Synthesis of Pyrano[3,4-*c*]pyrazole and Pyrazolo[3,4-*d*][1,2]diazepine Derivatives

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By the action of thionyl chloride on 3(5)-*R*-4-phenacylpyrazole-5(3)-carboxylic acid (**3c,d**), 3-*R*-5-phenylpyrano[3,4-*c*]pyrazole-7-(1*H*)ones (**4c,d**) were obtained. When **4c,d** were treated with hydrazine hydrate followed by refluxing in ethanol containing acetic acid, 4,7-dihydro-3-*R*-5-phenylpyrazolo[3,4-*d*][1,2]-diazepin-8-(1*H*)ones (**6c,d**) were formed. Compounds **6c,d**, in turn, were refluxed in ethanol saturated with hydrochloric acid to yield 6-amino-1,6-dihydro-3-*R*-5-phenyl-7*H*-pyrazolo[3,4-*c*]pyridin-7-ones (**7c,d**). Compounds **7c,d** could be obtained directly from **5c,d**. The starting materials **3c,d** were prepared by hydrolysis of the oxime of 3(5)-*R*-4-phenacyl-5(3)carboalcoxypyrazoles (**1a,b**). Structural assignments rested on correct elemental analysis, molecular weights determined by mass spectrometry, and spectroscopic evidence.

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Pyrano[3,4-*c*]pyrazole derivatives were previously obtained: i) by 1,3-dipolar cycloaddition of diazomethane on β,γ-unsatured δ-lactones (1,4); ii) by intramolecular cycloadditions of nitrilimines on acetylenic groups (5); iii) by the action of hydrazine on 4-ethynyltetrahydropyranoles (6,7); and iv) by condensation of *N*-methyl-4-iodopyrazolecarboxylic acids with copper acetylide (8).

On the other hand, a few examples of pyrazolo[3,4-*d*]-[1,2]diazepine derivatives are reported in the literature. This ring system was previously obtained by $4\pi + 2\pi$ 1,3 dipolar cycloaddition of diazoalkanes on 1,2-diazepines (9-11).

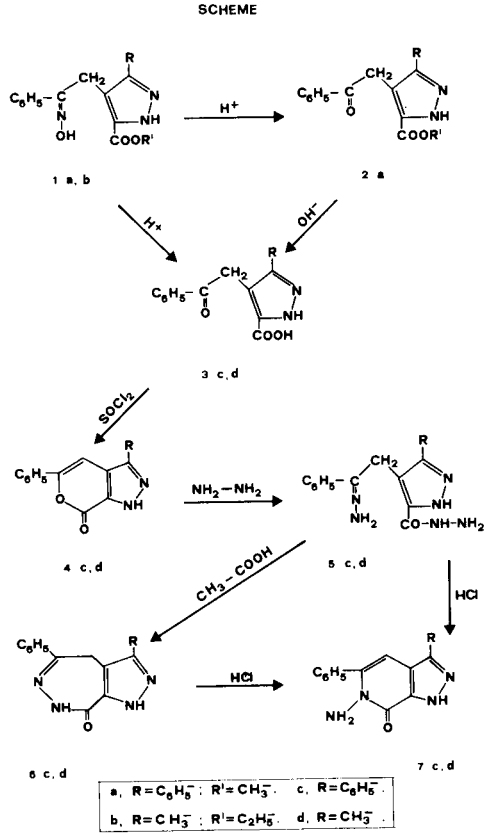
In this paper, we wish to describe a facile route to pyrano[3,4-*c*]pyrazole and pyrazolo[3,4-*d*][1,2]diazepine derivatives outlined in the Scheme.

The starting materials 3-(5)phenyl-4-phenacylpyrazole-5-(3)carboxylic acid (**3c**) and 3-(5)methyl-4-phenacylpyrazole-5-(3)carboxylic acid (**3d**) were prepared by two routes: a) by acid hydrolysis of the oxime of 3-(5)phenyl-4-phenacyl-5-(3)carbomethoxypyrazole (**1a**) (12), which lead to 3-(5)phenyl-4-phenacyl-5-(3)carbomethoxypyrazole (**2a**), followed by alkaline hydrolysis; and b) by acid hydrolysis of the oxime of 3-(5)methyl-4-phenacyl-5-(3)carbomethoxypyrazole (**1b**) (12).

