35.49 / 35.55	4.17 / 4.08	41.39 / 41.52	18.95 / 18.70	
3n	Carbeth-oxymethyl	Methyl	A	19.8	103-105 (CH:EtOAc)	$C_7H_{12}N_4O_2S$ (216.26)	38.87 / 38.75	5.59 / 5.63	25.91 / 25.76	14.83 / 15.01	
4n				11.1	129-131 (EtOAc)	$C_7H_{12}N_4O_2S$ (216.26)	38.87 / 38.75	5.59 / 5.70	25.91 / 25.88	14.83 / 14.64	
3o	1-Carb-ethoxy-ethyl	Methyl	B	39.1	99-101 (EtOAc)	$C_8H_{14}N_4O_2S$ (230.29)	41.72 / 41.60	6.13 / 6.35	24.33 / 24.12	13.92 / 13.88	
3p	2-Cyano-ethyl	Methyl	A	38.2	142-143 (H_2O)	$C_6H_9N_5S$ (183.24)	39.32 / 39.20	4.95 / 5.10	38.22 / 38.16	17.50 / 17.65	
4p				10.8	118-119 ($EtOH:H_2O$)	$C_6H_9N_5S$ (183.24)	39.32 / 39.45	4.95 / 5.18	38.22 / 38.35	17.50 / 17.28	
3q				37.8	103-105 (CH:2-PrOH)	102-105 [2]					
4q	Methyl	Benzyl	A	11.2	87-89 (EtOAc)	87-89 [2]					
5q				2.1	167-168 (EtOH)	$C_{10}H_{12}N_4S$ (220.30)	54.52 / 54.48	5.49 / 5.55	25.44 / 25.38	14.56 / 14.60	

The very different ms splitting scheme of derivatives **6** from those of derivatives **3-5** made possible their easy separation. On the other hand the extent to which the ms spectra of derivatives **3-5** differed from each other depended greatly on the nature of R substituents thus the ms method could be used for their differentiation only in some special cases [4,5].

After selection of derivatives **6** the ir spectra of the remaining derivatives **3-5** made it possible to separate into three distinct groups, one characterised with two strong ν C=N bands between 1670-1500 cm^{-1} and the other two with three strong bands in the 1670-1500 cm^{-1} region, one of the latter two being accompanied by one or two strong bands between 1310-1285 cm^{-1} (Table I) in good agreement with our earlier observations [2]. Nevertheless no decision could be made as to which group corresponded to structures **3, 4** or **5**, respectively [6]. The two NH signals appearing in the ^{1}H-nmr spectra [7] of derivatives **6** enabled again their easy differentiation from those of derivatives **3-5** characterised with one NH_2 singlet. On the other hand the very slight differences among the corresponding chemical shifts of the SCH_3 and NH_2 groups of derivatives **3-5**, respectively, made it impossible to formulate any general rule for their certain differentiation (compare *e.g.* **3a**: δ SCH_3 = 2.47 ppm, δ NH_2 = 6.5 ppm with **4a**: δ SCH_3 = 2.57 ppm, δ NH_2 = 5.3 ppm and **5a**: δ SCH_3 = 2.48 ppm, δ NH_2 = 5.9 ppm; or **3e**: δ SCH_3 = 2.46 ppm, δ NH_2 = 6.6 ppm with **4e**: δ SCH_3 = 2.54 ppm, δ NH_2 = 5.3 ppm and **5e**: δ SCH_3 = 2.45 ppm, δ NH_2 = 6.1 ppm; or **3h**: δ SCH_3 = 2.45 ppm, δ NH_2 = 6.55 ppm with **4h**: δ SCH_3 = 2.58 ppm, δ NH_2 = 5.4 ppm and **5h**: δ SCH_3 = 2.40 ppm, δ NH_2 = 5.9 ppm; or **3j**: δ SCH_3 = 2.44 ppm, δ NH_2 = 6.4 ppm with **4j**: δ SCH_3 = 2.58 ppm, δ NH_2 = 5.4 ppm and **5j**: δ SCH_3 = 2.41 ppm, δ NH_2 = 6.3 ppm; all spectra taken in DMSO solution).

The uv spectra of derivatives **3-5** (Table I) could be again separated into three distinct groups, one of them being fully analogous to those of derivatives **6**, but again no decision could be made as to which corresponded to structures **3, 4** or **5**. Moreover they strongly depended on the nature of the R-substituents.

Scheme I



To exclude the above uncertainties derivatives **3-5** were converted into their Schiff bases **8-10** (Scheme 2, Table II) where as a consequence of the prolonged conjugation a bathochromic shift of the highest maxima of derivatives **8** and **10** is expected as compared with those in derivatives **9**. In addition to the case of derivatives bearing the same R groups a hypsochromic shift of the highest maxima of derivatives **10** by about 5-10 nm's was observed as compared with those of the corresponding derivatives **8** (compare

