

A New Route for the Preparation of Pyrazolo[4,3-*c*]pyridines

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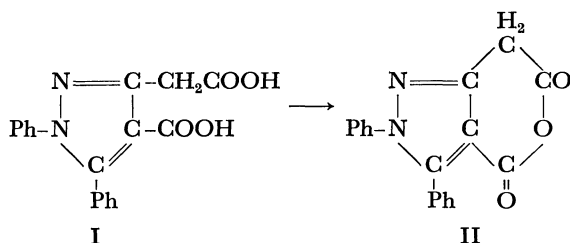
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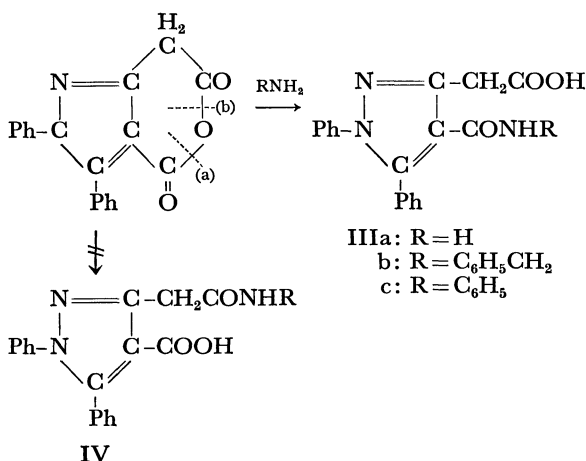
The anhydride (II) of 4-carboxy-1,5-diphenylpyrazole-3-acetic acid (I) has been prepared. The reactions of II with primary amines resulted in the formation of the monoamides IIIa—c. 2,3-Diphenylpyrazolo[4,3-*c*]pyridine-(5*H*,7*H*)-4,6-dione (VIIa), has been obtained by heating the ammonium salt of I in a vacuum at 220 °C. The ring closure of IIIc with acetyl chloride in benzene afforded VIIb. Compound VIIb was coupled with benzenediazonium chloride to give the 7-phenylazo derivative (XII) and also condensed with aromatic aldehydes giving 7-arylidene derivatives (XV).

We recently, prepared 4-carboxy-1,5-diphenylpyrazole-3-acetic acid (I) through the condensation of 1-benzoyl-1-phenylhydrazine with diethyl acetonedicarboxylate.¹⁾ We wish to report on some reactions of this acid.

We have found that the acid anhydride (II) was directly obtained by dehydration of the dibasic acid (I) with acetyl chloride in anhydrous dioxane.

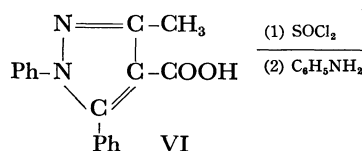
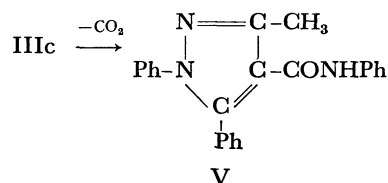


The reaction of II with primary amines in anhydrous dioxane resulted in the ring opening of the anhydride at position (a) with the formation of the corresponding amides IIIa—c, rather than at position (b) to give IV.

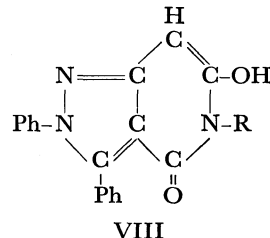
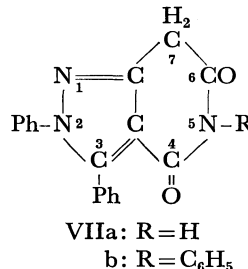


The structural elucidation of compounds III and confirmation of the ring opening of the anhydride (II) at position (a) were carried out as follows:

