

CCA-788

547.3

Original Scientific Paper

Synthesis of Di(*s*-triazinyl) Sulphides and Disulphides. The Promoting Effect of Oxidants on the Cleavage of the Thioether Bond

P. Mildner, Branka Mihanović, and M. Poje

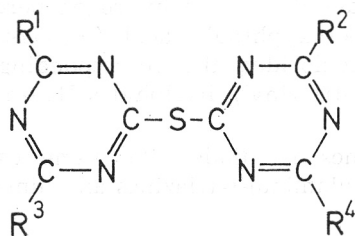
Laboratory of Biochemistry, Faculty of Technology, University of Zagreb,
41000 Zagreb, Croatia, Yugoslavia

Received March 27, 1973

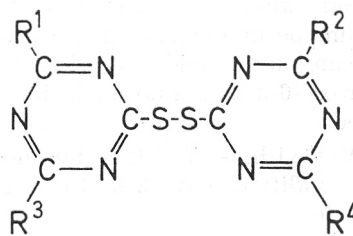
Synthesis of a number of di(*s*-triazinyl) sulphides and disulphides is described. The behaviour of these compounds on oxidative attack has been examined. It has been found that instead of the expected sulphoxide and/or sulphone formation upon oxidation, a simple scission of the thioether linkage takes place, yielding a hydroxytriazine and the corresponding disulphide.

INTRODUCTION

Since the application of 2-methylthio-4,6-bis(alkylamino)-*s*-triazines as agricultural herbicides in the early nineteen sixties, their chemical and biological properties have been studied intensively¹. More recently, however,



I



II

| | R ¹ | R ² | R ³ | R ⁴ |
|-----|-----------------|-----------------|-----------------|-----------------|
| Ia | -Cl | -NHEt | -NHEt | -NHEt |
| Ib | -Cl | -NH <i>i</i> Pr | -NHEt | -NHEt |
| Ic | -Cl | -NHEt | -NH <i>i</i> Pr | -NHEt |
| Id | -Cl | -NH <i>i</i> Pr | -NH <i>i</i> Pr | -NHEt |
| Ie | -Cl | -NHEt | -NH <i>i</i> Pr | -NH <i>i</i> Pr |
| If | -Cl | -NH <i>i</i> Pr | -NH <i>i</i> Pr | -NH <i>i</i> Pr |
| IIa | -NHEt | -NHEt | -NHEt | -NHEt |
| IIb | -NHEt | -NH <i>i</i> Pr | -NHEt | -NH <i>i</i> Pr |
| IIc | -NH <i>i</i> Pr | -NH <i>i</i> Pr | -NH <i>i</i> Pr | -NH <i>i</i> Pr |

we were also engaged in a reasearch project to investigate *S*-substituted triazines in plant tissue². The sulphanyl group has long been known to be involved in biochemical transformations of a number of thioether-linkage containing compounds. The observed effect of an oxidation agent on the degradation rate of methylthiotriazines³ suggested the intermediate formation of a sulfoxide and/or sulphone⁴. Nevertheless, the corresponding 2-hydroxy-triazine was the only metabolite found in resistant plant species, and so far nothing could be said about the fate of the alkylthio group in plant tissue. The obvious difficulty in studying the degradation of an alkylthiotriazine is to follow the highly interacting aliphatic sulphur-containing moiety within living systems. Therefore it was advantageous to synthesize some *s*-triazines, *viz.* di(*s*-triazinyl) sulphides and disulphides where with them it should be easier to follow the transformations within the tissue, including the sulphanyl function, if ever formed.

RESULTS

The IR spectra of di(*s*-triazinyl) sulphides and disulphides are alike in their essential features, with three main regions of absorption: near 3300 cm⁻¹, between 1660 and 1430 cm⁻¹, and just beyond 830 cm⁻¹. The first region contains the N—H stretching absorptions, and the second is where the »in-plane« vibrations of the triazine ring are expected, containing 3—4 large bands. The most outstanding one is a strong broad absorption band at 1550 cm⁻¹. The third region of interest, just beyond 830 cm⁻¹, contains in particular a sharp, medium strength band at 815 cm⁻¹, and has been assigned to on »out-of-plane« motion of the ring. This band is constant both in position and intensity in the spectra of di(*s*-triazinyl) sulphides and disulphides.

