Ring Contraction of 7-Chloro-3-phenyl-2*H*-1,2,4-benzothiadiazine

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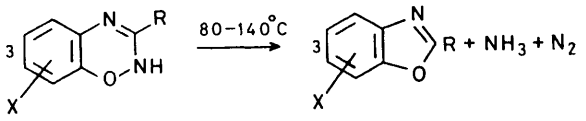
7-Chloro-3-phenyl-2*H*-1,2,4-benzothiadiazine (2) undergoes ring contraction to 6-chloro-2-phenylbenzothiazole (3) when it is heated in inert solvents above 180°. The reaction is markedly promoted by tervalent phosphorus compounds and in the presence of triphenylphosphine or triethyl phosphite, the ring contraction occurs even at room temperature. Photochemical ring contraction has also been observed. The benzothiadiazine (2) can act as a chlorinating agent at high temperatures: this remarkable property is ascribed to its reaction through the tautomeric structure (5a).

We have recently found that 1,2,4-benzoxadiazines (1) undergo ring contraction when they are heated in inert solvents at 80 °C or higher, the products being the corresponding benzoxazoles, ammonia, and nitrogen (Scheme 1).[1] The reaction formally involves the extrusion of a fragment NH from the benzoxadiazines, and no close analogies for such a process appear to exist. A mechanism has been suggested in which the first step is the cleavage of the N–O bond, and, on this basis, other related heterocyclic compounds with heteroatoms at positions 1 and 2 might be expected to show similar thermal instability.



(1)

SCHEME 1

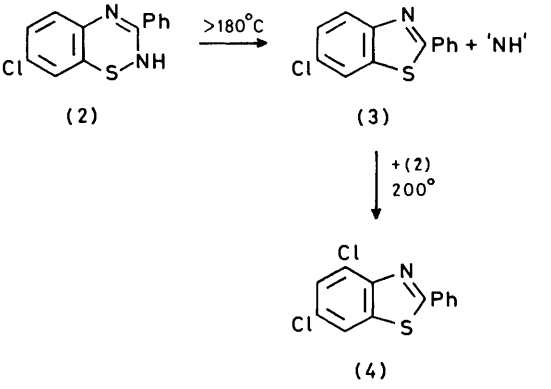
One such compound is 7-chloro-3-phenyl-2*H*-1,2,4-benzothiadiazine (2), which has been prepared by Kresze and his co-workers from *N*-(4-chlorophenyl)-benzamidine.[2]

We find that this compound also undergoes thermal ring contraction, but at much higher temperatures (180—215 °C) than the benzoxadiazines. The ring contraction takes place much more readily in the presence of tervalent phosphorus compounds, however. These and related reactions of the benzothiadiazine (2) are reported in this paper.

The benzothiadiazine (2) was recovered after prolonged heating in solution of dimethylformamide or chlorobenzene. When a solution of the benzothiadiazine was heated in 1,2-dichlorobenzene at 180 °C for 8 h, 6-chloro-2-phenylbenzothiazole (3) was isolated (10%) together with starting material (20%). Higher yields of the benzothiazole (3) were obtained by the use of *N*-methylpyrrolidone as solvent, but at temperatures above 180 °C a second ring contraction product was isolated. This was identified as 4,6-dichloro-2-phenylbenzothiazole (4) from its analytical data and spectra. The formation of the dichlorobenzothiazole was suppressed when the pyrolysis was conducted in 1,4-dimethoxybenzene, and 6-chloro-2-phenylbenzothiazole (3) was isolated in 68% yield. 1,4-Dimethoxybenzene would be expected to react preferentially with any chlorine cations generated in the reaction mixture, and thus prevents the formation of dichlorobenzothiazole.

The results of the solution pyrolyses of the benzothiadiazine (2) are summarized in the Table.

