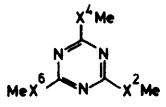
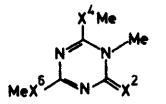
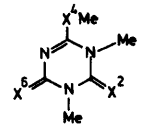
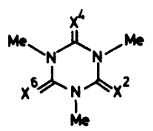
Regioselective Reactions in Heteroaromatic Systems. Rules for Methyl Migration and Nucleophilic Substitution in Methyl Cyanurates and Thiocyanurates

By **Maria Livia Tosato** * and **Laura Soccorsi**, Laboratories of Toxicology, Istituto Superiore di Sanità, 00161 Rome, Italy

A comparative analysis carried out on 19 methyl cyanurates and thiocyanurates (some of which reported for the first time) allowed the following general conclusions to be drawn about their reactivity in nucleophilic substitution and thermal isomerisation reactions. The nucleophilic substitution of the methylthio-groups by methoxide anions is always possible, but requires different experimental conditions which are specific for the molecular region in which the methylthio is located; the thermal isomerisation reaction of the methoxy-derivatives into the corresponding *S*- or *N*-methyl isomers requires temperature conditions which are also largely dependent upon the molecular site of the methoxy-group. In both reactions the reactivity is enhanced by local asymmetry of substitution at the ring carbon atom to which the XMe (X = S or O) group is bound.

WE have recently reported [1] a synthetic procedure which by means of methanolysis and isomerisation allowed four trimethyl dithiocyanurates and four trimethyl monothiocyanurates to be obtained from (1)† and (9).† A preliminary study of the two reactions allowed us (i) to point out the selectivity of nucleophilic attack in methanolysis and (ii) to develop some rules for the methyl group migration in the thermal isomerisation reactions.

		X^2	X^4	X^6
	(18)	S	S	S
	(19)	S	O	S
	(20)	O	O	S
	(21)	O	O	O
	(9)	S	S	S
	(10)	S	O	S
	(11)	O	S	S
	(13)	O	O	S
	(22)	O	O	O
	(27)	S	S	O
	(28)	S	O	O
	(29)	O	S	O
	(1)	S	S	S
	(2)	S	O	S
	(3)	S	S	O
	(5)	S	O	O
	(14)	O	S	O
	(16)	O	O	O
	(24)	O	S	S
	(25)	O	O	S
	(6)	O	O	S
	(17)	O	O	O
	(23)	S	O	S
	(26)	S	S	S

By means of a similar, or different, procedure seven new methyl thiocyanurates (19), (20), (23)—(25), (28), and (29) have been synthesized. Therefore, all the trimethyl-substituted isomeric derivatives of cyanuric and mono-, di-, and tri-thiocyanuric acids listed above, with the exception only of (27), were available to us for a complete comparative study of their behaviour. As a result the correlations between their structure and reactivity were clarified on qualitative grounds.

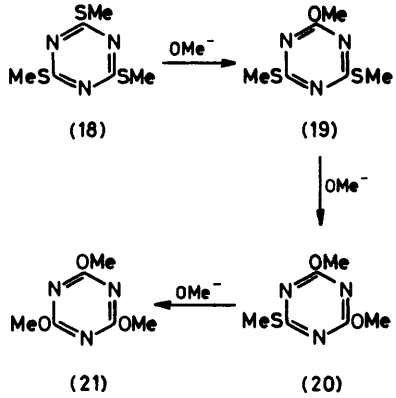
† In order to simplify the necessary references, compounds already mentioned previously [1] retain the same identification numbers. Compounds not cited therein (either known or new ones) are here numbered from (18) onwards.

In the present paper the synthesis of the new compounds is reported; the reactivity of the 12 methylthio-derivatives with respect to nucleophilic substitution of methanethiolate by methoxide, and the thermal stability of the 12 methoxy-derivatives with respect to isomerisation are examined; conclusions about the rules governing both nucleophilic substitution and the thermal rearrangement are drawn and a discussion of the molecular origin of these rules is presented.

RESULTS

Nucleophilic Substitutions.—The methylthio-derivatives so far examined were reported [1] to undergo substitution of methanethiolate by methoxide in methanol with trace amounts of NaOMe added at room temperature; a higher temperature or nucleophile concentration brought about *O*-demethylation of the products.

