PREPARATION AND THE TAUTOMERIC STRUCTURE OF 3-METHOXY-1,2,4-TRIAZIN-5-ONE AND 5-METHOXY-1,2,4-TRIAZIN-3-ONE*

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Methoxytriazinones *II*—*VI* have been prepared by methanolysis of methylthiotriazinones *VII*, *IX*—*XI* and *XIV*. The ease of this conversion decreases in the following order: *VII*, *X*, *XI* > *IX* ≫ ≫ *XIV*. The S_NAr2 substitution on the triazine nucleus is followed by the S_N2 reaction of the methanethiolate ions with methoxytriazinones under formation of the corresponding triazinediones *I*, *VIII*, and *XII*. The ease of this demethylation decreases in the order: *V*, *VI* > *IV* > > *II* ≫ *III*. From spectral data considerable predominance of the N^2-H forms *IIa* or *IIIa* in the tautomeric equilibrium of mobile methoxytriazinones *II* or *III*, resp., follows. Acid ionization constants of methoxytriazinones *II* and *III* have been measured.

In recent years we studied the preparation of N-methyl derivatives[1] of 1,2,4-triazine-3,5(2*H*, 4*H*)-dione (6-azauracil; *I*), which we used as model substances for a physico-chemical[2,3] investigation of the lactam-lactim tautomery of triazinedione *I* and during the structure determination of its more complex derivatives. The necessary O-methyl- or N, O-dimethyl derivatives of this dione could not be prepared at that time. As the substances of the mentioned type weree interesting for us also in connection with the study of Hilbert–Johnson's method of alkylation of methoxy-1,2,4-triazines, we again focussed our attention to their preparation. In the present paper we concentrate on 5-methoxy-1,2,4-triazin-3-one (O^4-methyl-6-azauracil; *II*), isomeric 3-methoxy-1,2,4-triazin-5-one (O^2-methyl-6-azauracil; *III*) and their N-methyl derivatives (N, O-dimethyl-6-azauracils; *IV*—*VI*).

Methoxy derivatives of heterocyclic compounds are usually prepared by methanolysis of chloro derivatives. However, the corresponding chloro-1,2,4-triazinones which were suitable intermediates for the preparation of the mentioned O-methyl derivatives of triazinedione *I* are not available. Therefore we tried to carry out their preparation by methanolysis of easily accessible methylthio-1,2,4-triazinones[4]. The choice of this approach was stimulated both by good results achieved during methanolysis of related methylthio-1,3,5-triazinones[5] and by the finding that in the methylation of

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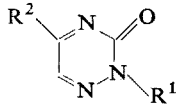
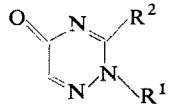
5-thio-1,2,4-triazine-3,5-dione with excess methyl iodide and methanolic sodium methoxide methanolysis of the intermediary 2-methyl-5-methylthio-1,2,4-triazin-3(2*H*)--one (*VII*) to 5-methoxy-2-methyl-1,2,4-triazin-3(2*H*)-one (*IV*) takes place.

However, the methanolysis of methylthiotriazines has been described for the first time by Hofmann[6] who on reaction of 2,4,6-tris(methylthio)-1,3,5-triazine with sodium methoxide *via* the unisolated 2,4,6-trimethoxy-1,3,5-triazine obtained 4,6-dimethoxy-1,3,5-triazin-2(1*H*)-one. In the field of 1,2,4-triazines several methoxy derivatives[7-9] have been prepared by this method recently.

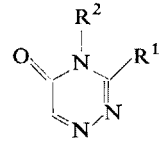
On methanolysis of 2-methyl-5-methylthio-1,2,4-triazin-3(2*H*)-one (*VII*) with equimolar amount of methanolic 0·33M sodium methoxide (room temperature, 20 minutes) the corresponding methoxytriazinone *IV* was obtained in a high preparative yield (94%). According to thin-layer chromatography the reaction took place quantitatively immediately after the dissolution of the starting material. A side-product of this reaction is 2-methyl-1,2,4-triazine-3,5(2*H*, 4*H*)-dione (*VIII*) which can be easily separated in the form of its sodium salt. The proportion of dione *VIII* in the mixture increases with reaction time and increase in temperature. At 120°C (8 hours, sealed tube) N-methyl derivative *VIII* is the main reaction product. The formation of dione *VIII* during methanolysis of methylthiotriazinone *VII* may be explained easily by a subsequent aliphatic S_N2 reaction of the primarily formed methoxytriazinone *IV* with methanethiolate ions, set free during methanolysis. The second product of demethylation is dimethyl sulfide which was detected in the mixture by gas chromatography. The presence of methyl iodide in the mixture during the above mentioned



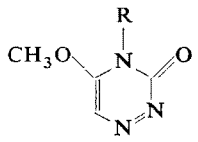
IIa, $R^1 = H$; $R^2 = OCH_3$
IV, $R^1 = CH_3$; $R^2 = OCH_3$
VII, $R^1 = CH_3$; $R^2 = SCH_3$
IX, $R^1 = H$; $R^2 = SCH_3$



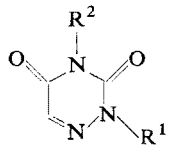
IIIa, $R^1 = H$; $R^2 = OCH_2$
V, $R^1 = CH_3$; $R^2 = OCH_3$
X, $R^1 = CH_3$; $R^2 = SCH_3$
XIV, $R^1 = H$; $R^2 = SCH_3$