Table I, continued

Spectral Data

	IR (cm^{-1})					UV, λ max (nm) (ε • 10^{-3}) 96% EtOH	10% EtOH + 90% 0.1 *N* NaOH	10% EtOH + + 90% 0.1 *N* HCl
3a						238 sh (2.3)	238 sh (2.7)	213 (8.9)
								237 sh (4.3)
4a						228 sh (4.1)	228 sh (3.8)	253 (4.9)
						247 (3.6)	245 (4.1)	
5a	3360	3310	1630	1565		220 (5.9)	220 (5.1)	210 (8.3)
	3170		1504			244 sh (4.0)	244 sh (3.7)	238 sh (3.0)
6a	3250	3120	1620	1520		220 sh (6.1)	218 (6.5)	213 (9.3)
						243 sh (1.8)	245 sh (2.8)	240 sh (4.1)
3b	3360	3320	1653	1573	1300	219 sh (8.8)	218 (6.1)	214 (7.9)
	3130		1511			245 sh (2.7)	238 sh (3.5)	242 sh (2.6)
4b	3350	3310	1630	1545		230 sh (4.1)	226 sh (4.0)	201 (6.9)
	3210					250 (4.1)	245 (4.4)	246 (5.7)
6b	3240	3035	1620	1520		217 sh (4.2)	245 sh (1.8)	209 (6.6)
						243 sh (1.1)		240 sh (2.5)
3c	3360	3320	1640	1545	1295	220 sh (5.2)	218 (4.8)	244 sh (3.9)
	3210	3160	1495			247 sh (3.3)	239 sh (4.4)	
4c	3430	3330	1635	1550		228 (4.1)	227 (4.7)	230 (3.8)
	3220	3190				249 (3.9)	245 (4.6)	249 (4.1)
6o	3310	3140	1625	1540	1290	219 sh (7.2)	218 (5.4)	214 (12.0)
	3070					245 sh (1.5)	243 sh (2.5)	248 sh (4.4)
3d						218 sh (6.5)	237 sh (4.0)	213 (9.8)
						239 sh (2.8)		238 sh (4.6)
4d						231 (4.0)	244 (4.3)	255 (5.4)
						247 (4.0)		
6d	3200		1595	1500		220 sh (8.8)		
			1490			244 sh (2.9)		
3e						240 sh (3.8)	240 sh (4.1)	206 (16.2)
								240 sh (5.0)
4e						230 sh (5.3)	247 (5.5)	256 (5.6)
						248 sh (4.5)		
5e	3280	3120	1670	1580		226 sh (5.3)	245 sh (3.6)	205 (15.2)
			1500			250 sh (3.8)		237 sh (3.5)
6e	3230	3130	1635	1535		220 sh (10.1)	227 sh (5.3)	205 (19.6)
	3040		1500			242 sh (3.0)	241 sh (4.2)	242 sh (4.9)
3f	3320	3180	1655	1565	1300	219 sh (7.9)	217 (7.1)	204 (24.2)
			1500			245 sh (2.9)	244 sh (4.5)	241 sh (5.3)
4f	3450	3310	1635	1550		255 sh (5.2)	217 (7.7)	254 (11.8)
	3200	3170				261 sh (4.7)	248 (6.6)	261 sh (10.7)
3g						218 (16.3)	239 (4.7)	220 (19.7)
						241 (4.0)		238 (6.0)
4g						219 (14.4)	246 (5.0)	219 (14.0)
						250 (4.6)		256 (5.6)
5g	3270	3110	1670	1580		220 (17.6)	248 sh (3.8)	220 (18.3)
			1495			250 sh (3.9)		241 sh (3.1)
6g	3260	3030	1620	1525		220 sh (17.1)	219 (18.5)	220 (21.4)
						245 sh (4.8)	245 sh (3.6)	245 sh (6.3)
3h	3410	3310	1635	1570	1300	236 sh (7.9)	236 sh (7.5)	236 sh (9.0)
	3210	3180	1505			285 (4.1)	284 (3.4)	284 (3.8)

Table I, continued

Spectral Data

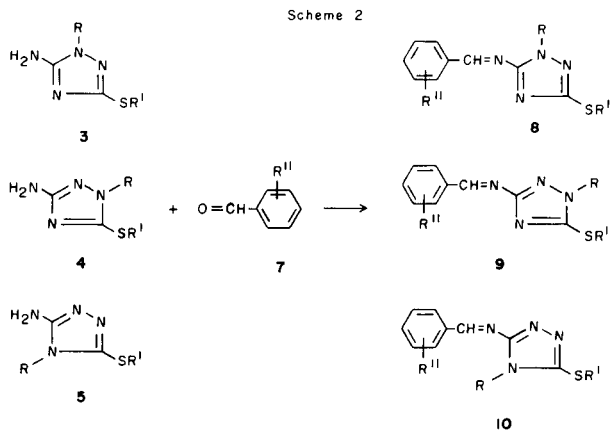
	IR (cm^{-1})					UV, λ max (nm) (ε • 10^{-3}) 96% EtOH	10% EtOH + 90% 0.1 *N* NaOH	10% EtOH + + 90% 0.1 *N* HCl
4h	3450	3330	1640	1550		237 (8.2)	236 (7.8)	240 (7.2)
	3230	3190				284 (4.2)	283 (3.5)	280 sh (5.3)
5h	3270	3120	1665	1580		233 (7.6)	232 (7.7)	236 sh (6.9)
	3100		1505			285 (3.7)	284 (3.7)	284 (3.6)
6h	3270	3230	1640	1550		241 sh (6.9)	230 (8.0)	237 sh (9.9)
	3180	3130				285 (3.9)	284 (3.7)	284 (3.9)
3i	3360	3320	1650	1560	1290	216 sh (14.9)	241 sh (3.5)	238 sh (4.2)
	3220	3200	1495		1305	242 sh (2.6)		
4i	3340	3310	1635	1545		215 sh (11.9)	218 (9.4)	214 sh (14.0)
	3210	3170				250 (3.6)	246 (4.8)	248 (4.2)
3j						218 sh (16.1)	240 sh (3.2)	216 sh (17.9)
						241 sh (2.7)		240 sh (4.3)
4j						220 sh (13.3)	245 (4.8)	220 sh (11.6)
						249 (4.7)		256 (5.7)
5j	3460	3320	1640	1565		219 sh (14.1)	225 (11.5)	218 sh (16.4)
	3230	3180	1500			282 (2.0)	282 (1.6)	281 (2.0)
						290 (1.8)	290 (1.5)	290 (1.7)
6j	3240	3140	1610	1515	1285	221 sh (23.7)	226 (6.9)	215 sh (23.8)
						243 sh (5.3)	246 sh (5.1)	242 sh (6.2)

