

Halogeno-1,4-dioxans and their Derivatives. Part VIII.¹ Direct Replacement of Chlorine in 2,3-Dichloro-1,4-dioxan by Sulphur and by Nitrogen. Conformations of the Products, of a Rigid *cis*-Fused Hexahydro-1,4-dioxino[2,3-*b*][1,4]dioxin, and of Bi-1,3-dithian-2-yl

By Robert E. Ardrey and Leslie A. Cort,* Joseph Kenyon Research Laboratories, University of Surrey, Guildford, Surrey GU2 5XH

The preparation of *SS'*-(1,4-dioxan-2,3-diyl)dithiuronium dichloride and of 2,3-bis-(*N*-methyl-*p*-tolylsulphonylamino)-1,4-dioxan is described. Analysis of ¹H n.m.r. spectra shows these compounds to be *trans*-isomers, with the former having a rigid conformation. ¹H N.m.r. parameters obtained by rigorous analysis are reported for two (-)-hexahydro-1,4-dioxino[2,3-*b*][1,4]dioxin-2,3-dicarboxylate esters and for bi-1,3-dithian-2-yl.

THERE is only one report² of the direct replacement of chlorine in *trans*-2,3-dichloro-1,4-dioxan by sulphur; reaction with thiols leads to rearrangement products.³ We have found that reaction with thiourea leads to *SS'*-(1,4-dioxan-2,3-diyl)dithiuronium dichloride (I); this compound is unstable, but rigorous analysis of the ¹H n.m.r. spectrum of a freshly prepared sample by using the LAOCOON 1968 program⁴ gives coupling constants for the CH₂·CH₂ unit consistent only with the *trans*-configuration and a chair conformation¹ (see Table I). The fact that the signal of the axial proton (A) is at lower field (by 0.5 p.p.m.) than that of the equatorial proton (B) indicates that there is some group (electronegative) other than hydrogen in the *cis*-axial position (compare the chemical shifts⁵ for H-5_{ax} and H-5_{eq} of β-D-xylopyranose and β-D-lyxopyranose in deuterium oxide). Both the substituents must therefore be axial, a conclusion supported by the chemical shift values of H-2.

TABLE I

¹H N.m.r. parameters [*J* in Hz (±0.2 Hz)] for the CH₂·CH₂ unit in *SS'*-(1,4-dioxan-2,3-diyl)dithiuronium dichloride (I)

Solvent:	D ₂ O	(CD ₃) ₂ SO	CF ₃ ·CO ₂ H
τ _A	5.55	5.75	5.34
τ _B	6.06	6.12	5.98
<i>J</i> _{AA'}	11.1	10.8	10.7
<i>J</i> _{AB} = <i>J</i> _{A'B'}	-12.8	-12.8	-12.8
<i>J</i> _{AB'} = <i>J</i> _{A'B}	2.9	2.9	2.8
<i>J</i> _{BB'}	0.7	0.5	0.5

The *trans*-configuration is accounted for by two S_N2 reactions. Although after the first the stereochemical

¹ Part VII, R. E. Ardrey and L. A. Cort, *J.C.S. Perkin II*, 1975, 959.

² W. R. Driveley, A. H. Haubein, A. D. Lohr, and P. B. Moseley, *J. Amer. Chem. Soc.*, 1959, **81**, 139.

³ M. Pröstenik and K. Balenović, *J. Org. Chem.*, 1952, **17**, 379.

requirements (*E2*) for loss of HCl can be met, addition of thiourea to the resulting olefin would lead to a final *cis*-product. The instability of compound (I) is due to the tendency to eliminate thiourea. In the mass spectrum the heaviest ion detected is at *m/e* 160 [*S*-(5,6-dihydro-1,4-dioxin-2-yl)isothiourea], and after attempted alkaline hydrolysis addition of benzoyl chloride led to *N*-benzoylthiourea. In the formation of 2,3-bis-(diethoxyphosphinothioylthio)-1,4-dioxan both *cis*- and *trans*-products are obtained,² and the *trans*-product alone readily undergoes thermal elimination to give a dihydro-dioxin.

The dichloride (I) was decomposed by nitrous acid in hydrochloric acid, but in acetic acid a tetranitroso-derivative was obtained which separated as a salt (II) of the starting base (*cf.* the dinitroso-derivative⁶ of *S-p*-tolylisothiourea); this product was insoluble in all common solvents, and explosive. Similar salts [(III) and (IV)] were obtained from *SS'*-ethylene- and *SS'*-trimethylenedithiuronium dibromides.