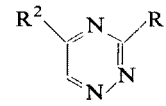
IIIb, $R^1 = OCH_3$; $R^2 = H$
VI, $R^1 = OCH_3$; $R^2 = CH_3$
XI, $R^1 = SCH_3$; $R^2 = CH_3$



IIb, R = H
XVI, R = CH_3



I, $R^1 = R^2 = H$
VIII, $R^1 = CH_3$; $R^2 = H$
XII, $R^1 = H$; $R^2 = CH_3$
XIII, $R^1 = R^2 = CH_3$



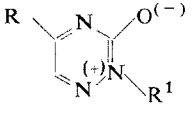
IIc, $R^1 = OH$; $R^2 = OCH_3$
IIIc, $R^1 = OCH_3$; $R^2 = OH$
XV, $R^1 = R^2 = OCH_3$

reaction of thiotriazinedione with excess sodium methoxide affects the yield of methoxytriazinone *IV* favourably because methyl iodide reacts with methanethiolate ions more rapidly than methoxy derivative *IV*, thus paralysing the unwanted subsequent demethylation. As the aromatic S_NAr2 substitution of the methylthio group on the triazine nucleus takes place in the case described substantially faster than the aliphatic S_N2 substitution on the methyl carbon of the methoxy group of triazinone *IV*, it is possible – keeping optimum temperature and reaction time constant – to achieve a high yield of triazinone *IV* even without the use of the competing methylation reagent.

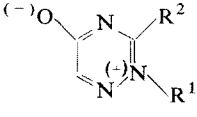
With respect to its acid character we carried out the methanolysis of 5-methylthio--1,2,4-triazin-3(2*H*)-one (*IX*) with two equivalents of methanolic sodium methoxide. However, at room temperature the reaction took place in this case much more slowly even when higher concentrations of the reagent (1M-$NaOCH_3$) were used. A quantitative substitution of the methylthio group could be achieved only when the reaction mixture was refluxed. Under these condition the subsequent demethylation reaction also took place, leading to a mixture of 5-methoxy-1,2,4-triazin-3-one (*II*) and triazinedione *I*. The use of a competing methylation reagent for the prevention of the unwanted demethylation of methoxytriazinone *II* is unsuitable because N-methylation of the triazine nucleus would take place in this case. Under optimum conditions we were able to achieve a 87% yield of methoxytriazinone *II*.

N-Methyl derivatives of 3-methylthio-1,2,4-triazin-5-one (*X* and *XI*) undergo methanolysis easily (in 0·33M-$NaOCH_3$) even at room temperature under formation of corresponding N-methyl derivatives of 3-methoxy-1,2,4-triazin-5-one (*V* and *VI*). The reaction takes place comparatively as easily as in the case of the isomeric 5-methylthio derivative *VII*, but in these cases the subsequent demethylation to corresponding N-methyltriazinediones *VIII* and *XII* is more pronounced. Under optimum conditions we were, however, able to achieve good preparative yields in both cases.

In the mixture after methanolysis of 3-methylthio derivative *XI* we proved chromatographically in addition to the already mentioned products *VI* and *XII* also the presence of 2,4-dimethyl-1,2,4-triazine-3,5(2*H*, 4*H*)-dione (*XIII*) which is formed evidently by mutual reaction of methoxytriazinone *VI* with the anion of 3-methyltriazinedione *XII*. Hence, as the anion *XII* competes in the reaction with the methanethiolate ions it may be judged that it is a nucleophile of roughly the same strength. The isomeric anion of 1-methyltriazinedione *VIII* is much less nucleophilic and, therefore, it is no longer capable of competing with the methanethiolate ions. Thus, in the



A



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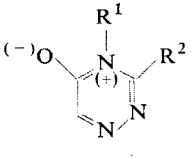

C

methanolysis of 2-methyl-3-methylthiotriazinone *X* the formation of dimethyl derivative *XIII* practically does not take place. As the supposition is justified that the nucleophilicity of the same type of substances is approximately proportional to their basicity, the observed differences in nucleophilicity of the mentioned anions may also be expected on the basis of the known ionization constants[1] of methyl derivatives *VIII* (p*K*a 6·99) and *XII* (p*K*a 9·52); from them it follows that the anion of methyl derivative *VIII* is more stable and hence less basic than the anion of methyl derivative *XII*.

The methanolysis of the acid 3-methylthio-1,2,4-triazin-5(2*H*)-one (*XIV*) takes place with great difficulty. We succeeded in obtaining the corresponding 3-methoxytriazinone *III* in a low yield (35%) only when the boiling with two equivalents of methanolic 1M sodium methoxide was prolonged (240 hours). In addition to methoxytriazinone *III* we succeeded in isolating triazinedione *I* and the starting methylthio derivative *XIV* during the chromatographic work-up of the reaction mixture. An increase in temperature to 120°C (88 hours, sealed tube) causes a quantitative substitution of the methylthio group on one hand, but methoxytriazinone *III* is practically quantitatively demethylated to triazinedione *I* under these conditions.

