Studies on the Synthesis of Heterocyclic Compounds. Part IV. Further Investigation of the Pschorr Reaction with Some Pyrazole Derivatives

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Thermal decomposition of the diazonium sulfate derived from *N*-methyl-(1-phenyl-3-methylpyrazol-5-yl)-2-aminobenzamide afforded products formulated as 1-phenyl-3-methyl[2]benzopyrano[4,3-*c*]pyrazol-5-one (yield 10%), 1,4-dimethyl-3-phenylpyrazolo[3,4-*c*]isoquinolin-5-one (yield 10%), *N*-methyl-(1-phenyl-3-methylpyrazol-5-yl)-2-hydroxybenzamide (yield 8%) and 4'-hydroxy-2,3'-dimethyl-1'-phenylspiro[isoindoline-1,5'-[2]pyrazolin]-3-one (yield 20%). Decomposition of the diazonium sulfate derived from *N*-methyl-(1,3-diphenylpyrazol-5-yl)-2-aminobenzamide gave products formulated as 7,9-dimethyldibenzo[*e,g*]pyrazolo[1,5-*a*][1,3]diazocin-10-(9*H*)one (yield 8%), 4-methyl-1,3-diphenylpyrazolo[3,4-*c*]isoquinolin-5-one (yield 7%) and 4'-hydroxy-2-methyl-1',3'-diphenylspiro[isoindoline-1,5'-[2]pyrazolin]-3-one (yield 10%).

The spiro compounds **6a,b** underwent thermal and acid-catalysed conversion into the hitherto unknown 2-benzopyrano[4,3-*c*]pyrazole ring system **7a,b** in good yield. Analytical and spectral data are presented which supported the structures proposed.

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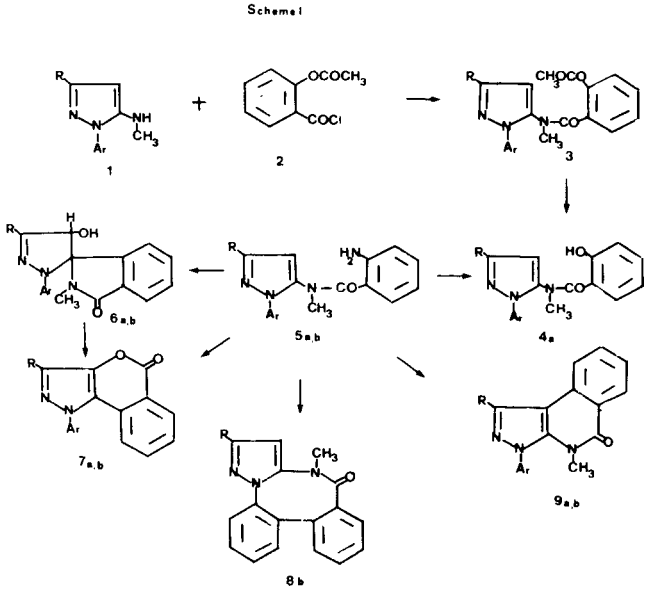
In the preceding article (1), it was reported that diazotisation of *N*-methyl-(1-phenyl-3-*R*-pyrazol-5-yl)-2-aminobenzamides **5a,b**, followed by the Pschorr reaction, afforded the desired pyrazolo[3,4-*c*]isoquinolin-5-one derivatives **9a,b**, together with some additional products, which were separated by column chromatography. The structural elucidation of these compounds and a complete study of the reaction mixtures led us to reinvestigate the Pschorr reaction of the above amines **5a,b**, which was carried out by the method previously described (1).

Thermal decomposition of the diazonium sulfate derived from amine **5a** resulted in the isolation and identification of four products. On the basis of analytical and spectral data these compounds were formulated as *N*-methyl-(1-phenyl-3-methylpyrazol-5-yl)-2-hydroxybenzamide (**4a**), 4'-hydroxy-2,3'-dimethyl-1'-phenylspiro[isoindoline-1,5'-[2]pyrazolin]-3-one (**6a**), 1-phenyl-3-methyl[2]benzopyrano-[4,3-*c*]pyrazol-5-one (**7a**) and 1,4-dimethyl-3-phenylpyrazolo[3,4-*c*]isoquinolin-5-one (**9a**), which was described in an earlier paper (1).