Table I, continued

Spectral Data

	IR (cm^{-1})					UV, λ max (nm) (ε • 10^{-3}) 96% EtOH	10% EtOH + 90% 0.1 *N* NaOH	10% EtOH + + 90% 0.1 *N* HCl
3k	3400	3330	1660	1575	1300	258 (19.6)	258 (18.7)	257 (19.1)
	3190		1505					
4k	3470	3330	1630	1545		258 (22.3)	257 (20.9)	258 (23.8)
	3420	3210						
3l	3430	3330	1680	1655	1310	215 sh (19.2)	219 sh (15.0)	216 (33.8)
	3190	3150	1610	1575		238 sh (4.9)	242 sh (5.6)	270 (27.8)
			1510			270 (18.0)	276 (16.4)	277 (26.7)
4l	3445	3335	1675	1640		219 sh (16.3)	219 (13.5)	216 (15.6)
	3240	3180	1610	1580		267 (18.5)	274 (16.7)	269 (18.5)
			1545	1515				
3m	3410	3310	1640	1565	1305	216 sh (6.6)	235 sh (3.2)	204 sh (10.9)
	3220	3180	1505			240 sh (2.8)		237 sh (4.1)
4m	3390	3330	1650	1635		251 (4.1)	246 (4.2)	249 (4.6)
	3220	3180	1555					
3n	3400	3320	1745	1660	1310	213 sh (7.9)	237 sh (3.5)	212 (9.8)
	3120		1575	1510		238 sh (2.8)		234 sh (5.0)
4n	3390	3320	1745	1635		230 (4.0)	245 (4.2)	254 (4.4)
	3220	3180	1560	1545		250 (4.0)		
3o	3400	3320	1650	1635	1305	214 sh (8.1)	239 sh (3.6)	213 (9.6)
	3230	3150	1565	1505		239 sh (2.7)		236 sh (4.4)
3p	3350	3300	1700	1530	1290	218 sh (7.0)	220 (6.4)	213 (10.1)
	3100		1495			240 sh (3.1)	240 sh (3.3)	234 sh (4.9)
4p	3380	3280	1625	1550		234 sh (3.5)	232 sh (3.7)	256 (5.3)
	3170	3100				251 (3.9)	247 (4.6)	
3q						215 sh (16.3)	246 (3.0)	214 sh (13.6)
						249 sh (2.6)		252 sh (3.3)
4q						216 sh (11.9)	256 (3.9)	217 sh (8.0)
						258 (4.1)		263 (5.1)
5q	3340	3300	1635	1560		217 sh (9.8)	251 sh (4.1)	217 sh (11.6)
	3100		1515	1505		253 (4.6)		252 sh (2.6)

Scheme 2



e.g. **8e**: λ max = 333 nm, **9e**: λ max = 304 nm and **10e**: λ max = 325 nm; or **8g**: λ max = 331 nm, **9g**: λ max = 302 nm and **10g**: λ max = 324 nm) (Table II). Nevertheless the dependence of these maxima on the nature of the R groups enabled us to formulate a general rule only for the differentiation of isomers **9** (λ max = 297-308 nm). The range of the absorption maxima of derivatives **8** (λ max = 325-341 nm) overlapped the corresponding range of derivatives **10** (λ max = 314-325 nm).

The certain differentiation among derivatives **3-5** made possible their ^{13}C-nmr spectra [7] where the triazole carbon atoms 3 and 5 appeared with the chemical shifts of δ C_3 = 155.1-158.4 ppm and δ C_5 = 157.9-160.3 ppm; or of δ C_3 = 151.1-153.5 ppm and δ C_5 = 163.0-165.5 ppm; or of δ C_3 = 145.4-146.1 ppm and δ C_5 = 156.9-157.8 ppm, respectively. Their unambiguous assignment to structures **3, 4** and **5**, respectively, made possible their coupling scheme arising from the ^{3}J(C,H) couplings among the triazole carbon atoms and the protons of the R and R′ groups. Thus *e.g.*, the carbon atoms 3 of derivatives **3f, 4f, 5f** (R = benzyl, R′ = methyl) had to appear as a quartet, multiplet and multiplet, respectively, while the corresponding carbon atoms 5 of the above derivatives had to appear as a triplet, singlet and triplet, respectively.

