SYNTHESIS OF 2H-PYRAZOLO[3,4-*a*]QUINOLINE DERIVATIVES BY ONE POT REARRANGEMENT OF PHENYLHYDRAZONES OF 3-ACYLINDOLES*

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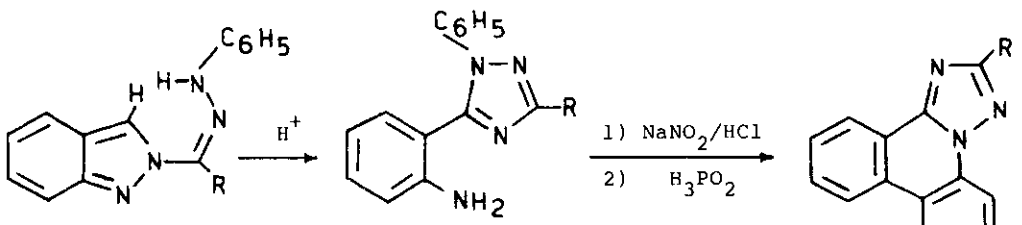
Abstract - The phenylhydrazones **4a-g** of 3-acylindoles led to the 2-phenyl-2H-pyrazolo[3,4-*a*]quinoline derivatives **9a-e** and **10a-b.** The reaction mechanism proposed involves an acid catalyzed 6 π heteroelectrocyclic reaction and a ring opening to the pyrazole derivatives **8** followed by a spontaneous ring closure of the latter compounds.

In the last few years considerable attention has been paid to the synthesis of condensed heterocyclic systems. Among the various synthetic approaches it seems to us of particular interest a stepwise building of the condensed ring system through addition and rearrangement reactions followed by transformation of functional groups. Thus we have reported a simple and efficient procedure for the synthesis of the substituted 1,2,4-triazolo[1,5-*f*]phenanthridines **3a-c** via a rearrangement reaction of the phenylhydrazones **1a-c** to the 3-substituted 5-(2-aminophenyl)-1,2,4-triazoles **2a-c** followed by dediazonation and Pschorr-type cyclization.[1]



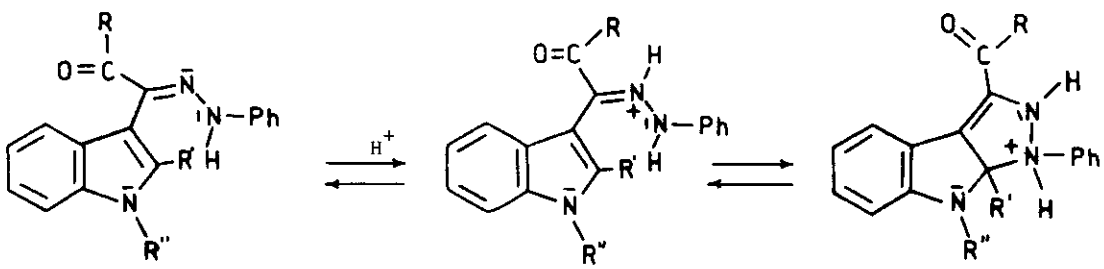
1a-c **2a-c** **3a-c**

a: R = COOEt; b: R = COMe; c: R = Ph

In order to generalize the application of this procedure to the synthesis of other nitrogen containing polycondensed heterocyclic systems, we now report the

rearrangement reaction of the phenylhydrazones **4a-g**[2] to the pyrazole derivatives **8** which are valuable intermediates for the synthesis of the pyrazolo[3,4-*c*]quinoline ring system for which only a few occasional synthetic pathways have been described.[3]

In the starting materials used, a methyl or phenyl group is present as a substituent in the pyrrole ring, but independently of the present substituents, **4a-e** and **4f-g** are different in that they contain an ester and an acetyl group, respectively. Moreover the phenylhydrazones **4a-b** have an Z configuration[2] whereas **4c-g** have a E configuration.[2]

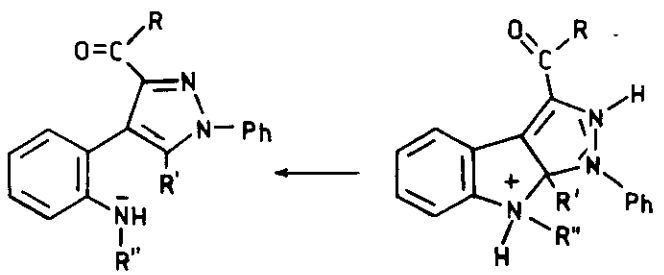


4a-g (**E**-isomers)

5

6

4	R	R'	R"
a	OEt	H	H
b	OEt	H	Me
c	OEt	Me	H
d	OEt	Me	Me
e	OEt	Ph	H
f	Me	Me	H
g	Me	Ph	H



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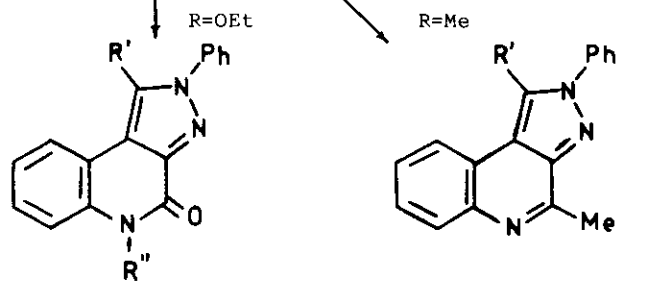
9	R'	R"
a	H	H
b	H	Me
c	Me	H
d	Me	Me
e	Ph	H

8

R=OEt

R=Me



9a-e

10a-b

10	R'
a	Me
b	Ph

For the *rearrangement*, compounds **4a-g** were refluxed in ethanol containing hydrochloric acid. This reaction allowed us to isolate directly the 4,5-dihydro-2H-pyrazolo [3,4-*c*] quinolin-4-one derivatives **9a-e** (from **4a-e**) and the 2H-pyrazolo [3,4-*c*] quinoline derivatives **10a,b** (from **4f-g**). Compounds **4a-b** (Z-isomers) give the final products with moderate yield (24-51%), because of partial hydrolysis involving the side chain,[4] whereas compounds **4c-g** (E-isomers) furnish the final products in high yields (81-93%).