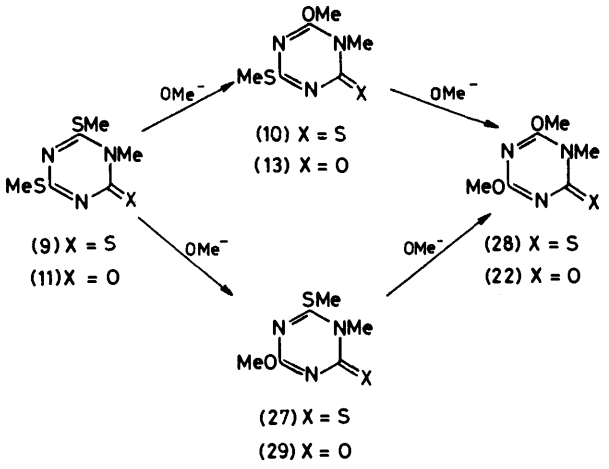
Methanolysis of compound (18). Upon refluxing a methanolic solution of (18) with *ca.* 1 equiv. NaOMe, a mixture of four components could be obtained with a controlled reaction time. After separation, the four components were identified as the starting compound (18), 2,4,6-trimethoxy-1,3,5-triazine (21), 2-methoxy-4,6-bismethylthio-1,3,5-triazine (19), and 2,4-dimethoxy-6-methylthio-1,3,5-triazine (20). Since, under the same controlled methanolysis conditions, (19) gave (20) and (21), and (20) changed into (21), the full methanolysis of (18) can be written as in Scheme 1. Neither (18), nor (19), nor (20) reacted at room



SCHEME 1

temperature; neither (19), nor (20), nor (21) gave *O*-demethylation products whatever the methoxide concentration and reflux time.

Methanolysis of compounds (9) *and* (11). These reactions were previously reported to produce (10) and (13), respectively. However, the above reported methanolysis of (18) suggested that it could be possible to substitute the other, less reactive, SMe group which is bound [both in (9) and (11)] to a ring carbon adjacent to two imidic nitrogen atoms, and thus to obtain (27) and/or (28) from (9), and (29) and/or (22) from (11), as shown in Scheme 2.



SCHEME 2

In practice we could never obtain (27) from (9) nor (29) from (11); (28) and (22) were isolated from the reaction mixtures obtained upon refluxing the methanolic solutions of (9) and (11), respectively, under controlled conditions of time and nucleophile concentration.

Methanolysis of compound (24). This compound (see Experimental section) changed quantitatively into (25) in methanol with trace amounts of NaOMe added at room temperature. A higher temperature and methoxide anion concentration led to the *O*-demethylated derivative.

Methanolysis of compound (13). This compound [1] underwent methanolysis to (22) upon refluxing a methanolic solution with about an equimolar amount of NaOMe added.

Thermal Rearrangements.—The thermal conversions of the OMe derivatives so far examined [1] into isomers were ireversible methyl shift reactions from the methoxide group either to a sulphur atom (O ⟶ S isomerisation) or, in the absence of a thione group available for methyl attack, to a ring nitrogen atom (O ⟶ N isomerisation).

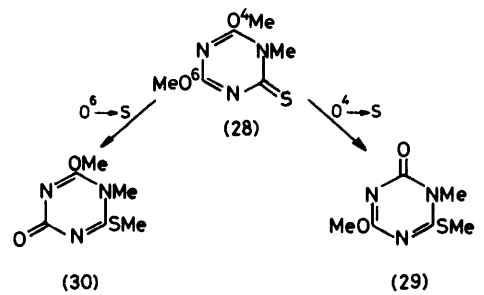
Whereas all the OMe derivatives may isomerise,[1–4] their actual thermal stability appeared to be largely dependent both on the nature of the isomerisation and on the molecular symmetry of the starting compound: all the O ⟶ S isomerisations occurred in the solid phase at room temperature; all the O ⟶ N isomerisations occurred, in the solid phase, at *ca.* 100 °C. The only exception was the O ⟶ N isomerisation of (21) into (17) that took place in the melt at *ca.* 200 °C. In terms of the proposed reaction mechanism [5] this deviant result was attributed to the high molecular symmetry of (21) among all the OMe derivatives examined, which could prevent the OMe bond from easily dissociating in the first reaction step.

Isomerisation of compounds (19) *and* (20). These two rather symmetric structures underwent O ⟶ N isomerisation in the melt at *ca.* 200 °C; their isomerisation products were, respectively, (11) and (14).