The structures of compounds **3c,d** are based on correct elemental analysis and spectroscopic data. Ir spectra showed the characteristic stretchings at 1715-1720 cm^{-1} and 1690 cm^{-1} for two carbonyl groups, along with the absorption band due to pyrazolic NH group at 3280-3300 cm^{-1}. Nmr spectra exhibited the resonance of a methylene group at δ 4.42-4.60 and a mobile proton at δ 13.01 for the pyrazolic NH.

When compounds **3c,d** were refluxed in benzene with thionyl chloride, the bicyclic systems 3,5-diphenylpyrano-[3,4-*c*]pyrazol-7-(1*H*)one (**4c**) and 3-methyl-5-phenylpyrano-[3,4-*c*]pyrazol-7-(1*H*)one (**4d**) were obtained. The ir spectra of these products showed the absorption band due to the lactonic group at 1725-1740 cm^{-1}. The more significant feature of the nmr spectrum of **4d** was the appearance of a methyne singlet (1H) at δ 7.29 due to H-4 of the pyrone nucleus; the H-4 signal in compound **4c** overlapped the multiplet of the aromatic protons.

SCHEME



Compounds **4c,d**, in turn, were refluxed with hydrazine hydrate to give the 4-hydrazones of 3-(5)phenyl-4-phenacylpyrazole-5-carboxylic acid hydrazide (**5c**) and of 3-(5)methyl-4-phenacylpyrazole-5-(3)carboxylic acid hydrazide (**5d**). These were converted into 4,7-dihydro-3,5-

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diphenylpyrazolo[3,4-*d*][1,2]diazepin-8-(1*H*)one (**6c**) and 4,7-dihydro-3-methyl-5-phenylpyrazolo[3,4-*d*][1,2]diazepin-8-(1*H*)one (**6d**), by refluxing in ethanol containing a few drops of acetic acid.

The assigned structures were substantiated by analytical and spectroscopic data, and by molecular weight determined by mass spectrometry. The nmr spectra exhibited a methylene resonance at δ 3.80-4.05 and two exchangeable proton signals at δ 10.85-11.10 and δ 13.37-14.02, attributable to the diazepinic NH and the pyrazolic NH, respectively.

Furthermore, the assigned structures were confirmed by the facile conversion in acidic medium of **6c,d** into **7c,d**. A similar nuclear contraction of 1,2-diazepine to *N*-aminopyridine has been previously reported (13).

The structures of 6-amino-1,6-dihydro-3,5-diphenyl-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (**7c**) and 6-amino-1,6-dihydro-3-methyl-5-phenyl-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (**7d**) were in agreement with analytical and spectral data. Significantly, the nmr spectra of **7c,d** showed NH_2 signals at δ 5.55-5.62 exchangeable with deuterium oxide; the ir spectrum showed bands at 3300-3175 cm^{-1}, attributable to NH and NH_2 stretching. Compounds **7c,d** were also obtained directly by the cyclization of **5c,d** in refluxing ethanol saturated with hydrochloric acid.

The facile availability (12) of various different starting compounds of type **1**, led us to consider this reaction a general procedure to obtain these ring systems.

EXPERIMENTAL

All melting points were taken on Büchi-Tottoli capillary melting point apparatus and are uncorrected. Ir absorption spectra were determined with a Perkin-Elmer Infracord 299, using nujol mulls. Nmr spectra (DMSO-d_6) (unless otherwise specified) were measured using TMS as the internal standard with FT-80A Varian spectrometer. The mass spectra were measured with a Jeol JMS-01SG-2 double focusing mass spectrometer at 75 eV (100 μ A). The sample was directly introduced and heated at about 200°.

3-(5)Phenyl-4-phenacyl-5-(3)carbomethoxypyrazole (**2a**).