The results achieved range the methylthiotriazinones investigated according to decreasing ease of methanolysis in the following sequence: *VII*, *X*, *XI* > *IX* ⩾ *XIV*. From the presently described nucleophilic methatheses of 3,5-disubstituted 1,2,4-triazines[10–12] it followed that the position 5 is more reactive then the position 3. The differences observed in the reactivity of methylthiotriazinones do not, however, correspond to the mentioned rule. For the explanation of the reactivity of triazinones the fact should be taken into consideration that these compounds are resonance hybrids to the structure of which aromatic zwitterionic forms A–C also contribute (R^1 = H, CH_3; R^2 = SCH_3, OCH_3). In consequence of the resonance the triazine nucleus of these compounds is actually partly cationized and it is therefore electron attracting. On the basis of this situation it may be expected[11,12] that an activation toward nucleophilic substitution in *ortho* and *para* positions with respect to the cationized nitrogen might take place, while in view of the electrostatic factor the *ortho* position should be preferred in the reaction with anionic nucleophiles and the *para* position in the reaction with neutral nucleophiles. Anionization of the substrates leads, on the contrary, to a strong deactivation toward nucleophilic substitution[11,12].

In acid methylthiotriazinones *IX* and *XIV* the partial cationization has a reversible character. In a strongly basic reaction medium anionization of these substrates takes place and in consequence of this a strong deactivation towards methanolysis. We suppose that only reactive non-ionized molecules present in the solution in the frame of Brönsted's equilibrium enter the reaction easily. The concentration of these molecules, to which the rate of the biomolecular methanolysis is also proportional, depends, however, on their acidity. Therefore it is understandable that the deceleration appears more pronouncedly in the case of the relatively strongly acid methylthio-

triazinone *XIV* (p*K*a 5·94) (ref.[4]) than in the case of the substantially less acid isomer *IX* (p*K*a 9·18) (ref.[4]).

In neutral N-methyl derivatives *VII*, *X* and *XI* partial cationization of the triazine nucleus is irreversible, so that activation may also take place in strongly basic medium. From a comparison of the ease of methanolysis of the *para*-substituted methylthiotriazinone *VII* with that of 3-methoxy-5-methylthio-1,2,4-triazine[13] on one hand, and the ease of these changes in *ortho*-substituted isomers *X* and *XI* with the 5-methoxy--3-methylthio-1,2,4-triazine[13] on the other hand it follows that the activation effect of the partial positive charge is more pronounced in *ortho*-substituted triazinones *X* and *XI* than in *para*-substituted triazinone *VII*, which is in agreement with the above indicated supposition.

The ease of aliphatic S_N2 demethylation of methoxytriazinones decreases in the following order: *V*, *VI* > *IV* > *II* ≫ *III*. Generally it may be supposed that the demethylation of the mentioned compounds will take place the easier the more stable the anion of the triazinedione formed will be, and hence the more acid will be the corresponding conjugated acid. According to this it could be expected that methoxytriazinones *II*–*IV* which on demethylation afford relatively strongly acid triazinediones *I* (p*K*a 7·00) (ref.[1]) or *VIII* (p*K*a 6·99) (ref.[1]) will be more reactive than methoxy derivative *VI* the demethylation of which leads to substantially less acidic triazinedione *XII* (p*K*a 9·52) (ref.[1]). The observed dependence indicates, however, that aliphatic S_N2 demethylation of methoxytriazinones is affected, similarly as the aromatic S_NAr2 substitution of methylthiotriazinones, predominantly by the deactivating effect of anionization and the activating effect of partial cationization. The activating effect of the positive charge is again more pronounced, according to expectation, in *ortho*-substituted methoxytriazinones *V* and *VI* than in the *para*-substituted isomer *IV*.

Acid thermodynamical ionization constants of methoxytriazinones *II* and *III* (Table I) differ from each other considerably (Δ p*K*a = 3·25). Similar differences in acidity were also observed in analogous ethoxypyrimidones[14] (Δ p*K*a = 2·52).

TABLE I

Thermodynamic Ionization Constants at 25°C

Compound	Solvent	p*Ka*
II	water	9·91 ± 0·03
II	methyl cellosolve(80%)–water(20%)	10·72 ± 0·04
III	water	6·66 ± 0·03
III	methyl cellosolve(80%)–water(20%)	7·21 ± 0·03

In comparison with pyrimidine analogues, however, methoxytriazinones are more acidic because the substitution of the CH group of the heterocyclic nucleus by the isoelectronic atom of nitrogen leads to the stabilization of the negative charge in the anion and thus also to the increase in acidity of corresponding conjugated acids. The basic ionization constants of methoxy derivatives *II* – *VI* were not measured due to the instability of these substances in strongly acid medium.

The potentially tautomeric methoxytriazinones *II* and *III* may in principle occur in several forms, *IIa* – *c* and *IIIa* – *c*. The tautomeric N^1-H forms of these compounds may be excluded reliably on the basis of spectral data of the recently prepared 1-substituted triazinones with a betaine structure[15–18]. In analogy to the 1,2,4-triazinones[9,19–23] studied up to now, in the case of methoxytriazinones the predominance of the N^2-H forms *IIa* and *IIIa* could be expected. In order to determine the predominating tautomeric form of these compounds we made use of ultraviolet, infrared and ^{1}H-NMR spectra. We also extended[13] the set of the above described model substances with a fixed tautomeric structure by 3,5-dimethoxy-1,2,4-triazine (*XV*).

