

Communications to the Editor

[Chem. Pharm. Bull.]
[24(9)2267-2269(1976)]

UDC 547.773.04 : 547.292-931.04

Novel Rearrangement of Pyrazole N-Imines with Acetic Anhydride

2-Amino-1,3-dimethylindazolium mesitylenesulfonate (I) was allowed to react with a large excess of acetic anhydride in the presence of anhydrous sodium acetate to give the unexpected rearrangement products, 3-acetoxymethyl-1-methylindazole (IV), 3-acetylaminomethyl-1-methylindazole (V) and the deaminated product, 1,3-dimethylindazole (II), and the desired product, pyrazolo[2,3-*b*]indazole derivative (III), could not be obtained. Likewise, the same reactions of 2-amino-1,3,5-trimethylpyrazolium mesitylenesulfonate (VII) and 2-amino-1,3,4,5-tetramethylpyrazolium mesitylenesulfonate (VIII) gave the rearrangement products, 5-acetoxymethyl-1,3-dimethylpyrazole (IX) and 5-acetoxymethyl-1,3,4-trimethylpyrazole (X), respectively. This is the first example of a rearrangement reaction of aromatic amine N-imine with acid anhydride. The desired product (III) was obtained by the reaction of 2-amino-1-methylindazolium mesitylenesulfonate (XIV) with acetylacetone in the presence of triethylamine, followed by oxidation with lead tetraacetate.

It is well known that aromatic amine N-oxides react with acid anhydrides to yield rearrangement products.¹⁾ On the other hand, as we previously reported,²⁾ the reaction of aromatic amine N-imines, isoelectronic with aromatic N-oxides, with acid anhydrides resulted in the formation of N-acylated N-imines or cyclized products and did not give any rearrangement products. This cyclization reaction was successfully utilized for the syntheses of nitrogen-bridged heteroaromatics such as pyrazoloazines^{2a,b)} and pyrazoloazoles.^{2c,d)} In the course of an extension of this cyclization method to the syntheses of pyrazoloisoazoles from isoazole N-imines, we have found that a novel rearrangement occurs when pyrazole N-imines are allowed to react with acetic anhydride.

In this paper, we report the first example of a rearrangement reaction of aromatic amine N-imine with acid anhydride. The N-amino compound, 2-amino-1,3-dimethylindazolium mesitylenesulfonate (I), mp 205°, prepared by the reaction of 1,3-dimethylindazole (II) with O-mesitylenesulfonylhydroxylamine, was heated with a large excess of acetic anhydride and anhydrous sodium acetate by refluxing for 12 hours. The expected cyclization product, pyrazolo[2,3-*b*]indazole derivative (III), was not obtained, but rearrangement products, IV (68.6%) colorless oil, C₁₁H₁₂O₂N₂, *m/e*: 204 (M⁺), IR $\nu_{\max}^{\text{liq}}$ cm⁻¹: 1744, 1224 (-COO-), NMR (CDCl₃) δ : 2.08 (3H, s, CH₃CO-), 4.04 (3H, s, N-CH₃), 5.44 (2H, s, -CH₂O-), 7.15—7.50 (3H, m), 7.60—7.85 (1H, m), V (10.5%), mp 152—153° colorless needles, C₁₁H₁₃ON₃, *m/e*: 203 (M⁺), IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3295 (NH), 1638 (CO), NMR (CDCl₃) δ : 2.03 (3H, s, CH₃CO-), 3.99 (3H, s, N-CH₃), 4.75 (2H, d, *J*=5 Hz, -CH₂NH), 6.30 (1H, broad s, D₂O exchangeable, NH), 7.15—7.50 (3H, m), 7.60—7.85 (1H, m), and the deaminated product II (9.1%) were isolated. The compound (IV)³⁾ was easily hydrolyzed by heating with 18% hydrochloric acid to afford the corresponding alcohol (VI), colorless oil, C₉H₁₀ON₂, *m/e*: 162 (M⁺), IR $\nu_{\max}^{\text{liq}}$ cm⁻¹: 3320 (OH), NMR (CDCl₃) δ : 3.90 (3H, s, N-CH₃), 5.00 (2H, s, -CH₂OH), 3.34 (1H, broad s, D₂O exchangeable, -CH₂OH), 7.15—7.40 (3H, m), 7.65—7.85 (1H, m).

- 1) a) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, p. 290; b) A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, London and New York, 1971, p. 353.
- 2) a) M. Hirobe, Y. Minamoto, and T. Okamoto, Abstracts of Papers, the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, August, 1970, p. II-47; b) K. Kasuga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **22**, 1814 (1974); c) H. Koga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **22**, 482 (1974); d) H. Koga, M. Hirobe and T. Okamoto, Abstracts of Papers, The 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April, 1974, p. II-141.
- 3) M.A. Kazanbieva, B.A. Tertov, and F.T. Pozharskii, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, **1965**, 125 [*Chem. Abstr.*, **63**, 4272 (1965)].