These results indicate that the benzothiadiazine (2) undergoes a thermal ring contraction (Scheme 2) which is analogous to that observed with 1,2,4-benzoxadiazines, but that much higher temperatures are required. The increased strength of the heteroatom–heteroatom bond at positions 1 and 2 is probably the reason for the higher activation energy. The unexpected feature of the reaction is that the benzothiadiazine (2) is able to act as a chlorinating agent at high temperatures, so that 4,6-dichloro-2-phenylbenzothiazole is formed in appreciable quantities. When equimolar amounts of 7-chloro-3-phenyl-1,2,4-benzothiadiazine (2) and 6-chloro-



(2) (3) (4)

SCHEME 2

Pyrolysis of 7-chloro-3-phenyl-2*H*-1,2,4-benzothiadiazine

Solvent	Temp. (°C)	Time (h)	Products (%) (2)	(3)	(4) *
Dimethylformamide	152	30	100		
1,2-Dichlorobenzene	178	8	20	10	
N-Methylpyrrolidone	180	30		56	3
N-Methylpyrrolidone	202	16		21	43
Tetralin	208	14		30	20
1,4-Dimethoxybenzene	213	16		68	
Triethyl phosphate	215	16		28	18

* Yields of (4) are calculated on the assumption that two moles of starting material are required per mole of product.

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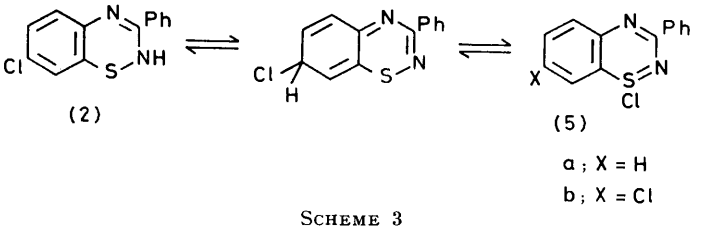
2-phenylbenzothiazole (3) were heated at 200 °C in *N*-methylpyrrolidone, a mixture of 6-chloro- and 4,6-dichloro-2-phenylbenzothiazoles was obtained, indicating that chlorination could occur after ring contraction.



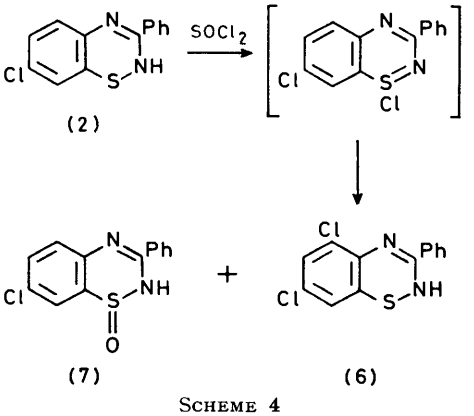
SCHEME 3

A possible explanation for the behaviour of the benzothiadiazine (2) as a chlorinating agent at high temperatures could be its rearrangement to the cyclic sulphinimidoyl chloride (5a) (Scheme 3), the latter could then act as a source of chlorine cations. Compounds of this type, *e.g.* (5b), have previously been isolated from the reaction of *N*-arylamidines with sulphur dichloride.[3] Indeed, we found that when the benzothiadiazine (2) was treated with thionyl chloride at room temperature, a mixture of 5,7-dichloro-3-phenyl-1,2,4-benzothiadiazine (6) and 7-chloro-3-phenyl-2*H*-1,2,4-benzothiadiazine 1-oxide (7) was obtained after chromatography. The products (6) and (7) are those to be expected from rearrangement and hydrolysis of (5b) (Scheme 4). On the other hand, we were unable to detect other products which might be expected from the action of the sulphinimidoyl chloride (5a) as the chlorinating agent; for example, no 2-phenylbenzothiazole or 3-phenyl-1,2,4-benzothiadiazine were found in the pyrolysis mixtures. The mechanism of chlorine transfer therefore remains a tentative one.

