# Studies on the Synthesis of Heterocyclic Compounds. Part I. The Pschorr Reaction in the Pyrazole Series



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Preparation and structural evidence of *N*-methyl-(1,3-R,R′-pyrazol-5-yl)-*o*-nitrobenzamides (VIIIa,b) are discussed. Diazotisation of related *o*-aminobenzamides XIa,b followed by the Pschorr reaction afforded a very complex mixture from which pyrazolo[3,4-*c*]isoquinolin-5-ones XIIa,b in 7-10% yields together with *N*-methyl-(1,3-R,R′-pyrazol-5-yl)-*o*-hydroxybenzamides (XIIIa) in 15-20% yields were isolated.

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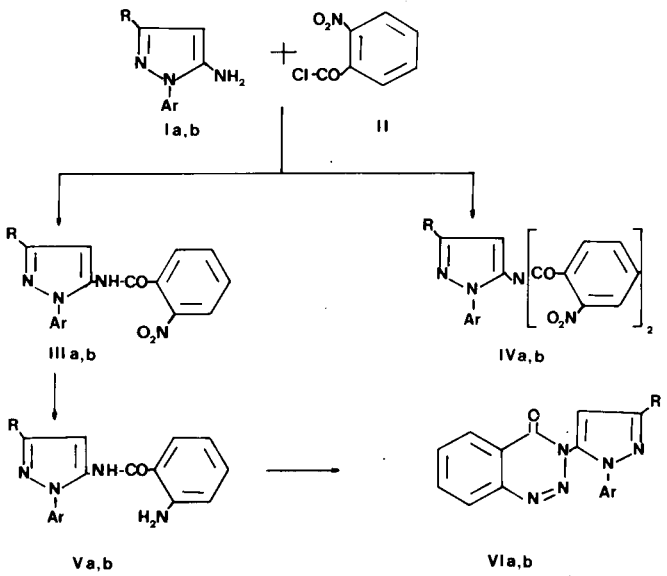
Previous synthesis of pyrazolo[3,4-*c*]isoquinoline derivatives have involved either the route of condensation of aminopyrazolinones with enaminoketones leading to hexahydroderivatives of the tricyclic system XII (1) or a thermal cyclization of ureas of pyrazole compounds (2).

The purpose of the present work was to investigate the Pschorr reaction in the pyrazole series, in order to develop a new method of synthesis of pyrazolo[3,4-*c*]-isoquinolines. The initial approach toward this synthetic goal involved the use of *N*-R-(1,3-R,R′-pyrazol-5-yl)-*o*-aminobenzamides, as starting materials, in which, to eliminate the formation on diazotisation of the hitherto unknown 3-pyrazolylbenzotriazinones VIa,b (Scheme I), R shoule be an alkyl group (*e.g.*, R = $CH_3$).

SCHEME I




a R = $CH_3$, Ar = $C_6H_5$

b R = Ar = $C_6H_5$.