Scheme I



a. R=CH_3 Ar=C_6H_5
b. R=Ar=C_6H_5

The identity of the first product **4a** was readily confirmed by an independent synthesis outlined in the scheme I (2).

The second product **6a** had a molecular weight of 307 (mass spectrum) and a molecular formula of $C_{18}H_{17}N_3O_2$ (analytical data). Support of the spiroisoindolinone structure **6a** was provided by spectral data and the reactions of the compound. The infrared spectrum showed a broad absorption band centered at 3250 cm^{-1} (hydroxyl group) and an intense band at 1690 cm^{-1} (amidic carbonyl group). The most significant features of the nmr spectrum determined at 90 MHz were the resonance band of the hydroxyl group splitted into a doublet at δ 6.40 (J = 5.4 Hz) and the shift of the methyne signal to higher field (*ca.* 1 ppm) with respect the H-4 absorption of the pyrazole nucleus. This signal, seen as a doublet at δ 5.40 (J = 5.4 Hz) was attributable to a methyne group of CH-OH group. On addition of deuterium oxide, the OH signal disappeared and the C*H*-OH peaks were replaced by a single peak.

The spiro compound **6a** underwent the thermal or acid-catalysed conversion into 1-phenyl-3-methyl[2]benzopyrano[4,3-*c*]pyrazol-5-one (**7a**) in good yield. This facile conversion suggested that the compound was an intermediate in the thermal decomposition of the diazonium salt to the 2-benzopyranopyrazolo **7a**.

The assigned structure **7a** was consistent with the molecular weight (mass spectrum), molecular formula (analytical data) and spectral data. The ir spectrum of the

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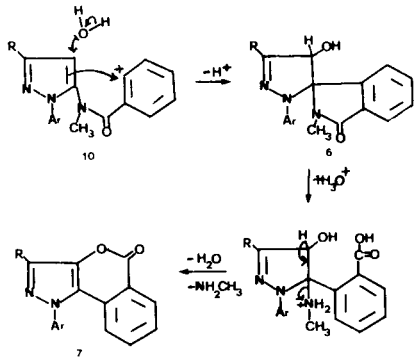
SCHEME II



compound displayed two carbonyl bands at 1725 and 1745 cm^{-1}, probably due to Fermi resonance (3). The nmr spectrum lacked an absorption at the chemical shift attributable to a methyne proton of a pyrazole nucleus and exhibited, besides other signals for the remaining protons, a multiplet (1H) centered at δ 8.4, likely due to the H-6 of the benzopyrano ring deshielded by the anisotropy of the carbonyl group.

The product **7a** is an example of the hitherto unreported 2-benzopyrano[4,3-*c*]pyrazolo ring system.

Thermal decomposition of the diazonium sulfate derived from amine **5b** gave three products formulated as 4'-hydroxy-2-methyl-1',3'-diphenylspiro[isoindoline-1,5'-[2]pyrazolin]-3-one (**6b**), 7,9-dimethyldibenzo[*e*,*g*]pyrazolo-[1,5-*a*][1,3]diazocin-10-(9*H*)one (**8b**) and 4-methyl-1,3-diphenylpyrazolo[3,4-*c*]isoquinolin-5-one (**9b**), previously described (1).

Compound **6b** underwent the facile acid-catalysed and thermal conversion into **7b** previously observed with the corresponding **6a**. The structures of the compounds **6b** and **7b** were supported by analytical data and spectral evidences. The infrared and nmr spectra were similar in essential detail to those above reported for the analogous spiroisoindolinone **6a** and benzopyranopyrazolo **7a**.