Upon oxidation of di(*s*-triazinyl) sulphides Ia—f with hydrogen peroxide, potassium permanganate, nitric acid, monoperoxyphthalic acid, (+)-*cis*-monoperoxyamphoric acid, and iodobenzene dichloride⁵, the corresponding 2,4-dihydroxy-6-alkylamino-*s*-triazines and di(*s*-triazinyl) disulphides IIa—c were obtained.

2-Methylthio-4,6-*bis*(alkylamino)-*s*-triazines III under the same experimental conditions gave 2-hydroxy-4,6-*bis*(alkylamino)-*s*-triazines and dimethyl-disulphide.

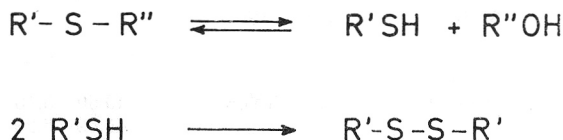
The reactions were followed by TLC and IR spectra. The characteristic IR absorption of sulfoxides near 1050 cm⁻¹, as well as two bands of sulphones in the 1350—1300 and 1160—1140 cm⁻¹ regions, were absent from all the spectra.

When heated in aqueous acetic acid, 4-chloro-4'-ethylamino-6,6'-*bis*(isopropylamino)-di(*s*-triazinyl-2)sulphide Id affords 2,4-dihydroxy-6-isopropylamino-*s*-triazine and 2-mercapto-4-ethylamino-6-isopropylamino-*s*-triazine. An analogous reaction took place with 2-methylthio-4-ethylamino-6-isopropylamino-*s*-triazine IIIa, which gave 2-hydroxy-4-ethylamino-6-isopropylamino-*s*-triazine and methylmercaptane.

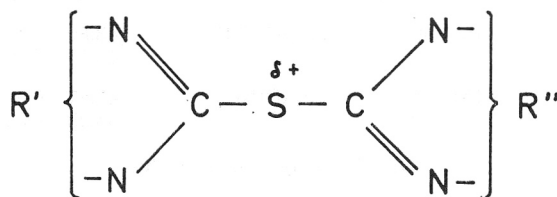
DISCUSSION

On the basis of the results obtained it is obvious that the behaviour of di(*s*-triazinyl) sulphides and methylthiotriazines is qualitatively the same. In both cases the valence state of sulphur remains unchanged at the end of the reaction, thus giving strong support to the statement that there are no

sulphoxides and/or sulphones involved in the breakdown of the thioether bond. The hydrolytic attack favored by oxidative removal of the mercapto compound as appropriate disulphide can be illustrated:



The fact that sulphoxide and sulphone formation in *s*-triazine series fails is best explained by their *S*-substituted-isothiourea-like structure in which sulphur has marked sulphonium character, and consequently low affinity to make a semipolar bond with oxygen.



EXPERIMENTAL

Melting points are uncorrected. The IR spectra were determined on a Perkin-Elmer Infracord 137 in KBr discs; TLC was conducted on Silica Gel HF (E. Merck) using chloroform—benzene—ethanol (9 : 7 : 1). Spots were visualized in UV (254 nm).

2-Mercapto-4,6-bis(alkylamino)-*s*-triazines were prepared according to the original method of Urquhart⁶.

2,4-Dichloro-6-alkylamino-*s*-triazines were synthesized according to Diels⁷.

2-Chloro-4,6-bis(alkylamino)-*s*-triazines were synthesized according to Pearlman and Banks⁸.

2-Methylthio-4,6-bis(alkylamino)-*s*-triazines were purchased from a commercial source.

Di(s-triazinyl) Sulphides Ia—f. General procedure

To a stirred solution of the corresponding 2,4-dichloro-6-alkylamino-*s*-triazine (0.03 mol) in 50 ml acetone, the equimolar amount of appropriate 2-mercapto-4,6-bis(alkylamino)-*s*-triazine dissolved in 30 ml. 40% NaOH was added dropwise at 50 °C. The heating and stirring was continued for 5 h. whereupon the solvent was evaporated. On recrystallization from chloroform—petroleum ether Ia—f were obtained as white irregular prisms. For analysis a sample was subjected to preparative TLC. The yields and analytical data are given in Table I.

Di(s-triazinyl) Disulphides IIa—c. General procedure

To 0.01 mol of appropriate 2-mercapto-4,6-bis(alkylamino)-*s*-triazine dissolved in 10 ml 1 M NaOH, 10 ml 1 M iodine was added gradually at room temperature, under stirring. The precipitate was filtered off, washed with water and dried. Upon recrystallization from chloroform—petroleum ether compounds IIa—c were obtained as white prisms. For analysis, samples were recrystallized twice from chloroform—petroleum ether. The yields and analytical data are given in Table I.