Likewise, the same reaction of VII (mp 175°) or VIII (mp 214°), obtained by the reaction of 1,3,5-trimethyl- or 1,3,4,5-tetramethylpyrazole with O-mesitylenesulfonylhydroxylamine, gave the rearrangement product (IX) (65.5%) or (X) (76.9%). The products (IX and X) were also easily hydrolyzed to the corresponding alcohols XI (66.7%) and XII (71.4%) respectively, when heated with 18% hydrochloric acid. The structure of XI was confirmed by comparison with the alcohol, obtained by the reduction of 1,3-dimethyl-5-ethoxycarbonylpyrazole (XIII)⁴⁾ with lithium aluminum hydride. Therefore, the structure of IX was established to be 5-acetoxymethyl-1,3-dimethylpyrazole. The structure of X and XII was assumed to be 5-acetoxymethyl-1,3,4-trimethylpyrazole and its corresponding alcohol by comparing their spectral properties⁵⁾ with those of IX and XI.

The cleavage reaction of nitrogen bond of pyrazole N-imine derivative was also found in the reaction of 2-amino-1-methylindazolium mesitylenesulfonate (XIV) with dimethyl acetylenedicarboxylate (DAC). The quaternary salt (XIV), mp 198° (decomp.), which was obtained by treating 1-methylindazole with O-mesitylenesulfonylhydroxylamine, was allowed to react with DAC in the presence of potassium carbonate in N,N-dimethylformamide (DMF) to give 2-aminofumaric acid dimethylester (XV) in 27% yield. The structure of XV was confirmed by comparison of its IR and NMR spectra with those of an authentic sample.⁶⁾ On the other hand, the reaction of XIV with acetylacetone in the presence of triethylamine in DMF at room temperature for a long while, afforded a cyclized product XVI (mp 72—75°).

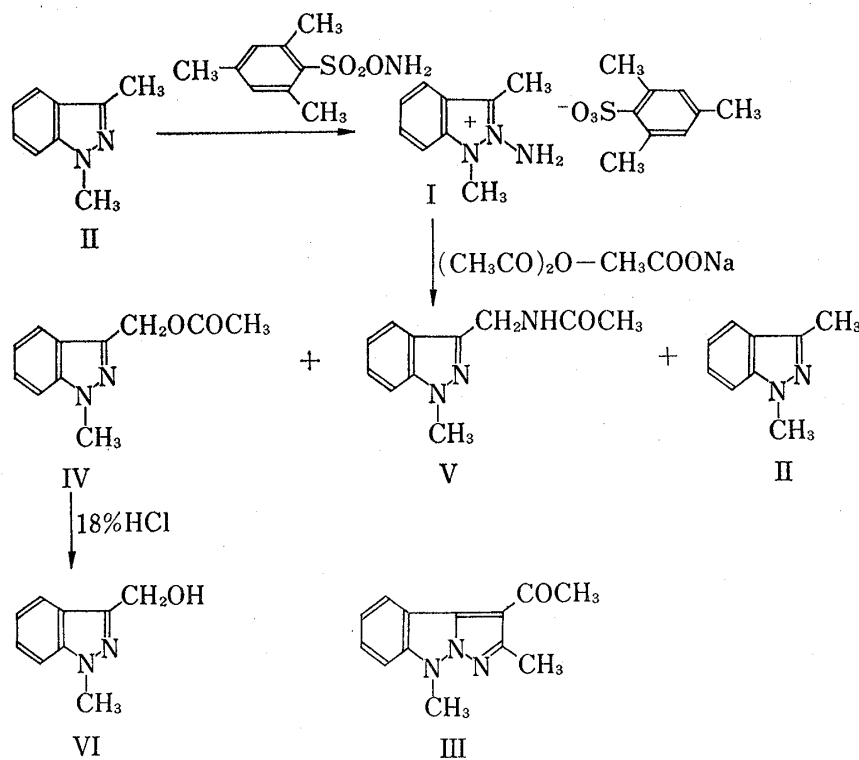


Chart 1

4) J. Elguero, R. Jacquier, G. Tarrago, and H.C.N. Tien Duc, *Bull. Soc. Chim. France*, **1966**, 293.