The product, which was assigned structure **8b**, had a molecular weight of 351 (mass spectrum) and a molecular formula of $C_{23}H_{17}N_3O$ (analytical data). The infrared spectrum showed an absorption band at 1655 cm^{-1} attributable to an amidic carbonyl group. Significantly, the nmr spectrum showed a singlet at δ 6.48 (1H), characteristic of the H-4 pyrazole resonance. The above evidences suggested that the compound was the pyrazolodibenzodiazocinone **8b**, whose formation implies an electrophilic attack of the phenyl-cation **10**, resulting from elimination of the nitrogen atoms of the diazonium salt, in the *ortho*-position of the *N*-phenyl group of the pyrazole ring.

The formation of **6a,b** can be outlined as follows (see Scheme II). Furthermore, a plausible mechanism for the acid-catalysed reaction of the spiro compounds **6a,b** involves the initial hydrolysis of the amidic bond followed by cyclodehydration and elimination of methylamine to give the benzopyranopyrazoles **7a,b**. The results obtained, by assuming a heterolytic SN_1 mechanism for the uncatalysed decomposition of the diazonium salts in aqueous solution, illustrate that the phenyl-cation **10** derived from these pyrazole substrates is highly reactive but unselective.

In order to maximize the yields of the products **9a,b**, decomposition of diazonium sulfates derived from the amines **5a,b** was attempted by adjusting the solution to *p*H 6.5. In a less acidic medium the weakly basic 2-nitrogen of the pyrazole ring is not protonated and a favourable intramolecular nucleophilic attack at position 4, where the electronic density is greatest, was expected. Decomposition of the diazonium salts under these conditions gave complex mixtures and also proved unsatisfactory in raising the yields of the pyrazoloisoquinolinones **9a,b**.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Infrared spectra were determined in nujol mull (unless otherwise specified) with a Perkin-Elmer 137 spectrophotometer; nmr spectra were obtained with a Varian EM-390 90MHz spectrometer (TMS as internal reference). A Jeol-JMS-01-SG-2 mass spectrometer was employed for determination of low resolution 75 eV mass spectra.

Decomposition of the Diazonium Sulfate Derived from *N*-Methyl-(1-phenyl-3-methylpyrazol-5-yl)-2-aminobenzamide.

The amine **5a** (1) (6.12 g.) was dissolved in concentrated sulphuric acid (15 ml.) and water (200 ml.) and the solution cooled at 0-5°. A solution of sodium nitrite (1.4 g.) in water (20 ml.) was added dropwise and the solution stirred for a further 1 hour in the ice-bath. The yellow solution was then filtered and gently warmed on a water-bath to 70° for 1.5 hours.

The suspension thus obtained was adjusted to *p*H 7 with aqueous sodium hydroxide and extracted with chloroform (3 × 150 ml.). The combined extracts were dried (sodium sulfate) and the chloroform was evaporated. The red-brown residue (6 g.) was then chromatographed on a column of silica gel with 15% of water (500 g.), using chloroform as the eluent. The initial colourless eluate and the successive yellow fractions F_{1-15} (each 50 ml.) were neglected. The combined fractions 16-23 (each 50 ml.) were evaporated and the product, which solidified, was crystallized from ethanol.

1-Phenyl-3-methyl[2]benzopyrano[4,3-*c*]pyrazol-5-one (**7a**).

This compound was obtained, m.p. 171-173°; molecular weight by mass spectroscopy m/e 276; ir: cm^{-1} 1725 and 1745 (CO); nmr (deuterochloroform): δ 2.50 (3H, s, CH_3), 6.40-7.40 (8H, m, aromatic protons), 8.40 (1H, m, H-6).

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.83; H, 4.32; N, 10.26.

Further elution with chloroform F_{24-33} (each 50 ml.) afforded a residue, which was crystallized from ethanol. The crystalline material was chromatographed by preparative tlc on silica gel (benzene-ethyl ether 1:1, as eluent) to give the pyrazoloisoquinolone **9a**, previously described (1), and further quantities of the benzopyranopyrazolo **7a** (overall yield of compound **7a** was 10%). Evaporation of fractions 34-73 (each 50 ml.) gave a residue, which was crystallized from ethanol; 1,4-dimethyl-3-phenylpyrazolo[3,4-*c*]isoquinolin-5-one (**9a**) was obtained (1).

