Pyrazoles. II. Reactions of 1-Methyl-5-amino-4-pyrazolecarboxamide and Nitrous Acid Introduction of a Nitro Group at Position 5 in the Pyrazole Ring (1)

C. C. Cheng

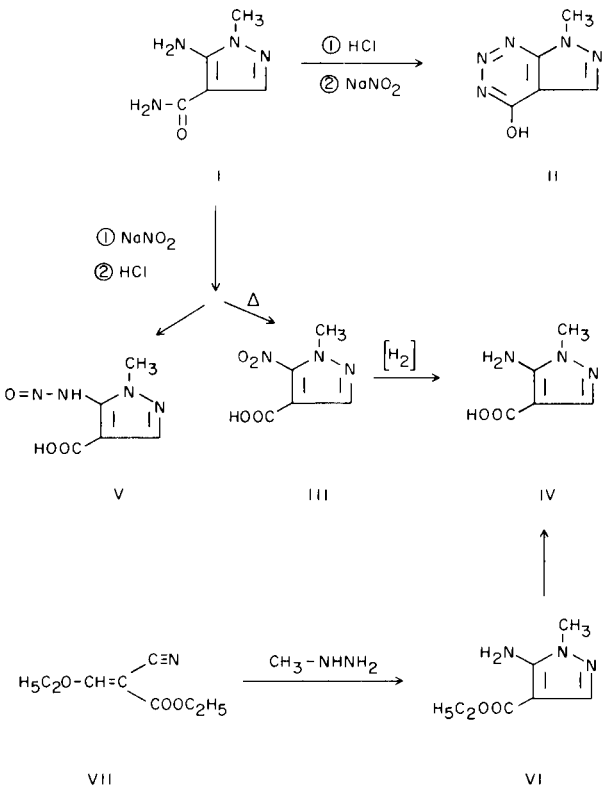
Midwest Research Institute

Addition of sodium nitrite to a mixture of hydrochloric acid and 1-methyl-5-amino-4-pyrazolecarboxamide, at either high or low temperature, yielded 1-methyl-4-hydroxypyrazolo-[3,4-*d*]-*v*-triazine. On the other hand, addition of hydrochloric acid to an aqueous mixture of sodium nitrite and 1-methyl-5-amino-4-pyrazolecarboxamide gave, at high temperature (~ 100°), 1-methyl-5-nitro-4-pyrazolecarboxylic acid and at low temperature (~ 0°), 1-methyl-5-nitros-amino-4-pyrazolecarboxylic acid.

It is generally believed that *o*-aminocarboxamides form 4-hydroxy-1,2,3(*v*)-triazines upon the treatment with nitrous acid (2). Notable exceptions are 5-amino-4-imidazolecarboxamide (3) and 5-amino-4-pyrazolecarboxamide (4) which yield the corresponding diazocarboxamides. These diazo derivatives are quite stable under ordinary storage conditions, and can be readily cyclized to 4-hydroxy-*v*-triazines in acidic, basic, or neutral aqueous solution (3,4).

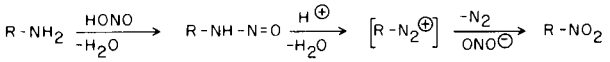
As expected, addition of excess sodium nitrite to a mixture of hydrochloric acid and 1-methyl-5-amino-4-pyrazolecarboxamide (5) (I), either at low or high temperature, yielded 1-methyl-4-hydroxypyrazolo[3,4-*d*]-*v*-triazine (II), m.p. 150° dec. However, addition of acid to an aqueous mixture of sodium nitrite and I gave, depending on the reaction temperature, different products. When the addition of acid was carried out at room temperature, and the resulting suspension boiled for a short time, a yellow solid (product A) was obtained, m.p. 161-163°. On the other hand, when the reaction temperature was kept at 0° throughout the reaction, a brown solid (product B) was isolated, m.p. 189-191°.

Elemental analysis of product A gave $C_5H_5N_3O_4$ as its empirical formula. An examination of the nmr spectrum revealed that the N-CH_3 and =CH- protons of product A showed strong paramagnetic shifts when compared with that of the starting material (1), indicating the presence of a powerful electron-withdrawing group. Product A was found to be extremely soluble in ether. This information, together with the fact that a new band at 1570 cm^{-1} was noted in the infrared spectrum of product A, suggested that the compound was 1-methyl-5-nitro-4-pyrazolecarboxylic acid (III). Since the preparation of pyrazole compounds having a nitro group at the "non-aromatic" position is uncommon (6), structure III for product A was substantiated by the following reaction: Catalytic reduction of product A gave 1-methyl-5-amino-4-pyrazolecarboxylic acid (IV). The latter was found to be identical with that prepared by the condensation of ethyl ethoxymethylenecyanoacetate with methylhydrazine, followed by base hydrolysis (7). This unambiguous preparation also rules out the possibility that product A might contain a nitrite group rather than a nitro group.