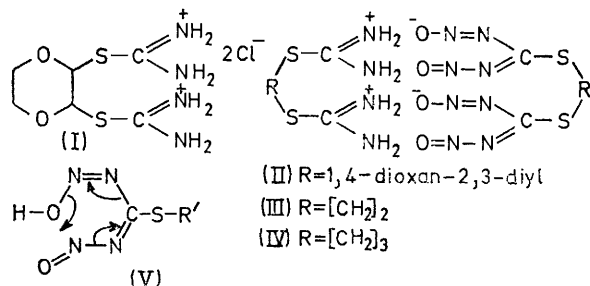
That these salts are as formulated and are not zwitterions of half the molecular weight follows from the fact that decomposition of the ethylene and trimethylene compounds with hydrochloric acid or by heating in acetic acid or dimethyl sulphoxide yielded not only the corresponding dithiocyanate (from the anion) but also the corresponding original cation, isolable as the dipicrate. Similar decomposition of the dioxan compound destroyed the anion (only a derivative of glyoxal was isolated), but the cation could again be isolated as the dipicrate. The thiocyanate group can arise by collapse

⁴ R. K. Harris and J. Stokes, 'A Library of Computer Programs for Nuclear Magnetic Resonance Spectroscopy,' Science Research Council, January 1971.

⁵ R. U. Lemieux and J. D. Stevens, *Canad. J. Chem.*, 1966, **44**, 249.

⁶ F. Arndt, *Annalen*, 1913, **396**, 1.

of the *O*-protonated system (V); this behaviour parallels that⁶ of the *S*-*p*-tolyl analogue, but the dioxan anion can undergo alternative decomposition (*e.g.* by protonation of a ring oxygen atom).



Direct replacement of chlorine in *trans*-2,3-dichloro-1,4-dioxan by nitrogen has been accomplished by reaction with *N*-methyltoluene-*p*-sulphonamide in diethyl ether, to give *trans*-2,3-bis-(*N*-methyl-*p*-tolylsulphonylamino)-1,4-dioxan. The ¹H n.m.r. spectrum shows a singlet signal from the CH₂•CH₂ unit. Of the possibilities accounting for this, a single boat conformation of the *cis*-isomer, or a single chair conformation of the *trans*-isomer with fortuitously the same chemical shifts for the axial and equatorial protons, or a chair conformation of the *trans*-isomer undergoing rapid inversion, the last is the most likely (*trans*-2,3-diphenyl-1,4-dioxan exhibits⁷ the same phenomenon).

The yield could not be raised above 16% by changing reactant proportions or solvent, and when the reaction time was extended by five months the material which then separated was bis-1-(*N*-methyl-*p*-tolylsulphonylamino)ethyl peroxide. In the mass spectrum the heaviest ion detected was at *M*/2; this may indicate ready thermal dissociation. The product had the expected ¹H n.m.r. spectrum, and liberated iodine on treatment with potassium iodide in acetic acid.

Diethyl (+)-tartrate condenses with *trans*-2,3-dichloro-1,4-dioxan to give diethyl (-)-hexahydro-1,4-dioxino-[2,3-*b*][1,4]dioxin-2,3-dicarboxylate (VI) in which the ring fusion is *cis*.⁸ The ¹H n.m.r. spectrum for the CH₂•CH₂ unit in deuteriochloroform appears as an AMNX pattern, indicating a single conformation. For a solution in benzene sufficient of the MN part of the spectrum from the dimethyl ester is available to permit analysis by the LAOCOON 1968 program.⁴ With these results, similar analysis of the diethyl ester spectrum is possible; experimental and theoretical spectra are shown in Figure 1,* and the chemical shifts and coupling constants are given in Table 2.

These parameters are of interest since this is so far the sole example of a 1,4-dioxan with *cis*-2- and -3-substituents only (the fused ring) which adopts a single chair conformation (VII) in solution. {The parent *cis*-hexa-

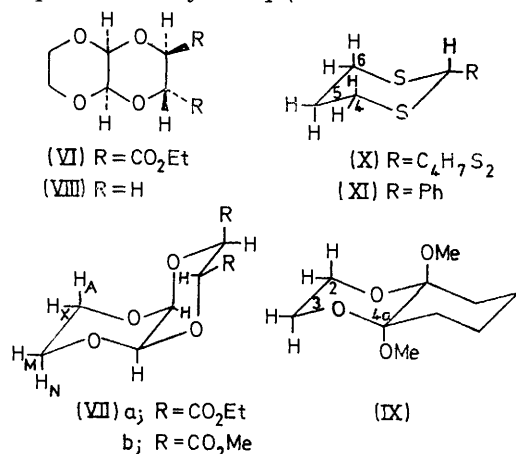
* Figures 1 and 2 are available in the Supplementary Publication.