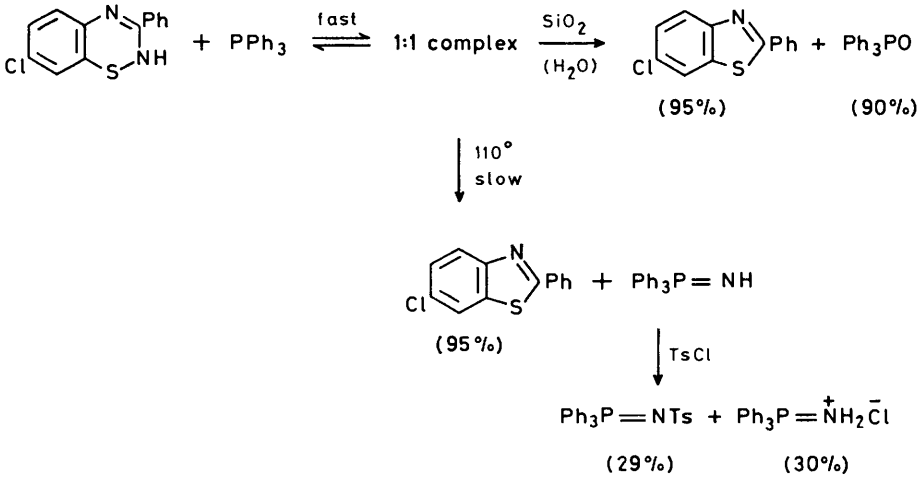
The dichlorobenzothiadiazine (6), which was made available by the chlorination shown in Scheme 4, also underwent ring contraction when heated in *N*-methylpyrrolidone, giving 4,6-dichloro-2-phenylbenzothiazole (4) in 66% yield. Both the benzothiadiazines (2) and (6) were also found to undergo the same ring contraction when they were irradiated in tetrahydrofuran, the corresponding benzothiazoles (3) and (4) being isolated in moderate yields.

The effect of tervalent phosphorus compounds on the thermal ring contraction proved to be a very marked one. Initially, triphenylphosphine was added in order to intercept the fragment NH which is lost from the benzothiadiazines, but it soon became apparent that the phosphine was participating at an early stage in the reaction. Equimolar quantities of the benzothiadiazine (2) and triphenylphosphine were dissolved in benzene at room temperature, and the solution was left for 6 h; an analysis of the mixture by t.l.c. on silica showed that both components had been consumed, and column chromatography on silica gave 6-chloro-2-phenylbenzothiazole (3) and triphenylphosphine oxide in high yields. Remarkably, it was found that if toluene-*p*-sulphonyl chloride were added to the reaction mixture before chromatography (the objective being to intercept any triphenylphosphine imide), the benzothiazole (3) was isolated in only 40—50% yield, and 50—60% of the starting benzothiadiazine could now be recovered. Thus, it appears that triphenylphosphine reacts with the benzothiadiazine (2) rapidly and reversibly at room temperature; the adduct is irreversibly converted into 6-chloro-2-phenylbenzothiazole and triphenylphosphine oxide by silica, but if triphenylphosphine is removed from the system before chromatography by complexation with toluene-*p*-sulphonyl chloride, the benzothiadiazine (2) can be recovered. Further evidence for the rapid complexation was obtained by passing a solution of triphenylphosphine down a column of silica on which the benzothiadiazine (2) was adsorbed; the yellow colour of the benzothiadiazine was discharged instantly on contact with the triphenylphosphine, and 6-chloro-2-phenylbenzothiazole (3) was isolated in high yield after elution from the column. The complex formed between triphenylphosphine and 7-chloro-2-phenylbenzothiadiazine is also slowly and irreversibly destroyed by heat: the components were heated under reflux in toluene for 12 h, toluene-*p*-sulphonyl chloride was added, and the mixture was heated for a further 1 h. No starting material was now recovered, the products being 6-chloro-2-phenylbenzothiazole (95%), triphenylphosphine imide hydrochloride (30%), triphenylphosphine *N*-*p*-tolylsulphonylimide (29%), and triphenylphosphine oxide (9%). The results of these experiments are summarized in Scheme 5. The same type of ring contraction is observed when 5,7-dichloro-3-phenylbenzothiadiazine (6) is heated with triphenylphosphine in toluene: 4,6-dichloro-2-phenylbenzothiazole (4) (97%) and triphenylphosphine oxide (89%) were isolated by column chromatography of the mixture on silica.