The complete series of model substances still lacks 5-methoxy-4-methyl-1,2,4-triazin-3(4*H*)-one (*XVI*) which, however, could not be prepared[24] as yet in consequence of its considerable instability due to the presence of the N=N double bond in the ring. The instability of 1,2,4-triazines with a forced N=N double bond in the ring was surmized earlier on the basis of quantum chemical calculations[25], and it was found later experimentally in connection with the study of the tautomeric structure of 6-azacytosine[19,20] and 1,2,4-triazinone[23]. These results justify the supposition that the N^4—H form *IIb* of 5-methoxy-1,2,4-triazin-3-one does not participate in the tautomeric equilibrium of this compound.

TABLE II

Ultraviolet Spectra of Methoxy-1,2,4-triazinones and 3,5-Dimethoxy-1,2,4-triazine

Compound	Solvent or pH	Form[a]	λ_{max}; nm (log ε_{max})
II	[b]	N	278 (3·43)
III	[b]	N	223 (3·58); 255 (3·47)
III	3·43	N	226 (3·61); 253 (3·62)
III	8·91	A	209 (3·65); 221 (3·62); 276 (3·63)
IV	[b]	N	210 (3·99); 286 (3·55)
V	[b]	N	228 (3·81); 263 (3·72)
V	3·43	N	228 (3·77); 262 (3·73)
VI	[b]	N	278 (3·77)
VI	3·43	N	275 (3·70)
XV[c]	[b]	N	212 (3·82); 274 (3·81)

[a] N, neutral form; A, anion; [b] 96% ethanol; [c] for the preparation see ref.[13].

The ultraviolet spectra (Table II) of the methoxytriazinones studied were measured in ethanol or in a weak buffer in view of their possible hydrolysis. Only in the case of a somewhat more stable 3-methoxy derivative *III* the spectrum was also measured in a weakly basic medium. The spectrum of the neutral form of 3-methoxy-1,2,4--triazin-5-one is rather similar to the spectrum of 2-methyl derivative *V* and it differs from the spectra of 4-methyl derivative *VI* and 3,5-dimethoxy-1,2,4-triazine(*XV*). From this it follows that this substance occurs in neutral aqueous or alcoholic solutions predominantly in the N^2-H form *IIIa* with a *para*-quinoid conjugation of the double bonds in the molecule. From the comparison of the spectra of 5-methoxy-1,2,4--triazin-3-one and the model substances *IV* and *XV* it follows – keeping in view the proved instability of the N^4-methyl derivative *XVI* – that the N^2-H form *IIa* predominates in neutral medium.

Methoxy derivatives *II* – *VI* and *XV* represent the so far missing models of partially or completely fixed lactim-lactam or dilactim tautomeric forms of triazinedione *I* to which the dilactam structure[2,3] was assigned earlier on the basis of spectral comparison with uracil or with the N-methyl derivatives of this dione. The proof based on the ultraviolet spectra was thus strengthened by the finding that the absorption maximum of 2,4-dimethyltriazinedione *XIII* may be derived additively from the shifts of the position of the absorption band of triazinedione *I* under the effect of the substitution of the hydrogens in the positions 2 and 4 by methyl groups[3]. Of course, the mentioned proofs supposed a clear difference of the spectra of O- and N-methyl derivatives of triazinedione *I*. However, it is evident now that the spectra of O-methyl derivatives *II* – *VI* and *XV* do not differ too much from those of N-methyl derivatives of this dione. The practical agreement of the absorption maxima of 2,4-dimethyl-1,2,4-triazine-3,5-dione (*XIII*) and 3,5-dimethoxy-1,2,4-triazine (*XV*), which represent models of the dilactam or the dilactim form of triazinedione *I*, is especially striking. In addition to this the absorption maxima of both isomeric dimethyl derivatives may be derived additively from the contributions of both O- and N-substitution on triazinedione *I*. The mentioned circumstances exclude, of course, the use of ultraviolet spectrophotometry for the determination of the tautomeric form of this compound. A similar situation was observed earlier in the case of the ultraviolet spectra of 5-azauracil[26] and its methyl derivatives.

More reliable conclusions on the tautomeric form of methoxy-1,2,4-triazinones and also 1,2,4-triazinediones are possible due to ^{1}H-NMR spectrometry; in order to prevent a possible hydrolysis of methoxy derivatives the ^{1}H—NMR spectra were measured in hexadeuteriodimethyl sulfoxide (Table III). However, the obtained results permit the supposition that the conclusions on the tautomery of the compounds, following from the measurements in hexadeuteriodimethyl sulfoxide, are also valid for aqueous medium. The comparison of the ^{1}H—NMR spectra of tautomeric methoxytriazinones *II* and *III* with their N^2-methyl derivatives *IV* and *V* shows that the chemical shifts of $H_{(6)}$ are approximately equal in the corresponding pairs and that

they differ distinctly from the position of the $H_{(6)}$ signals of other model substances. From this we conclude that the tautomeric equilibrium of the methoxytriazinones investigated comprizes at least 95% of N^2—H forms *IIa* or *IIIa*. The analogous comparison of the chemical shifts of $H_{(6)}$ of triazinediones *I*, *VIII*, *XII*–*XIII*, methoxytriazinones *II*–*VI*, and dimethoxytriazine *XV* affords an unequivocal proof of the dilactam structure of triazinedione *I* and thus confirms the older conclusions on the tautomeric form of these compounds[2,3].