A mixture of **1a** (12) (0.5 g.) and 10% aqueous hydrochloric acid (30 ml.) was refluxed for 30 minutes. After standing, the precipitate was filtered and crystallized; m.p. 185° (ethanol) (yield 70%); ir: cm^{-1} 3250 (NH), 1720 and 1670 (CO); nmr: δ 3.68 (3H, s, CH_3), 4.55 (2H, s, CH_2), 7.46-8.10 (10H, m, 2 × C_6H_5), 13.78 (1H, s, NH, exchangeable with deuterium oxide); ms: 320 (M^+).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.75. Found: C, 71.18; H, 5.08; N, 8.90.

3-(5)Phenyl-4-phenacylpyrazole-5-(3)carboxylic Acid (**3c**).

A mixture of **2a** (0.5 g.) and ethanol-water (1:1) potassium hydroxide solution 2.5% (30 ml.) was refluxed for 30 minutes. After evaporation under reduced pressure, the residue was acidified and the precipitate was crystallized, m.p. 200° (ethanol) (yield 50%); ir: cm^{-1} 3280 (NH), 1715 and 1690 (CO); nmr: δ 4.60 (2H, s, CH_2), 7.45-8.11 (10H, m, 2 × C_6H_5), 13.01 (1H, s, NH, exchangeable with deuterium oxide); ms: 306 (M^+).

Anal. Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.49; H, 4.71; N, 9.20.

3-(5)Methyl-4-phenacylpyrazole-5-(3)carboxylic Acid (**3d**).

A mixture of **1b** (0.5 g.) (12) and 10% aqueous hydrochloric acid (30 ml.) was refluxed for 2 hours. After standing, the precipitate was filtered and crystallized, m.p. 295° (butanol) (yield 70%); ir: cm^{-1} 3300 (NH), 1720 and 1690 (CO); nmr: δ 2.12 (3H, s, CH_3), 4.42 (2H, s, CH_2), 7.51-8.10 (5H, m, C_6H_5), 13.01 (1H, s, NH, exchangeable with deuterium oxide); ms: 244 (M^+).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 64.05; H, 4.95; N, 11.50.

General Procedure for the Preparation of **4c,d**.

A mixture of **3c,d** (1 mmole), dry benzene (40 ml.) and thionyl chloride (10 ml.) was refluxed for 4 hours. On cooling, the solid precipitate was filtered and crystallized.

3,5-Diphenylpyrano[3,4-*c*]pyrazol-7-(1*H*)one (**4c**).

Compound **4c** had m.p. 275° (ethanol) (yield 65%); ir: cm^{-1} 3210 (NH), 1725 (CO); nmr: δ 7.20-8.10 (11H, m, 2 × C_6H_5 and -CH=), 14.50 (1H, broad, NH, exchangeable with deuterium oxide); ms: 288 (M^+).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 75.06; H, 4.39; N, 9.83.

3-Methyl-5-phenylpyrano[3,4-*c*]pyrazol-7-(1*H*)one (**4d**).

Compound had m.p. 185° (ethanol) (yield 60%); ir: cm^{-1} 3500 (NH) 1740 cm^{-1} (CO); nmr (acetone-d_6): δ 2.53 (3H, s, CH_3), 7.29 (1H, s, -CH=), 7.41-7.98 (5H, m, C_6H_5), 13.08 (1H, broad, NH, exchangeable with deuterium oxide); ms: 226 (M^+).

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 69.14; H, 4.38; N, 12.35.

General Procedure for the Preparation of **5c,d**.

A mixture of **4c,d** (4.5 mmoles) and hydrazine hydrate (5 ml.) was refluxed for 2 hours. After standing overnight, a solid precipitated which was filtered and crystallized.

3-(5)Phenyl-4-phenacylpyrazole-5-(3)carboxylic Acid, Hydrazide, 4-Hydrazone (**5c**).

Compound **5c** had m.p. 275° (ethanol) (yield 75%); ir: cm^{-1} 3330, 3310, 3280 (NH and NH_2), 1640 (CO); nmr: δ 4.26 (2H, s, CH_2), 4.46 (2H, s, NH_2, exchangeable with deuterium oxide), 6.59 (2H, s, NH_2, exchangeable with deuterium oxide), 7.03-7.29 (10H, m, 2 × C_6H_5), 9.35 (1H, s, NH, exchangeable with deuterium oxide), 13.19 (1H, s, NH, exchangeable with deuterium oxide); ms: 334 (M^+).

