Polyhalogenonitrobenzenes and Derived Compounds. Part 3.[1] Reactions of 1,2,3,4-Tetrachloro-5,6-dinitrobenzene with Bidentate Nucleophiles

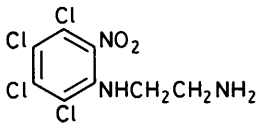
Alan Heaton,* Mark G. Hill, and Michael H. Hunt
Chemistry and Biochemistry Department, Liverpool Polytechnic, Byrom Street, Liverpool L3 3AF
Frederick G. Drakesmith
Electricity Council Research Centre, Capenhurst, Chester CH1 6ES

1,2,3,4-Tetrachloro-5,6-dinitrobenzene (TCDNB) has been treated with a number of bidentate nucleophiles, all of which contained at least one amino or methylamino group. Diamines of the type $H_2N(CH_2)_nNHR$ (R = H or Me, n = 2, 3, or 5), reacted *via* the primary amino group displacing a nitro group from TCDNB. The resulting products were inert to further reaction, *i.e.* cyclisation or further nucleophilic substitution. Both 2-hydroxyethylamine and ethyl glycinate behaved similarly, although ethyl diazoacetate was a by-product in the latter reaction.

The reaction of TCDNB with hydrazine hydrate was very sensitive to the conditions employed, *i.e.* rapid addition of excess of reagent (2.2:1 molar ratio) gave 3,4,5,6-tetrachloro-*o*-phenylenediamine (reduction had occured). Slow addition of an equimolar amount yielded 2,3,4,5-tetrachloro-6-nitrophenylhydrazine, *i.e.* nucleophilic substitution. *N,N'*-Dimethylethylenediamine and 2-hydroxy-*N*-methylethylamine reacted with TCDNB to give cyclised products, *i.e.* both nucleophilic centres reacted. The course of these reactions was investigated. In contrast 2-acetoxyethylamine, glycine, urea, 2,2'-iminodiethanol and butane-1,1,4,4-tetra-amine were all unreactive towards TCDNB.

Following our earlier studies on the reactions of 1,2,3,4-tetrachloro-5,6-dinitrobenzene (TCDNB) with primary and secondary aliphatic[1,2] amines we now report the results of reactions of TCDNB with bidentate nucleophiles. In all cases at least one of the nucleophilic centres was an amino or methylamino group.

When a bidentate nucleophile, such as ethylenediamine, reacts with TCDNB there are three broad categories of results possible. The first is a straight forward replacement of either a nitro group or a chlorine atom by one of the nucleophile's reactive centres. Our earlier results would suggest that primary amino groups will replace a nitro group whereas secondary amino groups will prefer to replace a chlorine atom adjacent to the nitro group, *i.e.* products like (**1**) and (**2**) respectively will be formed.

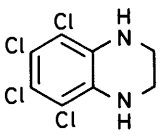


(**1**)

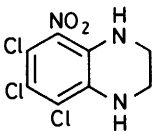
(**2**)

If, however, both nucleophilic centres react, then after initial attack as just described under (*i*) the second attack can take place either (*ii*) intramolecularly leading to a chlorinated benzheterocycle such as (**3**), (**4**), or (**5**), or (*iii*) intermolecularly giving a bridged product such as (**6**).

It is interesting to note that Qvist has reported[3] that 2,3,5,6-tetrachloro-1,4-dinitrobenzene reacted with hydrazine, ethylenediamine, and *p*-phenylenediamine, to give, in each case, a monosubstituted product in which a nitro group had been displaced. Preferential displacement of the nitro group was also found in the reaction of 1,2-dichloro-4,5-dinitrobenzene with the amino group of 2-hydroxyethylamine.[4] With hydrazine the same substrate yielded 5,6-dichlorobenzotriazol-1-ol. Newbold[5] and Haszeldine[6] showed that pentachloronitrobenzene and pentafluoronitrobenzene also reacted with hydrazine to yield the corresponding tetrahalogenobenzotriazol-1-ol.



(**3**)



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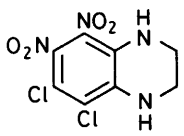
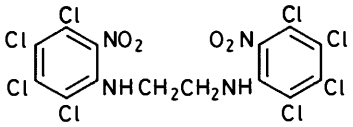


(**5**)



(**6**)

Suschitzky[7] obtained similar results with pentachloronitrobenzene but he also reported in addition that a small amount of pentachlorophenylhydrazine was isolated. In contrast, the reaction of 2,4-dinitrochloro (and fluoro) benzene with a variety of diamines resulted in the halogen atom being replaced.[8] However, since in these cases the nitro groups are *meta* to each other, the carbons to which they are attached will not be so activated towards nucleophilic attack as when they are *ortho* or *para*, which they were in the examples discussed earlier in which nitro group displacement therefore occurred in preference to halogen displacement.

