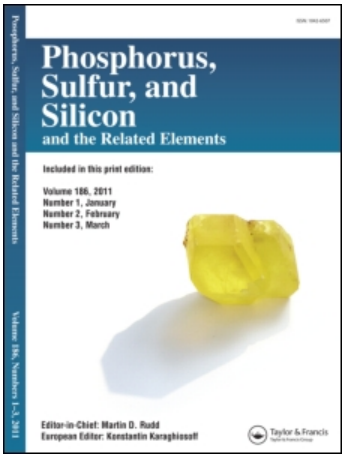

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

BIS-(SULFONYLFORMYL)-DIAMINES AS POTENTIAL CYTOSTATIC AGENTS

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To cite this Article Skorini, Sámal Jensí and Senning, Alexander(1980) 'BIS-(SULFONYLFORMYL)-DIAMINES AS POTENTIAL CYTOSTATIC AGENTS', Phosphorus, Sulfur, and Silicon and the Related Elements, 9: 2, 193 — 195
To link to this Article: DOI: 10.1080/03086648008078239
URL: http://dx.doi.org/10.1080/03086648008078239

Phosphorus and Sulfur, 1980, Vol. 9, pp. 193–196
0308-664X/80/0902-0193$06.50/0

BIS-(SULFONYLFORMYL)-DIAMINES AS POTENTIAL CYTOSTATIC AGENTS

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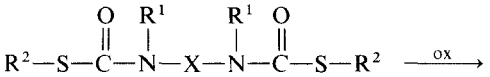
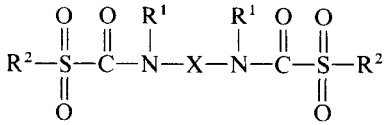
(*Received December 17, 1979*)

Four bis-(sulfonylformyl)-diamines IIa–c,e have been prepared by oxidation of the corresponding bis-thiolcarbamates I with 3-chloroperbenzoic acid. Bis-thiolcarbamate Id could not be oxidized because of insufficient solubility. Bis-thiolcarbamates IXa,b decomposed upon attempted oxidation.

Our general interest in difunctional acylating agents for chemotherapeutic screening[1,2] induced us to synthesize a series of bis-(sulfonylformyl)-diamines, II, which have not yet been reported in the literature. These compounds can be prepared



I

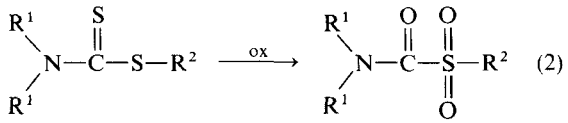


II (1)

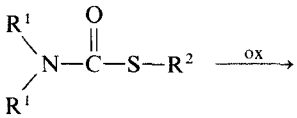
by oxidation of the corresponding bis-thiolcarbamates, I (Eq. (1)) analogous to the known procedures for the preparation of C-sulfonylformamides, IV, from different precursors, *i.e.* (2),[3] (3),[3–5] and (4).[6] These reactions are closely related

I, II	$R^1 = X$	R^2
a	CH_2CH_2	CH_3CH_2
b	CH_2CH_2	C_6H_5
c	CH_2CH_2	4-$CH_3C_6H_4$
d	CH_2CH_2	4-ClC_6H_4
e	CH_2CH_2	4-FC_6H_4

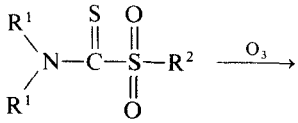
to similar procedures for the synthesis of carbamoyl sulfoxides[7] and thiocarbonate S,S-dioxides,[8] respectively.