5) IX: colorless oil, C₈H₁₂O₂N₂, *m/e* 168 (M⁺), IR $\nu_{\text{max}}^{\text{liq}}$ cm⁻¹: 1746, 1228 (-COO-), NMR (CDCl₃) δ : 2.07 (3H, s, CH₃CO), 2.21 (3H, s, 3-CH₃), 3.81 (3H, s, NCH₃), 5.03 (2H, s, -CH₂O-), 6.05 (1H, s, 4-H). X: colorless oil, C₉H₁₄O₂N₂, *m/e* 182 (M⁺), IR $\nu_{\text{max}}^{\text{liq}}$ cm⁻¹: 1745, 1228 (-COO-), NMR (CDCl₃) δ : 2.04 (3H, s, CH₃CO), 2.14 (3H, s, 3-CH₃), 3.77 (3H, s, NCH₃), 5.02 (2H, s, -CH₂O-), 1.97 (3H, s, 4-CH₃). XI: colorless oil, C₆H₁₀ON₂, *m/e* 126 (M⁺), IR $\nu_{\text{max}}^{\text{liq}}$ cm⁻¹: 3250 (OH), NMR (CDCl₃) δ : 2.16 (3H, s, 3-CH₃), 3.75 (3H, s, NCH₃), 4.53 (2H, s, -CH₂OH), 5.90 (1H, s, 4-H), 3.30 (1H, broad s, D₂O exchangeable, OH), XII: mp 106°, C₇H₁₂ON₂, *m/e* 140 (M⁺), IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3210 (OH), NMR (CDCl₃) δ : 2.11 (3H, s, 3-CH₃), 3.67 (3H, s, NCH₃), 4.48 (2H, s, -CH₂OH), 1.90 (3H, s, 4-CH₃), 3.20 (1H, broad s, D₂O exchangeable, OH).

6) R. Huisgen, K. Herbig, A. Siegel, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

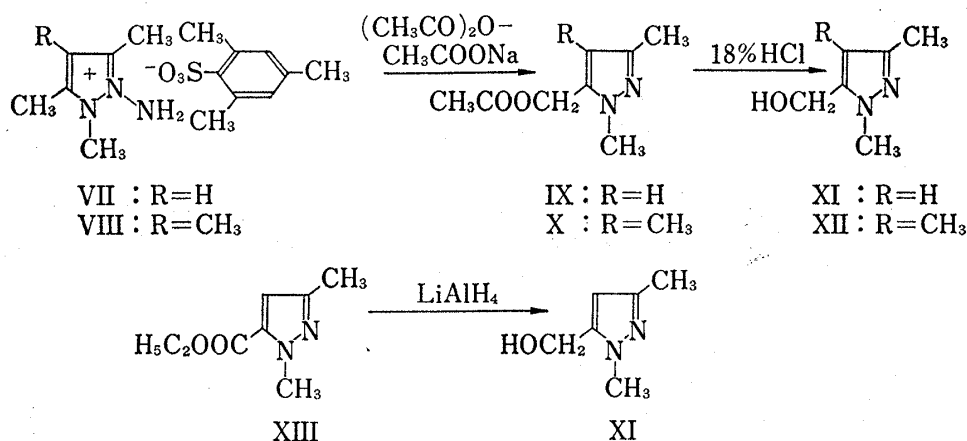


Chart 2

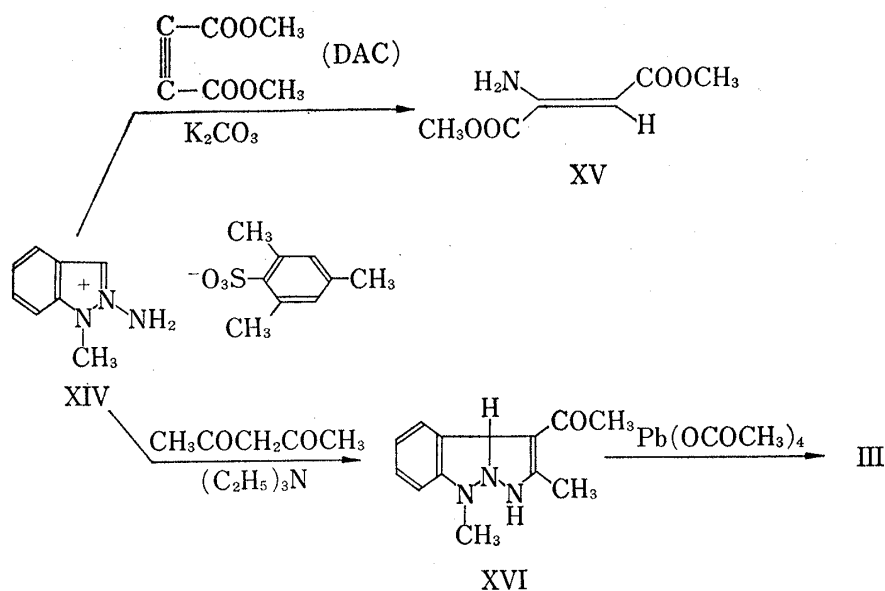


Chart 3

in 30.1% yield, which was oxidized with lead tetraacetate to give the desired product (III) in 13.3% yield, mp 127—128°, IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1620 (CO), NMR (CDCl_3) δ : 2.56, 2.72 (3H, each, s, CH_3), 3.82 (3H, s, NCH_3), 7.20—7.90 (4H, m), $\text{C}_{13}\text{H}_{13}\text{ON}_3$, m/e 227 (M^+).

Such a rearrangement reaction of aromatic amine N-imines would serve to elucidate the mechanism of the rearrangement of aromatic amine N-oxides with acid anhydride which has not exactly been clarified to date.^{1a,b)} Details of the mechanism of these reactions will be reported in connection with that of the reaction in N-oxides.

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Received May 13, 1976