In order to judge the predominant tautomeric forms of methoxytriazinones we further used the infrared spectra of methoxyderivatives *II*–*VI* and *XV* (Table IV). The spectra of chloroform solutions of tautomeric methoxytriazinones II and *III* show ν(NH) bands at 3409 cm^{-1} and 3421 cm^{-1}. This excludes the predominance of the OH forms *IIc* and *IIIc* in the tautomeric equilibrium of these compounds, and according to Mason's[27] rule it indicates an *ortho*-quinoid type of conjugation for methoxytriazinone *II* and a *para*-quinoid type of conjugation for methoxytriazinone *III*. A comparison of ν(CO) and ν(ring) bands in the spectra of tautomeric methoxytriazinones *II* and *III* with the position of these bands in the spectra of corresponding N^2-methyl derivatives *IV* and *V* shows an approximate agreement for the corresponding pairs. This similarity is well evident especially from the spectra measured in dimethyl sulfoxide. The mentioned facts permit the supposition that the studied tautomeric methoxytriazinones exist both in solutions and probably in

TABLE III

^{1}H-NMR Spectra of 1,2,4-Triazinediones, Methoxy-1,2,4-triazinones and 3,5-Dimethoxy-1,2,4-triazine in Hexadeuteriodimethyl Sulfoxide

Compounds	δ; p. p. m.
I	7·34[a] (d, H^6); 12·29 (bs, N^2—H); 11·91 (bs, N^4—H)
VIII	7·37[b] (s, H^6); 3·46 (s, N^2—CH_3); 12·10 (bs, N^4—H)
XII	7·42[b] (s, H^6); 12·52 (bs, N^2—H); 3·15 (s, N^4—CH_3)
XIII	7·46 (s, H^6); 3.53 (s, N^2—CH_3); 3·18 (s, N^4—CH_3)
II	7·72 (s, H^6); 12·75 (bs, N^2—H); 3·92 (s, C^5—OCH_3)
IV	7·77 (s, H^6); 3·62 (s, N^2—CH_3); 3·94 (s, C^5—OCH_3)
III	7·50 (s, H^6); 13.0—13·8 (bs, N^2—H); 3·92 (s, C^3—OCH_3)
V	7·52 (s, H^6); 3.62 (s, N^2—CH_3); 3·94 (s, C^3—OCH_3)
VI	8·19 (s, H^6); 3.29 (s, N^4—CH_3); 4·10 (s, C^3—OCH_3)
XV[c,d]	8·72 (s, H^6); 4·01 (s, C^3—OCH_3); 4·08 (s, C^5—OCH_3)

[a] $J_{6,NH} = 1·7$ Hz; [b] $0 < J_{6,NH} < 1$ Hz; [c] the signals of the OCH_3 groups were assigned according to the spectra of isomeric methoxymethylthiotriazines[34]; [d] the preparation is described in the subsequent paper[13].

TABLE IV

Infrared Spectra of Methoxy-1,2,4-triazinones and 3,5-Dimethoxy-1,2,4-triazine

Compound	Medium	ν(NH)	ν(CO)	ν(ring), δ(NH), δ(CH_3)						
III	$CHCl_3$[a]	3 421[f]	1 675m, br	1 600s	1,571vs		1 476s	1 436w		1 332s
III	DMSO[b]	[g]	1 666vs	1 601s, sh	1 574vs		1 479s	[g]		[g]
III	KBr	~2 810m, vbr	1 657m	1 604m	1 555s, br	1 534m, sh	1 462s	1 449m, sh	1 387m	1 353m, sh	1 339m
V	$CHCl_3$[a]	—	1 668vs	1 601vs	1 588s, sh	1 527vs	1 474s	1 420s	1 406s	1 348m	1 330m
V	DMSO[b]	—	1 665vs	1 600vs	1 590s, sh	1 523vs	1 472s	[g]	[g]	[g]	[g]
VI	$CHCl_3$[a]		1 702vs								
		—	1 691vs, sh	1 656m	1 566vs	1 517vs	1 473s	1 448m	1 413s	1 381s	
	DMSO[b]	—	1 695vs	1 651m	1 566vs	1 518vs	1 472s	[g]	[g]	[g]	[g]
II	$CHCl_3$[c]	3 409[f]	1 705s	1 600vs	1 569m		1 462s		1 387s		
II	DMSO[b]	[g]	1 680vs								
		[g]	1 692vs, br	1 599vs	1 570s		1 464s		[g]		
II	KBr	~3 165m, br 3 075, br	1 673s, br	1 638m, br, sh	1 599s	1 599s	1 469s	1 445m	1 389s	1 358m	1 325m 1 316s
IV	$CHCl_3$[d]	—	1 682vs	1 601vs	1 547s		1 461s		1 390s	1 327s, sh	1 314vs
IV	DMSO[b]	—	1 682vs	1 600vs	1 550s		1 463s		[g]	[g]	[g]
XV[h]	$CHCl_3$[e]	—	—	1 568vs	1 554vs	1 483s	1 453s	1 403m	1 307vs	1 351vs	1 341vs

[a] Concentration: 1·5%; [b] 2·5%; [c] saturated solution (0·5 mm); [d] 2%; [e] 3%; [f] $3 \cdot 10^{-3}$ M; [g] solvent absorption; [h] for the preparation see ref. [13].

the solid state predominantly in N^2—H forms *IIa*, or *IIIa*, respectively. The infrared spectra of methoxy derivatives *II* – *VI* and *XV* differ distinctly from those of N-methyl derivatives of triazinedione I which confirms sufficiently the correctness of an older proof of the dilactam tautomeric form of this dione, based on infrared spectra of triazinedione *I* and its N-methyl derivatives[2].