TABLE I
 Di(*s*-triazinyl) sulphides

| Compd. No. | Yield % | M. p./°C | Formula | Analyses | | | | |
|--------------------------------------|---------|----------|--|---------------|------|------|-------|-------|
| | | | | Calc'd. Found | | | | |
| | | | | % C | % H | % Cl | % N | % S |
| Ia | 87 | 150—1 | C ₁₂ H ₁₈ ClN ₉ S | 40.50 | 5.10 | | 35.43 | |
| | | | | 40.69 | 5.29 | | 35.60 | |
| Ib | 90 | 138—9 | C ₁₃ H ₂₀ ClN ₉ S | 42.21 | 5.45 | | 34.08 | |
| | | | | 42.63 | 5.77 | | 34.16 | |
| Ic | 83 | 113—4 | C ₁₃ H ₂₀ ClN ₉ S | 42.21 | 5.45 | | | |
| | | | | 42.20 | 5.47 | | | |
| Id | 80 | 106—7 | C ₁₄ H ₂₂ ClN ₉ S | 43.80 | 5.78 | 9.24 | 32.84 | 8.35 |
| | | | | 43.64 | 5.99 | 9.36 | 32.60 | 8.64 |
| Ie | 84 | 163—4 | C ₁₄ H ₂₂ ClN ₉ S | 43.80 | 5.78 | | 32.84 | |
| | | | | 43.16 | 5.86 | | 32.35 | |
| If | 81 | 151—2 | C ₁₅ H ₂₄ ClN ₉ S | 45.27 | 6.08 | | 31.68 | |
| | | | | 45.25 | 6.38 | | 31.70 | |
| Di(<i>s</i> -triazinyl) disulphides | | | | | | | | |
| IIa | 75 | 173—5 | C ₁₄ H ₂₄ N ₁₀ S ₂ | 42.41 | 6.10 | | | |
| | | | | 42.74 | 6.31 | | | |
| IIb | 69 | 180 | C ₁₆ H ₂₈ N ₁₀ S ₂ | 45.26 | 6.65 | | 32.99 | 15.10 |
| | | | | 45.15 | 6.81 | | 32.75 | 14.96 |
| IIc | 66 | 213—4 | C ₁₅ H ₃₂ N ₁₀ S ₂ | 47.76 | 7.13 | | | |
| | | | | 47.68 | 7.12 | | | |

Reaction of 4-Chloro-4'-ethylamino-6,6'-bis(isopropylamino)-di-(s-triazinyl-2) sulphide Id with Hydrogen Peroxide

To a solution of 5.0 g (0.013 mol) Id in 20 ml acetone and 20 ml 20% acetic acid, an equimolar amount H₂O₂ was added (30%, 1.5 ml). The reaction mixture was heated 2 h. To the mixture 50 ml water was added, and adjusted with 20% NaOH to pH = 7. The precipitate was filtered off and washed. TLC showed three spots: A with R_f 0.05, B R_f 0.20, and C (unreacted Id) R_f 0.44, respectively.

The crude product (0.5 g) was subjected to preparative TLC, the zones of A and B were scrapped off, and percolated with absolute methanol. 0.18 g (65.3%) B, obtained after removal of the solvent, was recrystallized from chloroform-petroleum ether; m. p. 180 °C. No m. p. depression on admixture with IIb was observed, and their R_fs as well as the IR spectra were identical.

Anal. C₁₆H₂₈N₁₀S₂ (424.60) calc'd.: C 45.26%; H 6.65%; S 15.10%
 found: C 45.20%; H 6.81%; S 15.41%.

0.20 g (90.4%) A was recrystallized from methanol; needles m. p. 235—6 °C (decompn.). The compound was identical with 2,4-dihydroxy-6-isopropylamino-*s*-triazine obtained by hydrolysis with 50% sulphuric acid from 2,4-dichloro-6-isopropylamino-*s*-triazine. The IR spectrum showed a strong peak at 1730 cm⁻¹ (=C=O).

Reaction of 2-Methylthio-4-ethylamino-6-isopropylamino-*s*-triazine IIIa with Hydrogen Peroxide

22.7 g (0.1 mol) IIIa was dissolved in 50 ml acetone and 50 ml 20% acetic acid. Soon afterwards, an unpleasant odour could be perceived. After addition of an equimolar amount H_2O_2 (30%, 11 ml) the smell disappeared, and the reaction mixture was heated 2 h. Then the pH was adjusted to 7 with 10% NaOH, and the precipitate filtered off and washed.