The analogous chemical shift of the triazole carbon atoms of derivatives **6** (δ C_3 = 155.7-158.8 ppm, δ C_5 = 155.8-159.9 ppm) with those of derivatives **3** strongly supports the idea that, at least in DMSO solution, is the dominant tautomeric form of derivatives **6** the 1*H*-tautomeric form (see as depicted on Scheme 1) which is in agreement with the uv measurements recorded in ethanolic solution (Table I).

Table II

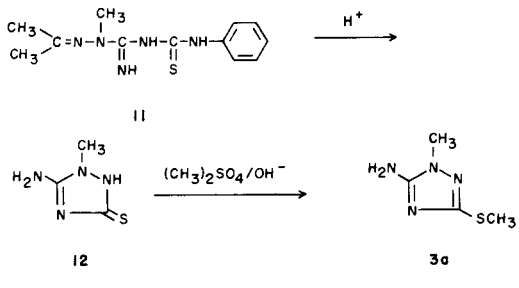
Compound No.	R	R′	R″	Isolated Yield (%)	Mp (°C) (crystallised from)	Molecular formula or Reference Mp	Analysis % Calcd./Found C	H	N	S	Hal	UV λ max (nm) (ε • 10^{-3}) 96% EtOH
8a	Methyl	Methyl	H		85-86 (2-PrOH)	85-86 [2]						217 sh (14.4) 278 (15.5) 328 (12.6)
9a	Methyl	Methyl	H		86-87 (2-PrOH)	86-87 [2]						215 (15.0) 262 (13.0) 301 (13.3)
10a	Methyl	Methyl	H	80.5	113-115 (2-PrOH)	$C_{11}H_{12}N_4S$ (232.30)	56.87 56.98	5.21 5.45	24.12 24.08	13.80 13.66		217 sh (14.2) 265 (11.6) 325 (12.7)
8d	Allyl	Methyl	H	42.9	80-82 (CH_3CN)	$C_{13}H_{14}N_4S$ (258.34)	60.44 60.21	5.46 5.60	21.69 21.55	12.41 12.35		275 (13.5) 331 (11.0)
8e	Benzyl	Methyl	H		102-103 (2-PrOH)	102-103 [2]						276 (15.7) 333 (12.6)
9e	Benzyl	Methyl	H		115-116 (EtOAc)	115-116 [2]						263 (14.3) 304 (14.3)
10e	Benzyl	Methyl	H	54.2	130-131 (CH_3CN)	$C_{17}H_{16}N_4S$ (308.40)	66.20 66.28	5.23 5.43	18.17 18.05	10.40 10.44		267 (12.1) 325 (13.2)
8g	4-Chloro-benzyl	Methyl	H		112-113 (2-PrOH)	111-113 [2]						219 (25.4) 275 (15.4) 331 (12.2)
9g	4-Chloro methyl	Methyl	H		114-115 (2-PrOH)	114-115 [2]						218 (25.9) 263 (14.8) 302 (14.6)
10g	4-Chloro benzyl	Methyl	H	44.2	145-147 (2-PrOH)	$C_{17}H_{15}ClN_4S$ (342.85)	59.55 59.66	4.41 4.65	16.34 16.24	9.35 9.33	10.34 10.25	219 (24.7) 261 (8.8) 324 (8.2)
8h	3,4-Methylenedi-oxybenzyl	Methyl	H	98.2	110-112 (2-PrOH)	$C_{18}H_{16}N_4O_2S$ (352.41)	61.34 61.23	4.58 4.75	15.90 15.76	9.10 9.07		218 sh (17.8) 280 (17.7) 329 (12.0)
9h	3,4-Methylenedi-oxybenzyl	Methyl	H	85.1	127-128 (2-PrOH)	$C_{18}H_{16}N_4O_2S$ (352.41)	61.34 61.45	4.58 4.66	15.90 15.88	9.10 9.14		221 sh (16.8) 289 (16.2) 308 (13.8)

