Derivatives of $NPCl_2(NSOCl)_2$ and $(NPCl_2)_2NSOCl$. Part 17.[1] The Dimethylaminolysis Pattern of *cis*-$NPCl_2(NSOCl)_2$ †

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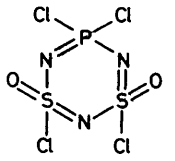
The sequence of chlorine substitution of *cis*-$NPCl_2(NSOCl)_2$ by dimethylamine in acetonitrile is S(1)–Cl, P–Cl, S(2)–Cl, P–Cl. The stereoselectivity of the consecutive steps shows similarities with that of the dimethylaminolysis of $(NPCl_2)_3$, but differs from it by the profound influence of the oxygen ligands, particularly if they are in mutual *cis* position. The relative weakness of the sulphur–chlorine bond(s) does not only result in an unusual mechanism of the first substitution step, but also in substantial isomerization phenomena as long as such bonds are present in the molecule. The isomerizations contribute considerably to the formation ratio of the products, particularly in reactions with an excess of amine. Isomerizations of selected derivatives can be induced by dimethylamine hydrochloride as well as catalytic amounts of antimony(v) chloride.

Recently we described the preparation [2] and structure elucidation [2,3] of dimethylamino-derivatives of the inorganic ring system *cis*-$NPCl_2(NSOCl)_2$ (1). The knowledge of the structure of nearly all these derivatives enables a detailed investigation of the substitution pattern, not only with respect to the regiospecificity of the consecutive steps, but also with respect to their stereoselectivity. Baalmann *et al.*[4] have already described reactions of (1) with piperidine, and have shown that, using acetonitrile as a solvent, the order of chlorine substitution is S(1)–Cl, P–Cl, S(2)–Cl, P–Cl; however, as no general method for the determination of the structures of the piperidino-derivatives was available, the stereoselectivity of the substitution steps could not be investigated in detail.

Whereas the first substitution step has already been discussed in a former report,[2] this paper primarily deals with the determination of the subsequent substitution pattern, while, in particular, isomerization phenomena will be treated in some detail.

Results and Discussion

Isomerization Phenomena.—It has been reported that, in dimethylamino-derivatives of $(NPCl_2)_3$ with phosphorus–chlorine bonds labilized by the electron release of four amino-substituents, a relatively fast *cis–trans* isomerization occurs by interaction with dimethylamine hydrochloride.[6] For this isomerization a mechanism was proposed in which the



(1)

ionization of a chlorine atom is the initiating step. In view of the previously observed weakness of the S–Cl bond(s) in (1) (which is one of the reasons for its unexpected substitution behaviour with secondary amines in acetonitrile),[2,4] similar isomerization phenomena of (1) and its derivatives should be taken into consideration. In order to clarify this, a number of isomerization experiments was carried out, using some pure derivatives, *viz.* (1), *cis*-$NPCl_2(NSOCl)(NSONMe_2)$ (2), (1α,3α,5β)-$NPCl(NMe_2)(NSOCl)(NSONMe_2)$ (4), and *cis*-$NP(NMe_2)_2(NSONMe_2)_2$ (10). Isomerization conditions and results of the most important experiments are summarized in Table 1. The ratio of the products was determined by means of ^1H n.m.r. spectroscopy; in none of the cases should the observed ratio be considered as the equilibrium ratio. The

