Polyhalogenonitrobenzenes and Derived Compounds. Part 1. Reactions of 1,2,3,4-Tetrachloro-5,6-dinitrobenzene with Amines

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The relationship between amine structure and the nature of the products obtained in their reaction with 1,2,3,4-tetrachloro-5,6-dinitrobenzene has been investigated. Primary amines react by displacing a nitro group whereas acyclic secondary amines, in general, reacted by replacing a chlorine atom from a position *ortho* to a nitro group. The reactivity of cyclic secondary amines, *e.g.* piperidine was more variable. These results have been rationalised in terms of steric and electronic effects.

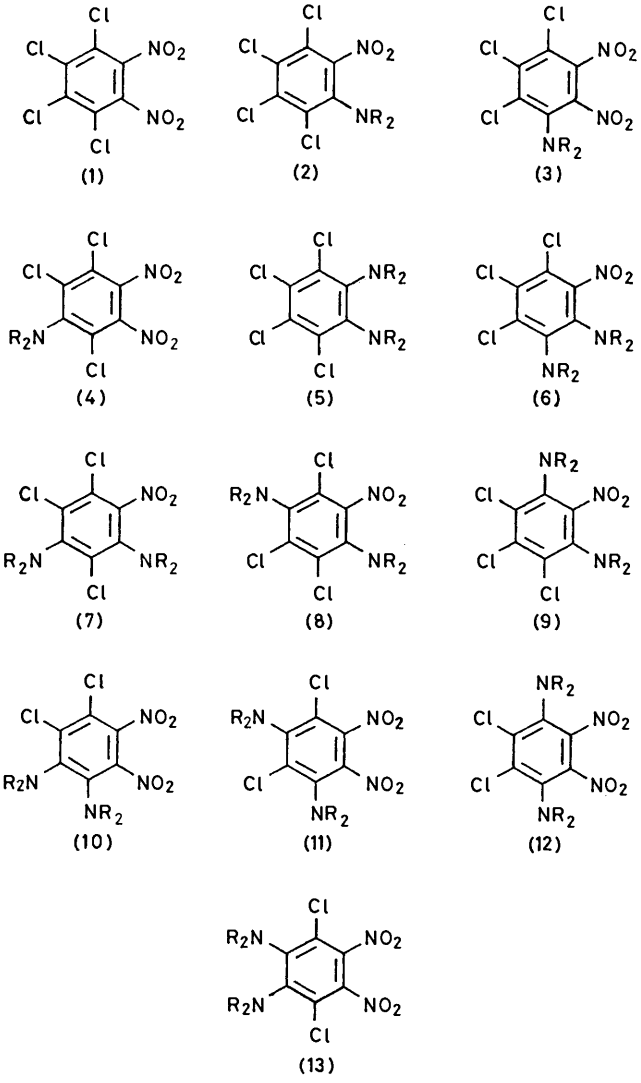
POLYHALOGENOBENZENES containing nitro groups are of interest because nucleophiles can react with them to displace either halogen, nitro, or both groups. The products obtained will depend on the structure of the reacting amine. Qvist has therefore investigated the reactions of 1,4-dichloro-2,3-dinitrobenzene [1] and 1,2-dichloro-4,5-dinitrobenzene [2] with amines. In the first

[1] W. Qvist, *Acta Acad. Aboensis, Math. Phys.*, 1953, **19** (4), 3.

[2] W. Qvist, *Acta Acad. Aboensis, Math. Phys.*, 1953, **19**, (5), 3.

case primary amines replaced a nitro group and secondary amines a chlorine, whereas in the second case both types of amine reacted by replacing a nitro group. However in the latter case use of an excess of amine at a higher temperature gave a disubstituted product in which one chlorine and one nitro group had been displaced.