III IV (2)

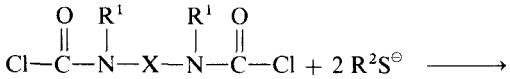


V IV (3)

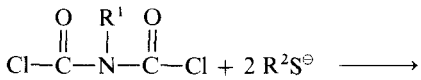


VI IV (4)

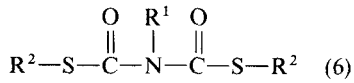
The choice of (1) as the preferred route to II was based upon the ready accessibility of Ia–e starting with the known key intermediate VII ($R^1 = X = CH_2CH_2$)[9] according to (5). Similarly, IXa–b



VII $I + 2\,Cl^{\ominus}$ (5)



VIII



IX (6)

could be obtained from the known VIII ($R^1 = CH_3$)[10] (Eq. (6)). Other methods for the preparation of thiolcarbamates have already been described in the literature.[11] The group R^2 of II was chosen so as to include both +I and −I substituents. The fluoro compound IIe was prepared when the chloro compound Id turned out to be of so extremely low solubility that it could not readily be oxidized to IId. Oxidation of IX according to

TABLE I

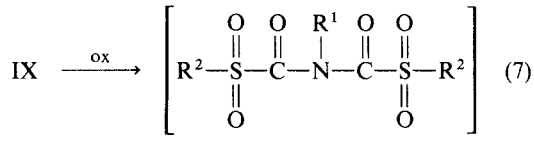
Comp.	Yield (%)	Mp (°C)	IR ($H\nu_{C=O}cm^{-1}$)	^1H NMR (δ, $CDCl_3$)	MS (*m/e*, M underlined)
Ia	96	90.5–91 (abs. EtOH)	1650	1.32 (t,J 7Hz, 6H) 2.98 (q,J 7Hz, 4H) 3.60 (s, 8H)	262, 247, 233, 201, 273
Ib	99	188–9 (CH_3CN)	1660	3.70 (s, 8H) 7.33–7.66 (m, 10H)	358, 249, 221
Id	97	240–1	1650	3.63 (s, 8H) 7.50 (s, 8H) (in DMSO)	426, 391, 283
Ie	82	224–5 ($CHCl_3$)	1665	3.68 (s, 8H) 6.90–7.70 (m, 8H)	394, 267, 239, 127
IXa	97	144–5 (abs. EtOH)	1670	3.43 (s, 3H) 7.30–7.60 (br.s. 10H)	303, 246, 218
IXb	68	133–4 (CH_3CN)	1670–1685 (doublet)	2.38 (s, 6H) 3.44 (s, 3H) 7.29 (dd,J 9Hz, 8H)	331, 274, 246, 123, 91

TABLE II

Comp.	Yield (%)	Mp (°C)	IR (cm^{-1})	^1H NMR (δ, $CDCl_3$)	MS (*m/e*)
IIa	97	188–9 (CH_3CN)	1685 ($\nu_{C=O}$) 1124, 1300 (ν_{SO_2})	1.42 (t,J 7Hz, 6H) 3.38 (q,J 7Hz, 4H) 3.60–4.22 (m, 8H)	249, 233, 204
IIb	95	213–4 (CH_3CN)	1705–20 ($\nu_{C=O}$) 1145, 1300 (ν_{SO_2})	too insoluble	281, 250, 141, 125, 109
IIc	56	222–3 (CH_3CN)	1670–80 ($\nu_{C=O}$) 1140, 1285–1315 (ν_{SO_2})	too insoluble	418, 406, 390
IIe	94	228–9 (CH_3CN)	1690–1700 ($\nu_{C=O}$) 1145, 1300–1320 (ν_{SO_2})	too insoluble	299, 159, 143, 127

TABLE III

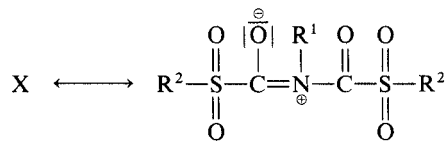
Comp.	Formula (mass)				
				C	H
Ia	$C_{10}H_{18}N_2O_2S_2$	(262.4)	Calcd.	45.77	6.93
			Found	45.92	7.09
Ib	$C_{18}H_{18}N_2O_2S_2$	(358.5)	Calcd.	60.30	5.07
			Found	60.39	5.04
Id	$C_{18}H_{16}Cl_2N_2O_2S_2$	(427.4)	Calcd.	50.58	3.78
			Found	50.40	3.85
Ie	$C_{18}H_{16}F_2N_2O_2S_2$	(394.5)	Calcd.	54.80	4.10
			Found	55.19	4.19
IXa	$C_{15}H_{13}NO_2S_2$	(303.4)	Calcd.	59.38	4.32
			Found	59.54	4.40
IXb	$C_{17}H_{17}NO_2S_2$	(331.4)	Calcd.	61.60	5.17
			Found	61.58	5.27
				S	N
IIa	$C_{10}H_{18}N_2O_6S_2$	(326.4)	Calcd.	19.65	8.58
			Found	18.90	8.54
IIb	$C_{18}H_{18}N_2O_6S_2$	(422.5)	Calcd.	15.18	6.63
			Found	15.21	6.71
IIc	$C_{20}H_{22}N_2O_6S_2$	(450.6)	Calcd.	14.23	6.22
			Found	14.25	6.19
IIe	$C_{18}H_{16}F_2N_2O_6S_2$	(458.5)	Calcd.	13.99	6.11
			Found	13.95	6.17