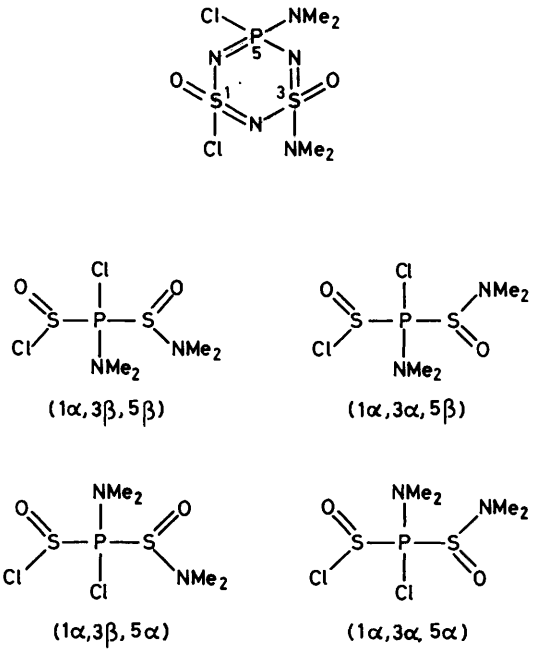


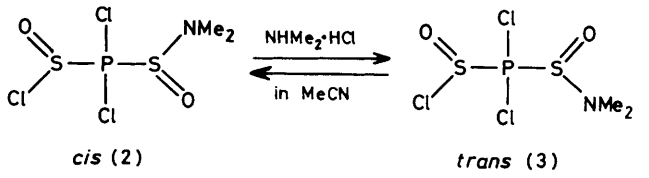
Figure. Representation and stereochemical nomenclature of the four isomers of 1,5-dichloro-3,5-bis(dimethylamino)-1λ⁶,3λ⁶,2,4,6,5λ⁵-dithiatriazaphosphorine-1,3-dioxide. In the schematic representations nitrogen atoms are omitted for the sake of clarity

† 1,3,5,5-Tetrachloro-1λ⁶,3λ⁶,2,4,6,5λ⁵-dithiatriazaphosphorine-1,3-dioxide.

Nomenclature: In order to distinguish stereoisomers, the α and β descriptors, employed in Chemical Abstracts (Index Guide, 1977, Appendix IV) are used for compounds having three 'stereogenic' centres. If only two such centres are present the prefixes '*cis*' and '*trans*' suffice. The order of preference of substituents in this nomenclature is determined using the I.U.P.A.C. sequence rule procedure (Cl > O > NMe_2).[5] An example is given in the Figure.

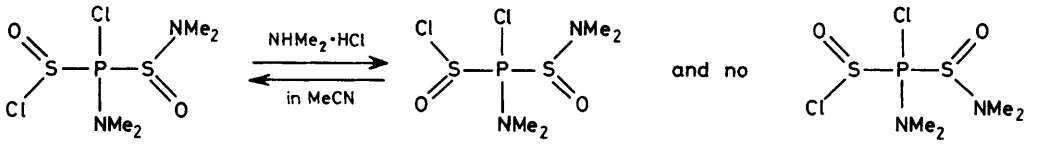
Table 1. Isomerization experiments with derivatives of *cis*-$NPCl_2(NSOCl)_2$ in acetonitrile

Reaction number	Starting material	Reagent(s)	Ratio	θ_c/°C	t/h	Products
(i)	(1)	None		80	20	85% (1) + sticky material
(ii)	(1)	$NHMe_2$·HCl	1 : 10	20	160	40% (1) + sticky material
(iii)	(2)	None		80	20	100% (2)
(iv)	(2)	$NHMe_2$·HCl	1 : 1	20	20	92% (2) + 8% (3)
(v)	(2)	$NHMe_2$·HCl	1 : 1	20	160	80% (2) + 20% (3)
(vi)	(4)	$NHMe_2$·HCl	1 : 10	20	20	75% (4) + 25% (6)
(vii)	(10)	$NHMe_2$·HCl	1 : 10	20	20	100% (10)
(viii)	(10)	$NHMe_2$	1 : 10	20	20	100% (10)
(ix)	(10)	$NHMe_2$·HCl + $NHMe_2$	1 : 10 : 10	20	160	100% (10)



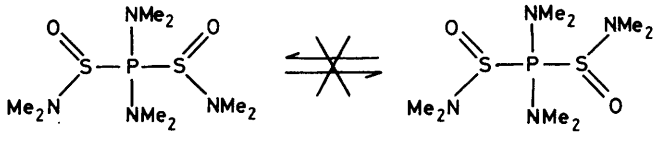
cis (2) *trans* (3)

Scheme 1.



(1α, 3α, 5β) (4) (1α, 3β, 5α) (6) (1α, 3β, 5β)

Scheme 2.



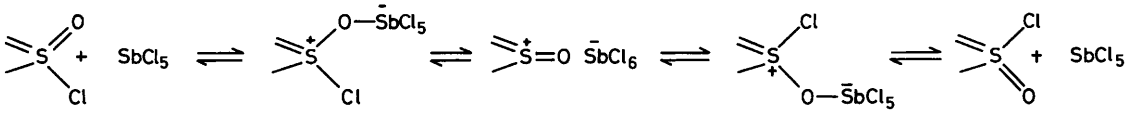
cis (10) *trans* (11)

Scheme 3.

sticky material obtained in the reactions (i) and (ii) is insoluble in diethyl ether and probably polymeric; the *trans* isomer of (1) was not found. The monosubstituted compound (2) shows a clear isomerization tendency (Scheme 1) under relatively mild conditions. Interestingly, the disubstituted compound (4), the (1α,3α,5β) isomer, is readily converted into the (1α,3β,5α) isomer (6), and not into the (1α,3β,5β) isomer (Scheme 2). This observation is the incontestable proof that the isomerization is indeed caused by inversion of the SOCl centre, and not by inversion of the $SONMe_2$ centre. The experiments with the fully substituted derivative (10) (Scheme 3) also show that a $SONMe_2$ centre is not inverted by interaction with the hydrochloride or with free amine, or by the combined action of salt and amine.