The 1 : 1 complex which is formed between the phosphine and the benzothiadiazine in these reactions must be capable of being transformed either into starting materials or into products under very mild conditions. We believe that the initial reaction probably occurs at the sulphur atom of the benzothiadiazines, partly because the thermal reactions of the 1,2,4-benzoxadiazines (1) were unaffected by the presence of triphenylphosphine. A possible mechanism for the reaction is shown in Scheme 6.



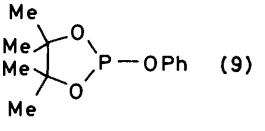
SCHEME 4



SCHEME 5

Recently, it has been reported that acyclic sulphenamides are cleaved by reaction with triphenylphosphine; a mechanism involving nucleophilic attack of the phosphine on sulphur, analogous to that shown in Scheme 6, is proposed for these reactions.[4]

In an attempt to detect an intermediate in the reaction, by increasing the potential lifetime of a phosphorane intermediate such as (8), phosphites were used in place of triphenylphosphine. Triethyl phosphite and the cyclic phosphite 4,4,5,5-tetramethyl-2-phenoxy-1,3,2-dioxaphospholan (9)[5] were used, both in equi-



(9)

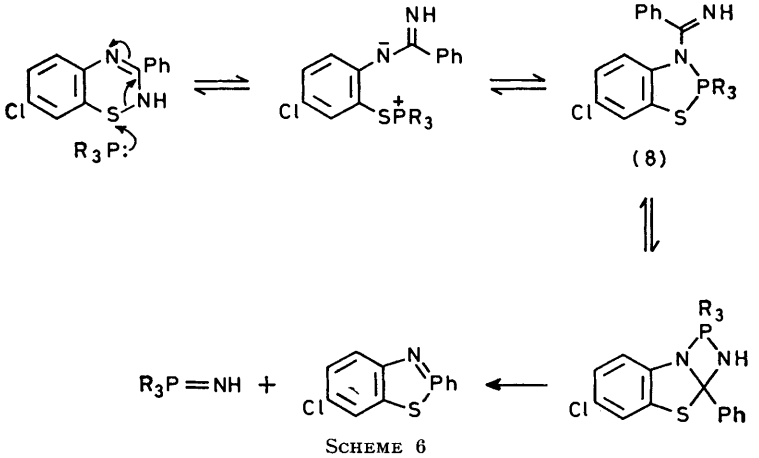
molar quantities. The cyclic phosphite (9) in particular might be expected to form a reasonably stable phosphorane. The only result was, however, that the phosphites proved to be even better than triphenylphosphine at promoting ring contraction. Triethyl phosphite completely converted the benzothiadiazine (2) into benzothiazole (3) within 14 h at room temperature, and with the phosphite (9) the reaction was complete within 2 h. No intermediates could be detected spectroscopically.

In summary, the thermal ring contraction of the benzothiadiazines represents a second example of the formal NH extrusion reaction first observed with benzoxadiazines, and extends the scope of the reaction. The phosphine-catalysed process, although it leads to the same product as the thermal contraction, is probably limited to sulphur-containing heterocycles and involves a different mechanism to that of the thermal process.

EXPERIMENTAL

7-Chloro-3-phenyl-2H-1,2,4-benzothiadiazine (2).—The compound was prepared according to the procedure previously described [2] and had m.p. 164—165 °C (decomp.) [lit.,[2] 166.5 °C (decomp.)]; δ(220 MHz; $CDCl_3$) 6.35 (1 H, d, *J* 8 Hz, H-6), 6.70 (1 H, H-8), 6.89br (1 H, H-5), 7.40—7.50 (3 H, m), and 7.58—7.68 (2 H, m).