The empirical formula for product B was found to be $C_5H_6N_4O_3$. Its absorption band at 1450 cm^{-1} (-N-N=O) and the paramagnetic shifts of the N-CH_3 and the =CH- protons suggested that product B was 1-methyl-5-nitrosamino-4-pyrazolecarboxylic acid (V). Conversion of an amino group substituted on a tetrazole ring system into a nitrosamino group has previously been reported by Strollé and co-workers (8).

The formation of compound III from I is perhaps the result of a nucleophilic attack by the nitrite anion (which is in equilibrium with the nitro anion) on the unstable diazonium intermediate. The formation of compound V is probably due to the inability to protonate the insoluble nitrosamino intermediate under the milder reaction conditions which otherwise would lead to the formation of the diazonium salt by dehydration (9).



EXPERIMENTAL (10)

1-Methyl-5-amino-4-pyrazolecarboxamide (I).

This compound was prepared by the method described previously (5). The infrared spectrum showed absorption bands at 3410 and 3380 cm^{-1} (NH_2), and 1600 cm^{-1} ($CONH_2$). The ultraviolet spectrum showed the following absorption maxima: *p*H 1 at 221 (ϵ, 9,400) and 245 mμ (ϵ, 7,400); *p*H 11 at 228 (ϵ, 7,600) and 252 mμ (ϵ, 8,000). The nmr spectrum (d_6-DMSO) showed a singlet (3H) at δ 3.44 ppm. (N-CH_3) and another singlet at 7.47 ppm. (1 H, proton C_3 on the pyrazole ring).

1-Methyl-4-hydroxypyrazolo[3,4-*d*]-*v*-triazine (II).

Method A.

To a solution of 130 ml. of concentrated hydrochloric acid in 200 ml. of water was added 46 g. (0.33 mole) of finely powdered 1-methyl-5-amino-4-pyrazolecarboxamide (I). The suspension was cooled to 0° and, with stirring, 30 g. (0.43 mole) of sodium nitrite dissolved in 60 ml. of water was added in one portion. The mixture was stirred at 0-5° for 10 minutes and then slowly heated to 70°. It was maintained at this temperature for 1 hour during which time the color of the solid gradually changed from white to light yellow. The reaction mixture was then cooled and the product was collected by filtration. The yield was 42.6 g. (85%), m.p. 144-145° dec. Recrystallization from water gave light golden yellow plates, m.p. 150° dec. The ultraviolet spectrum showed the following absorption maxima: *p*H 1 at 284 mμ (ϵ, 5,300); *p*H 11 at 300 mμ (ϵ, 7,600).

Anal. Calcd. for $C_5H_5N_5O$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.80; H, 3.60; N, 46.34.

Method B.

To 150 ml. of 2 *N* hydrochloric acid was added 20 g. (0.14 mole) of I. To the stirring suspension cooled at 0-5° was added 10 g. (0.14 mole) of sodium nitrite dissolved in 40 ml. of water. The color of the white solid turned into yellow immediately and the suspension, which became difficult to stir for a short while, was stirred for 4 hours at room temperature then permitted to stand overnight. The yellow solid was isolated by filtration to give 17.9 g. (83% yield) of product. It was found to be identical with that prepared by Method A.

1-Methyl-5-nitro-4-pyrazolecarboxylic Acid (III).

To a suspension of 28.5 g. (0.2 mole) of 1-methyl-5-amino-4-pyrazolecarboxamide (I) in 130 ml. of water was added 20 g. (0.3 mole) of sodium nitrite. With vigorous stirring, 115 ml. of concentrated hydrochloric acid was added as quickly as possible. After the initial foaming subsided, the resulting suspension was gradually heated to boiling whereupon all the solids dissolved. After the solution was boiled for 1 hour, it was cooled and a yellow solid separated on cooling. The yellow product was collected by filtration and washed with a small amount of water (the product was found to be very soluble in ether) to give 27 g. (78% yield), m.p. 157-163°. Recrystallization from water gave yellow crystals, m.p. 161-163°. The infrared spectrum showed absorption bands at 1710 (COOH) and 1570 cm^{-1} (NO_2). The ultraviolet spectrum showed the following absorption maxima: *p*H 1 at 269 mμ (ϵ, 5,100); *p*H 11 at 278 mμ (ϵ, 5,800). The nmr spectrum (d_6-DMSO) showed a singlet (3H) at δ 4.01 ppm. (N-CH_3) and another singlet at 7.70 ppm (1 H, proton C_3 on the pyrazole ring).

