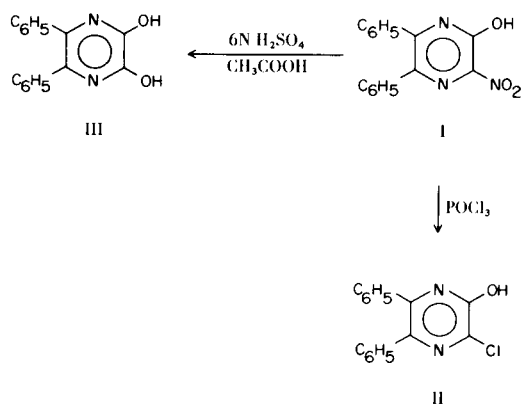


A Study of Some Halogen Displacements on 2-Hydroxy-3-nitro-5,6-diphenylpyrazine

Albert Hirschberg (1) and Paul E. Spoerri

Departments of Chemistry, Connoly College, Long Island
University and Polytechnic Institute of Brooklyn

While a notable characteristic of the pyrazine nucleus is its resistance to electrophilic substitution (2), the hydroxyl group apparently exerts an activating effect, for in 1953 Karmas and Spoerri (3) reported the preparation of 2-hydroxy-3-nitro-5,6-diphenylpyrazine (I) from the corresponding 2-hydroxy compound by nitration under mild conditions. A study (4) of the properties of this nitro-hydroxypyrazine I showed that the compound shared the typical properties of aromatic nitrophenols, being sufficiently acidic to dissolve in aqueous sodium bicarbonate as well as being stable in strong alkali. It was also found that the nitro group was capable of being displaced in strongly acidic media. Thus, the attempted preparation of 2-chloro-3-nitro-5,6-diphenylpyrazine failed because heating I with phosphorus oxychloride resulted in displacement of the nitro group leading to 2-hydroxy-3-chloro-5,6-diphenylpyrazine (II).



A survey of the literature reveals a few examples of similar displacements of an α -nitro group by halogen under acidic conditions in the pyridine series. Thus, 2-nitro-3-ethoxypyridine undergoes reaction with concentrated hydrobromic acid to yield 2-bromo-3-ethoxypyridine (5), while 3-hydroxy-2-chloropyridine was prepared by treating 3-hydroxy-2-nitropyridine with a mixture of phosphorus trichloride and phosphorus oxychloride (6).

In view of the reactivity of the nitro group on the pyrazine nucleus, a study was undertaken to determine which

chlorinating agent would be most effective in producing a good yield of the hydroxy-chloro compound II. These data are summarized in Table I.

Our initial experiments using dry hydrogen chloride were carried out using glacial acetic acid as solvent. At room temperature no reaction took place while at reflux temperature a 92% yield of 2,3-dihydroxy-5,6-diphenylpyrazine (III) was obtained. Since it had been previously determined that a quantitative yield of the dehydroxy compound III was obtained from the hydroxy-nitro compound I by refluxing in aqueous mineral acid (3), it seems reasonable that the small amount of water present in glacial acetic acid caused the hydrolysis to take place. Using dry dioxane as solvent afforded a 50% yield of the desired hydroxy-chloro compound II.

In an analogous fashion the displacement of the nitro group by bromide was carried out using several different brominating agents. These data are also summarized in Table I.

TABLE I

Displacements on 2-Hydroxy-3-nitro-5,6-diphenylpyrazine
Using Various Halogenating Reagents

Reagent	Yield (%)
PCl ₃	43
CH ₃ COCl	78
SOCl ₂	52
Dry HCl in dry dioxane	50
ICl	52
CH ₃ COBr	45
IBr	43
Dry HBr in dry dioxane	41

The number of brominating agents which could be used to displace the nitro group proved to be somewhat limited. In attempts using thionyl bromide or phosphorus tribromide under a variety of conditions, the only product isolated proved to be 2,3-dibromo-5,6-diphenylpyrazine (4) as determined by mixture melting point and comparison of its infrared spectrum with that of the known compound. Apparently polybromination takes place using these reagents.

The successful use of a variety of chlorinating and brominating reagents suggested using analogous iodinating compounds. Unfortunately the use of acetyl iodide, dry hydrogen iodide in dry dioxane, and phosphorus triiodide led to reductive degradation of the pyrazine nucleus. Similar reductive degradations have previously been reported by Stoehr and Gutknecht (7,8) using iodine and potassium iodide in attempts to prepare iodopyrazines.

There was no study of mechanisms, but it appears likely that pyrazinium cations and their tautomeric carbonium ions are intermediates in each of these reactions.

EXPERIMENTAL (9)

2-Hydroxy-3-nitro-5,6-diphenylpyrazine (I).

This compound was prepared in 67% yield following the procedure of Karmas and Spoerri (3).

2-Hydroxy-3-halo-5,6-diphenylpyrazine.

A mixture of 1.0 g. (0.0068 mole) of 2-hydroxy-3-nitro-5,6-diphenylpyrazine (I) and 30 ml. of the appropriate halogenating reagent was allowed to reflux for two hours. The mixture was then cooled and cautiously poured into 250 ml. of ice water (containing 5.0 g. of sodium bisulfite in the cases where iodine chloride and iodine bromide were used). The resulting yellow precipitate was filtered, dried in air and recrystallized from ethanol as yellow needles.

In the procedure involving dry hydrogen halides, a solution of

1.0 g. of I in 50 ml. of dry dioxane was allowed to reflux for one hour while the dry gas was bubbled into the refluxing mixture. The resulting solution was then cooled, poured into water and worked up as above.

The observed melting point for 2-hydroxy-3-chloro-5,6-diphenylpyrazine (II) was 227-229° dec. (lit. (4) 229-231° dec.) The observed melting point for 2-hydroxy-3-bromo-5,6-diphenylpyrazine was 219-222° dec. (lit. (4) 222-225° dec.).

REFERENCES

- (1) To whom all inquiries should be addressed at Long Island University.
- (2) I. J. Krems and P. E. Spoerri, *Chem. Rev.*, **40**, 328 (1947).
- (3) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **75**, 5517 (1953).
- (4) G. Karmas and P. E. Spoerri, *ibid.*, **78**, 4071 (1956).
- (5) H. J. den Hertog, F. R. Schepman, J. De Bruyn, and G. J. E. Thyse, *Rec. Trav. Chim.*, **69**, 1281 (1950).
- (6) T. Takashi and F. Yoneda, *Pharm. Bull. (Tokyo)*, **5**, 350 (1957); *Chem. Abstr.*, **52**, 13722^h (1958).
- (7) C. Stoehr, *J. Prakt. Chem.*, **51**, 445 (1895).
- (8) H. Gutknecht, *Chem. Ber.*, **12**, 2291 (1879).
- (9) All melting points are uncorrected. In each case the identity of the product was confirmed by mixture melting point and comparison of infrared spectra. Infrared spectra were obtained using a Perkin-Elmer model 137 B Infracord Spectrophotometer, using potassium bromide disks.

Received July 24, 1969

Brooklyn, N. Y. 11201