X

IX, X	R^1	R^2
a	CH_3	C_6H_5
b	CH_3	4-$CH_3C_6H_4$

(7) did not lead to well-defined products, probably because of inherent instability of X. Instability of X in contrast to the stability of II and IV can be predicted as a consequence of the reduced mesomeric donor properties of the nitrogen atom due to



X^1

the destabilization of mesomeric structures such as X^1. This is in keeping with the lability of Schank's α-ketosulfones[12] where no mesomerism is possible.

EXPERIMENTAL

The 60 MHz ^{1}H-NMR spectra were recorded in $CDCl_3$ with TMS as internal standard. The mass spectra were obtained with a CEC 21-104 mass spectrometer with direct inlet and an ionizing potential of 70 eV. IR spectra were recorded in KBr with a Beckman IR-18A spectrometer. The melting points are uncorrected.

1,4-Piperazinedicarbothioic acid S,S-diethyl ester, Ia. In a three-necked 250 ml flask equipped with a mechanical stirrer and a reflux condenser 4.0 g (0.06 mole) ethanethiol is dissolved in 75 ml abs. ethanol. Sodium, 1.4 g (0.06 mole), is added in small pieces and when the gas evolution has finished 6.4 g (0.03 mole) 1,4-bis-chloroformylpiperazine, VII (R^1 = X = CH_2CH_2),[9] is added at once and the mixture stirred under reflux for 3 hr. After cooling, the mixture is poured into water. The colorless precipitate is collected, air dried, and recrystallized from abs. ethanol to yield 7.5 g (96%) pure product.

The thiocarbamates, Ib, Ic, and Ie, were prepared analogously while Ic was obtained according to a literature procedure.[13] Compound Id was purified by extraction with boiling ethanol since it was too insoluble for recrystallization.

Compounds IXa and IXb were prepared like I expect that the carbamoyl chloride VIII (R^1 = CH_3)[10] was slowly injected through a rubber septum and the reflux period was reduced to 30 min. Since IXb did not precipitate in crystalline form it was isolated by extraction with chloroform and usual work-up of the chloroform extract.

1,4-Bis-ethylsulfonylformyl)-piperazine, IIa. In a three-necked 1 l flask equipped with a mechanical stirrer, dropping funnel, and a salt/ice cooling bath (−16°C) 11.0 g (0.052 mole) 3-chloroperbenzoic acid (85%, tech.) is suspended in 200 ml methylene chloride. 1,4-Piperazinedicarbothioic acid S,S-diethyl ester, Ia, dissolved in 150 ml methylene chloride, is added dropwise. After the addition, the cooling bath is removed and stirring continued for another 5 hr. The precipitated 3-chlorobenzoic acid is removed by filtration and the filtrate washed 3-4 times with 5% aqueous $NaHCO_3$ and 2-3 times with water. After drying with $MgSO_4$, rotary evaporation, and recrystallization from acetonitrile 4.1 g (97%) IIa is obtained.

Compounds IIb, IIc, and IIe were obtained analogously.

In our unsuccessful attempts to prepare Xa and Xb column chromatography of the raw products failed to provide the desired compounds. Only cleavage products were observed.

ACKNOWLEDGMENT

The authors express their gratitude to Bayer AG, Leverkusen (Germany), for a generous gift of VIII (R^1 = CH_3).

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