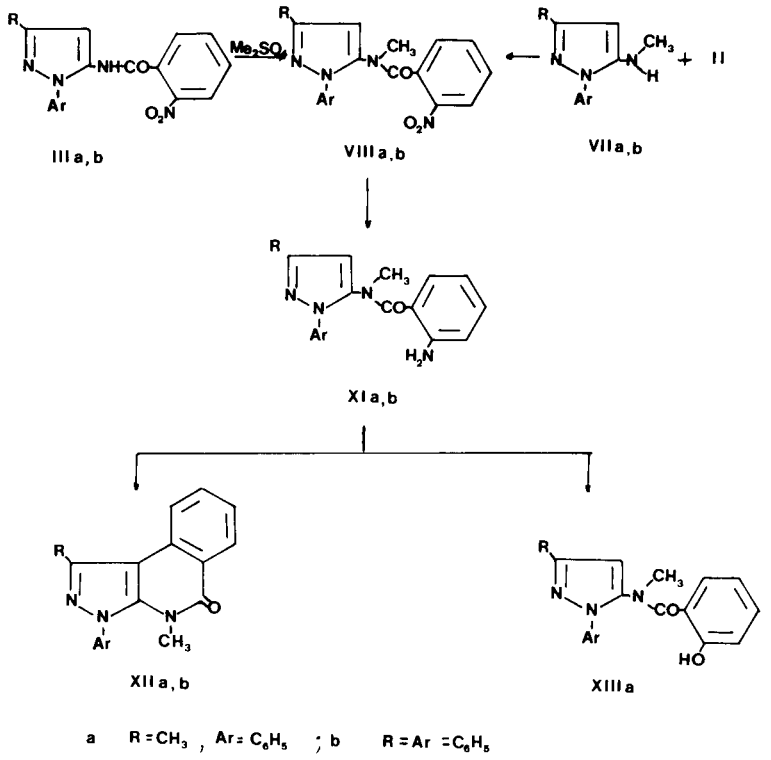
Particularly, as a route to the compounds VIIIa,b we proposed the condensation of Ia,b with *o*-nitrobenzoylchloride (II) in the presence of triethylamine, as recently reported by some of us (3), followed by methylation and successive reduction to give the desired compounds XIa,b. In these compounds the 4-position of pyrazole nucleus is available for electrophilic substitutions and the two positions in the aromatic nuclei between which the new internuclear bond is to be formed are near enough to permit the creation of the six-membered ring under the Pschorr reaction conditions, which involved diazotisation and the complete elimination of the nitrogen atoms (Scheme II).

Concerning the methylation reaction of IIIa,b which was carried out with dimethylsulfate in aqueous potassium hydroxide solution, three possible methylderivatives could be formed, depending upon whether the substitution reaction takes place at the exocyclic nitrogen (VIIIa,b), the pyrazolic nitrogen (Xa,b) or the oxygen atom (IXa,b). However, the presence in the ir spectrum of an amide I absorption strong band at 1700 $cm^{-1}$ eliminated the structures IXa,b. In order to decide between the structures VIII and X, we condensed the 5-methylaminopyrazoles VIIa,b with II. The products obtained were found to be identical with the compounds prepared by methylation of IIIa,b, so that we believe the assigned structures VIIIa,b to be correct. The 5-methylaminopyrazoles VIIa,b were prepared by the method shown in Scheme III.

The nmr spectra of these compounds in deuteriochloroform were completely explained in terms of structures VIIa,b, which showed a doublet at δ 2.80-2.85 (J = 5.0 Hz) attributable to a methyl group of the NH-$CH_3$ group and a broad NH signal at δ 3.70. On addition of deuterium oxide, the NH signal disappeared and the 5-N-$CH_3$ peaks were replaced by a single peak.

It is interesting to note that the more convenient route to VIIIa,b (yield 65-70%) is the condensation of the 5-methylaminopyrazoles with II, because the methylation reaction of IIIa,b was unsatisfactory (yield 10-12%) for recovering unreacted *N*-(1,3-R,R′-pyrazol-5-yl)-*o*-nitrobenzamides.

SCHEME II



a R = $CH_3$ , Ar = $C_6H_5$ ; b R = Ar = $C_6H_5$

The starting compounds *N*-blocked *o*-aminobenzamide derivatives XIa,b were obtained in high yield either by reduction of VIIIa,b by means of iron and acetic acid or by catalytic reduction with palladium on charcoal. Thus, by boiling an aqueous solution of diazonium sulfate prepared *in situ* from XIa,b, a very complex reaction mixture was obtained from which the pyrazolo[3,4-c]-isoquinolin-5-one derivatives XIIa,b in 7-10% yield together with *N*-methyl-(1,3-R,R′-pyrazol-5-yl)-*o*-hydroxybenzamides XIIIa in 15-20% yield were isolated (4).