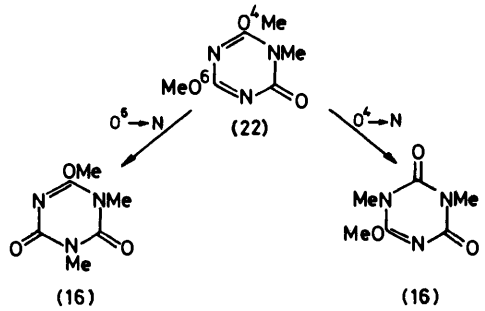
Isomerisation of compound (28). Compound (28) contains two non-equivalent methoxide groups and a thioxo-group available to methyl attack. According to previous results it should, in principle, isomerise as a solid at room temperature into both (29) and (30) (Scheme 3). However, a single isomerisation product, identified as (29), was formed in the solid state at any temperature below the m.p.

As (29) cannot be formed except by means of the O^4-methyl shift to the sulphur atom, the O^6-methyl group is not involved in solid-state isomerisation. This first example of a methoxide group bound to an unsymmetric structure which gives rise neither to a O ⟶ S nor to a O ⟶ N solid-state isomerisation* rules out the hypothesis of a direct correlation between thermal stability and both the molecular symmetry and the nature of the isomerisation.

In order to investigate this point further we have re-examined the thermal isomerisation of (22) [4] which is the only other compound with two non-equivalent methoxide groups, the same molecular symmetry as (28), and an apparently equivalent steric and electronic distribution. Compound (22) was reported to undergo O ⟶ N isomerisation to (16): whether the migrating group is the O^4- or the O^6-bound methyl (or both) cannot be established (Scheme 4). However, analysis of the isomerisation product of the



SCHEME 3



SCHEME 4

deuterium-labelled (22) O^4CD_3 (see Experimental section) established that the O^4-bound methyl group was shifted to the ring nitrogen.

This result is in line with the previous one; further evi-

* O⁶ ⟶ S isomerisation would give either (30) or its thermal rearrangement product (14). O⁶ ⟶ N isomerisation would give (5) or its thermal rearrangement product (6).[1] None of these products was formed in the solid.

dence to discount a correlation between thermal stability and molecular symmetry was given by the thermal behaviour of the unsymmetric (29).

Isomerisation of compound (29). This compound underwent thermal isomerisation into (14), but no reaction was observed in the solid; its complete conversion into (14) occurred at *ca.* 200 °C.

Isomerisation of compound (25). The O ⟶ S isomerisation of this compound into (14) occurred at room temperature.

DISCUSSION

A comparative analysis of the present and previous results allows us to identify the molecular origin of the different reactivities in the series of the SMe and OMe derivatives, respectively. As a consequence the general rules for both methanolysis and thermal isomerisation are given.

Rules for Methanolysis.—All the methanolysis reactions so far examined are listed in Table 1. With respect to the reaction conditions we distinguish two classes of substrates.

Compounds (1), (3), (9), (11), (14), (24), and (29) of the first class undergo methanolysis under ' very mild ' conditions, *i.e.* room temperature and trace amounts (or in the absence) of nucleophile.

Compounds (10), (13), and (18)—(20) of the second class only react upon refluxing methanolic solutions in the presence of approximately equimolar amounts of nucleophile.

The following observations point to a correlation between reactivity and electron distribution at the reaction centre of the two classes of compounds.

In the compounds of the first class the SMe group undergoing substitution is bound to a ring carbon atom which is located between two nitrogen atoms in different valence states (one is a pyridine-like, the other a pyrrole-like nitrogen). [We label SMe_{us} those groups which are located in an unsymmetric site of the molecule (Scheme 5a) and are easily substituted.] In the second class of compounds, the SMe group undergoing substitution is bound to a ring carbon atom between two equivalent pyridine-like nitrogens. [We label SMe_{ss} those groups which are located in a symmetric site of the molecule (Scheme 5b) and are uneasily substituted.]

If, as seems likely, the molecular site of the methanethiolate is the determining factor for rearrangement or removal, whenever both kinds of SMe groups are present in a molecule at the same time, as in (9) and (11), regioselective nucleophilic attack at the most reactive unsymmetric site should occur, and the corresponding monomethoxylated derivatives should be formed in higher yield than the others. In practice, whatever the methoxylation conditions, (9) and (11) changed quantitatively into (11) and (13), respectively, by substitution of their SMe_{us} groups. No monomethoxylation occurred at the symmetric site, since (27) and (29) were not found in the reaction mixture.

