Synthesis of Nitrogen-Containing Heterocycles. 8 [1]. Preparation and Ring-Opening of Spiro[cycloalkane-[1',2',4']triazolo[1',5'-*c*]pyrimidine] Derivatives

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Diaminomethylene- and aminomethylthiomethylenehydrazones [2] of cyclic ketones **1-8** readily reacted with ethoxymethylenemalononitrile to give spiro[cycloalkane-1,2'-[1',2',4']triazolo[1',5'-*c*]pyrimidine-8'-carbonitrile] derivatives **12-19** through the electrocyclic reaction of the initially formed condensation products **26** in moderate to high yields. The spiro[cyclopentanetriazolopyrimidine] derivatives underwent ring-opening at the cycloalkane moiety upon heating in solution to give 2-alkyl-5-substituted-[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carbonitriles **20-23**. When an alkyl substituent was introduced into the cyclopentane ring, cleavage of the spiro compounds occurred preferentially at the cyclopentane moiety between the spiro carbon and the more branched one. In contrast, the cyclohexane ring, especially of spiro-5-amino-triazolopyrimidines **17** and **18** strongly resisted to ring-opening under similar conditions, but those of 5-methylthiotriazolopyrimidines **14** gave up to 17 percent of cleavage after prolonged heating in hot ethanol. 2-*t*-Butyl-5-methylthio-2,3-dihydro[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carbonitrile **25** [R^3 = $C(CH_3)_3$] was highly susceptible to the cleavage even at room temperature and produced the corresponding 2-unsubstituted triazolopyrimidine **24** with loss of the *t*-butyl group.