Elemental analysis, molecular weights (MS), ir and nmr spectra were in agreement with the assigned structures. Concerning the structures XIIa,b, proof that substitution occurred at the 4-position of the pyrazole nucleus was discernible from the nmr spectra which lacked an absorption at a chemical shift attributable to 4-H of the pyrazole ring.

No attempt was made to maximize the XIIa,b recovery.

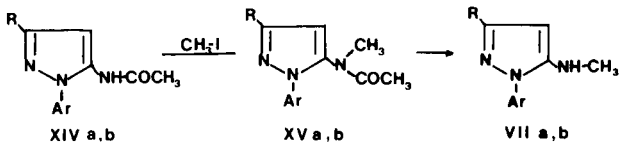
## EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Infrared spectra were determined in nujol mull with Perkin Elmer infracord 137 spectrophotometer, nmr spectra were obtained with a Jeol C-60H spectrometer (TMS as internal reference). A Jeol JMS-10SG-2 mass spectrometer was employed for determination of low resolution 75 eV mass spectra.

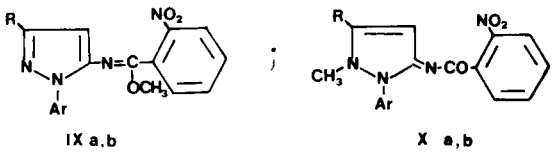
*N*-(1,3-Diphenylpyrazol-5-yl)-*o*-nitrobenzamide (IIIb) and *N,N′*-(1,3-Diphenyl-pyrazol-5-yl)bis-*o*-nitrobenzamide (IVb).

Compound Ib (5) (10 mmoles) was dissolved in 100 ml. of chloroform and 10 mmoles of *o*-nitrobenzoylchloride (II) was added. Triethylamine (10 mmoles) was added in one portion and the mixture was refluxed for 3 hours. The solution was evaporated

SCHEME III



a R = $CH_3$ , Ar = $C_6H_5$ ; b R = Ar = $C_6H_5$



a R = $CH_3$ , Ar = $C_6H_5$ ; b R = Ar = $C_6H_5$

under reduced pressure and the resulting crude solid was refluxed with ethanol (100 ml.). The insoluble material was filtered off and recrystallized to give IVb (yield 12-15%), m.p. 242-244° (ethylacetate); ir $cm^{-1}$: 1720-1740 (CO); nmr (DMSO-$d_6$): δ 7.18-8.40 (m, aromatic protons).

*Anal.* Calcd. for $C_{29}H_{19}N_5O_6$: C, 65.27; H, 3.59; N, 13.13. Found: C, 65.23; H, 3.51; N, 13.16.

The ethanolic solution concentrated to small volume left IIIb (yield 45-50%), m.p. 230-232° (ethanol); ir $cm^{-1}$: 3140 (NH), 1690 (CO); nmr (DMSO-$d_6$): δ 7.08 (1H, s, pyrazole CH), 7.30-8.20 (14H, m, 2 x $C_6H_5$ and $C_6H_4$), 11 (1H, s, NH).

*Anal.* Calcd. for $C_{22}H_{16}N_4O_3$: C, 68.74; H, 4.20; N, 14.58. Found: C, 68.71; H, 4.20; N, 14.60.

*N*-(1,3-Diphenylpyrazol-5-yl)-*o*-aminobenzamide (Vb).

Catalytic hydrogenation of IIIb as described for Va (3) afforded Vb (yield 65%), m.p. 190-192° (ethanol); ir: multiple bands in the 3 μ region and 1680 $cm^{-1}$ (CO); nmr (DMSO-$d_6$): δ 6.20-8.00 (m, aromatic protons and $NH_2$).

*Anal.* Calcd. for $C_{22}H_{18}N_4O$: C, 74.55; H, 5.12; N, 15.81. Found: C, 74.56; H, 4.97; N, 15.89.

General Procedure for 3-Pyrazolylbenzo-1,2,3-triazin-4(3*H*)ones (VIa,b).