Our results for the reaction of TCDNB with a variety of bidentate nucleophiles, each of which contained at least one amino or methylamino substituent, are summarised in Table 1. The first point to note is that in no case was a product of type (**6**) detected *i.e.* the one in which the second nucleophilic centre attacks a second molecule of TCDNB. Secondly, diamines, fitting the general formula $H_2N(CH_2)_nNHR$ (n = 2, 3, or 5; R = H or Me) attack TCDNB *via* the primary amino group to displace one of the nitro groups to give products of type (**1**). This is consistent with our earlier findings for simple primary amines, and the same explanation, based on stereoelectronic effects plus hydrogen bonding between the amine and nitro group of TCDNB,[2] may be cited here. Another similarity is the lack of

Table 1. Reaction of TCDNB with bidentate nucleophiles in toluene or under phase transfer conditions[a] (in brackets)

Nucleophile	Conditions	Products (% yield)
$N_2H_4 \cdot H_2O$	(i) Rapid addition; 1 h reflux	3,4,5,6-Tetrachlorophenylene-1,2-diamine (33)
	(ii) Slow addition (15 min); 2 h reflux	2,3,4,5-Tetrachloro-6-nitrophenylhydrazine (58)
$H_2NCH_2CH_2NH_2$	3 h reflux	1,2,3,4-Tetrachloro-5-(2,2-diaminoethyl)-6-nitrobenzene (66)
$H_2NCH_2CH_2NHMe$	1 h reflux	5-(2-Aminoethyl-*N*-methylamino)-1,2,3,4-tetrachloro-6-nitrobenzene (72)
$MeNHCH_2CH_2NHMe$	(i) 1 h reflux	5,6,7-Trichloro-1,4-dimethyl-8-nitrotetrahydroquinoxaline (55)
	(ii) 24 h, room temp.	5,6,7-Trichloro-1,4-dimethyl-8-nitrotetrahydroquinoxaline (52)
$H_2N(CH_2)_3NH_2$	1.5 h reflux	*N*-(3-Aminopropyl)-2,3,4,5-tetrachloro-6-nitroaniline (67)
$H_2N(CH_2)_5NH_2$	1.5 h reflux	*N*-(5-Aminopentyl)-2,3,4,5-tetrachloro-6-nitroaniline (59)
$H_2NCH_2CH_2OH$	3 h reflux	1,2,3,4-Tetrachloro-5-(2-hydroxyethylamino)-6-nitrobenzene (63)
$MeNHCH_2CH_2OH$	1 h reflux	5,6,7-Trichloro-4-methyl-8-nitrotetrahydro-1,4-benzoxazine[b] (52)
$MeNHCH_2CH_2OH$ (excess)	1 h room temp.	Dichlorobis(2-hydroxy-*N*-methylamino)-dinitrobenzene[c] (52)
$AcNHCH_2CH_2OH$	3 h reflux	Unchanged TCDNB
$H_2NCH_2CO_2H$	3 h reflux in ethanol	Unchanged TCDNB
	3 h reflux in presence of $NaHCO_3$	Unchanged TCDNB
H_2NCH_2COEt	1 h reflux	*N*-(Ethylacetoxy)-2,3,4,5-tetrachloro-6-nitroaniline (83)
		Ethyl diazoacetate (17)
H_2NCONH_2	(i) 165 h reflux in EtOH	2,3,4,5-Tetrachloro-6-nitrophenylamine (7)
	(ii) 96 h reflux in MeCN	2,3,4,5-Tetrachloro-6-nitrophenylamine (5)
	(iii) 2 h room temperature in presence of NaH; DMF solvent	4 Products, none separated and identifed.
	(iv) 1 h reflux	Unchanged TCDNB
	(v) 18 h reflux; 18-crown-6 as phase transfer catalyst	Unchanged TCDNB

[a] In toluene–water in presence of Aliquat 336. [b] Minor products not isolated. [c] Precise structure not determined but believed to be 2,3-dichloro-1,4-bis(2-hydroxy-*N*-methylethylamino)-5,6-dinitrobenzene.

reactivity once one of the nitro groups of TCDNB has been replaced. Thus even reaction of products of type (**1**) with sodium metal to generate an anion at the NH_2 group did not bring about cyclisation.