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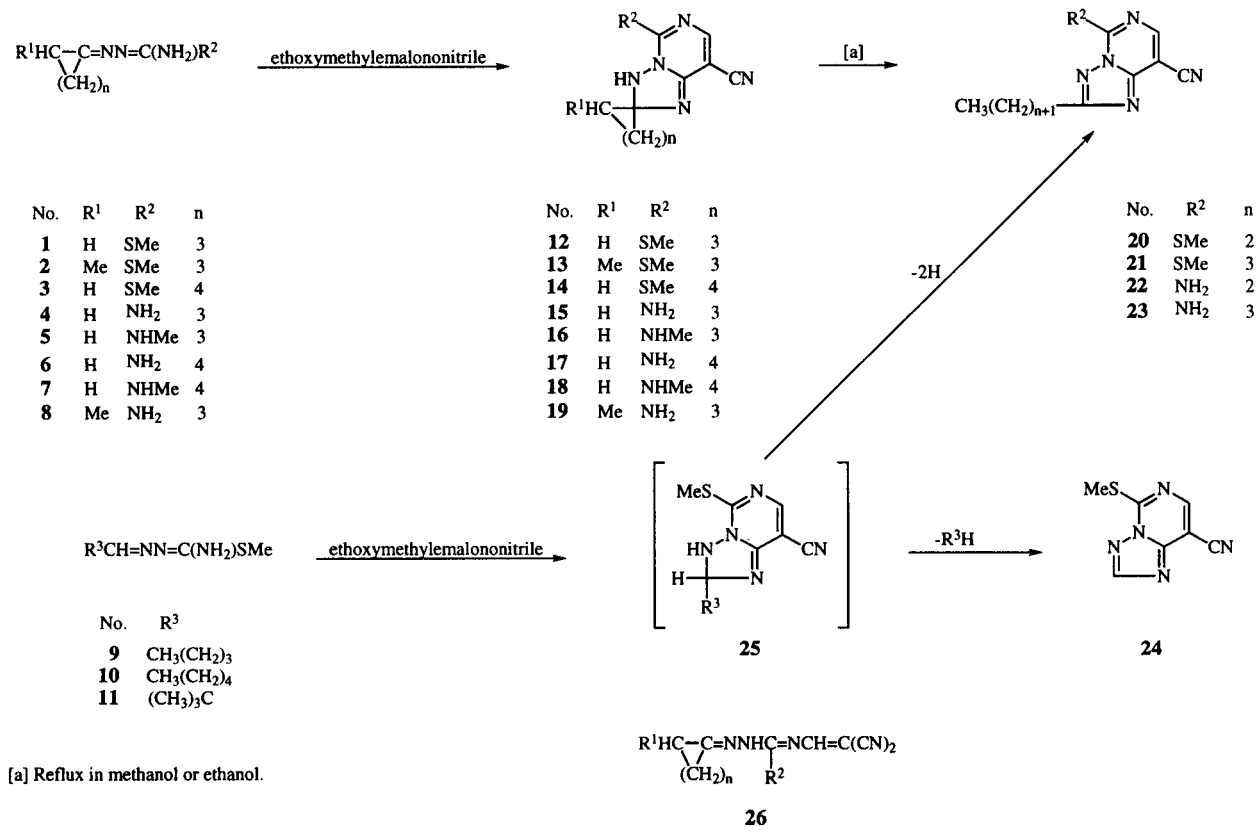
The utility of active ethoxymethylene compounds, in particular, ethoxymethylenemalononitrile, ethyl ethoxymethlyenecyanoacetate and diethyl ethoxymethylenemalonate, in the synthesis of heterocyclic compounds is well established [3]. We have previously reported the facile synthesis of di- and trisubstituted [1,2,4]triazolo-[1,5-*c*]pyrimidine derivatives by the electrocyclic reaction of the initial condensation products between the diaminomethylene- [4] and aminomethylthiomethylenehydrazones [5] of aromatic carbonyl compounds and the ethoxymethylene reagents. We have now attempted synthesis of spiro[cycloalkane-1,2'-[1',2',4']triazolo[1',5'-*c*]-pyrimidine] derivatives **12-19** starting with diaminomethylene- and aminomethylthiomethylenehydrazones of cyclic ketones **1-8** taking advantage of the characteristic feature of the electrocyclic reaction in which the benzylidene carbon of the starting hydrazone rehybridized to a tetrahedral carbon atom and appeared as a ring member of the condensed pyrimidine system. We also investigated the effects of the ring size of the spirocycloalkane product and nature of the substituents at the 5-position on the ease of the ring-opening reaction. As appreciated universally, five- and six-membered cycloalkane structures are extremely stable and, to the best of our knowledge, no report has been published as to such facile ring cleavage in a non-destructive solution at moderate temperature. Thus, we wish to report a simple synthetic route to the spirocycloalkanetriazolopyrimidine derivatives and cleavage of the carbon to a carbon single bond at the 2-position in the triazolopyrimidine system.

In general, the cyclization of aminomethylthiomethylenehydrazones of cycloalkanones **1-3** were performed by heating an equimolar mixture of the hydrazone and ethoxymethylenemalononitrile in ethanol at 80° for 5 minutes. The desired spiro compounds **12-14** crystallized out of the somewhat darkened solution and were isolated as crystalline compounds in 36-54% yields [6]. The products **12** and **13** thus obtained were more or less contaminated with the corresponding ring-cleaved compounds **20** and **21** as evidenced by the thiomethyl proton resonance at δ 2.80. The pure compounds were readily obtained by washing out the contaminants with warm benzene or ethanol. Compound **13** was obtained as a diastereoisomeric mixture from which the single stereoisomer could not be isolated.

The ring-opening reaction of the spiro compounds **12-14** could simply be achieved by heating them in ethanolic solution. Thus, for example, the ring-opening of compound **12** occurred in 89% in boiling ethanol within 4 hours and the cleaved compound **20** was isolated by means of high-performance liquid chromatography (hplc) on silica gel. It was identical with a compound produced by an alternative route in which compound **9** was allowed to react with ethoxymethylenemalononitrile with spontaneous dehydrogenation of the intermediate **25** [R^3 = $CH_3(CH_2)_3$]. Another spiro compound **13** which also has a five-membered alicyclic structure resisted ring-opening. Thus, the reaction occurred to the extent of about 60% over 16 hours and resulted in an incomplete reaction even after 38 hours in refluxing ethanol. Since the methylcyclopentane structure of **13** appeared as a linear alkyl