⁷ E. Caspi, T. A. Wittstruck, and D. M. Piatak, *J. Org. Chem.*, 1962, 27, 3183.

⁸ R. Bramley, L. A. Cort, and R. G. Pearson, *J. Chem. Soc. (C)*, 1968, 1213.

hydro-1,4-dioxino[2,3-*b*][1,4]dioxin (VIII) undergoes rapid inversion.⁹ The unexpectedness of the chemical shift data prompted an X-ray crystallographic analysis¹⁰ of the diethyl ester, which confirmed the conformation (VIIa).

Comparison of the chemical shift data with those¹¹ for *trans*-4a,8a-dimethoxyoctahydrocyclohexa[1,2-*b*][1,4]-dioxin (IX) shows that for H_A and H_X in compound (VIIa) there is good agreement. However, the signal for H_M (deuteriochloroform solution), instead of being to slightly higher field of that of H_X, is actually 0.5 p.p.m. downfield. The explanation for this is not clear, but it has also been shown¹ that introduction of equatorial chlorine at C-2 in the chair conformation of a dioxan effects predominantly H-6_{eq} (with a downfield shift), so



this may be a common feature with such electronegative substituents, including the equatorial oxygen in compound (VIIa).

TABLE 2

¹H N.m.r. parameters [*J* in Hz (±0.2 Hz)] for diethyl (VIIa) and dimethyl (VIIb) (-)-hexahydro-1,4-dioxino[2,3-*b*][1,4]dioxin-2,3-dicarboxylate

	(VIIa)		(VIIb)
	Solvent: CDCl ₃	C ₆ H ₆	C ₆ H ₆
τ _A	5.84	6.11	6.13
τ _M	6.01	6.65	6.64
τ _N	6.14	6.77	6.76
τ _X	6.49	7.15	7.14
J _{AM}	2.8	3.0	3.0
J _{AN}	11.1	11.1	11.1
J _{AX}	-11.8	-11.6	-11.7
J _{MN}	-12.0	-12.2	-12.1
J _{MX}	2.1	2.0	1.9
J _{NX}	2.7	2.6	2.7

The reaction of propane-1,3-dithiol with *trans*-2,3-dichloro-1,4-dioxan yields³ bi-1,3-dithian-2-yl (X). The 220 MHz ¹H n.m.r. spectrum (solvent deuteriochloroform) departs greatly from first order, but the iterative procedure⁴ yielded the chemical shifts and coupling constants given in Table 3; the experimental and theoretical spectra are shown in Figure 2.*

⁹ C. Altona and E. Havinga, *Tetrahedron*, 1966, 22, 2275.

¹⁰ R. E. Ardrey, M. J. Begley, M. F. C. Ladd, and D. C. Povey, *J. Cryst. Mol. Struct.*, 1973, 3, 171.

¹¹ R. R. Fraser and C. Reyes-Zamora, *Canad. J. Chem.*, 1967, 45, 929.

The only other 1,3-dithian unsubstituted in positions 4–6 which adopts a single conformation and for which there is a rigorous ^1H n.m.r. analysis (of a 220 MHz spectrum) is the 2-phenyl compound¹² (XI). In the

TABLE 3

^1H N.m.r. parameters [J in Hz (± 0.2 Hz)] for bi-1,3-dithian-2-yl (X) and 2-phenyl-1,3-dithian (XI)

	(X)	(XI) ¹²
Solvent:	CDCl_3	CCl_4
H-2ax	5.84	5.0
H-4eq = H-6eq	7.00	7.26
H-4ax = H-6ax	7.01	7.14
H-5eq	7.84	7.90
H-5ax	8.05	8.09
$4ax, 4eq = 6ax, 6eq$	See text	-13.9 †
$4ax, 5ax = 6ax, 5ax$	10.2	12.4
$4ax, 5eq = 6ax, 5eq$	1.3	2.3
$4eq, 5ax = 6eq, 5ax$	4.9	2.9
$4eq, 5eq = 6eq, 5eq$	6.0	4.4
$5ax, 5eq$	-14.5	-14.2 †

† In Table 1, ref. 12, these geminal couplings have been transposed; from the spectrum reproduced in Figure 4 it is clear that $|J_{5ax, 5eq}|$ is 14.2 Hz.

present work, $J_{4ax, 4eq}$ could be changed greatly (e.g. to -61 Hz) without affecting the appearance of the theoretical spectrum, and $J_{4eq, 5ax}$ could not be reduced below 4.3 Hz without sensibly affecting the appearance.