To a stirred solution of Va,b (10 mmoles) in acetic acid (150 ml.) at 0-5°, sodium nitrite (20 mmoles) in water (5 ml.) was added dropwise. Stirring was continued for 1 hour at 0-5° and then the solution was allowed to warm to room temperature. The white precipitate obtained from addition of water to the solution was filtered off, washed with water and recrystallized, yield 68-70%.

VIa.

The product melted at 112-114° (ethanol); ir: $cm^{-1}$ 1710 (CO); nmr (DMSO-$d_6$): δ 2.30 (3H, s, $CH_3$), 6.64 (1H, s, pyrazole CH), 7.10-8.40 (9H, m, $C_6H_5$ and $C_6H_4$).

*Anal.* Calcd. for $C_{17}H_{13}N_5O$: C, 67.31; H, 4.32; N, 23.09. Found: C, 67.44; H, 4.38; N, 23.05.

VIb.

The product melted at 189-190° (ethanol); ir: $cm^{-1}$ 1700 (CO); nmr (DMSO-$d_6$): δ 7.30-8.50 (m, aromatic protons).

*Anal.* Calcd. for $C_{22}H_{15}N_5O$: C, 72.31; H, 4.14; N, 19.17. Found: C, 72.28; H, 4.12; N, 19.19.

*N*-Methyl-(1,3-R,R'-pyrazol-5-yl)-acetamides (XVa,b).

To a solution of 7 g. of sodium in absolute ethanol (375 ml.) 0.23 mole of XIVa (6), XIVb (7) were added. While stirring, methyl iodide (0.30 mole) was added dropwise and the solution was kept at room temperature for 10 hours. After removal of ethanol under reduced pressure, the resultant residue was treated with water (100 ml.) and then with hydrochloric acid (36%), the solution was basified dropwise with sodium hydroxyde (30%) and the crystalline product which precipitated was collected (yield 90%).

XVa.

The product melted at 82-84° (petroleum ether, b.p. 40-70°); ir: $cm^{-1}$ 1680 (CO); nmr (deuteriochloroform): δ 1.84 (3H, s, $CH_3$), 2.34 (3H, s, $CH_3$), 3.10 (3H, s, $CH_3$), 6.10 (1H, s, pyrazole CH), 7.30 (5H, s, $C_6H_5$).

*Anal.* Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.14; H, 6.74; N, 18.19.

XVb.

The product melted at 120-122° (ethanol-water); ir: $cm^{-1}$ 1680 (CO); nmr (deuteriochloroform): δ 1.88 (3H, s, $CH_3$), 3.18 (3H, s, $CH_3$), 6.60 (1H, s, pyrazole CH), 7.20-8.00 (10H, m, 2 x $C_6H_5$).

*Anal.* Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.20; H, 5.90; N, 14.40.

1,3-R,R'-5-Methylaminopyrazoles (VIIa,b).

A solution of crude compounds XVa,b (48 g.) in ethanol (350 ml.) was treated with aqueous 5*N* potassium hydroxide (200 ml.) and refluxed for 10 hours.

VIIa.

After evaporation under reduced pressure the residue was extracted with ether (3 x 150 ml.) and the organic layer was shaken with aqueous *N* hydrochloric acid (3 x 100 ml.). The aqueous solution was washed with ether (2 x 100 ml.) and then basified with potassium hydroxide (30%) and extracted with ether. Drying (sodium sulfate) and evaporation left an oil (34 g.) which was purified by column chromatography over silica gel with 15% of water (chloroform as eluent); ir (film): $cm^{-1}$ broad bands in the 3 μ region (NH); nmr (deuteriochloroform): δ 2.22 (3H, s, $CH_3$), 2.70 (3H, d, N-$CH_3$, J = 5.0 Hz), 3.60 (broad, NH), 5.30 (1H, s, pyrazole CH), 7.10-7.80 (5H, m, $C_6H_5$).

*Anal.* Calcd. for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.54; H, 7.02; N, 22.53.

VIIb.