Scheme 1



No.	R^1	R^2	n
1	H	SMe	3
2	Me	SMe	3
3	H	SMe	4
4	H	NH_2	3
5	H	NHMe	3
6	H	NH_2	4
7	H	NHMe	4
8	Me	NH_2	3

No.	R^1	R^2	n
12	H	SMe	3
13	Me	SMe	3
14	H	SMe	4
15	H	NH_2	3
16	H	NHMe	3
17	H	NH_2	4
18	H	NHMe	4
19	Me	NH_2	3

No.	R^2	n
20	SMe	2
21	SMe	3
22	NH_2	2
23	NH_2	3

No.	R^3
9	$CH_3(CH_2)_3$
10	$CH_3(CH_2)_4$
11	$(CH_3)_3C$

25 **24** **26**

[a] Reflux in methanol or ethanol.

Table 1

Analytical and Physical Data for Diaminomethylene- and Aminomethylthiomethylenehydrazones

Compound No.	Yield (%)	Mp °C	Formula	Calcd./Found C	H	N	^{1}H NMR Spectra [a]
1	86	61-62	$C_7H_{13}N_3S$	49.11	7.65	24.55	1.75 (m, 4H, 2 x CH_2), 2.42 (s, 3H, CH_3), 2.46 (m, 4H, 2 x CH_2),
				49.04	7.50	24.67	5.16 (bs, 2H, NH_2)
2	80	73-74	$C_8H_{15}N_3S$	51.87	8.16	22.69	1.18 (d, J = 6.8, 3H, CCH_3), 1.27-2.68 (m, 7H, 3 x CH_2 + CH), 2.43
				52.05	8.19	22.99	(s, 3H, SCH_3), 5.10 (bs, 2H, NH_2)
3	[b]						
4	78	160-161	$C_6H_{12}N_4$	51.41	8.63	39.96	1.62 (m, 4H, 2 x CH_2), 2.22 (m, 4H, 2 x CH_2), 5.23 (bs, 4H,
				51.54	8.71	39.83	2 x NH_2)
5	78	80-82	$C_7H_{14}N_4 \cdot 1/2H_2O$	51.51	9.26	34.33	1.68 (m, 4H, 2 x CH_2), 2.40 (m, 2H, CH_2), 2.65 (m, 2H, CH_2),
				51.35	9.13	34.59	2.74 (s, 3H, CH_3), 4.53 (bs, 2H, NH_2)
6	45	127-128	$C_7H_{14}N_4$	54.52	9.15	36.33	1.55 (m, 6H, 3 x CH_2), 2.35 (m, 4H, 2 x CH_2), 4.44 (bs, 4H,
				54.22	9.00	36.16	2 x NH_2)
7	69	132-133	$C_8H_{16}N_4$	57.11	9.59	33.30	1.61 (bs, 6H, 3 x CH_2), 2.30 (m, 2H, CH_2), 2.55 (m, 2H, CH_2),
				57.30	9.30	33.10	3.01 (s, 3H, CH_3), 7.29 (bs, 3H, NH_2 + NH)
8	75	128-130	$C_7H_{14}N_4$	54.52	9.15	36.33	1.12 (d, J = 6.4, 3H, CH_3), 1.16-2.43 (m, 6H, 3 x CH_2), 2.51
				54.66	9.20	36.15	(quintet, J = 2.0, $CHCH_3$), 7.37 (bs, 4H, 2 x NH_2)
9	65	44-46	$C_7H_{15}N_3S$	48.54	8.73	24.26	0.92 (t, 3H, J = 7.3, CCH_3), 1.38 (sextet, 2H, J = 7.8, CH_2), 1.52
				48.55	8.77	24.46	(quintet, 2H, J = 7.8, CH_2), 2.30 (q, 2H, J = 5.9, CH_2CH=),
							2.43 (s, 3H, SCH_3), 5.31 (bs, 2H, NH_2), 7.74 (t, 1H, J = 5.4, CH=N)
10	73	oil	$C_8H_{17}N_3S$	51.31	9.15	22.44	0.90 (t, 3H, J = 6.8, CCH_3), 1.31-1.56 (m, 6H, 3 x CH_2), 2.29
				51.25	8.90	22.39	(q, 2H, J = 5.4, CH_2CH=), 2.44 (s, 3H, SCH_3), 5.27 (bs, 2H, NH_2),
							7.74, (t, 1H, J = 5.4, CH=N)
11	76	59-60	$C_7H_{15}N_3S$	48.54	8.73	24.26	1.10 [s, 9H, $C(CH_3)_3$], 2.43 (s, 3H, SCH_3), 5.31 (bs, 2H, NH_2),
				48.64	8.79	24.15	7.65 (s, 1H, CH=N)