The spectral proof of the tautomeric structure of methoxytriazinones *II* and *III* is also supported by quantum chemical calculation (HMO approximation) of resonance energies (Table V), which indicates a greater stability of N^2-H forms *IIa* or *IIIa* in comparison with corresponding N^4-H forms *IIb* and *IIIb*.

TABLE V
HMO Resonance Energies

Compound	*IIIa*	*IIIb*	*V*	*VI*	*IIa*	*IIb*	*IV*	*XVI*	*XV*[a]
R (β)	2·3666	1·6981	2·5338	2·8781	2·4528	1·9692	2·5895	2·0617	3·2830[b]

[a] For the preparation see ref. [13]. [b] Relative to the form with the N—N single bond.

EXPERIMENTAL

The melting points were determined on a Kofler block. Analytical samples were dried at 22°C/ /0·1 Torr for 8 hours. The solvents were evaporated on a rotatory evaporator at 35—40°C (bath temperature) and at 15 Torr. Thin-layer chromatography was carried out on fluorescent silica gel plates Silufol UV 254 (Kavalier, Votice, Czechoslovakia) in systems S_1 (ethyl acetate), S_2 (benzene–ethyl acetate 8 : 2), and S_3 (chloroform). Detection was carried out visually under UV light (Chromatolite). Column chromatography was carried out on macroporous silica gel according to Pitra[28] (Service laboratories of this Institute, Lysolaje near Prague) or on neutral alumina (Woelm, Eschwege, German Federal Republic) of activity II—III according to Brockmann.

Thermodynamical ionization constants were determined by potentiometric titration with tetramethylammonium hydroxide[29]. The ultraviolet spectra were measured on a single-beam spectrophotometer Optica Milano Model CF-4. The infrared spectra were recorded with a Zeiss Model UR-10 or UR-20 instrument. In the ν(NH) region the spectra were measured in 1 cm cells, while for the measurement in the 1 300—1 800 cm^{-1} region 0·1 mm (chloroform) and 0·07 mm (dimethyl sulfoxide) cells were employed. The ^{1}H-NMR spectra were measured on a Varian HA-100 instrument, the p.p.m. values are expressed in δ-scale, using tetramethylsilane as reference. The quantum chemical calculations were carried out using Hückel's semiempirical MO-LCAO method (HMO) with parameters according to Pullman and Pullman[30]. For the N=N double bond and the inductive effect of the methyl group the parameters according to Polansky and Derflinger[31] were used, and for —O—(CH_3) the parameter δ = 1·65 was applied.

5-Methoxy-1,2,4-triazin-3(2*H*)-one (*IIa*)

A) A solution of methylthiotriazinone[32] *IX* (2·86 g; 0·02 mol) in methanolic 1M-$NaOCH_3$ (40 ml) was refluxed for 2 hours (the condenser was fitted with a drying tube with KOH). After cooling the solution was decationized on an Amberlite IRC-50 [H^+] (100 ml) column, packed in methanol. The column was eluted with 300 ml of methanol and the eluate evaporated. The residue was extracted with a boiling mixture of ethyl acetate and methanol (9 : 1; 70 ml), the insoluble material was filtered off and the solution allowed to crystallize at room temperature overnight. After concentration of the mother liquors to half of their volume a total of 1·85 g of compound *IIa* were obtained, m.p. 163—165°C. The second mother liquor, containing according to thin-layer chromatography a larger amount of triazinedione *I* was filtered through a column of 10 g of alumina and the residue of the product was washed out with 50 ml of ethyl acetate. The dry residue of the eluate afforded on crystallization from ethyl acetate–methanol (9 : 1) methoxy derivative *IIa* (0·35 g). Total yield 2·20 g (87%) of compound *IIa*, m.p. 163—165°C; R_F 0·35 (S_1). A sample for analysis was recrystallized from ethanol (m.p. 165—166°C). Ionization constants and spectral data are given in Tables I—IV. For $C_4H_5N_3O_2$ (127·1) calculated: 37·80% C, 3·97% H, 33·06% N, 24·42% OCH_3; found: 38·10% C, 4·09% H, 33·26% N, 24·44% OCH_3. With increased reaction time (2·5 or 3·5 hours) the yield of methoxy derivative *IIa* dropped to 57 or 50%, respectively.