Decarboxylation of the monoanilide (IIIc) at 250 °C yielded 1,5-diphenylpyrazole-4-carboxanilide (V) prepared from 4-carboxy-1,5-diphenyl-3-methylpyrazole via the acid chloride.²⁾

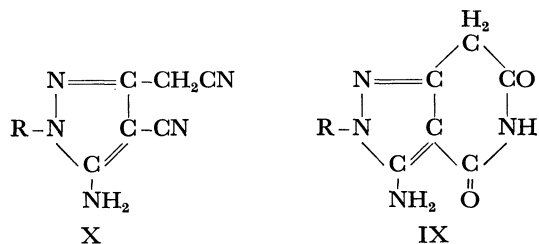


Heating of the ammonium salt of I at 220 °C in a vacuum gave 2,3-diphenylpyrazolo[4,3-*c*]pyridine-(5*H*,7*H*)-4,6-dione (VIIa). The 5-phenyl analogue (VIIb) was obtained by the action of acetyl chloride on the monoanilide (IIIc).



Compounds VII can also exist in the tautomeric structure VIII. However, the IR spectrum of the product shows two bands at 1720 and 1680 cm⁻¹ assignable to two carbonyl groups but no absorption in the OH region. This is in favor of the keto structure VII.

A similar compound (IX) which has the same ring structure as VII was prepared by acidic hydrolysis of compound X.³⁻⁵⁾



3) T. Sato, *J. Org. Chem.*, **24**, 963 (1959).

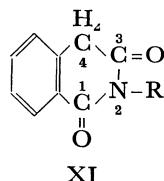
4) E. C. Taylor and K. S. Hartke, *J. Amer. Chem. Soc.*, **81**, 2452 (1959).

5) E. C. Taylor and K. S. Hartke, *ibid.*, **81**, 2456 (1959).

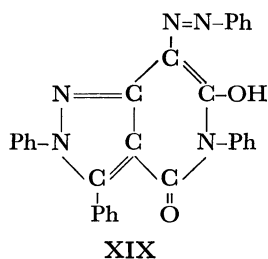
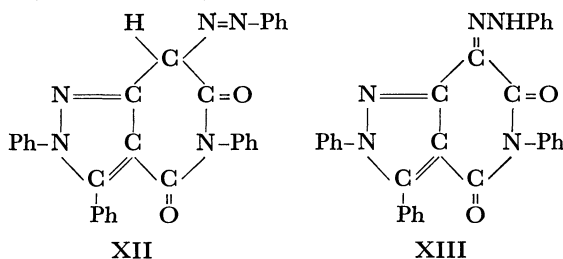
1) A. A. El-Sayed and M. Ohta, *This Bulletin*, **46**, 947 (1973).

2) K. V. Auwers and H. Holleman, *Ber.*, **18**, 313 (1885).

The reactivity of the methylene group at position 7 in pyrazolo[4,3-*c*]pyridine derivatives (VII) proved to be similar to that of the 4-methylene group in homophthalimides (XI).^{6,7}

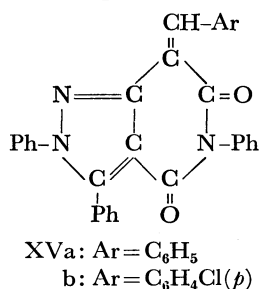


Thus, compound VII was coupled with benzenediazonium chloride to give the 7-phenylazo derivative (XII) which can also be formulated as either hydrazone (XIII) or azo-enol (XIV).⁸



However, the IR spectrum of the product shows two absorption bands in the carbonyl region (1710, 1680 cm^{-1}), but not in either the OH or NH regions. This indicates that it exists mainly in keto-azo form XII.

Compound VIIb was also condensed with aromatic aldehyde in acetic acid to furnish the 7-arylmethylene derivatives XV in the presence of sodium acetate.