[a] δ, J in Hz in deuteriochloroform; [b] Known compound [7].

Table 2

Analytical and Physical Data for Spiro[cycloalkane-1,2'-[1',2',4']triazolo[1',5'-*c*]pyrimidine-8'-carbonitriles]

Compound No.	Yield (%)	Mp °C [a]	Formula	Calcd./Found C	H	N	MS, m/z (Relative Intensity)	^{1}H NMR Spectra [c]
13 [b]	51	171-174	$C_{12}H_{15}N_5S$ (216)	55.16 55.29	5.79 5.85	26.81 27.00	261 (M^+, 17), 218 (100), 205 (26)	0.95 (d, J = 6.1, 3H, CCH_3), 1.60-1.95 (m, 7H, 3 x CH_2 + $CHCH_3$), 2.54 (s, 3H, SCH_3), 4.46 (bs, 1H, NH), 7.71 (s, 1H, H-7)
14	36	172-173	$C_{12}H_{15}N_5S$ (261)	55.16 55.18	5.79 5.84	26.81 26.79	261 (M^+, 18), 218 (50), 205 (100)	1.25-1.96 (m, 10H, 5 x CH_2), 2.54 (s, 3H, SCH_3), 4.46 (bs, 1H, NH), 7.72 (s, 1H, H-7)
16	61	172-203	$C_{11}H_{14}N_6$ (230)	57.38 57.49	6.13 6.18	36.50 36.78	230 (M^+, 7), 201 (62), 188 (100)	1.67-1.70 (m, 8H, 4 x CH_2), 2.83 (d, J = 4.4, 3H, NCH_3), 6.04 (s, 1H, H-3), 7.73 (q, J = 4.4, 1H, $NHCH_3$), 7.86 (s, 1H, H-7)
17	74	192-193	$C_{11}H_{14}N_6$ (230)	57.38 57.22	6.13 6.23	36.50 36.43	230 (M^+, 16), 187 (100), 174 (79)	1.38-1.62 (m, 10H, 5 x CH_2), 5.88 (s, 1H, H-3), 7.32 and 8.08 (each bs, 1H, NH), 7.75 (s, 1H, H-7)
18	67	192-198	$C_{12}H_{16}N_6$ (244)	59.00 58.78	6.60 6.63	34.40 34.34	244 (M^+, 15), 201 (93), 188 (100)	1.37-1.61 (m, 10H, 5 x CH_2), 2.94 (d, J = 4.4, 3H, NCH_3), 5.95 (s, 1H, H-3), 7.77 (q, J = 4.4, 1H, $NHCH_3$), 7.86 (s, 1H, H-7)
19 [b]	28	162-190	$C_{11}H_{14}N_6$ (230)	57.38 57.10	6.13 6.04	36.50 36.22	230 (M^+, 20), 187 (83), 174 (100)	0.84 (d, J = 6.3, 3H, CH_3), 1.58-1.83 (m, 7H, 3 x CH_2 + $CHCH_3$), 6.13 (s, 1H, H-3), 7.34 and 8.08 (each bs, 1H, NH), 7.76 (s, 1H, H-7)

[a] Broad melting ranges can be ascribed to partial ring-opening in the course of heating; [b] The data are those for the major component of the two diasteroisomers; [c] In deuteriochloroform for compounds **13** and **14** and in dimethyl-d_6 sulfoxide for others.