On cooling, a crystalline product was separated, m.p. 106-108° (benzene-petroleum ether); nmr (deuteriochloroform): δ 2.85 (3H, d, $CH_3$, J = 5.0 Hz), 3.70 (broad, NH), 5.80 (1H, s, pyrazole CH), 7.00-8.00 (10H, m, 2 x $C_6H_5$).

*Anal.* Calcd. for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.86. Found: C, 77.05; H, 6.05; N, 16.81.

*N*-Methyl-(1,3-R,R'-pyrazol-5-yl)-*o*-nitrobenzamides (VIIIa,b).

By Methylation of IIIa,b.

To a solution of 3 mmoles of IIIa,b in aqueous sodium hydroxide 10% (50 ml.) a slight excess of dimethylsulfate was added. After stirring for 24 hours at room temperature, the *N*-methylderivatives precipitated, which were collected and recrystallized from ethanol (yield 10-12%).

By adding ammonium chloride to the remaining alkaline solution, 500 mg. of unreacted III was separated.

VIIIa.

The product melted at 114-115°; ir: $cm^{-1}$ 1700 (CO); nmr (deuteriochloroform): δ 2.18 (3H, s, $CH_3$), 3.52 (3H, s, $CH_3$), 6.00 (1H, s, pyrazole CH), 6.30-8.10 (9H, m, $C_6H_5$ and $C_6H_4$).

*Anal.* Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.27; H, 4.80; N, 16.66. Found: C, 64.30; H, 4.79; N, 16.63.

VIIIb.

The product melted at 132-134°; ir: $cm^{-1}$ 1680 (CO); nmr (deuteriochloroform): δ 3.60 (3H, s, $CH_3$), 6.56 (1H, s, pyrazole CH), 7.20-8.00 (14H, m, 2 x $C_6H_5$ and $C_6H_4$).

*Anal.* Calcd. for $C_{23}H_{18}N_4O_3$: C, 69.33; H, 4.55; N, 14.06. Found: C, 69.30; H, 4.58; N, 14.03.

By *o*-Nitrobenzoylation of VIIa,b.

To a refluxed solution of equimolar amounts (20 mmoles) of VIIa,b and *o*-nitrobenzoylchloride (II) in 100 ml. of dry chloroform was added triethylamine (3 ml.) in four portions, each 1.5, 0.7, 2 X 0.4 ml., respectively, over a period of 5 hours. The solution was evaporated under reduced pressure. The residue was mixed with water (100 ml.) and extracted with ether (3 x 50 ml.). In the case of VIIb the product XIb precipitated during the

extraction. After standing for two hours, the solid was filtered off and recrystallized. The organic layer was shaken with 2*N* potassium hydroxide (100 ml.) for 10 minutes and washed with *N* hydrochloric acid (3 x 50 ml.) followed by 100 ml. of water and dried (sodium sulfate). The ether extracts evaporated left the products VIII identical with those prepared by the above method.

*N*-Methyl-(1,3-R,R'-pyrazol-5-yl)-*o*-aminobenzamides (XIa,b).

Catalytic hydrogenation of VIIIa,b, as described for compound Vb, afforded XI (yield 55%).

XIa.

The product melted at 142-144° (ethanol); ir: $cm^{-1}$ 3400 and 3500 ($NH_2$), 1660 (CO); nmr (deuteriochloroform): δ 2.25 (3H, s, $CH_3$), 3.36 (3H, s, $CH_3$), 4.30 (2H, s, $NH_2$), 6.04 (1H, s, pyrazole CH), 6.30-7.50 (9H, m, $C_6H_5$ and $C_6H_4$).

*Anal.* Calcd. for $C_{18}H_{18}N_4O$: C, 70.56; H, 5.92; N, 18.29. Found: C, 70.54; H, 5.89; N, 18.22.

XIb.

The product melted at 120-122° (ethanol); ir: $cm^{-1}$ 3360 3460 ($NH_2$), 1670 (CO); nmr (deuteriochloroform): δ 3.42 (3H, s, $CH_3$), 4.32 (2H, s, $NH_2$), 6.30-8.00 (14H, m, 2 x $C_6H_5$ and $C_6H_4$).