Experimental

4-Carboxy-1,5-diphenylpyrazole-3-acetic Acid Anhydride (II). To a solution of 2 g of 4-carboxy-1,5-diphenylpyrazole-3-acetic acid (I) in 50 ml of anhydrous dioxane was added 10 ml of acetyl chloride and the mixture was boiled on a water bath for 30 min. The solution was concentrated and cooled and the solid that separated (1.9 g) was crystallized from benzene

to give II as colorless prismatic crystals, mp 158 °C. Found: C, 71.32; H, 3.79; N, 9.41%. Calcd for C₁₈H₁₂O₃N₂: C, 71.04; H, 3.98; N, 9.21%. IR: 1795, 1760 cm^{-1} .

3-Carboxymethyl-1,5-diphenylpyrazole-4-carboxamide (IIIa).

Dry ammonia gas was bubbled slowly through a solution of 1.0 g of the anhydride (II) in 30 ml of anhydrous dioxane solution. The ammonium salt of the product IIIa was separated within a few minutes. Water was added after the dioxane solution has been saturated with ammonia and the clear light yellow solution was acidified with 10% hydrochloric acid solution. The resulting precipitate was filtered off to yield 0.8 g of IIIa, which was recrystallized from dilute acetic acid as colorless crystals, mp 228–230 °C. Found: C, 67.15; H, 4.50; N, 12.59%. Calcd for C₁₈H₁₅O₃N₃: C, 67.27; H, 4.71; N, 13.08%. IR: 3430, 3330, 1685, 1635 cm^{-1} .

3-Carboxymethyl-1,5-diphenylpyrazole-4-carboxamides (IIIb, c).

A solution of II (3 g; 1 mol) in anhydrous dioxane (50 ml) was treated with appropriate amines (2.2 mol) and the mixture was refluxed for 15 min and then cooled. The reaction mixture was diluted with water (20 ml) and acidified with 10% hydrochloric acid solution. The solid that separated was collected and crystallized from the proper solvent to give IIIb, c.

3-Carboxymethyl-1,5-diphenylpyrazole-4-carboxybenzylamide (IIIb). Colorless crystals from ethanol, mp 185 °C (85%). Found: C, 72.74; H, 5.70; N, 10.10%. Calcd for C₂₅H₂₁O₃N₃: C, 72.98; H, 5.14; N, 10.21%. IR: 3280, 1720, 1620 cm^{-1} .

3-Carboxymethyl-1,5-diphenylpyrazole-4-carboxyanilide (IIIc).

Colorless crystals from ethanol, mp 232–234 °C. Found: C, 72.22; H, 4.62; N, 10.64%. Calcd for C₂₄H₁₉O₃N₃: C, 72.53; H, 4.82; N, 10.57%. IR: 3400, 1698, 1665 cm^{-1} .

1,5-Diphenyl-3-methylpyrazole-4-carboxyanilide (V).

(Method A): Half a gram of IIIc was heated in a metal bath at 250 °C until the evolution of carbon dioxide stopped. The residue was triturated with ethanol and then crystallized from ethanol as colorless crystals, mp 178–180 °C.

(Method B): A suspension of 1.0 g of 4-carboxy-1,5-diphenyl-3-methylpyrazole (VI) in 20 ml of anhydrous benzene was treated with 3 ml of thionyl chloride and the mixture was refluxed until hydrogen chloride evolution stopped. The reaction mixture was distilled to dryness and the residue was dissolved in 50 ml of anhydrous benzene and treated with 0.7 g of aniline (2 mol). The reaction was refluxed for 2 hr, cooled and filtered to remove aniline hydrochloride. The filtrate was concentrated and cooled, and the precipitate formed was collected and recrystallized from ethanol, mp 180–181 °C. The products obtained by methods A and B were identical, as judged by mixed melting point determination and by comparison of infrared spectra. Found: C, 77.88; H, 5.38; N, 11.88%. Calcd for C₂₃H₁₉ON₃: C, 78.16; H, 5.42; N, 11.89%. IR: 3389, 1665 cm^{-1} .