Table 3

Analytical and Physical Data for 2-Alkyl[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carbonitriles

Compound No.	Mp °C	Formula	Calcd./Found C	H	N	MS, m/z (Relative Intensity)	^{1}H NMR Spectra [a]
21	104-105	$C_{12}H_{15}N_5S$ (261)	55.16 54.98	5.79 5.80	26.81 26.69	261 (M^+, 18), 205 (100)	0.91 (t, J = 6.6, 3H, CCH_3), 1.32-1.92 (m, 6H, 3 x CH_2), 2.79 (s, 3H, SCH_3), 2.99 (t, J = 7.6, 2H, $C_4H_9CH_2$), 8.43 (s, 1H, H-7)
22	185-186	$C_{10}H_{12}N_6$ (216)	55.55 55.41	5.59 5.63	38.86 38.79	216 (M^+, 8), 174 (100)	0.93 (t, J = 7.3, 3H, CH_3), 1.62-1.82 (m, 4H, 2 x CH_2), 2.84 (t, J = 7.8, 2H, $C_3H_7CH_2$), 8.43 (s, 1H, H-7), 8.66 and 9.09 (each bs, 1H, NH)
23	188-190	$C_{11}H_{14}N_6$ (230)	57.38 57.29	6.13 6.01	36.50 36.52	230 (M^+, 10), 174 (100),	0.88 (t, J = 7.3, 3H, CH_3), 1.34-1.78 (m, 6H, 3 x CH_2), 2.82 (t, J = 7.8, 2H, $C_4H_9CH_2$), 8.43 (s, 1H, H-7), 8.66 and 9.06 (each bs, 1H, NH)

group in the cleaved product **21**, the bond fission evidently occurred at the methylcyclopentane moiety between the spiro carbon and the methyl-bearing carbon atom and therefore produced the same cleaved compound as that derived from compound **14**. Thus, product **21** coincided with the compound obtained by the alternative route starting with **10** through **25** [$R^3 = CH_3(CH_2)_4$] with spontaneous dehydrogenation. The spirocyclohexane compound **14** vigorously resisted ring opening which required a time as long as 110 hours to achieve 84% cleavage under similar conditions. The cleavage of compound **14** can be accelerated by addition of pyridine to the reaction medium. Thus, the ring opening was completed within 91 hours when it was treated with hot ethanolic solution containing 10 v/v of pyridine. The facile and preferential bond fission at the more highly substituted carbon in the [1,2,4]triazolo[1,5-*c*]pyrimidine system was also observed in the behavior of dihydrotriazolopyrimidine **25**

Table 4

^{13}C NMR Chemical Shifts [a] of Ring Carbons in the Spiro[cycloalkane-1,2'-triazolopyrimidine-8'-carbonitriles]

Compound No.	C-2	C-5	C-7 [b]	C-8	C-9
12	86.3	161.3	157.0	97.1	145.8
13 [c]	86.1	161.0	157.0	98.3	145.5
14	89.3	161.6	156.9	86.6	145.7
15	78.1	147.2	159.8	95.8	151.8
16	78.8	147.3	159.4	96.0	150.7
17	78.3	147.1	159.8	87.9	152.1
18	79.0	147.1	159.5	88.1	150.9
19 [c]	77.9	147.2	159.8	96.9	151.7

[a] In deuteriochloroform for compounds **12** and **14** and in dimethyl-d_6 sulfoxide for the other compounds; [b] Appeared as a doublet, $^1J_{CH}$ = 180.1-191.1 Hz; [c] The values are those for the major component in a two-diastereoisomer mixture.

[$R^3 = (CH_3)_3C$] produced from compound **11**. It gave the 2-unsubstituted triazolopyimidine **24** with loss of R^3H upon standing, in a solution in chloroform at room temperature.