The facile loss of a chloride ion from the systems containing an NSOCl unit prompted us to carry out some experiments with antimony(v) chloride, $SbCl_5$, in order to examine whether the chloride elimination can also be accomplished by this chloride abstractor. Reactions of (2) and (4) with equimolar quantities of $SbCl_5$ in dichloromethane as well as in tetrachloromethane invariably lead to a vigorous degradation of the ring system within seconds. However, if (2) or (4) is allowed to react with $SbCl_5$ in tetrachloromethane in a 20 : 1 molar ratio (n.m.r. tube) at room temperature, the establishment of an equilibrium of the original compound (2) or (4) and its isomer (3) or (6) respectively can be observed within 5 min. The isomer ratios, as determined from the ^1H n.m.r. integration, are (2) : (3) = 85 : 15 and (4) : (6) = 80 : 20. This isomerization phenomenon can well be accounted for by assuming a salt-like intermediate, formed after a chloride abstraction from the ring. This abstraction is probably preceded by adduct formation, also encountered in reactions of $SbCl_5$ with sulphonyl halides [7] (see Scheme 4).

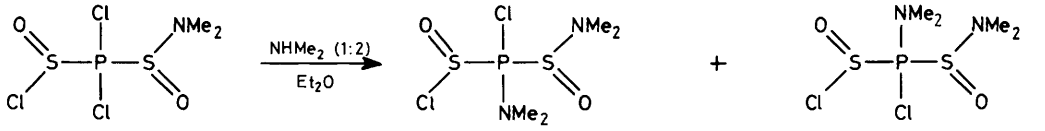
Second Substitution Step.—Reactions of *cis*-$NPCl_2(NSOCl)_2$ with dimethylamine in a 1 : 4 molar ratio lead to complex mixtures of mono-, bis-, and tris-(dimethylamino)-derivatives. A more convenient way of preparation of disubstituted compounds was found in 1 : 2 reactions of the monosubstituted derivatives (2) and (3) [in mixtures with (2)]. In Table 2 some



Scheme 4.

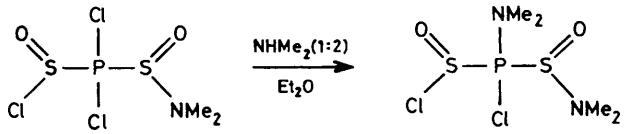
Table 2. Reactions leading to disubstituted compounds (θ_c = 20 °C, t = 17h)

Reaction number	Starting material	Reagent(s)	Ratio	Solvent	Products	Ratio
(x)	(2)	$NHMe_2$	1 : 2	Et_2O	(4), (5)	75 : 25
(xi)	(2) + (3) (1 : 1)	$NHMe_2$	1 : 2	Et_2O	(4), (5), (6)	35 : 15 : 50
(xii)	(2)	$NHMe_2$	1 : 2	MeCN	(4), (5), (6)	65 : 20 : 15
(xiii)	(2)	$NHMe_2$ + $NHMe_2$·HCl	1 : 2 : 10	MeCN	(4), (5), (6)	55 : 20 : 25



cis (2) (1α, 3α, 5β) (4) (1α, 3α, 5α) (5)

Scheme 5.



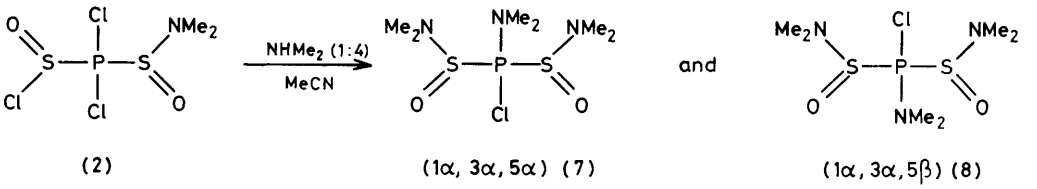
trans (3) (1α,3β,5α) (6)

Scheme 6.