Anal. Calcd. for $C_{18}H_{18}N_6O$: C, 64.65; H, 5.43; N, 25.14. Found: C, 64.75; H, 5.51; N, 25.18.

3-(5)Methyl-4-phenacylpyrazole-5-(3)carboxylic Acid, Hydrazide, 4-Hydrazone (**5d**).

Compound **5d** had m.p. 195° (ethanol) (yield 80%); ir: cm^{-1} 3460, 3340, 3200 (NH and NH_2), 1640 (CO); nmr: δ 1.84 (3H, s, CH_3), 4.09 (2H, s, CH_2), 4.40 (2H, s, NH_2, exchangeable with deuterium oxide), 6.76 (2H, s, NH_2, exchangeable with deuterium oxide), 7.13-7.68 (5H, m, C_6H_5), 9.22 (1H, s, NH, exchangeable with deuterium oxide), 12.67 (1H, s, NH, exchangeable with deuterium oxide); ms: 272 (M^+).

Anal. Calcd. for $C_{13}H_{16}N_6O$: C, 57.34; H, 5.92; N, 30.86. Found: C, 57.41; H, 6.03; N, 30.87.

General Procedure for the Preparation of **6c,d**.

A solution of **5c,d** (1.2 mmoles) in ethanol (20 ml.) with 1 ml. of acetic acid was refluxed for 2.5 hours. Upon evaporation under reduced pressure, the residue was treated with ice-water and stirred for 1 hour. The product separated was crystallized.

4,7-Dihydro-3,5-diphenylpyrazolo[3,4-*c*][1,2]diazepin-8-(1*H*)one (**6c**).

Compound **6c** had m.p. 253° (ethanol) (yield 55%); ir: cm^{-1} 3260 (NH), 1665 (CO); nmr: δ 4.05 (2H, s, CH_2), 7.29-7.96 (10 H, m, 2 × C_6H_5), 11.10 (1H, s, NH, exchangeable with deuterium oxide), 14.08 (1H, broad, NH, exchangeable with deuterium oxide); ms: 302 (M^+).

Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C,

71.45; H, 4.77; N, 18.50.

4,7-Dihydro-3-methyl-5-phenylpyrazolo[3,4-*d*][1,2]diazepin-8-(1*H*)one (**6d**).

Compound **6d** had m.p. 254° (ethanol) (yield 50%); ir: cm^{-1} 3180 (NH), 1660 (CO); nmr: δ 2.28 (3H, s, CH_3), 3.80 (2H, s, CH_2), 7.40-7.88 (5H, m, C_6H_5), 10.85 (1H, broad, NH, exchangeable with deuterium oxide), 13.37 (1H, broad, NH, exchangeable with deuterium oxide); ms: 240 (M^+).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 65.09; H, 4.99; N, 23.42.

6-Amino-1,6-dihydro-3,5-diphenyl-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (**7c**) and 6-Amino-1,6-dihydro-3-methyl-5-phenyl-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (**7d**).

A suspension of **6c,d** or **5c,d** (1 g.) in ethanol satured with hydrochloric acid (40 ml.) was refluxed for 3 hours. Upon evaporation under reduced pressure, the residue treated with ice-water was filtered off and crystallized.

Compound **7c**.

Compound **7c** had m.p. 290° (ethanol); ir: cm^{-1} 3300, 3175 (NH and NH_2), 1665 (CO); nmr: δ 5.62 (2H, s, NH_2, exchangeable with deuterium oxide), 6.77 (1H, s, -CH=), 7.37-7.98 (10H, m, 2 × C_6H_5), 14.26 (1H, broad, NH, exchangeable with deuterium oxide); ms: 302 (M^+).

Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.63; H, 4.82; N, 18.53.

Compound **7d**.

Compound **7d** had m.p. 250° (ethanol); ir: cm^{-1} 3300, 3190 (NH and NH_2), 1660 (CO); nmr: δ 2.40 (3H, s, CH_3), 5.55 (2H, s, NH_2, exchangeable with deuterium oxide), 6.51 (1H, s, -CH=), 7.45-7.64 (5H, m, C_6H_5), 13.61 (1H, s, NH, exchangeable with deuterium oxide); ms: 240 (M^+).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.85; H, 5.14; N, 23.45.

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