Since steric effects do not influence nucleophilic attack, the different reactivities of the two classes of compounds and the marked regioselectivity seem to be determined by the electron distribution at the reaction centres. According to the ' valence bond ' approach, the ground state of molecules may be represented in terms of a number of ' polarised ' structures: in azinones and azinethiones a dominant weight is commonly attributed to those structures where the electronic dissymmetry is such that the oxo and/or the thioxo groups are high electron density centres whereas the substituted nitrogens are low electron density centres and may be thought as partly cationized.[6] Thus, (i) the high rate of monosubstitution observed for the triazine-

TABLE 1

Methanolysis reactions of methyl thiocyanurates: substrates and products, reaction conditions, and ^1H n.m.r absorption frequencies of the SMe groups of the substrates

Methanolysis		Reaction conditions		^1H n.m.r. peaks (δ) of substrate [a]	
Substrates	Products	Nucleophile concentration [b]	Onset temperature [c]	SMe_{us} 2.67—2.58	SMe_{ss} 2.57—2.48
Trithiocyanurates	Dithiocyanurates				
(1)	(2)	Trace [d]	Room	2.65	
(9)	(10)	Trace [d]	Room	2.61	(2.57) [e]
(18) *	(19)	Equimolar	Boiling		2.48
Dithiocyanurates	Monothiocyanurates				
(3)	(5)	Trace	Room	2.59	
(11)	(13)	Trace	Room	2.59	(2.50) [e]
(19) *	(20)	Equimolar	Boiling		2.52
(10) *	(28)	Equimolar	Boiling		2.54
(24) *	(25)	Trace	Room	2.67	
Monothiocyanurates	Cyanurates				
(29) *	(22)	Trace	Room	2.58	
(14)	(16)	Trace	Room	2.59	
(20) *	(21)	Equimolar	Boiling		2.53
(13) *	(22)	Equimolar	Boiling		2.50

* Present work. [a] N.m.r. spectra were recorded in $CDCl_3$ with $SiMe_4$ as internal reference. [b] The OMe^- concentration is given relative to the substrate concentration. [c] The reactions were carried out in MeOH. [d] Compounds (1) and (9) also underwent methanolysis in the absence of NaOMe. [e] ^1H N.m.r. signal of the SMe group not undergoing substitution.

thiones and/or triazinones (1), (9), (11), (14), and (29), may be attributed to the fact that their reactive centre, which is located in an electron-deficient region (*ortho* to the cationized nitrogen), shows high affinity towards the nucleophile; as a consequence, a low activation energy is required for σ-complex formation, to which the role of intermediate is attributed according to the widely accepted mechanism of nucleophilic aromatic substitution.[6,7] (ii) The low reactivity of the remaining SMe derivatives may be interpreted as follows. Compounds (18)—(20) are triazines, so that no preferential polarized structures maybe written to represent their ground states. A rather high activation energy is consequently required for substitution to occur; (10) and (13), on the other hand, although a triazinethione and a triazinone respectively, have their reaction centre partly inactivated by the two flanking pyridine-like nitrogens which determine an electron-rich region between them. (iii) The selective methoxylation of (9) and (11) is the obvious consequence of the above items: the monosubstitution of the SMe_{ss} group is not observed because the reaction is controlled by the high rate of SMe_{us} substitution.

X = S → SMe_{us}
X = O → OMe_{us}

a

X = S → SMe_{ss}
X = O → OMe_{ss}

b

SCHEME 5 The two different molecular sites for the XMe (X = S or O) group: a, unsymmetric; b, symmetric

Experimental evidence for the different charge densities at the two reaction centres may be given by the measure of the chemical shifts of the respective SMe protons: in particular we expect the lower charge density site to determine the higher deshielding effect; as a matter of fact the ^1H n.m.r. spectra show that the SMe_{us} protons are all more deshielded than the SMe_{ss} protons: the corresponding signals range respectively in the intervals δ 2.67—2.58 and 2.54—2.48 (Table 1).

Rules for Isomerisation.—A similar trend is observed for the isomerisation reactions of the OMe derivatives listed in Table 2. Again, two classes of compounds can be distinguished, these undergoing isomerisation in the solid state (either at room temperature or at *ca.* 100 °C), and compounds undergoing isomerisation in the melt at *ca.* 200 °C.

The only structural feature which is common to all the compounds of the first class is the molecular site of the OMe group undergoing dissociation [5] in the isomerisation reaction; the group, which we label OMe_{us}, is located on a ring carbon atom bound to two non-equivalent nitrogen atoms (Scheme 5a). In the other class of compounds, the methoxy-group involved in the isomerisation process, that we label OMe_{ss}, is bound to a ring carbon adjacent to two equivalent, pyridine-like, nitrogen atoms (Scheme 5b).