B) A solution of methylthiotriazine[32] *IX* (1·43 g; 0·01 mol) in methanolic 1M-$NaOCH_3$ (20 ml) was heated in a sealed tube at 100°C for 6 hours. After cooling the precipitate of the sodium salt of 6-azauracil was filtered off under suction and washed with 50 ml of methanol. In contact with air humidity the sodium salt formed a monohydrate; yield 0·70 g (46%). For $C_3H_2NaN_3O_2.H_2O$ (153·1) calculated: 23·53% C, 2·64% H, 27·43% N; found: 23·80% C, 2·90% H, 27·71% N. On acidification of the hot saturated solution of the sodium salt with hydrochloric acid and cooling free triazinedione *I* was obtained; m.p. 280—281°C, undepressed on admixture of an authentic sample[33]; R_F 0·58 (S_1). The methanolic filtrate after the filtering off of the sodium salt was worked up as under *A*). A solution of the crude methoxytriazinone in ethyl acetate was filtered through a 10 g column of alumina, the column was washed with 50 ml of ethyl acetate and the filtrate evaporated. Crystallization of the residue from ethanol gave 0·55 g (43%) of methoxy derivative *IIa* in two fractions; m.p. 165—166°C, mixture melting point with the product obtained under *A* was undepressed.

5-Methoxy-2-methyl-1,2,4-triazine-3(2*H*)-one (*IV*)

A) A solution of methylthiotriazinone[4] *VII* (1·57 g; 0·01 mol) in methanolic 0·33M-$NaOCH_3$ (30 ml) was allowed to stand at room temperature for 20 minutes. According to thin-layer chromatography the reaction is over immediately after dissolution of the starting substance. After neutralization with solid carbon dioxide the mixture was evaporated and the residue triturated with 40 ml of ether. The insoluble fraction was filtered off and washed with ether. The filtrate was evaporated, the residue dissolved in 20 ml of hot benzene, the precipitate filtered off and the filtrate evaporated. Crystallization of the residue from a mixture of benzene and light petroleum gave, in two fractions, 1·33 g (94%) of methoxytriazinone *IV*; m.p. 67—68°C; R_F 0·52 (S_2). The spectral data are given in Tables II—IV. For $C_5H_7N_3O_2$ (141·1) calculated: 42·55% C, 5·00% H, 29·78% N, 21·99% OCH_3; found: 42·83% C, 5·25% H, 30·05% N, 22·26% OCH_3. The ether insoluble fraction of the sodium salts (according to thin-layer chromatography without traces of methoxy derivative *IV*) was dissolved in water, the solution was decationized with Dowex 50 W [H^+] and evaporated. Crystallization of the residue from ethanol gave dione *VIII* (0·025 g; 2%); m.p. 156—157°C, undepressed on admixture with an authentic sample[1]; R_F 0·62

(S_1). Prolongation of the reaction time to one hour caused the yield of methoxy derivative *IV* to decrease to 89%.

B) A mixture of 5-thio-1,2,4-triazine-3,5-dione[4] (6·45 g; 0·05 mol), methanolic 1M-$NaOCH_3$ (100 ml), and methyl iodide (10 ml) was allowed to react first spontaneously (exothermically) and it was then refluxed for one hour. Methanolic 1M-$NaOCH_3$ (100 ml) was again added to the neutral solution, followed by 5 ml of methyl iodide and the mixture was refluxed for another hour (neutral reaction). The solution was evaporated and the residue partitioned between water and chloroform. The organic layer was dried over sodium sulfate, filtered, and evaporated. Crystallization of the residue from benzene–light petroleum gave 5·0 g (70%) of compound *IV*; m.p. 67–68°C, undepressed on admixture of the product obtained by procedure *A*.

3-Methoxy-1,2,4-triazin-5(2*H*)-one (*IIIa*)

A solution of methylthiotriazinone[4] *XIV* (1·43 g; 0·01 mol) in methanolic 1M-$NaOCH_3$ (20 ml) was refluxed for 240 hours (condenser provided with a KOH tube). After cooling the mixture was filtered through a column of Amberlite IRC-50 [H^+] (50 ml), prepared in methanol. The column was washed with methanol (250 ml) and the eluate additioned with 10 g of silica gel and evaporated. The residue was dried in a vacuum (until it became powdery) and then applied in a suspension in ethyl acetate onto the top of a silica gel column (90 g), also prepared in ethyl acetate. The column was eluted with ethyl acetate (900 ml; fractions 1–45). Evaporation of fractions 5–9 gave 0·10 g (9%) of triazinedione *I*; m.p. 280–281°C (water), undepressed with an authentic sample[33]; R_F 0·58 (S_1). Working up of fractions 12–18 gave 0·60 g (42% of regeneration) of the starting triazinone *XIV*; m.p. 221–222°C (ethanol), undepressed with an authentic specimen[4]; R_F 0·35 (S_1). Fractions 20–41 afforded 0·45 g (35%) of a residue which consisted of compound *IIIa*; m.p. 167–169°C (ethanol); R_F 0·21 (S_1). Ionization constants and spectral data are given in Tables I–IV. For $C_4H_5N_3O_2$ (127·1) calculated: 37·80% C, 3·97% H, 33·06% N, 24·42% OCH_3; found: 37·77% C, 4·02% H, 32·93% N, 24·40% OCH_3.