The mother liquors were concentrated to dryness under reduced pressure and the residue was treated with aqueous potassium hydroxide 15% (30 ml.). After stirring for 5 minutes, the suspension was filtered off

and the solution was adjusted to *p*H 5 and extracted with chloroform (3 × 30 ml.). The organic phases were dried (sodium sulfate) and evaporated to leave a residue which was crystallized from petroleum ether b.p. 60-80°. *N*-methyl-(1-phenyl-3-methylpyrazol-5-yl)-2-hyroxybenzamide (**4a**) was obtained (yield 8%), m.p. 114-116°; ir (hexachlorobutadiene): broad band centered at 3100 cm^{-1} (OH) 1635 cm^{-1} (CO); nmr (deuterochloroform): δ 2.23 (3H, s, CH_3), 3.32 (3H, s, CH_3), 6.10 (1H, s, CH), 6.40-7.40 (9H, m, aromatic protons), 10.30 (1H, s, OH, exchangeable with deuterium oxide); molecular weight by mass spectroscopy m/e 307.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.33; H, 5.60; N, 13.75.

Fractions 74-114 were discarded and the successive combined fractions $F_{115-173}$ (each 50 ml.) were collected, the solvent removed and the product was crystallized from ethanol to give 4'-hydroxy-2,3'-dimethyl-1'-phenylspiro[isoindoline-1,5'-[2]pyrazolin]-3-one (**6a**) (yield 20%), m.p. 245-246°; molecular weight by mass spectroscopy m/e 307; ir: cm^{-1} 3250 (OH), 1690 (CO); nmr (DMSO-d_6): δ 2.15 (3H, s, CH_3), 2.58 (3H, s, CH_3), 5.30 (1H, d, CH, J = 5.4 Hz), 6.40 (1H, d, OH, J = 5.4 Hz, exchangeable with deuterium oxide), 6.55-8.00 (9H, m, C_6H_4 and C_6H_5).

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.30; H, 5.61; N, 13.71.

Decomposition of the Diazonium Sulfate Derived from *N*-Methyl-(1,3-diphenylpyrazol-5-yl)-2-aminobenzamide.

The amine **5b** (1) (5 g.) was dissolved in a solution of concentrated sulphuric acid (125 ml.) and water (540 ml.). After cooling at 0-5°, a solution of sodium nitrite (0.96 g.) in water (15 ml.) was added dropwise. After being stirred for 1.5 hours the yellow solution was filtered and gently warmed on a water-bath to 70° for 1.5 hours. The suspension thus obtained was adjusted to *p*H 7 with aqueous sodium hydroxide and extracted with chloroform (3 × 400 ml.). Evaporation of the dried (sodium sulfate) extracts left a red-brown residue (5 g.), which was chromatographed on a column of silica gel with 15% of water (460 g.), using chloroform as eluent. The first 350 ml. were neglected and the successive fractions 20-30 (each 50 ml.) were evaporated under reduced pressure to leave 7,9-dimethyldibenzo[*e*,*g*]pyrazolo[1,5-*a*][1,3]diazocin-10-(9*H*)one (**8b**), which was crystallized from ethanol (yield 8%), m.p. 188-190°; molecular weight by mass spectroscopy m/e 351; ir: cm^{-1} 1655 (CO); nmr (deuterochloroform): δ 3.25 (3H, s, CH_3), 6.47 (1H, s, CH), 7.03-7.83 (13H, m, 2 × C_6H_4 and C_6H_5).

Anal. Calcd. for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.59; H, 4.94; N, 12.06.

Further elution with chloroform (fractions 31-58) (each 50 ml.) afforded a residue, which was crystallized from ethanol. 4-Methyl-1,3-diphenylpyrazolo[3,4-*c*]isoquinolin-5-one (yield 7%), previously described, (1) was obtained.