The reaction of TCDNB with hydrazine hydrate proved to be very sensitive to the conditions employed. Firstly, when an excess of hydrazine hydrate (2.2:1 molar ratio) was added to TCDNB in ethanol and the mixture heated under reflux on a steam-bath, a precipitate began to form after 5 min. The reaction was allowed to continue for 1 h. After work-up, in addition to unchanged TCDNB, 3,4,5,6-tetrachloro-*o*-phenylenediamine was isolated. Here the hydrazine had acted as a reducing agent. In contrast, when equimolar amounts were used and the hydrazine hydrate added slowly over 15 min to a stirred solution of TCDNB in ethanol, the solution turned red. The solution was then heated under reflux for 2 h. From this mixture 2,3,4,5-tetrachloro-6-nitrophenylhydrazine was isolated and characterised by its formation of derivatives with benzaldehyde, acetophenone, and benzophenone. Clearly under these conditions hydrazine is reacting as a nucleophile. We did not, in either of these reactions, isolate any 4,5,6,7-tetrachlorobenzotriazol-1-ol which Newbold reported [5] was the product of the reaction between pentachloronitrobenzene and hydrazine hydrate.

Several bidentate nucleophiles having a primary amino group as one centre and an oxygen containing substituent as the second were also studied. The reactivity here was, predictably, variable. Where reaction did occur it was usually by the NH_2 group displacing a nitro group from TCDNB. Both 2-hydroxyethylamine and ethyl glycinate reacted in this way. Interestingly, in the latter case ethyl diazoacetate was also isolated as a by-product. This compound can be prepared by the diazotisation of ethyl glycinate.[9] Its formation in the TCDNB reaction can be explained by reaction of a second molecule of ethyl glycinate with the NO_2^- which has been displaced. Since the reaction is occuring at a temperature of 110 °C its formation and stability are quite surprising—especially since temperatures > 35 °C are normally avoided in its preparation because of the explosive nature of the compound! We have previously reported [10] similar behaviour in the reactions of primary aromatic amines with TCDNB. Attempts to get 1,2,3,4-tetrachloro-5-(2-hydroxyethylamino)-6-nitrobenzene to cyclise were unsuccessful (*cf.* diamines discussed earlier).

In contrast, 2-acetoxyethylamine, glycine, urea, 2,2′-iminodiethanol, and butane-1,1,4,4-tetra-amine all proved very unreactive towards TCDNB. Even the use of phase-transfer conditions with Aliquat 336, or 18-crown-6 failed to improve reactivity. The only sign of reaction was when TCDNB and urea were heated together in ethanol, under reflux, for 165 h. A small amount (*ca.* 10%) of 2,3,4,5-tetrachloro-6-nitrophenylamine

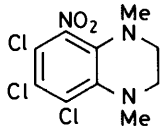
Table 2. Products obtained from the reaction of TCDNB with bidentate nucleophiles

Nucleophile	Structure type	M.p. (°C)	Lit. m.p. (°C)	Found (%) C	H	Cl	N	Required (%) C	H	Cl	N
Hydrazine hydrate (i)	*a*	233—235	233—234								
(ii)	(**1**)	176—178		Benzaldehyde deriv., m.p. 239—40 °C; benzophenone deriv., 154.5—6 °C.							
$H_2NCH_2CH_2NH_2$	(**1**)	110—111		30.15	2.55	44.75	13.3	30.12	2.21	44.46	13.17
$H_2NCH_2CH_2NHMe$	(**1**)	112—114		32.6	2.7	43.85	12.45	32.43	2.70	42.64	12.61
$MeNHCH_2CH_2NHMe$	(**3**)	115—116		39.0	3.5	33.75	13.65	38.67	3.25	34.25	13.53
$H_2N(CH_2)_3NH_2$	(**1**)	77—79									
$H_2N(CH_2)_5NH_2$	(**1**)	169—170									
$H_2NCH_2CH_2OH$	(1)	105—107									
$MeNHCH_2CH_2OH$	(**8**)	106—107		36.45	2.35	36.05	9.45	36.33	2.37	35.75	9.42
$MeNHCH_2CH_2OH$ (excess)	(**5**)	74—76		38.5	4.45	18.55	13.7	37.60	4.18	18.54	14.62
$AcNHCH_2CH_2OH$	Unchanged TCDNB recovered										
$H_2NCH_2CO_2H$	Unchanged TCDNB recovered										
$H_2NCH_2CO_2Et$	(**1**)	89—90									
H_2NCONH_2 (i)	*b*	163—165		26.2	0.95	51.0	10.15	26.12	0.74	51.39	10.15
(ii)	Same product as above										
(iii)	4 Products detected but none isolated										
(iv)	Unchanged TCDNB recovered										
(v)	Unchanged TCDNB recovered										

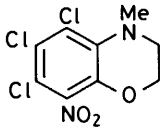
[a] Product was 3,4,5,6-tetrachlorophenylene-1,2-diamine. [b] Product was 2,3,4,5-tetrachloro-6-nitroaniline.

