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TAUTOMERISM OF UNSUBSTITUTED ALKYL GROUPS ON as-TRIAZINES[1]

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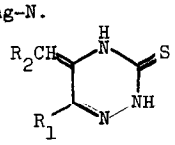
The reaction of thiosemicarbazide with 2,3-pentanedione and its higher homologs has given 5,6-disubstituted as-triazines I in which the alkyl groups at the 5-position display an unusual tautomerism of an α-proton to ring-N.

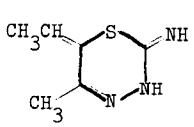
Ia $R_1 = CH_3$, $R_2 = CH_3$

Ib $R_1 = CH_3CH_2$, $R_2 = CH_3$

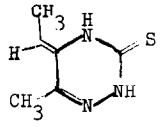
Ic $R_1 = CH_3CH_2CH_2$, $R_2 = CH_3CH_2$



I



II



III

The unexpected presence of alkylidene groups in I is demonstrated by a proton in the olefinic region of the p.m.r. spectra (in Me_2SO-d_6) which is split into a quartet for ethylidene compounds and into a triplet in the propylidene homolog. In addition, the methyl group R_2 in the 5-position substituent in Ia and Ib is split into a doublet as required for the ethylidene group. Consistent with structure I, two protons attached to nitrogen are readily discernible downfield and disappear on exchange with deuterium. The chemical shifts and splitting patterns are shown in Table I and the p.m.r. spectrum of Ia is shown in Figure 1.

The ethylidene group of Ia is assigned to the 5-position on the basis of the reported reaction of a similar acylhydrazide with the less hindered carbonyl of the pentanedione. Metze (2) has shown that acetylhydrazide reacts with 2,3-pentanedione to give an acetylmonohydrazone which with hydroxylamine gives the same product obtained from acetylhydrazide and 3-oximino-2-pentanone unequivocally prepared by nitrosation of 3-pentanone.

The possibility that the product might be the thiadiaza heterocycle II was ruled out by the following evidence: a) both protons attached to N were much further downfield than observed for analogous imino protons (3); b) the infrared spectrum's most intense band at 8.2 microns could only be attributed to the cyclic thioamide group (4) such as in I rather than the C=NH in II; (c) the solubility in base and insolubility in acid indicated the acidic triazine structure and not the basic thiadiazine II.

Table I. Chemical Shifts in 3-Thioxo-as-triazines[1]

	Substituent	Compound Ia	Compound Ib	Compound Ic
	NH	10.1(s), 11.4(s)	10.1(s), 11.4(s)	10.1(s), 11.4(s)
5-position	=CH-(CH_3 or C_2H_5)	4.85(q)	4.85(q)	4.8(t)
	=CH-CH_3	1.7(d)	1.7(d)	--
	=CH-CH_2CH_3	-	-	2.15-2.2(m)[2]
	=$CHCH_2$-CH_3	-	-	0.9 -0.95(t)[2]
6-position	-CH_3	1.9(s)	-	-
	-CH_2-(CH_3 or C_2H_5)	-	2.3(q)	ca. 2.3(m)[2]
	-CH_2-CH_3	-	1.0(t)	-
	-CH_2-CH_2CH_3	-	-	1.55(m)
	-CH_2CH_2-CH_3	-	-	0.9 -0.95(t)[2]

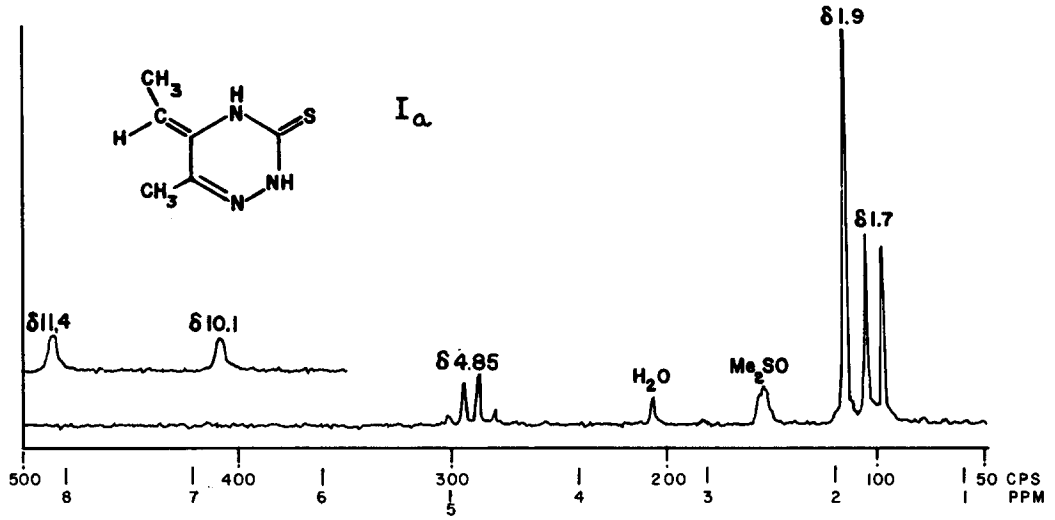
1. δ values in deutero-dimethyl sulfoxide, p.p.m. relative to tetramethylsilane, Varian A-60. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

2. Overlapping multiplets.

X-ray crystallography (5) has confirmed that the structure of Ia is as shown and also provided the additional information that the methyl group attached to the exocyclic double bond is trans to the 5,6-bond of the triazine ring as shown in III.