Fractions 60-94 (each 50 ml.) were discarded and the successive combined fractions 95-110 (each 50 ml.) were collected, the solvent removed and the product was crystallized from ethanol to give 4'-hydroxy-2-methyl-1',3'-diphenylspiro[isoindoline-1,5'-[2]pyrazolin]-3-one (**6b**) (yield 10%), m.p. 264-265° (ethanol); molecular weight by mass spectroscopy m/e 369; ir: cm^{-1} 3240 (broad) (OH), 1685 (CO); mmr (DMSO-d_6): δ 2.60 (3H, s, CH_3), 5.80 (1H, d, CH, J = 5.8 Hz), 6.65 (1H, d, OH, J = 5.8 Hz, exchangeable with deuterium oxide) 6.75-8.10 (14H, m, aromatic protons).

Anal. Calcd. for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.38. Found: C, 74.90; H, 5.24; N, 11.34.

N-Methyl-(1-phenyl-3-methylpyrazol-5-yl)-2-acethoxybenzamide (**3**).

Equimolar amounts of **1** (1) (10 mmoles) and 2-acetylsaliciloyl chloride (2) (4) in chloroform were stirred at room temperature for 24 hours. The solution was evaporated to dryness under reduced pressure; the residue was crystallized from diethylether, m.p. 114-115°; ir: cm^{-1} 1660 (amidic CO), 1765 (ester CO); molecular weight by mass spectroscopy m/e 349; nmr (deuterochloroform): δ 2.20 (6H, s, 2x, CH_3), 3.30 (3H, s, CH_3), 6.10 (1H, s, CH), 6.60-7.70 (9H, m, aromatic protons).

Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.91; H, 5.60; N, 12.02.

N-Methyl-(1-phenyl-3-methylpyrazol-5-yl)-2-hydroxybenzamide (**4a**).

A solution of **3** (0.9 g.) in ethanol (9 ml.) was treated with the stoichiometric quantity of potassium hydroxide and refluxed for 15 minutes. The resulting solution was extracted with benzene (2 × 20 ml.). The inorganic layer was neutralized and extracted with chloroform (2 × 20 ml.). The combined extracts were dried (sodium sulfate) and evaporated under reduced pressure to give 75% of **4a**. The product melted at 114-115° (petroleum ether) and was identical in all respects with a sample of *N*-methyl-(1-phenyl-3-methylpyrazol-5-yl)-2-hydroxybenzamide obtained by decomposition of diazonium salt derived from amine **5a**.

1-Phenyl-3-*R*-[2]benzopyrano[4,3-*c*]pyrazol-5-ones (**7a,b**).

Method A.

The spiro compounds **6a,b** were heated twenty degrees above their melting points for 5 minutes. The crude **7a,b** were purified by preparative tlc on silica gel (chloroform as eluent), yield 60%.

Method B.

A mixture of spiro compounds **6a,b** (200 mg.) dissolved in ethanol (5 ml.) and 5 ml. of aqueous hydrochloric acid (36.5%) was refluxed for 4 hours. Upon removal of the solvent under reduced pressure, the crude **7a,b** was worked up in the same manner described in the method A, yield 50%.

The compound **7a**, obtained by the above methods, was identical in all respects with 1-phenyl-3-methyl[2]benzopyrano[4,3-*c*]pyrazol-5-one, isolated from the reaction mixture obtained by decomposition of the diazonium salt derived from amine **5a**.

1,3-Diphenyl[2]benzopyrano[4,3-*c*]pyrazol-5-one (**7b**).

The product melted at 234-236° (ethanol); molecular weight by mass spectroscopy m/e 338; ir: cm^{-1} 1730-1760 (CO); nmr (deuterochloroform): δ 7.20-8.30 (13H, m, aromatic protons), 8.50 (1H, m, H-6).

Anal. Calcd. for $C_{22}H_{14}N_2O_2$: C, 78.09; H, 4.17; N, 8.28. Found: C, 78.21; H, 4.08; N, 8.34.

REFERENCES AND NOTES

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(2) The experimental data previously reported for compound **4a** (1), must be attributable to the spiro compound **6a**. The nmr spectrum determined at 90 MHz, was reinterpreted.

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(4) Ch. Weizmann, E. D. Bergmann and M. Sulzbacher, *J. Org. Chem.*, **13**, 796 (1948).