reaction conditions and results are summarized. Reaction (x) is represented in Scheme 5; no isomerization phenomena are observed. The predominant formation of the (1α,3α,5β) isomer (4) is in accordance with the results of most aminolysis studies at $(NPCl_2)_3$: going from the monosubstituted derivative $N_3P_3Cl_5(NRR')$ to the disubstituted one [in diethyl ether or tetrahydrofuran (thf)] the *trans* isomer is formed predominantly (with methyl- and dimethyl-amine, and piperidine). Observations like these have prompted previous investigators to postulate a '*cis* effect'[8] as well as a 'substituent-solvating effect'[9] in order to explain the '*trans*-preference.' Both theories can explain equally well the preponderance of the (1α,3α,5β) isomer in the product of reaction (x) (Table 2). However, neither is able to explain the much stronger stereoselectivity of the second substitution step of *trans*-$NPCl_2(NSOCl)(NSONMe_2)$ (3), which according to the results of reactions (x) and (xi) affords exclusively compound (6) (Scheme 6). In (3) the oxygen ligands are in mutual *cis* position and therefore its behaviour in substitution reactions will in principle resemble that of (1). It has been pointed out previously that the latter compound reacts in diethyl ether with a number of amines to give predominantly the (1α,3α,5α) isomer of $NPCl(NRR')(NSOCl)_2$, in which the amino-group NRR' is positioned *cis* with respect to the oxygen ligands.[10,11] It is to be expected that also (3) preferentially reacts to give the (disubstituted) isomer in which the phosphorus-bonded group is positioned *cis* with respect to the oxygen ligands. In this particular case the '*trans*-preference' principle co-operates with this 'steric directive effect,' resulting in a preponderance of (6) over the (1α,3β,5β) isomer in such a way that the latter cannot be detected. In acetonitrile [reaction (xii), Table 2] a phosphorus-bonded chlorine ligand is substituted as well. According to the results of the *X*-ray structure determination of (2),[3] the formation of a transition state with five-co-ordinated phosphorus is no longer hampered by steric repulsions as in (1) itself.[12] Hence, the most reactive centre (in the absence of such repulsions),[13] the PCl_2 centre, is now attacked. Apart from the (1α,3α,5β) and (1α,3α,5α) isomers (4) and (5) a significant amount of the (1α,3β,5α) isomer (6) is present in the product mixture. Its quantity is enhanced, at the expense of (4), by the addition of dimethylamine hydrochloride to the reaction mixture [reaction (xiii)]. Undoubtedly, (6) is formed *via* an isomerization, either of (2) or of (4). The reactions in acetonitrile represent examples of the influence of amine hydrochloride on the composition of the product mixture.

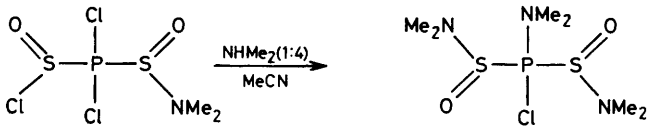
Third Step.—The exact course of the third substitution step is obscured seriously by the complexity of the mixtures, obtained after 1 : 6 molar ratio reactions with (1). Again, it was necessary to start from the monosubstituted derivatives (2) and (3) (1 : 4 molar ratio reactions). It appears that the reaction of (2) with dimethylamine in acetonitrile (in diethyl ether the reaction mainly stops at the disubstituted stage) affords a mixture, containing the trisubstituted derivatives (7)—(9) and considerable amounts of di- and tetra-substituted compounds. A rough estimation of the ratio of formation from the very complex ^1H n.m.r. spectrum [in the ^{31}P n.m.r. spectrum the signals of (7) and (9) coincide] affords (7) : (8) : (9) = 3 : 3 : 1, covering about 75% of the total amount of material (Scheme 7). If a 1 : 1 mixture of (2) and (3) is used as the starting material, the (1α,3β,5α) isomer (9) is the preponderant trisubstituted product (about 50% yield) (Scheme 8). The ratio of the numerous other compounds cannot even be estimated roughly. It appears that the third substitution step takes place at the second sulphur centre. The data suggest that the reaction proceeds mainly or exclusively according to an inversion mechanism. The presence of (9) in the product mixture or (2) can be explained conveniently by assuming a partial isomerization of (2) [or of the intermediate products (4) or (5)].

Fourth Step.—The effect of isomerization phenomena on the composition of the products is demonstrated in the clearest way by the results of substitution reactions in acetonitrile using an excess of dimethylamine, and starting from (1) as well as from (2). In addition, small-scale experiments were carried out with two trisubstituted isomers. The results are summarized in Table 3. Reactions (xvii) and (xviii) once again show that compounds without NSOCl centre(s) do not isomerize. This means that in the reactions (xiv)—(xvi) the



(2) (1α, 3α, 5α) (7) (1α, 3α, 5β) (8)

Scheme 7.



