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Steric Effect on the Smiles Rearrangement

During the course of an investigation[1] of the Smiles rearrangement in employing heterocyclics, we observed certain chemical behavior which seemed to indicate that the rearrangement is accelerated by the effect of bulky substituents. This communication deals with the experimental results concerning the above findings.

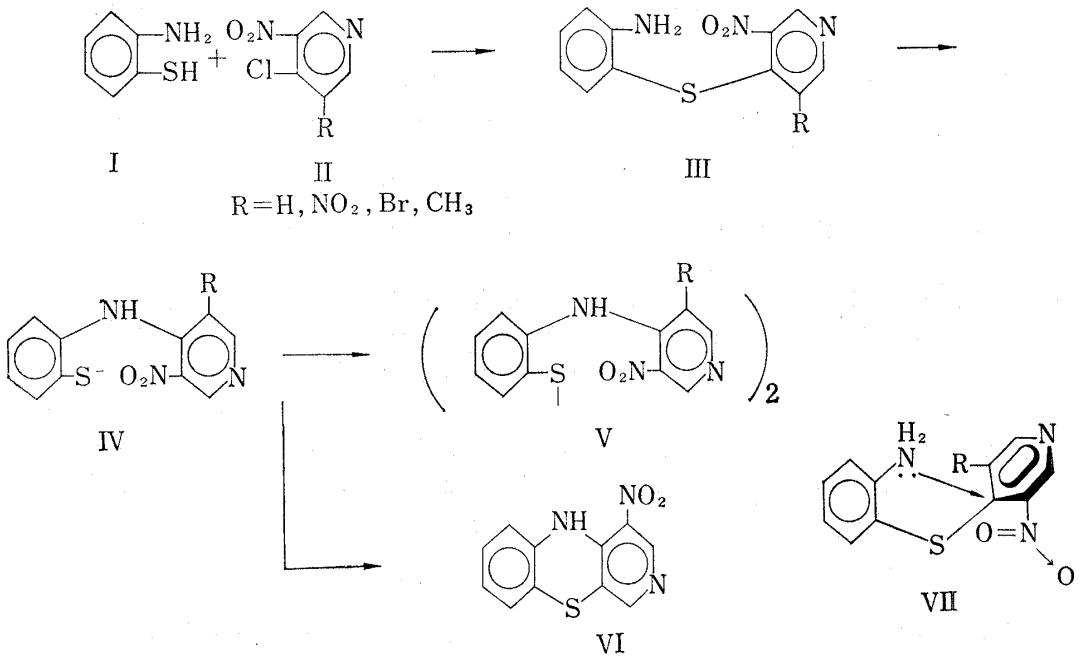

Chart 1

The reaction of equimolar quantities of *o*-aminothiophenol (I) and 3-nitro-4-chloropyridine (II: R=H) at 20° for 1 hr in ethanol containing an equivallent amount of sodium ethoxide gave 3-nitro-4-(*o*-aminophenylthio)pyridine (III: R=H)[1-3] in quantitative yield.

However, using precisely the same conditions, the condensation of I with 3-nitro-4-chloro-5-substituted pyridines (II: R=NO_2, Br, CH_3) did not afford the expected sulfides (III: R=NO_2, Br, CH_3), but rather the disulfides (V: R=NO_2, Br, CH_3) or 4-nitro-5*H*-pyrido[3,4-*b*][1,4]benzothiazine (VI). These products appear to be formed by rearrangement of the initially formed sulfides (III: R=NO_2, Br, CH_3) followed by autooxidation or cyclization as shown in Chartl.

Reaction of I and 3,5-dinitro-4-chloropyridine (II: R=NO_2) yielded two crystalline products, mp 142—143° and mp 183—184°, in yields of 69% and 7% respectively. The former was identical in melting point and infrared spectrum with authentic (V) prepared by Petrow's method.[4] The latter was to be 1-ethoxy-4-nitro-5*H*-pyrido[3,4-*b*][1,4]-benzothiazine by analysis and by comparison of its NMR spectrum with that of VI.

1) For previous papers in this series, see; Y. Maki, K. Yamane, and M. Sato, *Yakugaku Zasshi*, **86**, 50 (1966).
2) A.J. Saggiomo, P.N. Craig, and M. Gordon, *J. Org. Chem.*, **23**, 1906 (1958).
3) F.H. Clarke, G.B. Silverman, C.M. Watnick, and N. Sperber, *J. Org. Chem.*, **26**, 1126 (1961).
4) V.A. Petrow and E.L. Rewald, *J. Chem. Soc.*, **1945**, 591.

When 3-bromo-4-chloro-5-nitropyridine (II: R=Br) was allowed to react with I, VI and disulfide[5] (V: R=Br), mp 182—183°, were isolated in yields of 34% and 48% respectively.

The condensation of I with 3-nitro-4-chloro-5-methylpyridine (II: R=CH_3) proceeded to afford disulfide (V: R=CH_3), mp 183.5°, in 66% yield, together with small amounts of two minor products which were detectable by thin-layer chromatography.

On the basis of the above experimental facts, it is immediately apparent that both electron attracting groups (NO_2, Br) and the electron releasing group (CH_3) at position 5 in the pyridine ring of the unisolated sulfides (III: R=NO_2, Br, CH_3) lead to a rapid rearrangement into phenylpyridylamine derivatives (IV: R=NO_2, Br, CH_3), compared with the isolated sulfide (III: R=H). In particular, the rate accelerating effect of the methyl group would appear to indicate the presence of a more effective steric factor than an electronic factor in this type rearrangement.

We believe that bulky substituents at position 5 gives rise to the restricted rotation of sulfides (III: R=NO_2, Br, CH_3) and this steric effect results in the favorable conformation (VII)[6,7] for intramolecular SN_2 reaction.

(III: R=H) does not rearrange, but its acetate easily underwent rearrangement upon treatment with ethanolic caustic alkali to give the corresponding phenylpyridylamine derivatives.[1]

It has been generally considered[8,9] that an anionic nitrogen must first be formed in order for *o*-aminophenylsulfides to rearrange to diphenylamine. This is usually accomplished by conversion of the amine function into an amide which is acidic.

However, taking the present experimental facts into consideration, an acetyl group on the amino moiety of (III: R=H) may play a significant role in the rearrangement by virtue of its bulkiness thereby giving rise to restricted rotation in sulfide (III: R=H).[6]

Further work is in progress on the steric effect in the Smiles rearrangement and will be reported at a later date.

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5) The structure of the disulfides (V: R=Br, CH_3) was established by infrared spectrum, combustion analysis, molecular weight (Rast method) and ultraviolet spectral comparison with 3-nitro-4-(*o*-methylthiophenylamino)-5-bromopyridine, mp 90°, prepared by the condensation of *o*-methylthioaniline with (II: R=Br).

6) The restricted rotation of sulfide (III: R=NO_2, Br, CH_3) and acetate of (III: R=H) can be seen from Dreiding models.

7) In another type of the Smiles rearrangement in an *o*-hydroxydiphenylsulfone derivative, one example of steric acceleration by substituents has been reported by J.F. Bunnett and T. Okamoto (*J. Am. Chem. Soc.*, **78**, 5363 (1956)).

8) J.F. Bunnett and R.E. Zahler, *Chem. Rev.*, **49**, 369 (1951).

9) W.J. Evans and S. Smiles, *J. Chem. Soc.*, **1935**, 181.