Note: All compounds had the expected M^+ ions and isotopic ratios.

was formed alongside a larger amount of unchanged TCDNB. This was presumably formed either by the urea acting as a reducing agent or by urea acting as a nucleophile to displace a nitro group from TCDNB, followed by a cleavage process to leave only NH_2 attached to the aromatic ring. With both *N,N'*-dimethylethylenediamine and 2-hydroxy-*N*-methylethylamine, the nucleophilic centres reacted to give cyclised products (**7**) and (**8**) respectively. From our earlier work, and earlier discussion

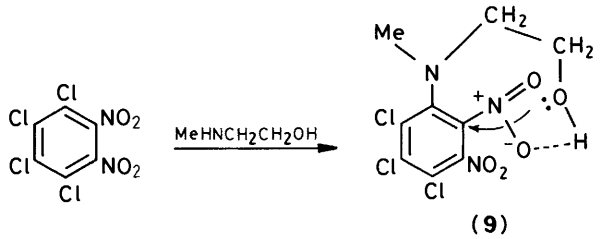


(**7**)



(**8**)

regarding the lack of reactivity once one nitro group has been displaced in TCDNB, the methylamino group will displace a chlorine atom adjacent to a nitro group. Nucleophilic displacement of the adjacent nitro group by either the second NHMe or OH groups will then complete the cyclisation. Intramolecular hydrogen bonding between these groups and the nitro group will aid this. Attempts were made to collect evidence in support of the above pathway both by following the reaction by t.l.c. and attempting to isolate the intermediate (**9**). Different



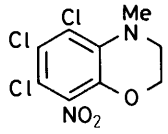
(**9**)

Scheme.

results were obtained for the two nucleophiles. With *N,N'*-dimethylethylenediamine the reaction was carried out under milder conditions (ambient temperature) with samples initially analysed by t.l.c. every hour. Only TCDNB and the cyclised product (**7**) were ever detected. Therefore the second (cyclisation) step must be very rapid.

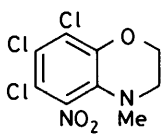
With 2-hydroxy-*N*-methylethylamine periodic t.l.c. analysis showed formation of an initial product followed later by a second product (**8**). As the reaction progressed the amount of the first product diminished whilst that of the second product increased. In an attempt to isolate the first product the reaction was quenched after 15 min and purification by column chromatography yielded a red oil which proved difficult to purify further. However, its i.r. and n.m.r. spectra were consistent with the intermediate (**9**) *i.e.* bands at 2 950 and 2 890 cm^{-1} (saturated C–H str) 1 560 and 1 340 cm^{-1} (C–NO_2 str) and a broad band centred at 3 480 cm^{-1} (O–H str); δ_H 2.30 (s, OH), 2.85 (s, NCH_3), 3.15 (t, OCH_2), and 3.65 (t, NCH_2).

An isomeric product (**8a**) is possible from this reaction *via* Smiles rearrangement of intermediate (**9**) (with interchange of the oxygen and nitrogen) and completion of the cyclisation by displacement of the adjacent nitro group by the NHMe group. However, we strongly favour structure (**8**) from our previous

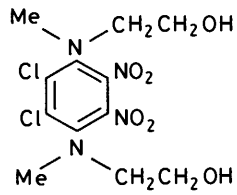


(**8**)

work with monodentate amines. An alternative second step is for (**9**) to react with a second molecule of the nucleophile to give (**10**), by analogy with our earlier work.[2] When the reaction was carried out using an excess of nucleophile, but at ambient temperature, a product believed to be (**10**) was indeed isolated.



(**8a**)



(**10**)

Experimental

Mass spectra were recorded on either an AEI MS9 or a V.G. Micromass 16B instrument. N.m.r. spectra were recorded on a Perkin-Elmer RS32 instrument at 90 MHz in deuteriochloroform with TMS as internal standard. The following description is typical of the method used.

Reaction with Ethylenediamine.—Ethylenediamine (0.92 g) was added to a solution of TCDNB (2.00 g) in toluene (50 cm^3). The solution was then heated under reflux for 3 h. After cooling the solution was washed with water, dried ($MgSO_4$), and filtered. Removal of the solvent under reduced pressure gave an orange solid. This was recrystallised from methanol to give the orange 1,2,3,4-tetrachloro-5-(2,2-diaminoethyl)-6-nitrobenzene (1.4 g, 64%), m.p. 110—111 °C *m/z* 323 (M^+ for ^{37}Cl) (Found C, 30.15; H, 2.55; Cl, 44.75; N, 13.3. $C_8H_7Cl_4N_3O_2$ requires C, 30.12; H, 2.21; Cl, 44.46; N, 13.17%).

Prior purification by column chromatography (silica gel 35—70 mesh) was necessary in some cases.

Acknowledgements

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