Solution Pyrolysis of the Benzothiadiazine (2).—Pyrolyses were performed on 300 mg (1.15 mmol) specimens of the benzothiadiazine in 5 cm^3 solvent, for the times specified in the Table. 6-Chloro-2-phenylbenzothiazole (3) was identified by comparison with a specimen synthesised by a standard route,[6] and had m.p. 157° (from ethanol) (lit.,[6] 157—157.5°). *4,6-Dichloro-2-phenylbenzothiazole* (4) had m.p. 151° (from cyclohexane) (Found: C, 55.7; H, 2.5;



SCHEME 6

N, 4.75; S, 11.6. $C_{13}H_7Cl_2NS$ requires C, 55.7; H, 2.5; N, 5.0; S, 11.4%); δ(220 MHz; $CDCl_3$) 7.49—7.53 (3 H, m), 7.93 (1 H), 8.02—8.08, (2 H, m), and 8.12 (1 H).

5,7-Dichloro-3-phenyl-2H-1,2,4-benzothiadiazine (6).—7-Chloro-3-phenyl-2*H*-1,2,4-benzothiadiazine (2) (261 mg, 1 mmol) was stirred with thionyl chloride (5 cm³) at room temperature for 24 h. The excess of thionyl chloride was removed and the solid residue was shaken with 10% aqueous sodium hydroxide (30 cm³) and chloroform (30 cm³). The organic solution was dried and evaporated and the residue was subjected to column chromatography (silica; 70 g). Elution with cyclohexane–butyl acetate (9 : 1) gave *5,7-dichloro-3-phenyl-2H-1,2,4-benzothiadiazine* (6) (160 mg, 54%), m.p. 170—171 °C (decomp.) (from ethanol) (Found: C, 52.9; H, 2.75; N, 9.3; S, 11.0. $C_{13}H_8Cl_2N_2S$ requires C, 52.9; H, 2.7; N, 9.5; S, 10.85%); δ(220 MHz; $CDCl_3$) 6.52 (1 H), 6.72 (1 H), 7.38—7.48 (3 H, m), and 7.55—7.62 (2 H, m). Starting material (2) (60 mg, 23%) was also recovered from the column. Acidification of the basic aqueous layer gave 7-chloro-1-oxo-3-phenyl-2*H*-1,2,4-benzothiadiazine (7) (70 mg, 23%), m.p. 235—237 °C (decomp.) (from methanol) (lit.,[2] 237—237.5 °C).

Pyrolysis of the Benzothiadiazine (6).—The benzothiadiazine (6) (100 mg, 0.34 mmol) was dissolved in *N*-methylpyrrolidone (5 cm³) and the solution was heated at 180 °C for 30 h. The solvent was removed by distillation and the residue was purified by column chromatography (silica–chloroform) to give 4,6-dichloro-2-phenylbenzothiazole (62 mg, 66%), m.p. 151° (from cyclohexane).

Photolysis of the Benzothiadiazines.—(a) The benzothiadiazine (2) (261 mg, 1 mmol) in dry, degassed tetrahydrofuran (120 cm³) was irradiated in a Rayonet reactor (Pyrex filter) for 6 h. The solid residue obtained by removal of the solvent was subjected to column chromatography (silica–chloroform). This gave 6-chloro-2-phenylbenzothiazole (80 mg, 33%).

(b) The benzothiadiazine (6) (295 mg, 1 mmol) gave, by the same procedure as described in (a), 4,6-dichloro-2-phenylbenzothiazole (100 mg, 35%).