This is the first report of such a prototropic shift in unsubstituted alkyl groups in azines. Recently several instances of groups with an acidic methylene proton produced by adjacent strong electron-withdrawing moieties have been reported (6,7) to tautomerize to the methine derivatives. However, in these instances the methine structure is favored either by hydrogen-bonding of the N-H proton to a carbonyl oxygen to form a 6-membered cyclic chelate or by conjugation with double or triple bonds in these moieties in addition to the acidity of the CH involved. In the several structures reported, unsubstituted alkyl groups did not tautomerize.

The existence of the alkylidene structure is dependent on the presence of an =NH-C=X moiety at the 3-position in the generalized structure VI but this alone in an azine is not sufficient (e.g., VII has no olefinic protons). In the 3-methylthio analog, produced by methylation in aqueous alkali, only the 5-ethyl form was evident in the p.m.r. spectrum. When the thione Ia was dissolved in alkaline Me_2SO, a 45:55 mixture of ethyl and ethylidene forms was present after a few minutes, changing only after 1-2 hours to more than 95% of the ethyl form in the thiol anion IV. In contrast, the reverse transformation was very rapid, more than 95% of IV being immediately converted to Ia on acidification of this alkaline Me_2SO solution. Displacement of the 3-methylthio group with sodium sulfanilamide yielded a 3-sulfanilamido-as-triazine which was a



Ia

FIG. 1

P.m.r. spectrum of 5-ethylidene-6-methyl-3-thioxo-2,3,4,5-tetrahydro-as-triazine; upper curve offset 200 c.p.s.

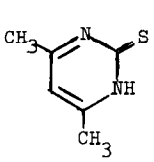
mixture of the ethyl (sulfonamido) and ethylidene (sulfonimido) VI forms with the latter predominating.

The 3-amino analog exists in the ethyl form in neutral Me_2SO but, on annular N-protonation (by dissolving in trifluoroacetic acid), is about 30% converted to the ethylidene iminium form V. The thione in TFA solution is about 15% converted to the ethyl form. No tendency toward exocyclic double-bond structure at the 6-position is evident in Ib or in 6-ethyl-3-thioxo-as-triazine (1) which shows the usual ethyl quartet-triplet splitting pattern without an olefinic proton and with only one downfield N-H proton.

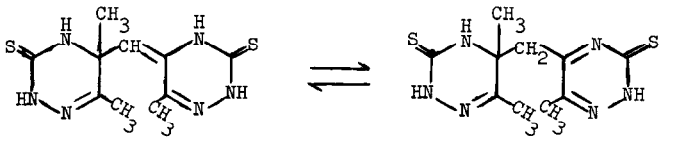
IV V VI

X = S, O, $\overset{+}{N}H_2$, NSO_2R

Reported preparations (8-11) of 5,6-dimethyl-1,2,4-triazine-3-thione failed, giving instead biacetyl bisthiosemicarbazone or mixtures containing the mono- and bis-thiosemicarbazones. It is now clear that inability to secure this triazine is only partly due to the greater tendency to form bisthiosemicarbazone when both alkyl groups are methyl. More importantly, the expected reactivity of the methylidene group in I when R_2 = H leads to formation of dimer VIII. Isolated biacetyl monothiosemicarbazone gave a product which on the basis of its p.m.r. spectrum



VII



VIII

(in Me_2SO-d_6) is a mixture of the tautomers shown in VIII. Mass spectrometry (12) has shown a peak at m/e = 282 (M^+) as well as the most abundant species at m/e = 141. The reported (13) 5,6-dimethyl-as-triazin-3-one appears from its p.m.r. spectrum to be the analogous dimer.

Extension of this work to other oxo analogs, to bicyclic 5,6-polymethylene-as-triazines and to other heterocycles will be described in later publications.

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References

1. Paper II on as-triazines; preceding paper: W. E. Taft and R. G. Shepherd, J. Med. Chem., 10, 883 (1967).

2. R. Metze, Chem. Ber., 91, 1861 (1958).

3. The chemical shift of the imino proton in 2-imino-1-methylpyrimidine is at 6.35 δ.

4. The infrared absorption of thioxo N-heterocycles is discussed by E. Spinner, J. Chem. Soc., 1237 (1960) and by C. N. R. Rao and R. Venkataraghavan, Spectrochim. Acta, 18, 539 (1962).

5. Personal communication, J. van den Hende of these Laboratories.

6. R. Mondelli and L. Merlini, Tetrahedron, 22, 3253 (1966); A. L. Borror and A. F. Haeberer, J. Org. Chem., 30, 243 (1965).

7. S. K. Chakrabartty and R. Levine, J. Heterocyclic Chem., 4, 109 (1967); W. von Philipsborn, H. Stierlin and W. Traber, Helv. Chim. Acta, 46, 2592 (1963).

8. J. Klosa, Arch. Pharm., 288, 465 (1955).

9. Ng. Ph. Buu-Hoï, Ng. D. Xuong and F. Binon, J. Chem. Soc., 713 (1956).

10. Societe belge de l'azote et des produits chimiques du Marly, S.A., Belgian patent 503,980 (1951); Chem. Abstr., 50, 404g (1956).

11. K. Bednarz, Dissertationes Pharm., 9, 249 (1957); Chem. Abstr., 52, 8083f (1958).

12. Determined by J. Karliner of these Laboratories.

13. W. Seibert, Chem. Ber., 80, 494 (1947).