The direct correlation observed between the OMe site and the thermal energy necessary to produce its dissociation is confirmed by the reported behaviour (see Results section) of (28) and (22) in which both kinds of OMe groups are present: the identification of their first isomerisation products and the analysis of the reaction

TABLE 2

Isomerisation reactions of the *O*-methyl cyanurates and thiocyanurates: starting compounds and isomerisation products, nature of methyl migration, reaction conditions, and m.p.s and ^1H n.m.r. absorption frequencies of the methoxy- groups of the starting compounds

Isomerisation		Me migration	Onset temperature of isomerisation in the			^1H N.m.r. peaks (δ) of starting compound [a]	
Starting compound	End product	from OMe to	Solid state	Melt	M.p. of starting compounds (°C)	OMe_{us} 4.15—4.04	OMe_{ss} 4.03—3.97
Dithiocyanurates							
(2)	(3)	S	Room		[b]	4.13	
(10)	(11)	S	Room		[b]	4.08	
(19) *	(11)	N		~200 °C	135—136		3.99
Monothiocyanurates							
$(28)_{OMe}$ *	(29)	S	Room		[b]	4.04	(3.99) [c]
(25) *	(14)	S	Room		[b]		
(5)	(6)	N	~100 °C		[b]	4.10	
(13)	(14)	N	~100 °C		[b]	4.06	
(29) *	(14)	N		~200 °C	169—170		3.97
(20) *	(14)	N		~200 °C	118—119		4.01
Cyanurates							
(22)	(16) [d]	N	~100 °C		~145 °C [e]	4.09	(3.98) [c]
(16)	(17)	N	~100 °C		~120 [e]	4.06	
(21)	(17)	N		200 °C	135—136		4.03

* Present work. [a] N.m.r. spectra recorded in $CDCl_3$ with $SiMe_4$ as internal reference. [b] M.p. not detectable since the isomerisation product is formed in the solid. [c] ^1H N.m.r. signal of the OMe group not involved in the isomerisation process. [d] Compound (16) was found in the isomerisation mixture, together with (17), when the isomerisation was carried out as described in the Experimental section. [e] Approximate m.p. detected when the bath temperature was rapidly raised in order to reduce the extent of isomerisation.

paths proved that only the methyl belonging to the OMe_{us} group was selectively removed in the thermal rearrangement.

The origin of the different ease and selectivity in methyl removal from the methoxide is again attributed to the different polarisation of the substrates; in the triazinones and triazinethiones (compounds of the first class) the polarisation is such as to favour OMe bond cleavage; in the triazines (18)—(20) and in the triazinethione (29) the weak polarisation at the reaction centres is such as to hinder OMe_{ss} cleavage.

Information about the trend of the charge distribution at the reaction centres may be given by the chemical shifts of the OMe protons: according to expectation the OMe_{us} protons are all more deshielded (δ 4.15—4.04) than the OMe_{ss} protons (δ 4.03—3.97) (Table 2).

As to the nature of the thermal rearrangements it was pointed out that whenever both the O ⟶ S and the O ⟶ N isomerisations were possible, selective migration of the methyl group to the extranuclear sulphur atom occurs. This fact supports the hypothesis that the sulphur atoms in the triazinethiones have high electron densities: the sulphur acts as a stronger nucleophile than the pyridine-like nitrogens towards the methyl groups: whenever in a molecule the loosely bound, rather deshielded, methyl belonging to a OMe_{us} group is coupled with a partly anionized thioxo-group, the energy required for the O ⟶ S transition falls to the order of the molecular vibration energy and a room temperature rearrangement is observed.

In previous work [5,8] the particular stability of the 2,4,6-trimethyl derivatives of cyanuric and trithiocyanuric acids was tentatively associated with the overall symmetry of substitution at the 1,3,5-triazine ring.

Our present findings show that the behaviour of these compounds with respect to both methanolysis and thermal isomerisation reactions is mainly determined by the extent of the dissymmetry of the charge distribution in the molecular region where the XMe (X = O or S) reacting groups are located.

EXPERIMENTAL

Instruments, experimental procedures, and conditions for recording spectra and for determining R_F values were the same as previously described,[1] unless stated differently. Preparative h.p.l.c. was performed by means of a Jobin Yvon Miniprep apparatus equipped with silica gel column; elution was with chloroform–hexane (1 : 1 v/v).