Reaction of the Benzothiadiazine (2) *with Triphenylphosphine.*—(a) A solution of the benzothiadiazine (2) (260 mg, 1 mmol) and triphenylphosphine (262 mg, 1 mmol) in benzene (120 ml) was kept at 20° for 6 h. The solvent was evaporated to leave a solid residue which, by column chromatography on silica in chloroform, gave 6-chloro-2-phenylbenzothiazole (230 mg, 94%) and triphenylphosphine oxide (260 mg, 95%).

(b) The benzothiadiazine (2) (75 mg, 0.28 mmol) and triphenylphosphine (75 mg, 0.28 mmol) in benzene (30 ml) were left at 20° for 16 h. When the mixture was examined by t.l.c. using silica plates, no starting material (2) could be detected. Toluene-*p*-sulphonyl chloride (80 mg, 0.42 mmol) was added. After a further 1 h, the mixture was subjected to layer chromatography (silica) which gave the benzothiadiazine (2) (40 mg, 55% recovery), 6-chloro-2-phenylbenzothiazole (30 mg, 44%), triphenylphosphine oxide (25 mg), and triphenyl-*p*-tolylsulphonylphosphonium chloride (70 mg).

(c) The benzothiadiazine (100 mg, 0.38 mmol) and triphenylphosphine (100 mg, 0.38 mmol) were dissolved in toluene (10 ml) and the solution was heated under reflux for 12 h. Toluene-*p*-sulphonyl chloride (72 mg, 0.38 mmol) was added and the solution was heated for a further 1 h. The solution was then cooled; a precipitate was filtered off and was identified as the hydrochloride of triphenylphosphine imide (35 mg, 30%), m.p. 232 °C (lit.,[7] 236 °C). The filtrate was evaporated to dryness and the residue was subjected to column chromatography (silica–chloroform). This gave toluene-*p*-sulphonyl chloride (45 mg, 60% recovery), 6-chloro-3-phenylbenzothiazole (90 mg, 95%), triphenylphosphine oxide (10 mg, 9%), and triphenylphosphine *N*-*p*-tolylsulphonylimide (48 mg, 29%), m.p. 192 °C (lit.,[7] 193 °C), identical with an authentic specimen.

(d) The benzothiadiazine (40 mg, 0.15 mmol) was applied to a silica column in chloroform. After the yellow benzothiadiazine had started to move down the column, a solution of triphenylphosphine (40 mg, 0.15 mmol) in chloroform was put on the top of the column. The faster moving triphenylphosphine discharged the colour of the benzothiadiazine as the two components came together on the column. 6-Chloro-2-phenylbenzothiazole (36 mg, 95%) and triphenylphosphine oxide (38 mg, 90%) were eluted.

Benzothiadiazine (2) *and Triethyl Phosphite.*—The benzothiadiazine (2) (100 mg, 0.38 mmol) and triethyl phosphite (63 mg, 0.38 mmol) in chloroform (5 cm³) were left at 20° for 14 h. The solvent was removed and the residue was crystallised from ethanol to give 6-chloro-2-phenylbenzothiazole (90 mg, 95%).

Benzothiadiazine (2) *and 4,4,5,5-Tetramethyl-2-phenoxy-1,3,2-dioxaphospholan* (9).—The benzothiadiazine (2) (100 mg, 0.38 mmol) and the dioxaphospholan (9) [5] (90 mg, 0.38 mmol) in dry benzene (30 cm³) were left at 20° for 2 h. The solvent was removed and the residue was washed with a little ice-cold acetone, leaving 6-chloro-2-phenylbenzothiazole (87 mg, 92%).

Benzothiadiazine (6) *and Triphenylphosphine.*—A solution of the benzothiadiazine (6) (100 mg, 0.34 mmol) and triphenylphosphine (89 mg, 0.34 mmol) in toluene (10 cm³) was heated under reflux for 12 h. 4,6-Dichloro-2-phenylbenzothiazole (92 mg, 97%) and triphenylphosphine oxide (84 mg, 89%) were isolated by column chromatography (silica–chloroform).

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