Qvist has also reported a similar series of reactions with 1,2,4,5-tetrachloro-3,6-dinitrobenzene.[3] Here nitro group displacement occurred exclusively with both types of amine. Newbold *et al.* have described the reactions of 1,2,3,4-tetrachloro-5,6-dinitrobenzene (TCDNB) (1) with a number of primary [4] and cyclic secondary amines.[5] They found that compounds of type (2), *i.e.* arising by



nitro group replacement were obtained using primary amines whereas cyclic secondary amines, such as morpholine and piperidine replaced a chlorine, *i.e.* gave (3) or (4). Which of these two possible structures represented the product was not established. Disubstituted products were not reported and all reactions were carried out in ethanol.

We have carried out a more extensive study of the reactions of TCDNB (1) with amines, including establishing the structure of products arising by chlorine(s) displacement and briefly studying the effect of varying the solvent with a particular amine. An attempt has also been made to rationalise the observed pattern of results in terms of steric and electronic factors.

Reaction of TCDNB with amines can result in the displacement of either chlorine or nitro groups leading to products having structures (2)—(4). If two of the substituents in TCDNB are replaced, then nine different products are possible, *viz.* (5)—(13). The structure of a particular product may be elucidated as follows. Elemental analysis will establish structures (2) and (5) (assuming no rearrangement has occurred), and will also distinguish the group (6)—(9) from (10)—(13). Identifying the structure from within these groups may be accomplished using ^{13}C n.m.r. spectroscopy.

Table 1 summarises the results of the reactions between TCDNB and amines.

Primary amines clearly react by displacement of a nitro group only, *i.e.* give (2) with the sole exception of aniline, which reacts mainly in this way but also gives some product arising from chlorine displacement, *i.e.* (3). Secondary amines, in contrast, generally displace a chlorine atom, *i.e.* give (3), although dimethylamine and piperidine react partly by chlorine and partly by nitro displacement. Pyrrolidine is exceptional in that it behaves like the primary amines by exclusively replacing a nitro group.

Consideration of the electronic effects of the chlorine and nitro groups suggests that TCDNB (1) should be susceptible to nucleophilic attack and that there should be a slight preference for attack at positions 5 and 6, *i.e.* at the carbons bearing the nitro groups. However since the benzene ring carries six bulky substituents steric effects will also clearly play a part in determining the position of attack by a nucleophile.

The preference of primary amines for attacking at C-5 may be explained by this being the most reactive position coupled with the fact that the nucleophile is sufficiently small to prevent steric effects from becoming very significant. In this latter context it should be borne in mind that position 5 is the most sterically hindered since NO_2 groups are much bulkier than Cl atoms. Secondary amines are obviously bulkier than primary amines and the steric factor now predominates. On purely steric grounds attack at position 2 would be expected since this carbon is flanked by two chlorines. However all primary and secondary amines will hydrogen bond to the nitro groups. This places them in a favourable position for attack at C-1 and -6 and in an unfavourable position for attack at C-2. Although positions 1 and 2 will be equally activated by the mesomeric effect of the nitro

[3] W. Qvist, *Acta Acad. Aboensis, Math. Phys.*, 1955, **20** (6), 3.
[4] G. T. Newbold, A. J. Lambie, and M. B. Purdew, B.P. 1,056,862.
[5] G. T. Newbold, A. J. Lambie, and M. B. Purdew, B.P. 1,069,991.

groups, their inductive effect will give greater activation at position 1 than 2. Thus overall position 1 is favoured over 2.

Although the major product from the reaction with aniline fits the pattern of the other primary amines, a minor product arising from chlorine displacement was isolated. Its formation is rather surprising, particularly since the bulkier *o*-anisidine reacts exclusively by nitro group replacement.