Anal. Calcd. for $C_5H_5N_3O_4$: C, 35.10; H, 2.95; N, 24.56; Mol. wt. 171. Found: C, 34.90; H, 2.95; N, 24.28; Mol. wt. 172.

1-Methyl-5-amino-4-pyrazolecarboxylic Acid (IV).

Method A.

A solution of 10 g. of 1-methyl-5-nitro-4-pyrazolecarboxylic acid (III) in 150 ml. of anhydrous methanol was hydrogenated with 1 g. of 5% platinum-on-charcoal at 40 psig. Within 15 minutes the theoretical amount of hydrogen was absorbed. The hydrogenation was allowed to continue for 3 hours. The catalyst was removed by filtration and the light yellow filtrate was evaporated to give 7 g. of yellow solid, m.p. 144-146° dec. Recrystallization from methanol gave 4.5 g. (55% yield) of analytically pure product as light yellow crystals, m.p. 155-156° dec. The ultraviolet spectrum at *p*H 1 showed on absorption maximum at 251 mμ (ϵ, 6,400) and at *p*H 11 a shoulder at 235 mμ.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.83; H, 4.75; N, 29.98.

Method B.

To a solution of 18.4 g. (0.4 mole) of methylhydrazine in 200 ml. of absolute ethanol was added 68 g. (0.4 mole) of ethyl ethoxymethylenecyanoacetate. Slight heat was produced during the addition. The resulting solution was refluxed with stirring for 1 hour, after which the solvent was evaporated under reduced pressure. The resulting solid, after washing with ether, gave 54 g. (79% yield) of ethyl 1-methyl-5-aminopyrazolecarboxylate, m.p. 98-99°. Recrystallization from water gave shining, white plates, m.p. 98-99°. The intermediate gave the following ultraviolet absorption maxima: *p*H 1 at 253 mμ (ϵ, 6,700), *p*H 11 at 253 mμ (ϵ 7,100).

Ten grams of the ester was boiled with 100 ml. of 4 *N* sodium hydroxide for 90 minutes. The solution was then cooled to 0° and acidified with concentrated hydrochloric acid to give 5.5 g. (66% yield) of white powder, m.p. 155-156° dec. A mixture melting point of products obtained from both Method A and Method B showed no depression. The ultraviolet and infrared spectra of this product were found to be identical with those prepared by Method A.

1-Methyl-5-nitrosamino-4-pyrazolecarboxylic Acid (V).

To a mixture containing 15.5 g. (0.11 mole) of 1-methyl-5-amino-4-pyrazolecarboxamide (I) in 300 ml. of water was added 10 g. (0.13 mole) of sodium nitrite. The reaction mixture was cooled to 0-5° and a solution of 11 ml. of concentrated hydrochloric acid in 90 ml. of cold water was added. An orange-red solid formed almost immediately. The reaction mixture was allowed to stir at 0° for 30 minutes. The resulting solid was isolated by filtration, washed successively with water, methanol, and ether, then dried to give 10 g. of brown solid, m.p. 175-180°. Recrystallization from water gave 9.3 g. (49% yield) of brown crystals, m.p. 189-191°. The infrared spectrum showed absorption bands at 3370 cm^{-1} (OH), 1650 cm^{-1} (COOH) and 1450 cm^{-1} (N-N-N=O). The ultraviolet spectrum showed the following absorption maxima: *p*H 1 at 275 mμ (ε, 6,000); *p*H 1 at 273 mμ (ε, 6,100). The nmr spectrum (d_6-DMSO) showed two singlets at δ 3.96 ppm (3 H, N-CH_3) and 7.64 ppm (1 H, proton C_3 on the pyrazole ring), respectively.

Anal. Calcd. for $C_5H_6N_4O_3$: C, 35.30; H, 3.55; N, 32.93. Found: C, 35.36; H, 3.64; N, 32.97.

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