New compounds were identified by means of elemental analysis, mass spectra, and the assignment of their ^1H n.m.r. peaks by use of the criteria given in ref. 1.

Methanolysis of (18). Prolonged refluxing of (18) with equivalent or higher amounts of sodium methoxide in methanol gave the product (21) of complete methanolysis; the products (19) and (20) of partial methanolysis (Scheme 1) were obtained, in largest yield, upon refluxing (18) (1 mmol) with NaOMe (0.35 mmol) in methanol (100 ml) for 80 min: the mixture contained (18)—(21) in the approximate ratio 5 : 7 : 3 : 5. Separation was carried out by preparative h.p.l.c. The R_F values, determined by means of t.l.c. on pre-coated silica gel plates (0.25 mm) with a fluorescent indicator and elution with chloroform–hexane (1 : 1), were: $R_{F(18)}$ 0.40, $R_{F(19)}$ 0.22, $R_{F(20)}$ 0.11; [$R_{F(21)}$ is not given because (21) does not appear as a fluorescent spot, in common with the cyanurates examined].

Compounds (18) and (21) were identified by comparison with authentic samples.

2-Methoxy-4,6-bismethylthio-1,3,5-triazine (19) formed crystals from methanol or water, m.p. 135—136 °C (Found: C, 35.3; H, 4.5; N, 20.7. $C_6H_9N_3OS_2$ requires C, 35.45; H, 4.45; N, 20.7%); δ 2.52 (6 H, SMe) and 3.99 (3 H, OMe); $\nu_{max.}$ 1 530s, 1 380m, 1 280m, 1 270w, 1 070w, and 820w cm^{-1}; *m/e* 203 (M^+). Isomerisation of (19) into (11) occurred at 200 °C.

2,4-Dimethoxy-6-methylthio-1,3,5-triazine (20) formed crystals from methanol or water, m.p. 118—119 °C (Found: C, 38.4; H, 4.9; N, 22.5. $C_6H_9N_3O_2S$ requires C, 38.5; H, 4.85; N, 22.45%); δ 2.53 (3 H, SMe) and 4.01 (6 H, OMe); $\nu_{max.}$ 1 560s, 1 530m, 1520m, 1 470m, 1 400m, 1 360s, 1 330m, 1 300m, 1 130w, 1 110m, 1 070m, 1 060m, 940w, and 820w cm^{-1}; *m/e* 187 (M^+). Isomerisation of (20) into (14) occurred at 200 °C.

Methanolysis of (9). The product (28) of complete methanolysis (Scheme 2) was obtained, in largest yield, upon refluxing a solution of (9) (1 mmol) in methanol (100 ml) and NaOMe (0.4 mmol) for 2 min. The mixture contained (28), (10), and (12)[1] whose yields, after separation by means of preparative h.p.l.c., were found to be *ca.* 25, 25, and 40%, respectively. Compounds (10) and (12) were identified by comparison with authentic samples.[1] Trace amounts of another product were present in the reaction mixture, whose molecular ion (*m/e* 173) and ^1H n.m.r. peaks [δ 3.65 (3 H, NMe) and 4.05 (3 H, OMe)] are consistent with a mono-*O*-demethylated product of (28).

Dihydro-3-methyl-4,6-dimethoxy-1,3,5-triazine-2-thione (28) formed crystals from water; m.p. not recorded since isomerisation of the compound to (29) starts in the solid at room temperature (Found: C, 38.6; H, 4.9; N, 22.4. $C_6H_9N_3O_2S$ requires C, 38.5; H, 4.85; N, 22.45%); δ 3.72 (3 H, NMe), 3.99 (3 H, 6-OMe), and 4.04 (3 H, 4-OMe). The assignment of the last two signals was based on the appearance of a single OMe signal at δ 3.99 for the 4-OCD_3 isomer of (28) [prepared upon refluxing in methanol the 4-OCD_3 isomer of (10) in the presence of NaOMe]; $\nu_{max.}$ 1 600s, 1 480m, 1 450w, 1 390m, 1 375m, 1 310m, 1 090m, and 950w cm^{-1}; *m/e* 187 (M^+); R_F 0.57.