Pyrrolidine reacted differently to the other secondary amines and in fact behaved like a primary amine. We ascribe this to the fact that the α-methylene groups, being constrained as part of a five-membered ring system, are held back thus making the molecule smaller than the general pattern for secondary amines. Dimethylamine was considered earlier to be intermediate between primary and most secondary amines and so the formation of a disubstituted product arising by displacement of chlorine and nitro is understandable. We tentatively assign structure (9) to this product on the basis that (a) ^{13}C n.m.r. results on other products show that whenever a chlorine is replaced it is always from a position adjacent to a nitro group and (b) since displacement of a nitro group renders the system unreactive, (9) is presumably formed by chlorine displacement followed by nitro displacement and on electronic grounds the nitro group *meta* to the dimethylamino group should be replaced more readily than the *o*-nitro group. In the reaction with

TABLE 1

Reactions of TCDNB (1) with amines

Amine	Solvent	Reaction conditions	Products [%]
(a) Primary amines			
Ethylamine	T	1 h reflux (or 72 h R.T.)	(2) [76, (64)]
n-Propylamine	T	1 h reflux (or 24 h R.T.)	(2) [83, (82)]
Isopropylamine	T	1 h reflux (or 21 h R.T.)	(2) [74, (88)]
n-Butylamine	T	1 h reflux (or 24 h R.T.)	(2) [78, (78)]
Isobutylamine	T	1 h reflux (or 25 h R.T.)	(2) [65, (60)]
s-Butylamine	T	1 h reflux (or 24 h R.T.)	(2) [68, (76)]
Allylamine	T	1 h reflux	(2) [64]
Cyclohexylamine	T	1 h reflux (or 24 h R.T.)	(2) [73, (64)]
Benzylamine	T	1 h reflux (or 24 h R.T.)	(2) [68, (59)]
Aniline	A	1 h reflux	(2) [17], (3) * [3]
o-Anisidine	A	1 h reflux	(2) [21]
(b) Secondary amines			
(i) Acyclic			
Dimethylamine	T	1.25 h reflux	(2) [41], (3) * [18]
Dimethylamine	T	72 h R.T.	(2) [44], (3) * [7], (9) [1.5]
Diethylamine	A	1 h reflux (or 18 h R.T.)	(3) [22, (33)]
Di-n-propylamine	T	1 h reflux (or 14 h R.T.)	(3) [28, (29)]
Di-n-butylamine	T	1.5 h reflux	(3) [34]
Di-isobutylamine	T	18 h reflux	(3) [44]
Diallylamine	T	22 h reflux	(3) [40]
(ii) Cyclic			
Pyrrolidine	T	1 h reflux (or 18 h R.T.)	(2) [53, (53)]
Piperidine	T	1 h reflux (or 24 h R.T.)	(2) [31, (40)], (9) [0.3, (0.4)], (3) [37 (36)], (12) [1.8 (1.0)]
Morpholine	T	1 h reflux	(3) [1], (12) [4]

T = toluene, A = acetonitrile, R.T. = room temperature.

* Insufficient sample for ^{13}C n.m.r. Structures therefore proposed by analogy with other compounds.

other secondary amines and more like a primary amine. In piperidine, since the ring is larger, the α-methylene groups are only slightly held back and it might therefore be expected to be intermediate in behaviour between pyrrolidine and the other secondary amines. The results agree with this because both (2) and (3) are formed. Dimethylamine also gives these two products and this may again be explained by its intermediate size.

Once a nitro group has been replaced the molecule becomes quite unreactive towards further attack, *e.g.* 1,2,3,4-tetrachloro-5-nitro-6-pyrrolidinobenzene was recovered after heating under reflux, in toluene, with pyrrolidine for 77 h. In contrast disubstituted products were actually formed during the reaction of TCDNB with dimethylamine, piperidine, and morpholine. In the latter case the two chlorines at positions 1 and 4 were replaced, *i.e.* (12) was formed, and this is consistent with piperidine formation of the two disubstituted products (9) and (12) can be similarly explained.