3-Methoxy-2-methyl-1,2,4-triazin-5(2*H*)-one (*V*)

A solution of methylthiotriazinone[4] *X* (1·57 g; 0·01 mol) in methanolic 0·33M-$NaOCH_3$ (30 ml) was allowed to stand at room temperature for one hour. According to thin-layer chromatography the reaction was over immediately after dissolution of the starting substance. After neutralization of the solution with solid carbon dioxide the mixture was evaporated, the residue dissolved in 20 ml of water, and the solution extracted with chloroform (4× 10 ml). After drying over sodium sulfate and evaporation of the chloroform layer 0·80 g (57%) of compound *V* were obtained; m.p. 118–119°C (benzene-light petroleum); R_F 0·16 (S_1). The spectral data are given in Tables II–IV. For $C_5H_7N_3O_2$ (141·1) calculated: 42·55% C, 5·00% H, 29·78% N, 21·99% OCH_3; found: 42·85% C, 4·97% H, 29·99% N, 22·10 OCH_3. The aqueous layer (according to thin-layer chromatography it did not contain any methoxy derivative *V*) afforded after deionization with Dowex 50 W [H^+] and evaporation 0·50 g (39%) of dione *VIII*; m.p. 156–157°C (ethanol), undepressed on admixture of an authentic sample[1]; R_F 0·62 (S_1).

3-Methoxy-4-methyl-1,2,4-triazin-5(4*H*)-one (*VI*)

A suspension of methylthiotriazinone[4] *XI* (1·57 g; 0·01 mol) in methanolic 0·33M-$NaOCH_3$ (30 ml) was stirred until dissolution (5 min) and then allowed to stand at room temperature for 55 minutes. According to thin-layer chromatography the reaction was finished immediately after the dissolution of the starting substance. After neutralization with dry ice the mixture was

evaporated and the residue mixed with ether (40 ml). The insoluble fraction of the sodium salts was filtered off, washed with ether and the filtrate evaporated. The residue was dissolved in 5 ml of chloroform and the solution applied onto a column of alumina (50 g) packed in chloroform. The column was eluted with 150 ml of chloroform and the eluate evaporated. Crystallization of the residue from benzene–light petroleum gave 0·85 g (60%) of compound *VI* in two crops; m.p. 100–101°C; R_F 0·38 (S_1). The spectral data are given in Tables II–IV. For $C_5H_7N_3O_2$ (141·1) calculated: 42·55% C, 5·00% H, 29·78% N, 21·99% OCH_3; found: 42·80% C, 5·02% H, 29·97% N, 21·86% OCH_3. According to thin-layer chromatography dimethyltriazinedione *XIII* prevails in the last mother liquors; R_F 0·33 (S_3), in agreement with an authentic sample[1]. A solution of the sodium salts in water (according to thin-layer chromatography it dose not contain any methoxy derivative *VI*) was decationized with Dowex 50 W [H^+] and evaporated. Crystallization of the residue from ethanol gave 0·28 g (22%) of dione *XII*; m.p. 171°C, undepressed with an authentic sample[1]; R_F 0·75 (S_1).

1,2,4-Triazine-3,5(2*H*, 4*H*)-dione (*I*)

A solution of methylthiotriazinone[4] *XIV* (2·86 g; 0·02 mol) in 40 ml of methanolic 1M-$NaOCH_3$ was heated in a sealed tube in an oil bath (120°C) for 88 hours. The separated salt of triazinedione *I* was filtered off after cooling and dissolved in a minimum amount of boiling water. The solution was acidified with hydrochloric acid and allowed to crystallize; yield 0·69 g (75%) of dione *I*; m.p. 280–281°C, undepressed with an authentic sample[33]; R_F 0·58 (S_1). The methanolic mother liquors after the sodium salt of dione *I* contained according to thin-layer chromatography only traces of methoxy derivative *III*.

2-Methyl-1,2,4-triazine-3,5(2*H*, 4*H*)-dione (*VIII*)

A) A solution of methylthio triazinone[4] *VII* (1·57 g; 0·01 mol) in methanolic 0·33M-$NaOCH_3$ (30 ml) was heated in a sealed tube at 120°C for 8 hours. Gas chromatography detected in the mixture dimethyl sulfide (comparison with a standard; on Carbowax, 3·2 m tube, 70°C). According to thin-layer chromatography the mixture does not contain any methoxy derivative *IV*. The mixture was evaporated, the residue dissolved in water, the solution deionized with Dowex 50 W [H^+] and evaporated. Crystallization of the residue from ethanol afforded 0·95 g (75%) of compound *VIII*; m.p. 156–157°C, undepressed on admixture of an authentic sample[1]; R_F 0·62 (S_1).

B) A solution of methylthio derivative[4] *X* (1·57 g; 0·01 mol) in methanolic 0·33M-$NaOCH_3$ (30 ml) was allowed to stand at room temperature for 24 hours. The sodium salt of dione *VIII* begins to precipitate from the solution already after 80 minutes. The mixture was neutralized with solid carbon dioxide and evaporated. The residue was triturated with ether (50 ml), the insoluble salts were filtered off, washed with ether and dissolved in water. According to thin-layer chromatography the solution did not contain any methoxy derivative *V*. The solution was decationized with Dowex 50 W [H^+] and evaporated. Crystallization of the residue from ethanol gave 0·86 g (68%) of compound *VIII*; m.p. 156–157°C, undepressed with an authentic sample[1]; R_F 0·62 (S_1). The ethereal filtrate after the elimination of the sodium salt by filtration was evaporated to give 0·26 g (19%) of methoxy derivative *V*; m.p. 118–119°C (benzene–light petroleum), undepressed on admixture of the above described sample.

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