It is interesting to compare the coupling constants (Table 3), especially since in each case agreement between theoretical and experimental spectrum is good. Although for the bidithianyl $J_{4ax, 5ax}$ is nearer the value expected (9.9–12.0 Hz) from other rigid 1,3-dithians,^{13–15} $J_{4eq, 5eq}$ is a little high (3.5–4.1 Hz expected). Although values for $J_{4ax, 5ax}$ and $J_{4eq, 5ax}$ suggest a flatter ring¹⁶ for the bidithianyl than for the 2-phenyldithian, the values for $J_{4ax, 5eq}$ and $J_{4eq, 5eq}$ suggest the opposite.

EXPERIMENTAL

^1H N.m.r. spectra were obtained at ambient temperature with Perkin-Elmer R10 (60 MHz) and Varian HA100 (100 MHz) instruments, and with the spectrometer (220 MHz) operated by I.C.I. Limited on contract to the S.R.C. *trans*-2,3-Dichloro-1,4-dioxan¹⁷ had m.p. 30–31°. Where indicated by an asterisk, further spectral data are available in Supplementary Publication No. SUP 21599 (9 pp.), which also contains Figures 1 and 2.†

trans-SS'-(1,4-Dioxan-2,3-diyl)dithiuronium Dichloride (I).—Thiourea (15.2 g) was dissolved in propan-1-ol (30 ml) under reflux with stirring. The dichlorodioxan (15.7 g) was added in portions, the exothermic reaction being allowed to subside between additions. The solid was filtered off, and washed with acetone to give the dichloride (I) (12.0 g), m.p. 168–169° (decomp.) (from methanol-acetone); dipi-

† For details of Supplementary Publications, see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

¹² H. R. Buys, *Rec. Trav. chim.*, 1970, **89**, 1244.

¹³ E. L. Eliel and R. O. Hutchins, *J. Amer. Chem. Soc.*, 1969, **91**, 2703.

¹⁴ R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 1965, 335.

¹⁵ J. Gelan and M. Anteunis, *Bull. Soc. chim. belges*, 1968, **77**, 423.

crate, m.p. 184–188° (decomp.) (from aqueous methanol). Satisfactory elemental analyses were not obtained. The dichloride had ν_{max} * (Nujol) 1 645s, 1 665s, 2 740sh, 3 250s, and 3350sh cm^{-1} , τ (60 MHz; D_2O) 3.77 (2 H), τ (CD_3)₂SO 3.48 (2 H) and 0.39br (8 H), τ ($\text{CF}_3\text{-CO}_2\text{H}$) 3.88 (2 H), 2.18 (4 H), and 1.85 (4 H) (see also Table 1), m/e *.

The dichloride reacted with benzoyl chloride in ethanolic potassium hydroxide to give *N*-benzoylthiourea.

The dichloride (10.0 g) was dissolved in glacial acetic acid (11 ml) and water (30 ml) and cooled in ice to $<5^\circ\text{C}$. With continuous stirring a similarly cooled solution of sodium nitrite (10.0 g) in water (20 ml) was added. The mixture was allowed to attain room temperature and after 2 h filtration yielded the nitroso-salt (II) (4.3 g), m.p. 117–119° (explodes) (Found: C, 24.3; H, 3.4; N, 27.7. $\text{C}_{12}\text{H}_{20}\text{N}_{12}\text{O}_8\text{S}_4$ requires C, 24.5; H, 3.4; N, 28.6%), ν_{max} * (Nujol) 1 270, 1 326m, 1 650, 1 670s, 2 780sh, and 3 410s cm^{-1} ; it was not possible to recrystallise this compound. An explosion occurred when it was treated with concentrated hydrochloric acid.

With aqueous picric acid, by use of the nitroso-salt (II) directly or after its decomposition with glacial acetic acid or dimethyl sulphoxide, was obtained the dipicrate of SS'-(1,4-dioxan-2,3-diyl)di-isothiurea, m.p. 184–188° (decomp.) (from methanol).

Derivatives of SS'-Ethylene-di-isothiurea.—The dihydrobromide¹⁸ had m.p. 252–253° (lit.,¹⁸ m.p. 236–237°, and reference to other m.p.s), and gave a dipicrate,¹⁹ m.p. 274–276° (decomp.) [lit.,¹⁹ 267° (decomp.)], τ * (60 MHz).