In general, the diamionmethylenehydrazones of cyclic ketones **4-7** showed comparable reactivity to that of the methylthio compounds toward ethoxymethylenemalononitrile. Thus, hydrazones **4-7** were allowed to react with ethoxymethylenemalononitrile by brief heating in acetonitrile to give the corresponding spirocycloalkanetriazolopyrimidines **15-18** in 61-79% yield. When the cyclization was carried out in refluxing methanol, significant amounts of ring-opening took place and the yield of the spiro compounds markedly diminished. Diaminomethylenehydrazone **6** was the most reactive compound which gave the cyclized product **17** in 74% yield within 30 minutes even at room temperature, while hydrazone **8** was unreactive at room temperature and gave the lowest yield (28%) of the spiro product **19** even at elevated temperatures. In view of the fact that hydrazone **4** gave the corresponding spirocyclopentanetriazolopyrimidine **15** in 79% yield within 3 minutes in boiling acetonitrile, it was quite evident that the methyl substituent on the cyclopentane ring of **8** decidedly inhibited the reactivity toward ethoxymethylenemalononitrile in this series.

The ring-opening of spiro compound **15** occurred in boiling methanol and proceeded in 86% yield within 3 hours giving the corresponding cleaved product **22**. The cleavage of the cycloalkane ring was promoted by introduction of a methyl substituent into the cycloalkane moiety, compound **19**, or the 5-amino nitrogen, compound **16**, resulting in complete ring-opening within 2 hours for these compounds.

The structures of the spirocycloalkanetriazolopyrimidine **12-19** and the ring-opened 2-alkyl compounds **20-23** were confirmed on the basis of the spectal data and elemental analyses which appears in Tables 2-4.

EXPERIMENTAL

Melting points were determined in open capillary tubes and uncorrected. The ^1H and ^{13}C nmr spectra were obtained with a JNM EX-400 (400 MHz) or a JNM FX-90Q (90 MHz) spectrometer. The chemical shift values were recorded in parts per million (ppm) on the δ scale with tetramethylsilane as the internal reference. The mass spectra (75 eV) were obtained on a JEOL JMS-D100 mass spectrometer. Preparative high-performance liquid chromatography (hplc) was carried out on a Kusano Kagaku KHLC-201 instrument with a 300 x 22 mm glass column packed with silica gel. Microanalyses were performed with a Perkin-Elmer 240D elemental analyser at the Microanalytical Laboratory of Kitasato University.

The diaminomethylene- and aminomethylthiomethylenehydrazones **1-8** used were prepared by literature methods [7] and are reported in Table 1.

Preparation of Spiro[cycloalkane-1,2'-(5'-substituted)-[1',2',4']-triazolo[1',5'-*c*]pyrimidine-8'-carbonitriles]. Spiro[cyclopentane-1,2'-(5'-methylthio)-[1',2',4']triazolo[1',5'-*c*]pyrimidine-8'-carbonitrile] (**12**).

A mixture of hydrazone **1** (1.71 g, 0.01 mole), ethoxymethylenemalononitrile (1.22 g, 0.01 mole) and ethanol (10 ml) was treated at 80° with agitation for 5 minutes and then cooled. The reddish yellow needles which formed upon cooling were filtered, washed with ethanol and then with benzene, and dried to give the desired product **12** as bright yellow needles (1.34 g, 54%) [homogeneous on a silica-gel plate developed with chloroform-methanol (98:2 v/v)], mp 164-166°; ^1H nmr (deuteriochloroform): δ 1.59-2.21 (m, 8H, 4 x CH_2), 2.55 (s, 3H, SCH_3), 4.39 (bs, 1H, NH), 7.73 (s, 1H, H-7); ms: m/z (relative intensity) 247 (M^+, 7), 218 (69), 205 (100).

Anal. Calcd. for $C_{11}H_{13}N_5S$: C, 53.43; H, 5.30; N, 28.33. Found: C, 53.63; H, 5.24; N, 28.54.

The spiro compounds **13** and **14** were similarly obtained and are reported in Table 2.

Spiro[cyclopentane-1,2'-(5'-amino)-[1',2',4']triazolo[1',5'-*c*]-pyrimidine-8'-carbonitrile] (**15**).