These results are broadly comparable with those of Qvist provided the differing steric effects are taken into account. Reactions of primary amines with TCDNB gave similar results to those reported by Newbold. However our studies on cyclic secondary amines, even in a non-polar solvent such as toluene, show that the reactions are more complex than Newbold reported. His work showed that only a single monosubstitution product was formed by both morpholine and piperidine in ethanol whereas we isolated two products in the first case and four in the second case (using toluene as solvent). In our hands carrying out these reactions in ethanol, albeit on a much smaller scale, gave a complex mixture of at least seven components and these could not be separated by column chromatography. In general we found that

the use of more polar solvents (*e.g.* excess amine, sulpholan, ethanol) led to complex mixtures which were difficult to separate.

Elucidation of the structures of products arising by chlorine displacement has been carried out using ^{13}C n.m.r. Prediction of chemical shifts for the ring carbons in polysubstituted benzenes generally leads to poor agreement with found values. This is due to the non-additivity of substituent effects, which is caused primarily by steric effects. We have shown that this may be overcome, for the compounds described in this paper, by taking hexachlorobenzene (in which a degree of steric

TABLE 2

^{13}C Chemical shifts (p.p.m. relative to Me_4Si)

R_2N	Structure	Found (F), calculated (C), difference (Δ)	Chemical shift C-1	C-2	C-3	C-4	C-5	C-6
Di-n-propylamino	(3)	F	139.5	142.1	142.7	137.6	137.6	122.1
		C	139.5	141.8	140.0	138.3	136.0	122.6
		Δ	0	0.3	2.7	0.7	1.6	0.5
Di-n-butylamino	(3)	F	142.0	142.5	142.5	139.0	137.5	121.9
		C	139.5	141.8	140.0	138.3	136.0	122.6
		Δ	2.5	0.7	2.5	0.7	1.5	0.7
Diallylamino	(3)	F	139.9	142.8	141.6	137.5	137.5	123.2
		C	139.5	141.8	140.0	138.3	136.0	122.6
		Δ	0.4	1.0	1.6	0.8	1.5	0.6
Morpholino	(3)	F	140.3	141.5	141.5	138.1	137.8	122.3
		C	139.9	141.6	138.2	138.1	136.4	123.4
		Δ	0.4	0.1	3.2	0	1.4	1.1
Morpholino	(12)	F	141.3	141.3	138.8	138.3	138.3	138.8
		C	141.1	141.1	136.2	137.6	137.6	136.2
		Δ	0.2	0.2	2.6	0.7	0.7	2.6
Piperidino	(2)	F	148.6	142.2	134.3	135.6	129.9	123.8
		C	149.2	139.1	134.2	135.2	130.0	123.7
		Δ	0.6	3.1	0.1	0.4	0.1	0.1
Piperidino	(3)	F	139.2	142.1	143.4	137.4	137.4	120.3
		C	139.5	141.3	139.9	137.8	136.0	122.1
		Δ	0.3	0.8	3.5	0.4	1.4	1.8
Piperidino	(12)	F	140.8	140.8	138.0	139.7	139.7	138.0
		C	140.4	140.4	136.6	136.9	136.9	136.6
		Δ	0.4	0.4	1.4	2.8	2.8	1.4
Piperidino	(9)	F	150.5	141.4	131.8	134.9	131.8	141.4
		C	150.1	138.2	130.9	134.3	130.9	138.2
		Δ	0.4	3.2	0.9	0.6	0.9	3.2