Table II, continued

Compound No.	R	R'	R''	Isolated Yield (%)	Mp (°C) (crystallised from)	Molecular formula or Reference Mp	Analysis % Calcd./Found C	H	N	S	Hal	UV λ max (nm) (ε • 10^{-3}) 96% EtOH
8m	Cyano-methyl	Methyl	H	61.5	138-140 (2-PrOH)	$C_{12}H_{11}N_5S$ (257.31)	56.01 / 56.11	4.31 / 4.54	27.22 / 27.08	12.46 / 12.34		218 sh (11.4) 279 (12.6) 330 (9.7)
9m	Cyano methyl	Methyl	H	34.2	59-62 (CH:EtOAc)	$C_{12}H_{11}N_5S$ (257.31)	56.01 / 56.15	4.31 / 4.44	27.22 / 27.20	12.46 / 12.31		220 sh (15.8) 265 (12.8) 302 (12.6)
8n	Carbeth-oxymethyl	Methyl	4-Chloro	64.2	99-101 (EtOAc)	$C_{14}H_{15}ClN_4O_2S$ (338.82)	49.63 / 49.61	4.46 / 4.60	16.54 / 16.51	9.46 / 9.40	10.47 / 10.66	219 sh (20.7) 230 sh (9.5) 325 (19.5)
9n	Carbeth-oxymethyl	Methyl	4-Chloro	94.4	110-112 (2-PrOH)	$C_{14}H_{15}ClN_4O_2S$ (338.82)	49.63 / 49.83	4.46 / 4.52	16.54 / 16.56	9.46 / 9.53	10.47 / 10.74	218 (14.9) 273 (15.8) 304 (16.2)
8p	2-Cyano-ethyl	Methyl	H	27.4	130-132 (Bz)	$C_{13}H_{13}N_5S$ (271.34)	57.54 / 57.50	4.83 / 4.93	25.81 / 25.77	11.82 / 11.90		218 (15.2) 275 (16.2) 328 (12.9)
9p	2-Cyano-ethyl	Methyl	H	58.1	136-138 (EtOH)	$C_{13}H_{13}N_5S$ (271.34)	57.54 / 57.58	4.83 / 4.88	25.81 / 25.77	11.82 / 11.65		215 sh (16.4) 263 (13.4) 298 (13.0)
8q	Methyl	Benzyl	H		88-89 (EtOH)	88.5-89.5 [2]						214 sh (23.0) 274 (15.6) 328 (12.7)
9q	Methyl	Benzyl	H		77-78 (2-PrOH)	77-78 [2]						214 sh (23.3) 265 (14.2) 297 (13.4)
10q	Methyl	Benzyl	H	49.5	114.5-116 (CH_3CN)	$C_{17}H_{16}N_4S$ (308.40)	66.20 / 66.12	5.23 / 5.30	18.17 / 18.11	10.40 / 10.47		216 (21.3) 269 (13.0) 314 (14.3)

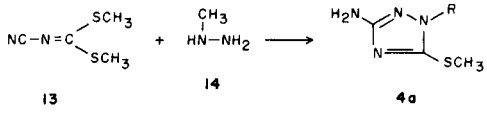
The structure of the *N*-monoalkylated derivatives **3, 4, 5** and **6** was also proved by preparative means. Thus 1-phenyl-5,7-dimethyl-4-imino-1,3,5,6-tetraazaoctane-2-thione (**11**) was converted by a known method [8] to 2,3-dihydro-1-methyl-5-amino-1*H*-1,2,4-triazole-3-thione (**12**) that was methylated to yield **3a** (Scheme 3).

Scheme 3



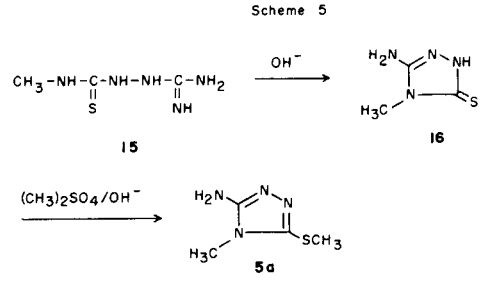
The isomeric **4a** was obtained as the main product of the reaction of *N*-cyanocarbonimidodithioic acid dimethyl ester (**13**) and *N*-methylhydrazine (**14**) [2]. In this reaction in addition to **4a** only **3a** could be formed which was prepared by a structure proving synthesis (see Scheme 3). As the product obtained differed from that of **3a** it had to have structure **4a** (Scheme 4).

Scheme 4



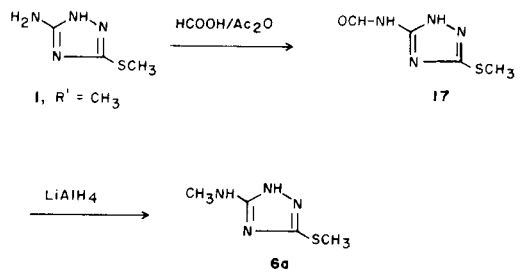
Compound **5a** was obtained by methylation of 2,3-dihydro-4-methyl-5-amino-4*H*-1,2,4-triazole-3-thione (**16**) prepared by a known method [9] from 1-methylthiocarbamoyl semicarbazide (**15**) (Scheme 5).

Scheme 5



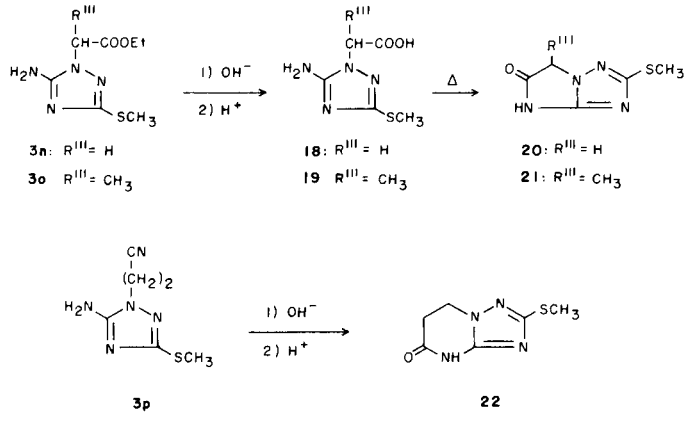
The remaining **6a** was synthesized by reduction of 3-methylthio-5-formylamino-1*H*-1,2,4-triazole (**17**) obtained by the formylation of **1** (R' = CH_3) (Scheme 6).

