Tetrahedron Letters No.17, pp. 1657-1662, 1967. Pergamon Press Ltd. Printed in Great Britain.

STUDIES ON THE SYNTHESIS OF NITROPHENOTHIAZINES BY SMILES REARRANGEMENT
BEHAVIOUR OF HALONITROBENZENES WITH o-AMINOTHIOPHENOL

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(Received 7 February 1967)

Nitrophenothiazines have mostly been obtained either by nitration of the respective phenothiazines (1,2,3,4) or by the ring closure of the appropiately substituted diphenylamines(5). As only a few references (6,7) deal with their synthesis by Smiles rearrangement, the behaviour of some halogenonitrobenzenes with o-aminothiophenol has been studied, and at the early stage of this investigation we wish to report some of the interesting findings.

It was noted that the formation of nitrophenothiazines did not take place unless both the positions ortho to the activated halogen atom in halogenonitrobenzenes are substituted either by the two nitro groups or by one nitro and one halogen atom. In the latter case where the reactive halogen atom had a nitro as well as a halogen atom in both of its ortho positions the cyclisation always took place by the elemination of the halogen atom in preference to the nitro group.

Thus 1,4-dichloro-2-nitro—(I), 1-chloro-2,4-dinitro-(II) and 1-chloro-5-methyl-2,4-dinitrobenzene (III) which had only a nitro group ortho to the activated halogen atom provided 2-amino-4'-chloro-2'-nitro—(A),2-amino-2',4'-dinitro—(B) and 2-amino-2',4'-dinitro-5'-methyldiphenylsulphide (C) but no phenothiazine. On the other hand, 2,6-dinitro—(IV), 2,4,6-trinitro—(V) and 4-chloro-2,6-dinitrochlorobenzene (VI) which possessed the two nitro groups ortho to the reactive halogen atom afforded 1-nitro—(D), 1,3-dinitro—(E) and 1-nitro-3-chlorophenothiazine(F) respectively, under the identical experimental conditions mentioned at the end. Since 1,2-dichloro—(VII), 1-chloro-2-bromo—(VIII) and 1-chloro-2-Iodo-4,6-dinitrobenzene (IX) in which the activated halogen atom had a nitro and a halogen atom at its ortho positions furnished 1,3-dinitrophenothiazine (E), identical to that obtained by treating 1-chloro-2,4,6-trinitrobenzene (V)with o-aminothiophenol under the same conditions, supported the fact that cyclisation had involved the replacement of the ortho halogen atom in preference to the ortho nitro group.

Halogenonitrobenzenes which are unsymmetrically substituted and possess two nitro groups, ortho to the activated halogen atom are thus expected to yield two isomeric phenothiazines depending upon the possibility as to which nitro group is involved in the cyclisation. Thus 1-chloro-2,4,6-trinitro-5-methylbenzene(X) under identical conditions furnished two isomeric phenothiazines, though the proportion of one isomer was very large as compared to the other. The reaction product consisting of the two isomeric phenothiazines was extracted with ethanol and the latter on

concentration and cooling provided a product which after recrystallisation from ethylacetate afforded a phenothiazine (15%) which melted at 178-9°. This phenothiazine was found to be identical to that obtained by treating 1-bromo-2-chloro-4,6-dinitro-5-methylbenzene (XI) with o-aminothiophenol, in which both the halogen atoms were involved in cyclisation. Hence this isomer is, obviously, 1,3-dinitro-2-methylphenothiazine (G). The residual ethanol insoluble portion upon recrystallisation with glacial acetic acid afforded the other isomeric phenothiazine (75%) melting at 185-6° which therefore must be 1,3-dinitro-4-methylphenothiazine (H).