The filtrate was concentrated *in vacuo*, extracted with 150 ml of ether, and the extract dried. Ether was evaporated and the remaining oil distilled (55 °C, 34 mmHg). A colorless liquid, identical with dimethyldisulphide, was obtained: 3.9 g (82.9%), b. p. 105–8 °C. Reduction with Zn in H_2SO_4 afforded methylmercaptan.

The precipitate was resuspended in 100 ml methanol, heated 1 h and filtered off, yielding 13.3 g (67.5%), m. p. 300 °C. IR spectrum showed a strong peak at 1710 cm^{-1} ($=\text{C}=\text{O}$).

2-Chloro-4-ethylamino-6-isopropylamino-*s*-triazine yielded the same compound on hydrolysis with 50% H_2SO_4 , *i. e.* 2-hydroxy-4-ethylamino-6-isopropylamino-*s*-triazine.

Acid Catalysed Hydrolysis of Id

A solution of 5.0 g (0.013 mol) Id in 20 ml acetone and 20 ml 20% acetic acid was heated 2 h. The mixture was then adjusted with 20% NaOH to pH = 7, the precipitate was filtered off and then in turn resuspended in 80 ml 70% ethanol, heated 1 h and filtered. The crude product was then resuspended in 50 ml 0.2 M NH_4OH , stirred 1 h and filtered off.

The solid was washed with water and dried. Upon recrystallization from methanol 0.46 g (20.8%) white needles were obtained; m. p. 234–6 °C (decompn.). IR spectrum showed a strong peak at 1730 cm^{-1} ($=\text{C}=\text{O}$). The mixed m. ps. showed no depression on admixture with 2,4-dihydroxy-6-isopropylamino-*s*-triazine.

The ammoniacal filtrate was adjusted with 10% acetic acid to pH = 7, the precipitate was filtered off, washed with water, and dried. On recrystallization from ethyl cellosolve 0.77 g (27.8%) of white crystals were obtained; m. p. 214 °C. IR spectrum showed a peak at 2560 cm^{-1} (SH). No m. p. depression on admixture with 2-mercapto-4-ethylamino-6-isopropylamino-*s*-triazine could be observed. On oxidation with iodine, IIB was obtained; m. p. 179–80 °C.

Acid Catalysed Hydrolysis of IIIa

22.7 g (0.1 mol) IIIa dissolved in 50 ml acetone and 50 ml 20% acetic acid was heated 2 h. The mixture was then adjusted to pH = 7 with 10% NaOH, and the precipitate was filtered off. The crude product was resuspended in 200 ml methanol, heated 1 h and filtered off yielding 4.1 g (20.8%) of 2-hydroxy-4-ethylamino-6-isopropylamino-*s*-triazine.

REFERENCES

1. P. Kearney and D. Kaufman, *Degradation of Herbicides*, Dekker Inc., New York, 1969, pp. 51–75.
2. P. Mildner, B. Mihanović, and M. Poje, *FEBS Letters*, **22** (1972) 117.
3. P. Müller, *Proc 463rd Meeting Biochem. Soc., Aberystwyth*, Colloq. Biochem. Herb., 1966, p. 1 P.
4. H. Gysin, *Chem. Ind.* (London) (1962) 1393.
5. G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc. (C)* (1968) 659.
6. G. Urquhart, J. Gates, and R. Counor, *Org. Synth.* **21** (1941) 36.
7. O. Diels, *Ber.*, **32** (1889) 691.
8. W. Pearlmann, and C. Banks, *J. Amer. Chem. Soc.* **70** (1948) 3726.

IZVOD**Sinteza di (s-triazinil) sulfida i disulfida. Učinak oksidansa pri cijepanju tioeterskog veza**

P. Mildner, Branka Mihanović i M. Poje

Opisana je sinteza većeg broja spojeva iz reda di-(s-triazinil)-sulfida i di-(s-triazinil)disulfida. Ispitano je ponašanje sulfida pri oksidaciji. Dokazano je da ne nastaju pripadni sulfoksidi ili sulfoni, već dolazi do cijepanja tioeterskog veza, pri čemu nastaju hidroksitriazin i merkapto derivat koji odmah prelazi u pripadni disulfid.

LABORATORIJ ZA BIOKEMIJU
TEHNOLOŠKI FAKULTET
SVEUČILIŠTA U ZAGREBU
41000 ZAGREB

Primljeno 27. ožujka 1973.