Scheme 6



Structure **3** of 1-(1-carboethoxymethyl)- and 1-(1-carboethoxyethyl)-3-methylthio-5-amino-1*H*-1,2,4-triazole (**3n** and **3o** respectively) as well as 1-(2-cyanoethyl)-3-methylthio-5-amino-1*H*-1,2,4-triazole (**3p**) was also corroborated by their cyclisation reactions to yield 5,6-dihydro-2-methylthio-4*H*-imidazo[1,2-*b*]-1,2,4-triazol-5-one (**20**), 5,6-dihydro-2-methylthio-6-methyl-4*H*-imidazo[1,2-*b*]-1,2,4-triazol-5-one (**21**) and 4,5,6,7-tetrahydro-2-methylthio-1,2,4-triazolo-[1,5-*a*]pyrimidin-5-one (**22**), respectively (Scheme 7).

Scheme 7



Using a hplc method the ratio of the monoalkylated derivatives **3, 4, 5** and **6** formed in the *N*-alkylation reactions according to Scheme 1 was also determined. As this determination was disturbed by the small amount of the polyalkylated products formed in these reactions before the hplc determination the monoalkylated derivatives were separated from the reaction mixture by passing it through a short column filled with silica-gel. The total amount of derivatives **3-6** thus obtained was then considered to be 100% (Table III).

Table III

Products of Alkylation	Reaction Temperature (°C)	Percentage Content of the *N*-Monoalkylated Products 3	4	5	6
3a-6a					
R = R′ = CH_3	25 ± 0.1	55	32	9	4
	0 ± 0.1	62	33	4	1
3e-6e	25 ± 0.1	63	30	5	2
R = CH_2Ph	50 ± 0.5	63	31	5	1
R′ = CH_3	75 ± 1	61	32	5	2
	98 ± 1	54	38	4	4

As it can be seen from Table III, the ratio of products **3, 4, 5** and **6** formed did not depend significantly on the nature of the R-substituent nor on the reaction temperature. The main product is in all cases derivative **3** offering a good chance for its preparation in those cases when it is formed in the reaction of *N*-cyanocarbonimidodithioic acid esters and the corresponding alkylhydrazines [2] as minor product only.

EXPERIMENTAL

Melting points were determined on a Koffler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using a Perkin-Elmer 577 spectrophotometer. The electron impact mass spectra were determined with a Varian MAS SM-1 spectrometer. The ultraviolet spectra were obtained by a Varian Cary 118 and a Pye Unicam SP 8-150 instrument. The hplc determinations were performed using a Varian 8500 pump, Variscan spectrophotometer, Varian Stop-Flow sampler and a Varian A-25 recorder.

General Methods for the Alkylation of Derivatives **1**.

Method A.

To a stirred mixture of 3.12 g (0.104 mole) of sodium hydride (Merck, 80% suspension in toluene) and 20 ml of absolute dimethylformamide a solution of 0.1 mole of the corresponding derivative **1** in 30 ml of absolute dimethylformamide was added at 0° during a period of 1 hour. The mixture was stirred at this temperature for ½ hour after which the appropriate alkyl halide (or its solution in a small amount of absolute dimethylformamide) was added keeping the temperature at 0°. The mixture was stirred for a further 3 hours at 0°, the cooling was then interrupted and the mixture left while stirring to warm to room temperature. The reaction was completed in the case of alkyl iodides by stirring at room temperature for a further 2 hours, in the case of alkyl bromides and benzyl chlorides by stirring for 5 hours, while in case of alkyl chlorides by stirring for 30 hours. The mixture thus obtained was treated with 200 ml of water and extracted with 2 × 100 ml of chloroform. The combined chloroform layers were dried over sodium sulfate, evaproated at reduced pressure to dryness and the residue chromatographed on a silica-gel column to obtain products **3-6** which were recrystallised from an appropriate solvent (Table I).

Method B.

A solution of 0.1 mole of the corresponding derivative **1**, 0.12 mole of the corresponding alkyl halide and 0.1 mole of triethylamine in 200 ml of acetonitrile was refluxed in the case of alkyl chlorides for 40 hours, while in the case of alkyl bromides for 15 hours. The reaction mixture was then evaporated at reduced pressure to dryness, the residue partitioned between 200 ml of water and 100 ml of chloroform, the aqueous phase extracted with 2 × 200 ml of chloroform, the combined chloroform layers extracted with 100 ml of water, dried over sodium sulfate, evaporated at reduced pressure to dryness and the residue chromatographed on a silica-gel column to obtain products **3-6** which were recrystallized from an appropriate solvent (Table I).

General Method for the Preparation of Schiff Bases, **8**, **9** and **10**.