TABLE 3

Products obtained from the reaction of TCDNB with amines

Amine group(s)	Structure	M.p. (°)	Lit. m.p. (°C)	Found (%) C	H	Cl	N	Formula	Required (%) C	H	Cl	N
Ethylamino	(2)	79—80	78—79 [a]									
n-Propylamino	(2)	91—92.5		34.2	2.7	44.8	8.9	$C_9H_8Cl_4N_2O_2$	34.0	2.5	44.6	8.8
Isopropylamino	(2)	63—63.5		34.1	2.6	45.2	8.6	$C_9H_8Cl_4N_2O_2$	34.0	2.5	44.6	8.8
n-Butylamino	(2)	45—46.5	46—47 [b]									
Isobutylamino	(2)	63—64.5		35.9	3.0	42.8	8.6	$C_{10}H_{10}Cl_4N_2O_2$	36.2	3.0	42.7	8.4
s-Butylamino	(2)	61.5—62		36.2	3.1	42.5	8.5	$C_{10}H_{10}Cl_4N_2O_2$	36.2	3.0	42.7	8.4
Allylamino	(2)	69—70		34.4	2.0	44.85	8.8	$C_9H_6Cl_4N_2O_2$	34.2	1.9	44.9	8.9
Cyclohexylamino	(2)	78—79	67—68 [c]									
Benzylamino	(2)	96—97		43.15	2.3	39.7	8.1	$C_{13}H_8Cl_4N_2O_2$	42.7	2.2	38.7	7.65
Anilino	(2)	142—144		41.0	1.6	40.1	7.8	$C_{12}H_6Cl_4N_2O_2$	41.0	1.7	40.3	8.0
	(3) *	195—197		40.0	1.7		11.6	$C_{12}H_6Cl_3N_3O_4$	39.75	1.7		11.6
o-Anisidino	(2)	136—137		40.6	2.2	37.1	7.2	$C_{13}H_8Cl_4N_2O_3$	40.9	2.1	37.1	7.3
Dimethylamino	(2)	67.5—68		31.5	1.9	46.7	9.2	$C_8H_6Cl_4N_2O_2$	31.6	2.0	46.65	9.2
	(3) *	118—119.5		30.5	1.9	33.5	13.5	$C_8H_6Cl_3N_3O_4$	30.55	1.9	33.8	13.4
	(9) *	121—125		39.0	3.8		13.2	$C_{10}H_{12}Cl_3N_3O_2$	38.4	3.9		13.4
Diethylamino	(3)	54—56		34.9	3.0	31.3	12.1	$C_{10}H_{10}Cl_3N_3O_4$	35.1	2.9	31.0	12.3
Di-n-propylamino	(3)	59.5—60		39.1	3.9	28.5	11.2	$C_{12}H_{14}Cl_3N_3O_4$	38.9	3.8	28.7	11.3
Di-n-butylamino	(3)	33—34		42.6	4.3	26.0	10.45	$C_{14}H_{18}Cl_3N_3O_4$	42.2	4.55	26.7	10.5
Di-isobutylamino	(3)	56—57.5		42.3	4.7	26.8	10.3	$C_{14}H_{18}Cl_3N_3O_4$	42.2	4.55	26.7	10.5
Diallylamino	(3)	83—84		39.6	3.0	28.6	11.5	$C_{12}H_{10}Cl_3N_3O_4$	39.3	2.75	29.0	11.5
Pyrrolidino	(2)	81—82.5		36.3	2.4	42.9	8.3	$C_{10}H_8Cl_4N_2O_2$	36.4	2.4	43.0	8.5
Piperidino	(2)	70.5—71.5	70—71 [c]									
	(9)	105—108		48.55	5.1	29.4	10.6	$C_{16}H_{20}Cl_3N_3O_2$	48.9	5.1	27.1	10.5
	(3)	114.5—115.5	107—109 [d]									
	(12)	218—218.5		47.5	4.9	17.35	17.3	$C_{16}H_{20}Cl_2N_4O_4$	47.7	5.0	17.6	17.6
Morpholino	(3)	122—123	123—124 [d]									
	(12)	259—260		41.2	4.1	17.2	14.0	$C_{14}H_{16}Cl_2N_4O_6$	41.3	4.0	17.4	13.8

* Insufficient sample for ^{13}C n.m.r. Structures therefore assigned by analogy with other compounds.