Dihydro-3-methyl-4-methylthio-6-methoxy-1,3,5-triazin-2-one (29) was obtained by thermal isomerisation of (28): the process was started at room temperature and was complete after (28) was kept at 60 °C for a few minutes; (29) formed crystals from water, m.p. 169—170 °C (Found: C, 38.5; H, 4.9; N, 22.3. $C_6H_9N_3O_2S$ requires: C, 38.5; H, 4.85; N, 22.45%); δ 2.57 (3 H, SMe), 3.48 (3 H, NMe), and 3.97 (3 H, OMe); $\nu_{max.}$ 1 700s, 1 570s, 1 500s, 1 460m, 1 420w, 1 370s, and 1 110w cm^{-1}; *m/e* 187 (M^+); R_F 0.46.

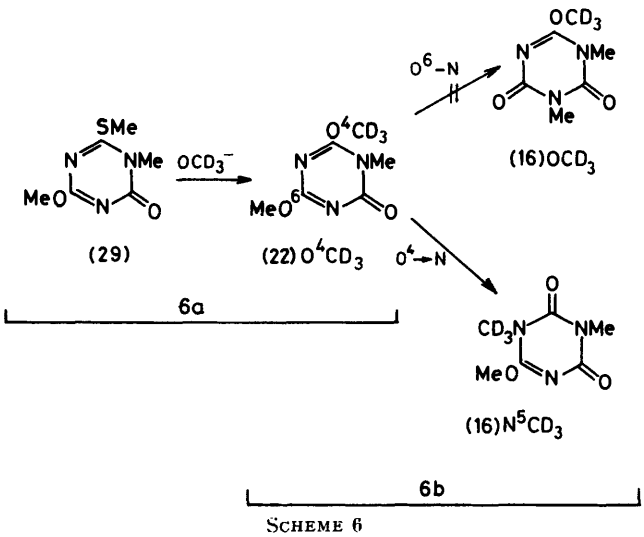
The thermal conversion of (29) into its isomer (14) occurred at 200 °C. By refluxing a methanolic solution of (29), containing trace amounts of sodium methoxide for a few minutes the methanolysis product (22) was obtained quantitatively by comparison with an authentic sample.

Methanolysis of (11).—The product (22) of complete methanolysis (Scheme 2), was obtained under the same conditions for the methanolysis of (9) to (28). The reaction mixture contained (22), (13), and (15), identified by com-

parison with authentic samples.[1,4] Their yields were *ca.* 10, 20, and 60%, respectively.

Synthesis of (23)—(25).—The two unknown dithiocyanurates (23) and (24), as well as their isomers (19), (3), and (11) (Table 1) were formed in approximately equivalent amounts by means of methylation of the dithiocyanuric acid (from a commercial sample of trithiocyanuric acid which was found to contain about equal amounts of the two acids). Methylation was carried out with diazomethane according to standard procedures. The isomeric products were separated by chromatography on a silica gel column using carbon tetrachloride as solvent; the compounds were eluted according to the order of their R_F values: $R_{F(23)}$ 0.70, $R_{F(19)}$ 0.65, $R_{F(24)}$ 0.61, $R_{F(3)}$ 0.59, and $R_{F(11)}$ 0.50. Compounds (19), (13), and (11) were identified by comparison with authentic samples.

Hexahydro-1,3,5-trimethyl-2,6-dithioxo-1,3,5-triazin-4-one (23) formed pale yellow crystals from methanol, m.p. 114—115 °C (Found: C, 35.45; H, 4.55; N, 20.8. $C_6H_9N_3OS_2$ requires C, 35.45; H, 4.45; N, 20.7%); δ 3.73 (3 H, 3-, 5-Me) and 4.20 (3 H, 1-Me); $\nu_{max.}$ 1 720s, 1 470s, 1 440m, 1 390s, 1 320m, 1 160w, and 1 100m cm^{-1}; *m/e* 203 (M^+).



SCHEME 6

Tetrahydro-1,3-dimethyl-4-methylthio-6-thioxo-1,3,5-triazin-2-one (24) formed yellow crystals from methanol, m.p. 192—194 °C (Found: C, 35.5; H, 4.55; N. 20.7. $C_6H_9N_3OS_2$ requires C, 35.45; H, 4.45; N, 20.7%); δ 2.67 (3 H, SMe), 3.71 (3 H, 1-Me), and 3.48 (3 H, 3-Me); $\nu_{max.}$ 1 720s, 1 540s, 1 430m, 1 380m, 1 340m, 1 290m, 1 180m, 1 140m, and 1 020m cm^{-1}, *m/e* 203 (M^+). Upon refluxing for a few minutes a methanolic solution of (24) with trace amounts of sodium methoxide, the methanolysis product (25) was obtained quantitatively.

