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REDUCTION OF N-ACETYL-2-NITRODIPHENYLAMINES BY TRIETHYL PHOSPHITE: FORMATION OF DIHYDROPHENAZINES INVOLVING A NOVEL AROMATIC REARRANGEMENT.

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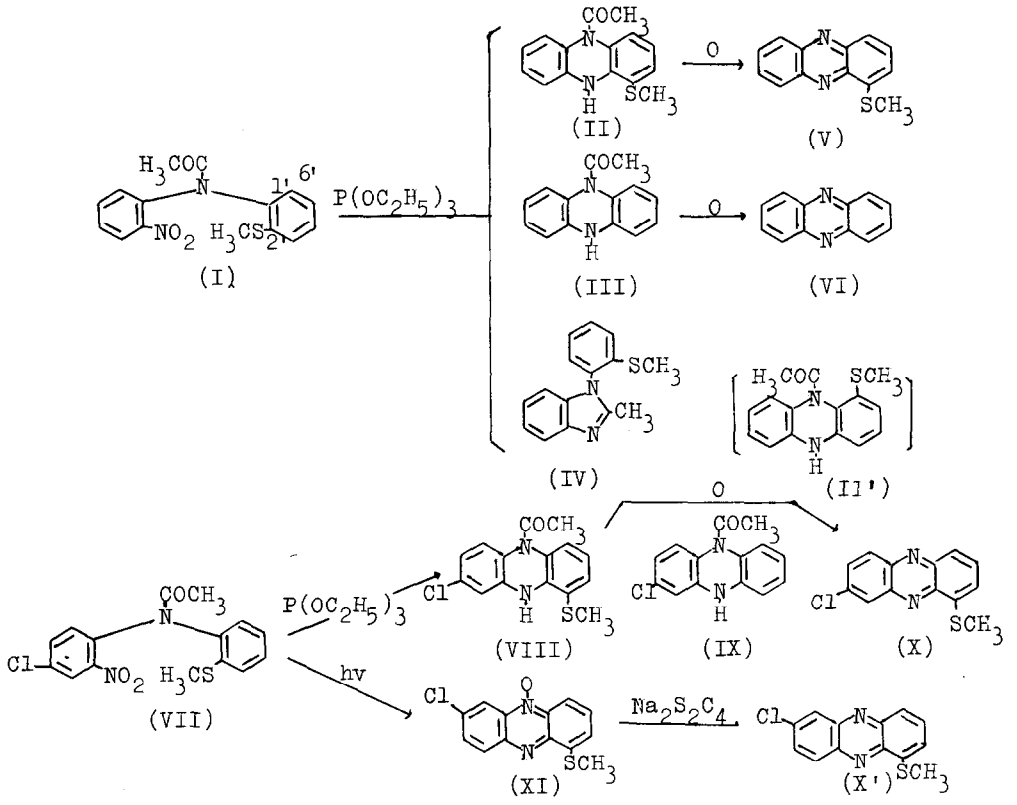
Cadogan and co-workers[1] have reported a new synthesis of phenothiazines employing reductive cyclization of 2-nitrophenyl phenyl sulphides with triethyl phosphite, which involves a new molecular rearrangement *via* arylnitrenes. Cadogan[2] has also commented on the difficulty of six-membered ring formation *via* a nitrene insertion reaction and, in fact, the molecular rearrangement in the phenothiazine formation may well proceed *via* a five-membered ring intermediate. Although Taylor and co-workers[3] suggested that nitrene insertion reactions are applicable, in principle, to the preparation of a variety of fused pyrazine heterocycles on the basis of their successful transformation of 1,3-dimethyl-5-nitro-6-anilino(or xylidino)uracil to alloxazines, there has been no example demonstrating the formation of dihydrophenazines(or phenazines) in the reaction of 2-nitrodiphenylamines with triethyl phosphite.

We have now confirmed that the reaction of N-acetyl-2-nitrodiphenylamines with triethyl phosphite leads to the formation of N-acetyl-dihydrophenazines involving a novel molecular rearrangement.

N-acetyl-2-nitro-2'-methylthiodiphenylamine(I), prepared readily by the Smiles rearrangement[4] of 2-nitrophenyl 2'-acetamidophenyl sulphide, was allowed to react with triethyl phosphite at 140-150° for 5 hr under nitrogen. After cooling, the reaction mixture was well mixed with a large amount of acidic alumina, without prior evaporation of triethyl phosphite, and dried as sufficient as possible. Removal of the triethyl phosphite was accomplished by

elution using petroleum ether. Successive elution(solvent: ether) gave 1-methylthio-5-acetyl-5,10-dihydrophenazine(II)(22%), 5-acetyl-5,10-dihydrophenazine(III)(1.7%), 1-(o-methylthiophenyl)-2-methylbenzimidazole(IV)(3.0%), 1-methylthiophenazine(V)(1.3%) and phenazine(VI)[5](trace).



Scheme 1

The phenazines(V and VI) were shown to be formed by autooxidation of the dihydrophenazines(II and III) initially formed by triethyl phosphite: 1) thin-layer chromatography of the reaction mixture revealed the absence of both (V) and (VI); 2) on standing in contact with air, (II) and (III) dissolved in ethanol were converted into (V) and (VI) respectively. The presence of an intramolecular hydrogen bond (-NH---SCH_3) in (II) may be supported by comparison of an NH absorption band of (II) with that of (III) in their i.r. spectra (3250 cm^{-1} for II and 3300 cm^{-1} for III, in dilute CCl_4 solution), excluding the possible alternative (II') which might be expected on the assumption of a direct

insertion reaction at position 6' in (I).