Thus it is interesting to note that although in the classical Smiles rearrangement (8) of the diphenylsulphides to diphenylamines, the activation is usually provided by the resonance effect of an ortho or a para nitro group, even then the reaction of halonitrobenzenes like I, II and III with o-aminothiophenol under the conditions referred at the end, did not provide the expected diphenylamines but only the diphenylsulphides i.e. the Smiles rearrangement of the product A, B and C did not occur. On the other hand the increased resonance effects due to the presence of the two nitro groups at both the ortho positions as in halogenonitrobenzenes like IV, V, VI and X,and the combined resonance and inductive mechanisms enforced by the one nitro and one halogen atom as in halonitrobenzenes like VII, VIII, IX and XI activated the Smiles rearrangement as well as the ring closure to such an extent that both the processes were instantaneous and in situ, therefore it was rather difficult to isolate the intermediates

TABLE

S.No.	Halonitro-benzene	Product	Yield %	Refluxing period hrs.	M.P. °C	Mol.Formula	Sulfur %	
							Found	Requires
1.	I	A	65	5	122 (9)	$C_{12}H_9ClN_2O_2S$	11.38	11.40
2.	II	B	85	2	142 (10)	$C_{12}H_9N_3O_4S$	10.97	10.99
3.	III	C	70	4	169	$C_{13}H_{11}N_3O_4S$	10.47	10.49
4.	IV	D	68	12	110 (11)	$C_{12}H_8N_2O_2S$	13.09	13.11
5.	V	E	95	2	184 (2)	$C_{12}H_7N_3O_4S$	11.06	11.07
6.	VI	F	90	2	176	$C_{12}H_7ClN_2O_2S$	11.48	11.49
7.	VII	E	95	2	184	$C_{12}H_7N_3O_4S$	11.06	11.07
8.	VIII	E	95	2	184	$C_{12}H_7N_3O_4S$	11.05	11.07
9.	IX	E	94	2	184	$C_{12}H_7N_3O_4S$	11.05	11.07
10.	X	a)G	15	2	178	$C_{12}H_9O_4N_3S$	10.54	10.56
		b)H	75	2	186	$C_{13}H_9O_4N_3S$	10.55	10.56
11.	XI	G	70	2	178	$C_{13}H_9O_4N_3S$	10.55	10.56

Lit.m.p. 128°, 148°, 111°, 188°C respectively.

like diphenylsulphides and the diphenylamines. The possibility of the formation of the nitrophenothiazines by the direct ring closure of the respective diphenylsulphides instead *via* Smiles rearrangement is ruled out on the grounds that if the rearrangement did not occur, the only possible products could be 4-nitro--(from IV), 2,4-dinitro—(from V, VII, VIII and IX),2-chloro-4-nitro—(from VI), 2,4-dinitro-3-methyl—,and 2,4-dinitro-1-methyl —(from X) and 2,4-dinitro-3-methylphenothiazine (from XI)which was not the case.

The general procedure followed was to reflux a mixture of halonitrobenzene (0.01M), *o*-aminothiophenol (0.015M), anhyd. sodium acetate (0.05M) and absolute ethanol (30 ml) on a water bath for several hrs (cf.table).The reaction mixture was then cooled, filtered and the product was washed well with water,dil. hydrochloric acid (10%) and finally with ice cold ethanol (50%).

The crude products A, B and D were crystallised with ethanol in yellowish-brown, yellow and violet crystals respectively, the product C from benzene-petroleumether (40^0-60^0)mixture (1:4) in yellow plates; E, F and H in violet needles from glacial acetic acid while G from ethylacetate in violet plates.

The phenothiazines E to H generally separated within 15 minutes after the start of refluxing but the period was extended for 2 hours in order to attain better yields.The phenothiazine D could be obtained in good yield by prolonging the refluxing period to 12 hrs.

The products I, II and III were also obtained by following in general procedure usually adopted for the synthesis of

diphenylsulphides which in brief is as follows. To an ice cold solution of potassium hydroxide (0.0142M) in 5 ml of water was added o-aminothiophenol (0.008M).Dioxan (6.5 ml) was then added to it in order to attain a clear solution. This was followed by the addition of the solution of the respective halonitrobenzene (0.0065M) in 8 ml of ethanol. The mixture after stirring in an ice chest for 4 hrs, was diluted and the product which separated was filtered, washed well with water, cold dil. alkali (10%) and finally with water. These products after recrystallisation were found to be identical to those obtained by the procedure referred above.

The detailed investigations on the peculiar behaviour of halonitrobenzenes with o-aminothiophenols including the Spectral studies are in progress.

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