*Anal.* Calcd. for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21. Found: C, 74.95; H, 5.51; N, 15.20.

1,4-Dimethyl-3-phenylpyrazolo[3,4-*c*]isoquinolin-5-one (XIIa).

*N*-methyl-(1-phenyl-3-methylpyrazol-5-yl)-*o*-aminobenzamide (6.12 g.) was dissolved in a solution of concentrated sulphuric acid (15 ml.) and water (200 ml.). After cooling to 0° a solution of sodium nitrite (1.4 g.) in water (20 ml.) was added dropwise.

After being stirred for 1 hour at 0° the yellow soluiton was filtered and gently warmed on a water-bath to 70° for 1.5 hours. The obtained suspension was adjusted to *p*H ~ 7 with aqueous sodium hydroxide and extracted with chloroform. Evaporation of the dried (sodium sulfate) extracts left a red-brown residue (6 g.), which was chromatographed over a column of silica gel (80 g.) with 15% of water, using chloroform as eluent.

Two fractions of 200 and 400 ml. were collected. Evaporation of the first fraction afforded a residue which was recrystallized from ethanol. The crystalline material was chromatographed by preparative tlc on silica gel (benzene-petroleum ether 1:1, as eluent) to give the pyrazoloisoquinolinone XIIa, and a product of $M^+$ = 276 (8% yield).

XIIa.

This compound had m.p. 227-228° (7-10% yield); molecular weight by mass spectroscopy m/e 289; ir: $cm^{-1}$ 1650 (CO); nmr (deuteriochloroform): δ 2.60 (3H, s, $CH_3$), 3.20 (3H, s, $CH_3$), 7.40-8.60 (9H, m, $C_6H_4$ and $C_6H_5$).

*Anal.* Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.53. Found: C, 74.70; H, 5.21; N, 14.56.

Evaporation of the second fraction gave the phenolic substance XIIIa (15-20% yield).

XIIIa.

This compound had m.p. 245-246° (ethanol); molecular weight by mass spectroscopy m/e 307; ir: $cm^{-1}$ 3250 (OH), 1690 (CO); nmr (DMSO-$d_6$): δ 2.08 (3H, s, $CH_3$), 2.58 (3H, s, $CH_3$), 5.30 (1H, s, OH), 6.30-8.00 (10H, m, pyrazole CH, $C_6H_4$ 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.

4-Methyl-1,3-diphenylpyrazolo[3,4-*c*]isoquinolin-5-one (XIIb).

Powdered *N*-methyl-(1,3-diphenylpyrazol-5-yl)-*o*-aminobenzamide (5 g.) was dissolved in a solution of concentrated sulphuric acid (125 ml.) and water (540 ml.). After cooling to 0° 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 hydroxicde and extracted with chloroform. Evaporation of the dried (sodium sulphate) extracts left a red-brown residue (5 g.), which was chromatographed on a column of silica gel with 15% of water (200 g.), using chloroform as eluent. The first 200 ml. were neglected and the successive combined fractions 2-8 (each 150 ml.) were evaporated under reduced pressure. The residue was recrystallized to give XIIb (7% yield). Further elution $F_{12-14}$ (each 150 ml.) afforded a substance (10% yield) of $M^+$ = 369 which melted at 264-265° (ethanol).

XIIb.

This compound had m.p. 260-261° (ethanol); molecular weight by mass spectroscopy m/e 351; ir: $cm^{-1}$ 1650 (CO); nmr (deuteriochloroform): δ 3.30 (3H, s, $CH_3$), 7.20-8.70 (14H, m, $C_6H_4$ and 2 x $C_6H_5$).

*Anal.* Calcd. for $C_{23}H_{17}N_3O$: C, 78.61; N, 4.88; N, 11.96. Found: C, 78.56; H, 4.81; N, 11.90.

## REFERENCES AND NOTES

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