2,3-Diphenylpyrazole[4,3-*c*]pyridine-(5H,7H)-4,6-dione (VIIa).

Three grams of acid I was treated with 10 ml of concentrated ammonium hydroxide solution and the resulting solution was heated on a boiling water bath to dryness and then heated in a metal bath at 220 °C under reduced pressure. The residue obtained was triturated with ethanol to give a yellow solid (1.8 g) of VIIa, which was recrystallized from ethanol as yellow crystals, mp 251–252 °C. Found: C, 71.08; H, 4.40; N, 13.80%. Calcd for C₁₈H₁₃O₂N₃: C, 71.27; H, 4.32; N, 13.86%. IR: 3180, 3055, 1715, 1685 cm^{-1} .

2,3,5-Triphenylpyrazolo[4,3-*c*]pyridine-(5H,7H)-4,6-dione (VIIb).

A suspension of 2 g of IIIc in 50 ml of anhydrous benzene was treated with 10 ml of acetyl chloride and the mixture was boiled on a water bath for 2 hr. The

6) A. Meyer and R. Vittenet, *Ann. Chim.*, (10) **17**, 272 (1937).

7) A. Meyer, *Bull. Soc. Chim. Fr.*, (4) **51**, 953 (1932).

8) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley & Sons, Inc., New York, (1952), p.439.

solution obtained was concentrated to dryness and the residue was triturated with ethanol to give a pale yellow solid (1.3 g) which was crystallized from acetic acid as pale yellow crystals, mp 217—219 °C. Found: C, 75.56; H, 4.37; N, 11.22%. Calcd for $C_{24}H_{17}O_2N_3$: C, 75.97; H, 4.52; N, 11.08%. IR: 1720, 1680 cm^{-1} .

*2,3,5-Triphenyl-7-phenylazopyrazolo[4,3-*c*]pyridine-(5H,7H)-4,6-dione (XII).* A solution of 0.5 g of VIIb in 50 ml of pyridine was cooled in ice and treated with a solution of an equimolar amount of benzenediazonium chloride (prepared from 0.15 g of aniline in 2 ml of concentrated hydrochloric acid, 2 ml of water and 0.1 g of sodium nitrite), left to stand in ice for 1 hr and then diluted with water (100 ml). The product that separated was filtered off, washed thoroughly with water and crystallized from dioxane as orange voluminous crystals, mp 262—266 °C. Found: C, 74.22; H, 4.44; N, 14.27%. Calcd for $C_{30}H_{21}O_2N_5$: C, 74.52; H, 4.38; N, 14.49%. IR: 1710, 1680 cm^{-1} .

Condensation of Compound VIIb with Aromatic Aldehyde.

A solution of VII (1 g) and anhydrous sodium acetate (2g) in glacial acetic acid (100 ml) was treated with an equimolar amount of appropriate aldehydes, and the mixture was refluxed for 1 hr. It was then cooled and the crystalline precipitate was filtered off. The arylidene derivatives XVa, b were yellow and gave red coloration with concentrated sulfuric acid.

*7-Benzal-2,3,5-triphenylpyrazolo[4,3-*c*]pyridine-(5H,7H)-4,6-dione (XVa).* This was recrystallized from acetic acid, mp 256—257 °C. Yield 90%. Found: C, 79.34; H, 4.46; N, 9.10%. Calcd for $C_{31}H_{21}O_2N_3$: C, 79.64; H, 4.53; N, 8.99%. IR: 1715, 1680 cm^{-1} .

*7-p-Chlorobenzal-2,3,5-triphenylpyrazolo[4,3-*c*]pyridine-(5H,7H)-4,6-dione (XVb).* This was recrystallized from acetic acid, mp 250—252 °C, yield 82%. Found: C, 73.88; H, 4.08; N, 8.29%. Calcd for $C_{31}H_{20}O_2N_3Cl$: C, 74.12; H, 3.95; N, 8.37%.