[a] G. E. Ficken, D. J. Fry, and K. J. Bannert, B.P. 1,132,528. [b] Ref. 4. [c] D. J. Berry, I. Collins, S. M. Roberts, H. Suschitzky, and B. J. Wakefield, *J. Chem. Soc.* (*C*), 1969, 1285. [d] Ref. 5.

interaction already exists) as a standard, rather than benzene. Satisfactory agreement between actual and predicted values was found and this coupled with the number of resonances observed enabled unambiguous structural assignments to be made. Full details of these results have been published elsewhere; [6] Table 2 shows the agreement between calculated and found chemical shift values.

Attempts have been made to support the ^{13}C n.m.r. structural assignments chemically. They have been based on the well established fact that *NN*-dialkyl-*o*-nitroanilines undergo cyclisation with a variety of reagents to form benzimidazole systems.[7] Therefore (3) should undergo this cyclisation whereas (4) should not. Although some reaction clearly occurred when trichlorodinitro-piperidino- or -morpholino-benzene were treated thermally,[7a] or with acetic anhydride–zinc chloride,[7b] no products could be isolated and identified. When iron(II) oxalate [7c] was treated with trichlorodinitropiperidinobenzene a product, believed to be trichloronitropiperidinophenylamine was isolated. The results were therefore inconclusive.

EXPERIMENTAL

Mass spectra were recorded on an AEI MS9 instrument. Molecular ions quoted are for the ^{37}Cl isotope; in each case the expected isotopic pattern and intensity was observed, *e.g.* for three chlorines four peaks each separated by two mass units and in the ratio 27 : 27 : 9 : 1. ^{13}C N.m.r. spectra were recorded on a Varian CFT 20 instrument at 20 MHz, at probe temperature in trichloromethane, with deuterium oxide as an external lock and using the 10 mm probe. I.r. spectra were recorded as potassium bromide discs on a Perkin-Elmer 457 instrument. M.p.s are uncorrected.

Reactions of TCDNB with Amines.—The following description is typical of the method used.

Reaction with Propylamine.—Propylamine (0.425 g) was added to a solution of TCDNB (1.0 g) in toluene (25 cm^3). The resulting yellow solution was heated under reflux conditions for 1 h. After cooling, the mixture was washed with water, dried ($MgSO_4$), and filtered. Removal of the solvent under vacuum gave an orange solid which was purified by column chromatography [silica gel; light petroleum (b.p. 60—80°)] and recrystallised from methanol to give the orange yellow *1,2,3,4-tetrachloro-5-nitro-6-propylaminobenzene* (0.86 g, 83%), m.p. 91—92.5°.

Details of the products obtained are summarised in Table 3.

Reaction between Iron(II) Oxalate and 1,2,3-Trichloro-4,5-dinitro-6-piperidinobenzene.—A mixture of 1,2,3-trichloro-4,5-dinitro-6-piperidinobenzene (1.0 g), iron(II) oxalate (1.014 g), and lead pellets was heated at 260° for 15 min, during which time a vigorous reaction took place with the evolution of thick orange fumes. When cool, the mixture was extracted with dichloromethane. The organic fractions were combined, washed with water, dried ($MgSO_4$), and filtered. Removal of the solvent under vacuum gave an orange solid which was purified by column chromatography [silica; light petroleum (b.p. 60—80°)] to give two fractions. The main fraction, recrystallised from hot methanol, was unchanged 1,2,3-trichloro-4,5-dinitro-6-piperidinobenzene (0.13 g), m.p. 113.5—114°. The other fraction was recrystallised from hot aqueous ethanol to give red needles, believed to be a trichloronitropiperidinophenylamine (0.013 g), m.p. 122—123°, *m/e* 329 (M^+).

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[6] C. A. Heaton, M. H. Hunt, and O. Meth-Cohn, *Org. Magnetic Resonance,* 1977, **10**, 102.

[7] (*a*) R. K. Grantham and O. Meth-Cohn, *J. Chem. Soc.* (*C*), 1969, **70**; (*b*) H. Suschitzky and M. E. Sutton, *Tetrahedron Letters,* 1967, **3933**; (*c*) R. H. Smith and H. Suschitzky, *Tetrahedron,* 1961, **16**, 80.