(3) (1α, 3β, 5α) (9)

Scheme 8.

Table 3. Reactions with excess of dimethylamine in acetonitrile [a]

Reaction number	Starting material	Ratio	t/h	Products	Ratio
(xiv)	(1)	1 : 13.6	20	(10) + (11) [b]	25 : 75
(xv) [c]	(1)	1 : 13.6	20	(10) + (11) [b]	10 : 90
(xvi)	(2)	1 : 10	20	(10) + (11) [b]	60 : 40
(xvii)	(8)	1 : 10	20	(10) (+8)	
(xviii)	(9)	1 : 10	140	(11)	

[a] θ_c = 20 °C. [b] Traces of (7) also present. [c] Ring solution added to amine solution.

ratio (10) : (11) already is fixed after the third substitution step. Assuming an inversion mechanism for the third substitution step, reaction (xvi) should lead to the *cis*-tetrasubstituted isomer (10). The observed product ratio indicates that 40% of the material isomerizes at one of the intermediate stages. In reactions (xiv) and (xv), where part of the compound (11) formed can be accounted for by the S_N1 type mechanism of the first step, the same effect is observed to an even larger degree. Particularly, in the case where a large excess of amine is present continuously [reaction (xv)], the isomerization phenomenon governs the formation ratio of the isomers to such an extent that, under these circumstances, this ratio seems to be almost thermodynamically controlled.

Experimental

Aminolysis Reactions.—The details of the preparation and identification of most of the compounds have been described recently.[2] In addition, the following compounds have been prepared and/or purified.

(1α,3β,5α)-$NPCl(NMe_2)(NSONMe_2)_2$ (9). To a stirred solution (−30 °C) of a 1 : 1 (^{1}H n.m.r.) mixture of *cis*- and *trans*-$NPCl_2(NSOCl)(NSONMe_2)$ (6.45 mmol) in acetonitrile (40 cm^3) was added in 0.5 h a 1.0 mol dm^{-3} solution (25.8 cm^3) of dimethylamine in acetonitrile. Stirring was continued at room temperature for 17 h. Extraction of the evaporated mixture with diethyl ether and cooling of the extract to −25 °C afforded crystals which were recrystallized twice from diethyl ether. Yield 18% of (9), m.p. 77.5—79.5 °C (Found: C, 21.45; H, 5.35; Cl, 10.6; N, 24.95; S, 19.15. $C_6H_{18}ClN_6O_2PS_2$ requires C, 21.4; H, 5.40; Cl, 10.5; N, 25.0; S, 19.0%). N.m.r.: (^{1}H, δ, $CDCl_3$) $PNMe_2$, 2.79 (1, d, 16.7 Hz); $SNMe_2$, 2.84 (1, d, 0.5 Hz), 2.79 (1, d, 0.7 Hz); (^{31}P, 85% H_3PO_4, $CDCl_3$) 28.4 (s).

trans-$NP(NMe_2)_2(NSONMe_2)_2$ (11). Compound (11) was purified from the reaction mixture of reaction (xv) (Table 3) by means of h.p.l.c. (25-cm Polygosil 60-D-10 CN column, diameter 10 mm) using diethyl ether–n-hexane (80 : 20) as eluant, and maintaining a flow rate of 3.6 cm^3 min^{-1}. The oily *trans* isomer is the component with the lowest retention time (Found: C, 27.5; H, 7.00; N, 27.95; S, 18.25. $C_8H_{24}N_7O_2PS_2$ requires C, 27.8; H, 7.00; N, 28.4; S, 18.6%). The *cis* isomer (10) could not be freed from traces of (7).

Isomerizations.—With dimethylamine hydrochloride. The ring compound (0.1 mmol) was stirred with the hydrochloride in dry acetonitrile (3 cm^3). After the desired reaction time the mixture was evaporated and extracted with diethyl ether. The ether was driven off *in vacuo* and the residue subjected to ^{1}H n.m.r. measurements (in $CDCl_3$). The ratio of isomers was determined from the integration data of the spectra.

With antimony(v) *chloride.* The ring compound (0.15 mmol) was dissolved in tetrachloromethane (0.5 cm^3) in a 5-mm n.m.r. tube. After the addition of three drops (50 mg) of a solution of $SbCl_5$ (0.15 mmol) in CCl_4 (1.0 g) an ^{1}H n.m.r. spectrum was taken immediately. The spectra did not change significantly within 24 h.

The results of the experiments are given in the text.

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