A similar treatment of N-acetyl-2-nitro-4-chloro-2'-methylthiodiphenylamine (VII) with triethyl phosphite gave 1-methylthio-5-acetyl-8-chloro-5,10-dihydrophenazine(VIII)(25%) and 5-acetyl-8-chloro-5,10-dihydrophenazine(IX)(6%). Repeated crystallizations of (VIII) resulted in the conversion to 1-methylthio-8-chlorophenazine(X). We attempted an unequivocal synthesis of the possible positional isomer (X') in order to distinguish (X) from (X'). Fortunately, it was found[6] that 1-methylthio-7-chlorophenazine-5-oxide(XI) was obtained in a moderate yield(50%) when (VII) in benzene was irradiated with a 100 W high-pressure mercury lamp through a pyrex filter for 24 hr. (XI) was readily reduced by sodium hydrosulphite to give (X'). Thus, (X') was prepared unambiguously. Depression in the mp of (X) by admixture with (X') and the apparent discrepancy in their spectra (i.r. and n.m.r.) showed clearly the formation of (X) *via* (VIII) from (VII).

Above experiments again point the formation of (II) rather than (II').

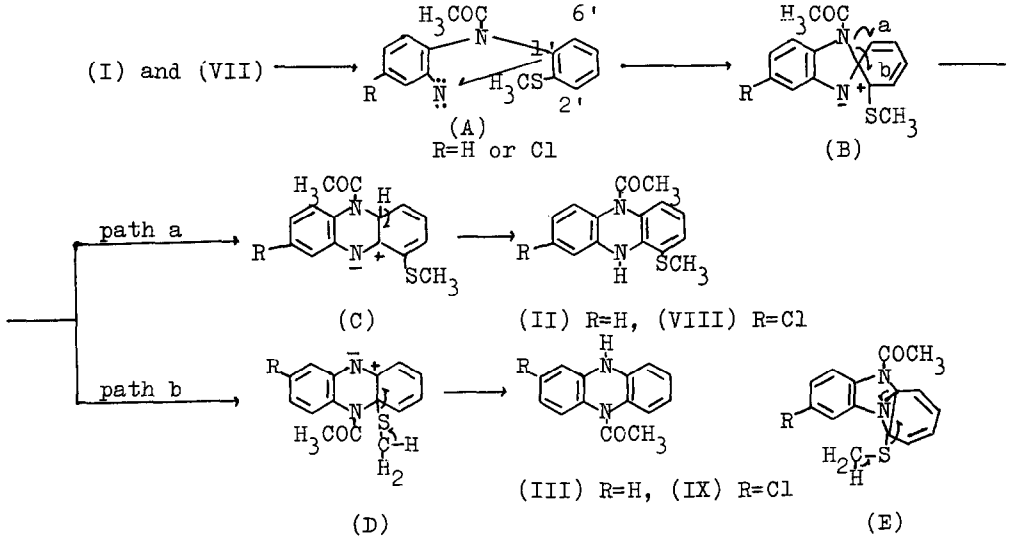
These results make it possible to propose the mechanism for the dihydrophenazine formation *via* arylnitrenes as shown in scheme 2: the first formed nitrene[7] (A) attacks the 1' position to give a five-membered intermediate (B) which then undergoes sigmatropic(migration of the N-acetyl group to the 6' position, path a) and prototropic shifts to give the observed 'rearranged' products (II and VIII). Thus, we can expand the mechanism analogous to the phenothiazine formation[1] to the dihydrophenazine formation.

The formation of (III and IX) is also explained as the migration of the N-acetyl group to the 2' position, path b in (B), followed by elimination of the methylthio group as shown in (D). In this case, however, it may be permitted to predict an azanorcaradiene intermediate (E) which has been postulated in thermal decomposition of 2-azido-2'-methoxydiphenylmethane[8].

It is worth noting that the concomitant formation of (IV) may involve the initial attack of a nitrene, probably a triplet nitrene, at the carbonyl carbon of the N-acetyl group in (I).

When 2-nitro-2'-methylthiodiphenylamine(deacetyl compound of I) was treated with triethyl phosphite, the reaction took place with complication and attempts

to isolate the reaction products were unsuccessful in accordance with previous observations[2] in 2-nitrodiphenylamine. The difficulty may arise from no protection on an NH group in 2-nitrodiphenylamines.



Scheme 2

Footnotes and References

1 J.I.G.Cadogan, S.Kulik, C.Thomson and M.J.Todd, J.Chem.Soc.(C), 1970, 2437; J.I.G.Cadogan and S.Kulik, Chem.Comm., 1970, 233.
2 J.I.G.Cadogan, Quart.Rev., 1968, 22, 222.
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4 W.J.Evans and S.Smiles, J.Chem.Soc., 1935, 181.
5 All compounds described herein gave satisfactory analyses and consonant i.r., n.m.r. and u.v. spectra for their structures.
6 This type of photochemical reaction provides a new synthetic approach leading to phenazine-N-oxides. The details involving mechanistic considerations will be repprted in a separated paper.
7 Recent studies on the dehydrogenation of aromatic nitro compounds by triethyl phosphite support the intermediacy of nitrene intermediates. (cf. a G.Solinsky and B.L.Feuer, J.Org.Chem., 1966, 31, 3882. b J.I.G.Cadogan and M.J.Todd, Chem.Comm., 1967, 178.)
8 C.R.Cliff and G.Jones, Chem.Comm., 1970, 1705.