A solution of 0.1 mole of the appropriate 1-, or 2- or 4-(alkyl-, or aralkyl)-3-(alkyl- or aralkylthio)-5-amino-1,2,4-triazole **3**, **4** or **5** in 100 ml of 2-propanol, 0.3 mole of the corresponding aldehyde and 1 ml of piperidine was refluxed for 5 hours. The solution was evaporated to dryness and

the residue recrystallised from an appropriate solvent (Table II).

1-Methyl-3-methylthio-5-amino-1*H*-1,2,4-triazole (**3a**).

To the stirred solution of 1.30 g (0.01 mole) of 2,3-dihydro-1-methyl-5-amino-1*H*-1,2,4-triazole-3-thione (**12**) [8] in 10.5 ml of 1*N* sodium hydroxide, 1.26 g (0.01 mole) of dimethyl sulfate dissolved in 2 ml of methanol was added keeping the temperature of the reaction mixture below 25°. After the reaction had ceased the reaction mixture was evaporated to dryness *in vacuo*, the residue triturated with ethyl acetate, the solution obtained again evaporated to dryness *in vacuo* and the residue (1.10 g, 76%) recrystallised from a small amount of ethyl acetate to yield 1-methyl-3-methylthio-5-amino-1*H*-1,2,4-triazole (**3a**), mp 111-112° (lit [2] mp 110-111°). The product is identical with that of **3a** obtained by direct alkylation (Table I).

2-Methyl-3-methylthio-5-amino-2*H*-1,2,4-triazole (**4a**).

Reiter's method [2] was used to prepare 2-methyl-3-methylthio-5-amino-2*H*-1,2,4-triazole (**4a**), mp 106-107° in 86% yield. The product is identical with that of **4a** obtained by direct alkylation (Table I).

3-Methylthio-4-methyl-5-amino-4*H*-1,2,4-triazole (**5a**).

To the stirred solution of 6.50 g (0.05 mole) of 2,3-dihydro-4-methyl-5-amino-4*H*-1,2,4-triazole-3-thione (**16**) [9] in 80 ml of 1 *N* sodium hydroxide, 4.75 ml of dimethyl sulfate was added and the reaction mixture kept at 85° for 9 hours. After cooling the mixture was evaporated to dryness *in vacuo* and the residue chromatographed on a silica gel column to yield 2.66 g (37%) of 3-methylthio-4-methyl-5-amino-4*H*-1,2,4-triazole (**5a**), mp 147-149° (acetonitrile). The product is identical with that of **5a** obtained by direct alkylation (Table I).

3-Methylthio-5-formylamino-1*H*-1,2,4-triazole (**17**).

A solution of 26.04 g (0.2 mole) of 3-methylthio-5-amino-1*H*-1,2,4-triazole (**1**, R′ = CH_3) in 42.5 ml (0.45 mole) of acetic anhydride and 22 ml (0.48 mole) of formic acid was heated at 80° for 1 hour. After cooling the crystals precipitated were filtered off to yield 26.4 g (83%) of 3-methylthio-5-formylamino-1*H*-1,2,4-triazole (**17**), mp 210-212° (butanol); ir: ν NH = 3280, 3200 and 3070 cm^{-1}; ν C=O = 1690 cm^{-1}, ν C=N = 1600 and 1555 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ SCH_3 = 2.60 s and 2.69 s ppm, δ CHO = 8.45 s and 8.98 s ppm, δ NH = 11.2 b, 11.6 b and 13.5 b ppm (a 1:1 mixture of the two rotamers [10]); uv (ethanol): λ max = 208 nm (ϵ = 16400), λ max = 233 nm (ϵ = 9000); (10% ethanol and 90% 0.1 *N* sodium hydroxide): λ max = 244 nm (ϵ = 8000); (10% ethanol and 90% 0.1 *N* hydrochloric acid): λ max = 209 nm (ϵ = 14,300), λ max = 236 nm (ϵ = 7400).

3-Methylthio-5-methylamino-1*H*-1,2,4-triazole (**6a**).

To a stirred mixture of 0.14 g (0.03 mole) of lithium aluminium hydride and 30 ml of tetrahydrofuran, 1.58 g (0.01 mole) of 3-methylthio-5-formylamino-1*H*-1,2,4-triazole (**17**) was added in small portions at room temperature. The mixture was then refluxed while stirring for 2 hours. After cooling the mixture was treated with 10 ml of water; evaporated *in vacuo* to dryness, the residue triturated with 2 × 25 ml of hot dimethylformamide and the solution obtained again evaporated *in vacuo* to dryness. 3-Methylthio-5-methylamino-1*H*-1,2,4-triazole (**6a**) (1.44 g, 100%) was thus obtained that melted after recrystallisation from 2-propanol at 191-193° and was identical with that of **6a** obtained by direct alkylation (Table I).

1-Carboxymethyl-3-methylthio-5-amino-1*H*-1,2,4-triazole (**18**).