A solution of diaminomethylenehydrazone (**4**) (0.14 g, 1 mmole) and ethoxymethylenemalononitrile (0.15 g, 1.2 mmoles) in acetonitrile (1 ml) was heated under reflux for 3 minutes during which time the starting materials went into solution and then the desired product rapidly separated. The crystals were collected by filtration and washed with acetonitrile to give **15** as a pale yellow crystalline powder (0.17 g, 79%), mp 194-206°; ^1H nmr (DMSO-d_6): δ 1.68 (m, 4H, 2 x CH_2), 1.71 (m, 4H, 2 x CH_2), 6.09 (s, 1H, H-3), 7.39 and 8.10 (each bs, 3H, NH_2 + NH), 7.77 (s, 1H, H-7); ms: m/z (relative intensity) 216 (M^+, 6), 187 (65), 174 (100).

Anal. Calcd. for $C_{10}H_{12}N_6$: C, 55.55; H, 5.59; N, 38.86. Found: C, 55.19; H, 5.53; N, 38.89.

When the reaction was carried out at room temperature for 30 minutes and the crystals were filtered, a linear intermediate **26** (R^1 = H, R^2 = NH_2, n = 3) was obtained as a pale yellow crystalline powder (0.14 g, 62%), mp 177-184°; ^1H nmr (DMSO-d_6): δ 1.70 (quin, 2H, J = 6.3, CH_2), 1.77 (quin, 2H, J = 6.8, CH_2), 2.04 (t, 2H, J = 7.3, =C-CH_2), 2.42 (t, 2H, J = 7.8, =C-CH_2), 7.66, 8.16 and 10.53 (each bs, 3H, NH_2 + NH), 8.25 (s, 1H,

-CH=); ms: m/z (relative intensity) 216 (M^+, 17), 187 (100).

Anal. Calcd. for $C_{10}H_{12}N_6$: C, 55.55; H, 5.59; N, 38.86. Found: C, 55.34; H, 5.62; N, 39.06.

It was readily converted into **15** by heating the methanolic solution for 5 minutes.

Other spiro compounds **16-19** were prepared similarly or with appropriate modifications and are reported in Table 2.

Ring-Opening of Spiro[cycloalkane-1,2'-(5'-substituted)-[1',2',4']triazolo[1',5'-*c*]pyrimidine-8'-carbonitriles]. Ring-Opening of Spiro Compound **12**.

Formation of 2-Butyl-5-methylthio-[1,2,4]triazolo[1,5-*c*]pyrimidine-8-cabonitrile (**20**).

A 0.5 g portion of product **12** was dissolved in ethanol (8 ml) and the solution was refluxed for 4 hours during which time ring-opening had proceeded in 89% yield. After evaporation of the solvent, the residue was subjected to hplc on silica gel with chloroform as the eluent to give the cleaved product **20** (0.18 g, 36%) as white crystals. Recrystallization from hexane gave the analytical sample of 2-butyl-5-methylthio[1,2,4]triazolo[1,5-*c*]-pyrimidine-8-carbonitrile (**20**) as white prisms, mp 81.5-82°; ^{1}H nmr (deuteriochloroform): δ 0.96 (t, J = 6.6, 3H, CCH_3), 1.25-1.95 (m, 4H, 2 x CH_2), 2.79 (s, 3H, SCH_3), 2.99 (t, J = 7.7, 2H, $C_3H_7CH_2$), 8.42 (s, 1H, H-7); ms: m/z (relative intensity) 247 (M^+, 12), 218 (34), 205 (100).

Anal. Calcd. for $C_{11}H_{13}N_5S$: C, 53.43; H, 5.30; N, 28.33. Found: C, 53.35; H, 5.18; N, 28.63.

Alternative Route to Cleaved Compound **20**.

A mixture of pentanal aminomethylthiomethylenehydrazone (**9**) (0.87 g, 5 mmoles), ethoxymethylenemalononitrile (0.91 g, 7.5 mmoles), triethylamine (0.2 ml) and acetonitrile (5 ml) was boiled under reflux for 6 hours and then evaporated under reduced pressure. The residue was subjected to preparative hplc on silica gel using dichloromethane as the eluent to collect homogeneous fractions from which compound **20** (0.09 g, 7%) was obtained as colorless prisms, mp 81-82° with no mp depression on admixture with the cleaved product from **12**. The ir (carbon tetrachloride) [8] and ^{1}H nmr spectra was identical with those from **12**.