Tetrahydro-1,3-dimethyl-4-methoxy-6-thioxo-1,3,5-triazin-2-one (25) crystallised as a powder from methanol; the m.p. was not recorded since (25) isomerises to (14) at room temperature (Found: C, 38.7; H, 4.9; N, 22.2. $C_6H_9N_3O_2S$ requires C, 38.5; H, 4.85; N, 22.45%); δ 3.73 (3 H, 1-Me), 3.39 (3 H, 3-Me), and 4.16 (3 H, OMe); $\nu_{max.}$ 1 730m, 1 600s, 1 500m, 1 430m, 1 310w, 1 170w, and 1 100m cm^{-1}; *m/e* 187 (M^+). Upon refluxing (25) in methanol with an equivalent amount of NaOMe added, the *O*-demethylation product, hexahydro-1,3-dimethyl-6-thioxo-1,3,5-triazine-2,4-dione, was obtained as identified from elemental analysis, *m/e* 173 (M^+); δ 3.64 (3 H, 1-Me) and 3.35 (3 H, 3Me).

Thermal Isomerisation of (22) *into* (16). *Identification of the Migrating Methyl.*—The *OON*-trimethyl cyanurate (22) undergoes thermal conversion into its *ONN*-trimethyl isomer (16) which, in turn, at a higher rate, changes into the *NNN*-trimethyl isomer (17). The major product found in the reaction mixture is therefore (17). In order to establish which of the two non-equivalent OMe groups dissociates in the thermal isomerisation of (22) to (16) we first found the isomerisation conditions which enabled us to obtain a sufficient amount of (16); we then prepared (22) with one labelled methoxy-group, and finally analysed its thermal isomerisation mixture.

A good yield of (16) was obtained when the thermal isomerisation of (22) was carried out at 130 °C for 15 min. The mixture contained (22), (16), and (17) in the ratio 31 : 24 : 45, evaluated from n.m.r. peaks areas. Compound (22) $_{O}4_{CD_3}$ was prepared by reacting (29) with [$^2H_4$]methanol at room temperature, in the presence of a trace amount of sodium (Scheme 6a).

Comparison of the n.m.r. spectrum of unlabelled (22) [δ 4.09 (3 H, OMe), 3.98 (3 H, OMe), and 3.38 (3 H, NMe)] with that of the labelled $(22)_{O^4CD_3}$ [δ 3.98 (3 H, 6-OMe) and 3.38 (3 H, NMe)] allowed as to assign the δ 4.09 peak to the 4-OMe group of (22).

Compound $(22)_{O^4CD_3}$ was then isomerised under the above conditions which gave isomer (16) in 27% yield, and the n.m.r. spectrum of the reaction mixture was recorded. On the basis of the peak assignments reported above, and of the known chemical shift of the OMe protons of (16), which is at δ 4.06, analysis of the spectrum in the OMe region was carried out (peak overlap does not allow us to examine the region of the NMe groups). From this we concluded that the methyl group bound to 4-OMe of (22) migrates in the thermal isomerisation to (16) (see Scheme 6b). In fact $(16)_{N^5CD_3}$ is present in the mixture and $(16)_{OCD_3}$ is not as (i) the OMe signal of (16) appears in the spectrum (δ 4.06) and (ii) the area corresponds to the amount of $(16)_{N^5CD_3}$ formed under the reported experimental conditions. The methyl transfer 6-O N does not occur in the thermal isomerisation under investigation, since $(16)_{OCD_3}$ is not present in the mixture.

[1/1280 *Received*, 11*th August*, 1981]

REFERENCES

1 M. L. Tosato, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1371.
2 L. Paoloni and M. L. Tosato, *Ann. Chim. (Rome)*, 1964, **54**, 897.
3 M. L. Tosato and L. Paoloni, *Ric. Sci.*, 1967, **37**, 259.
4 L. Paoloni and M. L. Tosato, *Ric. Sci.*, 1968, **38**, 552.
5 L. Paoloni, M. Cignitti, and M. L. Tosato, *J. Heterocycl. Chem.*, 1968, **5**, 533.
6 R. G. Shepherd and J. L. Fedrik, *Adv. Heterocycl. Chem.*, 1965, **4**, 145.
7 G. Illuninati, *Adv. Heterocycl. Chem.*, 1964, **3**, 285.
8 L. Paoloni, M. Cignitti, and M. L. Tosato, Second Jerusalem Symposia on Quantum Chem. and Biochem., 1970, p. 324.