To the solution of 1.0 g (0.0046 mole) of 1-carboethoxy-methyl-3-methylthio-5-amino-1*H*-1,2,4-triazole (**3n**) in 20 ml of methanol the solution of 0.3 g (0.0075 mole) of sodium hydroxide in 10 ml of methanol was added in one portion and the reaction mixture obtained left to stand at room temperature for three days. After the acidification of the reaction mixture with concentrated hydrochloric acid to p*H* = 4 the mixture immediately crystallised to yield after filtration 0.6 g (69%) of 1-carboxymethyl-3-methylthio-5-amino-1*H*-1,2,4-triazole (**18**), mp 225-228°; ir: ν C=O = 1680 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ SCH_3 = 2.45 s ppm, δ CH_2 = 4.72 s ppm, δ NH_2 = 6.5 bs ppm.

5,6-Dihydro-2-methylthio-4*H*-imidazo[1,2-*b*]-1,2,4-triazol-5-one (**20**).

1-Carboxymethyl-3-methylthio-5-amino-1*H*-1,2,4-triazole (**18**) (0.28 g, 0.0015 mole) was heated at 250° for 5 minutes. The dark brown solid obtained was triturated with 10 ml of hot ethyl acetate, treated with charcoal, filtered and evaporated to dryness. The crystalline residue was recrystallised from a small amount of ethyl acetate to yield 0.12 g (81%) of 5,6-dihydro-2-methylthio-4*H*-imidazo[1,2-*b*]-1,2,4-triazol-5-one (**20**), mp 202-205°; ir: ν C=O = 1692 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ SCH_3 = 2.55 s ppm, δ CH_2 = 4.66 s ppm; uv (ethanol): λ max = 212 nm (ϵ = 18,000), 238 sh nm (ϵ = 4100); (10% ethanol and 90% 0.1 *N* sodium hydroxide): λ max = 241 sh nm (ϵ = 14,000), 265 sh nm (ϵ = 6,000); (10% ethanol and 90% 0.1 *N* hydrochloric acid): (λ max = 212 nm (ϵ = 17,500), 236 sh nm (ϵ = 5500).

1-(1-Carboxyethyl)-3-methylthio-5-amino-1*H*-1,2,4-triazole (**19**).

To the solution of 1.2 g (0.005 mole) of 1-(1-carboethoxyethyl)-3-methylthio-5-amino-1*H*-1,2,4-triazole (**3o**) in 5 ml of methanol the solution of 0.3 g (0.0075 mole) of sodium hydroxide in 5 ml of methanol was added in one portion and the mixture left to stand at room temperature for three days. The reaction mixture was then acidified with concentrated hydrochloric acid to p*H* = 4 and allowed to crystallise. After filtration 0.6 g (59%) of 1-(1-carboethoxyethyl)-3-methylthio-5-amino-1*H*-1,2,4-triazole (**19**) was obtained, mp 213°; ir: ν C=O = 1680 cm^{-1}.

5,6-Dihydro-2-methylthio-6-methyl-4*H*-imidazo[1,2-*b*]-1,2,4-triazol-5-one (**21**).

1-(1-Carboethoxyethyl)-3-methylthio-5-amino-1*H*-1,2,4-triazole (**19**) (0.5 g, 0.0025 mole) was heated at 250° for 5 minutes. The dark solid obtained was triturated with a 1:2 mixture of benzene and ethyl acetate and chromatographed on a short silica-gel column to yield 0.35 g (73%) of 5,6-dihydro-2-methylthio-6-methyl-4*H*-imidazo[1,2-*b*]-1,2,4-triazol-5-one (**21**), mp 183-184°; ir: ν C=O = 1690 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ SCH_3 = 2.40 s ppm, δ CH = 4.95 qa ppm, δ CCH_3 = 1.55 d ppm, δ NH = 6.4 bs ppm; uv (ethanol): λ max = 213 nm (ϵ = 18,800), λ max = 238 sh nm (ϵ = 4200); (10% ethanol and 90% 0.1 *N* sodium hydroxide): λ max = 240 sh nm (ϵ = 13,800), 265 sh nm (ϵ = 5800); (10% ethanol and 90% 0.1 *N* hydrochloric acid): λ max = 212 nm (ϵ = 17,000), λ max = 235 sh nm (ϵ = 5000).

2-Methylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-5-one (**22**).

The mixture of 4.50 g (0.025 mole) of 1-(2-cyanoethyl)-3-methylthio-5-amino-1*H*-1,2,4-triazole (**3p**) and 10 ml of 5 *N* sodium hydroxide was refluxed for 2 hours. The solution obtained was acidified with 20% sulfuric acid (p*H* = 1) and allowed to crystallise for a few days. This way 1.70 g (37%) of 2-methylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-5-one (**22**) was obtained which melted after recrystallisation from a 2:1 mixture of methanol and water at 254-256°; ir: ν C=O = 1712 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ SCH_3 = 2.52 s ppm, δ CCH_2 = 2.88 m ppm, δ NCH_2 = 4.23 t ppm, δ NH = 9 b ppm; uv (ethanol): λ max = 212 nm (ϵ = 22,300), λ max = 236 sh nm (ϵ = 5450); (10% ethanol and 90% 0.1 *N* sodium hydroxide): λ max = 241 sh nm (ϵ = 8500), λ max = 263 nm (ϵ = 7000); (10% ethanol and 90% 0.1 *N* hydrochloric acid): λ max = 212 nm (ϵ = 21,000), λ max = 234 nm (ϵ 7300).

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