The dihydrobromide (5.0 g) in water (20 ml) with concentrated hydrochloric acid (3.2 g) was cooled to $<5^\circ\text{C}$. After addition dropwise with stirring of similarly cooled sodium nitrite (2.16 g) in water (15 ml) the mixture was set aside for 24 h. The solid that separated was ethylene dithiocyanate, m.p. and mixed m.p. 90°, identical (i.r. absorption) with authentic material.

The dihydrobromide (10.0 g) in water (60 ml) with glacial acetic acid (9.0 g) was cooled to $<5^\circ\text{C}$. After addition dropwise with stirring of sodium nitrite (9.0 g) in water (20 ml), the nitroso-salt (III) (3.6 g) separated; m.p. 138° (explodes) (Found: C, 20.4; H, 3.6; N, 35.6; S, 27.1. $\text{C}_8\text{H}_{16}\text{N}_{12}\text{O}_4\text{S}_8$ requires C, 20.3; H, 3.4; N, 35.6; S, 27.1%), ν_{max} * (Nujol). Decomposition of this salt with aqueous hydrochloric acid or by warming with glacial acetic acid gave ethylene dithiocyanate (identified by mixed m.p. and i.r. absorption) as the water-insoluble product, and the filtrate gave with picric acid the dipicrate (identified by m.p. and i.r. absorption) of SS'-ethylene-di-isothiurea. After decomposition of the salt in dimethyl sulphoxide the clear solution was divided: one part on addition of picric acid gave the foregoing dipicrate; the other after evaporation left a residue, the water-insoluble portion of which contained ethylene dithiocyanate (identified by i.r. absorption and 70 eV electron impact mass spectrum) [Found: M^+ 144, $M : (M + 1) : (M + 2)$ 100 : 7.0 : 9.1. Calc. for $\text{C}_4\text{H}_4\text{N}_2\text{S}_2$: $M : (M + 1) : (M + 2)$ 100 : 6.74 : 8.95].

Derivatives of SS'-Trimethylene-di-isothiurea.—The dihydrobromide¹⁹ had m.p. 202° and gave a dipicrate of m.p.

¹⁶ H. R. Buys, *Rec. Trav. chim.*, 1970, **89**, 1253.

¹⁷ R. K. Summerbell and H. E. Lunk, *J. Amer. Chem. Soc.*, 1957, **79**, 4802.

¹⁸ C. H. Grogan, L. M. Rice, and M. X. Sullivan, *J. Org. Chem.*, 1953, **18**, 728.

¹⁹ M. Jurečk and M. Večeřa, *Coll. Czech. Chem. Comm.*, 1951, **16**, 95.

228—229° (decomp.). The behaviour of the dihydrobromide paralleled that of the ethylene compound. The nitroso-salt (IV) had m.p. 98° (explodes), ν_{\max}^* (Nujol). The trimethylene dithiocyanate obtained from it had b.p. 135—140° at 0.1 mmHg, and i.r. absorption identical with that of an authentic sample; the dipicrate obtained from it was identical (m.p. and i.r. absorption) with the foregoing dipicrate of m.p. 228—229° (decomp.).

Derivatives of N-Methyltoluene-p-sulphonamide.—The sulphonamide (5.0 g) and the dichlorodioxan (2.1 g) were dissolved in dry diethyl ether (50 ml). After 3 months the solid was collected and recrystallised from acetone to give trans-2,3-bis-(N-methyl-p-tolylsulphonylamino)-1,4-dioxan (1.0 g), m.p. 228°, ν_{\max}^* (Nujol), τ^* (60 MHz; CDCl₃), m/e^* 454 (*M*). The filtrate after a further 5 months had deposited bis-1-(N-methyl-p-tolylsulphonamino)ethyl peroxide (2.5

g), m.p. 169° (Found: C, 52.8; H, 6.2; N, 6.1. C₂₀H₂₈N₂O₆S₂ requires C, 52.6; H, 6.1; N, 6.1%); ν_{\max}^* (Nujol), τ^* (60 MHz; CDCl₃), m/e^* .

Diethyl and Dimethyl (-)-Hexahydro-1,4-dioxino[2,3-b]-[1,4]dioxin-2,3-dicarboxylate.—These⁸ (VII) had m.p. 93 and 73°, respectively.

Bi-1,3-dithian-2-yl.—Prepared³ from the dichlorodioxan, this (X) had m.p. 140° and i.r. absorption identical with that reported; ²⁰ for 60 MHz ¹H n.m.r. spectrum see ref. 20.

We thank the S.R.C. for a studentship (to R. E. A.) and the staff of the ATLAS Computer Laboratory for help.

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²⁰ D. R. Williams, D. L. Coffen, P. E. Garrett, and R. N. Schwartz, *J. Chem. Soc. (B)*, 1968, 1132.