2-Hexyl-5-methylthio-[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carbonitrile (**21**) was obtained similarly by the three routes, *i.e.*, ring-opening of **13** and **14** and the cyclization of **10** with ethoxymethylenemalononitrile under the reaction conditions described for **20**.

Ring-Opening of Spiro Compound **15**. Formation of 5-Amino-2-butyl[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carbonitrile (**22**).

A solution of spiro compound **15** (0.1 g) in methanol (1 ml) was heated under reflux for 30 minutes and evaporated. The residue which contained about 90% of the cleaved product was subjected to hple on silica gel using chloroform as the eluent to give the desired product (0.07 g, 70%), mp 185-186°; ^{1}H nmr (DMSO-d_6): δ 0.93 (t, J = 7.3, 3H, CCH_3), 1.38 (sextet, J = 7.3, 2H, CH_2), 1.76 (quintet, J = 7.8, 2H, CH_2), 2.84 (t, J = 7.8, 2H, $C_3H_7CH_2$), 8.43 (s, 1H, H-7), 8.66 and 9.09 (each bs, 1H, 2 x NH) [9].

Anal. Calcd. for $C_{10}H_{12}N_6$: C, 55.55; H, 5.59; N, 38.86. Found: C, 55.41; H, 5.63; N, 38.79.

Cleavage of 2-*tert*-Butyl-2,3-dihydro-5-methylthio[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carbonitrile (**25**). Formation of 5-Methylthio[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carbonitrile (**24**).

A solution of aminomethylthiomethylenehydrazone **11** (0.43 g, 2.5 mmoles) and ethoxymethylenemalononitrile (0.30 g, 2.5 mmoles) in chloroform (2.5 ml) was allowed to stand at room temperature with occasional agitation for 2 hours and then evaporated at that temperature. The residual yellow crystals **25** (0.60 g, contaminated with *ca.* 8% of **24**); ^{1}H nmr (deuteriochloroform): δ 0.93 [s, 9H, $(CH_3)_3C$], 2.54 (s, 3H, SCH_3), 4.70 (d, J = 9.3, 1H, NH), 5.09 (d, J = 9.3, 1H, H-2), 7.71 (s, 1H, H-7); M^+ 249] were redissolved in chloroform (10 ml) and the solution was allowed to stand at room temperature for 75 hours during which time dealkylation had been completed and partial deposition of **24** was observed. The solvent was evaporated and the crystalline residue (0.35 g, 73%) was recrystallized twice from a benzene-ethanol mixture (5:3 v/v) with active charcoal to give compound **24** as colorless prisms, mp 204-205°; ^{1}H nmr (deuteriochloroform): δ 2.82 (s, 3H, SCH_3), 8.50 and 8.51 (each s, 1H, H-2 and H-7); ms: m/z (relative intensity) 191 (M^+, 100).

Anal. Calcd. for $C_7H_5N_5S$: C, 43.98; H, 2.64; N, 36.64. Found: C, 43.98; H, 2.60; N, 36.39.

REFERENCES AND NOTES

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[2] Although the term aminomethylthiomethylenehydrazones was used to emphasize the analogy of these compounds to the diaminomethylenehydrazones in structure, the former compounds are typically named as isothiosemicarbazones.

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[5] C. Yamazaki, *Bull. Chem. Soc. Japan*, **54**, 1767 (1981); C. Yamazaki, *J. Org. Chem.*, **46**, 3956 (1981).

[6] Throughout the text, the yields of the products were determined for the isolated, substantially pure compounds.

[7] C. Yamazaki, *Can. J. Chem.*, **53**, 610 (1975); Y. Miyamoto, *Chem. Pharm. Bull.*, **33**, 2678 (1985).

[8] The ir spectrum was recorded on a Perkin-Elmer Model 983 instrument in 1 mm-KRS-5 cells.

[9] The two protons of 5-amino group may be non-equivalent to each other, presumably due to intramolecular hydrogen bonding.