A reasonable reaction mechanism implies that i) the phenylhydrazones **4a-b** (Z-isomers) before rearrangement isomerize to **4a-b** (E-isomers); ii) **4a-g** (E-isomers) rearrange to the unisolated **6** by an acid catalyzed 6 π heteroelectrocyclic reaction;[5] iii) the pyrazole derivatives **8** are formed by ring opening of compounds **7** (in prototropic equilibrium with **6**); iv) intermediates **8** spontaneously afford **9a-e** or **10a,b** depending on the substituent at C-3.

Compounds **9a,c,e** either in ethanol solution or in the solid state are characterized by the oxo form. In fact their uv spectra closely resemble those of N-methyl derivatives **9b,d**; moreover their ir spectra (nujol) exhibit a strong band at 1665 cm^{-1} and a weak broad band centered at 3185 cm^{-1} assigned to the C=O and NH groups, respectively.

The nmr spectra (**Table**) show the NH signal of **9a,c,e** at δ 11.35-11.47 and the N-methyl signal of **9b,d** at δ 3.77 and 3.73, *according to the reported values for* N-methylquinolin-2-one derivatives.[6]

Table ^{1}**H-NMR** Spectra of **9a-e**

				Chemical shifts (δ)				
Compd.	R'	R"	Solvent	R'	R"	2-C_6H_5	H-9	Ar-H
9a	H	H	DMSO-d_6	9.47(s)	11.47(s)	8.01(m,o-H)[a]	8.01(m)[a]	d
9b	H	Me	$CDCl_3$	8.51(s)	3.77(s)	7.88(m,o-H)[a]	7.09(m)[a]	e
			DMSO-d_6	9.46(s)	3.69(s)	8.04(m,o-H)[a]	8.04(m)[a]	d
9c	Me	H	DMSO-d_6	2.74(s)	11.35(s)	7.64(s)	7.93(m)	d
9d	Me	Me	$CDCl_3$	2.73(s)	3.73(s)	7.51(s)	7.87(m)	e
			DMSO-d_6	2.73(s)	3.66(s)	7.64(s)	8.00(m)	d
9e	Ph	H	DMSO-d_6	7.48(s)[b]	11.43(s)	7.51(s)[b]	c	d

[a] Overlapping multiplets of ortho protons (o-H) of 2-phenyl and of H-9 proton. [b] Or reverse assignment. [c] Overlapped with signals of other Ar-H because of the shielding effect of the phenyl group in the 1-position. [d] Multiplet at 7.30-7.75. [e] Multiplet at 7.15-7.60.

In compounds **9a,b**, the ortho protons of the phenyl group appear, together with C-9 proton, as a downfield multiplet at δ 8.01-8.04, indicating that in these compounds the phenyl and pyrazole rings are coplanar; in compounds **9c-e**, where, due to the steric effect of the adjacent substituents, the coplanarity of the two rings is highly unlikely, the phenyl groups appear as singlets at δ 7.48-7.64.

The spectral data of compounds **10a,b** are in agreement with the structure assigned. The nmr spectra ($CDCl_3$) show the singlet due to the methyl group in the 4-position at δ 2.95 and 3.02. The phenyl group signals appear as singlets at δ 7.35-7.55 according to the steric effect already pointed out for compounds **9c-e**.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus; ir spectra (nujol mull) were determined with a Perkin-Elmer 257 instrument; uv spectra (ethanol) were determined with a Varian Superscan 3 spectrophotometer; ^1H nmr spectra were determined with a Varian FT-80 spectrometer (TMS as internal standard).

General method for the preparation of 2-phenyl-1-R'-5-R"-4,5-dihydro-2H-pyrazolo [3,4-*c*] quinolin-4-ones (**9a-e**) and 2-phenyl-4-methyl-1-R'-2H-pyrazolo[3,4-*c*]quinolines (**10a,b**).

A solution of 3-ethoxalyl-indole 3^1-(phenylhydrazones) **4a-e** (2 mmoles) or 3-pyruvoyl-indole 3^1-(phenylhydrazones) **4f-g** (2 mmoles) in ethanol (50 ml) and hydrochloric acid (36%, 0.4 ml) was refluxed for 4-9 hours. The solvent was evaporated to dryness in vacuo, the residue was treated with cold ethanol and the solid was collected by filtration.[4]

Compound **4a** (R=OEt,R'=R"=H) gave compound **9a** (R'=R"=H) which was recrystallized from chloroform, (yield 51%), mp 310°C; ir cm^{-1} : 3185 (NH), 1665 (C=O); uv nm λ_{max} (log ε) : 251sh(4.47),257 (4.33),274 (4.43), 297sh(4.15); Anal. Calcd. for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.20; H, 4.28; N, 16.22.

Compound **4b** (R=OEt,R'=H,R"=Me) gave compound **9b** (R'=H,R"=Me) which was recrystallized from ethanol, (yield 24%), mp 225-228°C; ir cm^{-1} : 1650 (C=O); uv nm λ_{max} (log ε) : 253sh (4.41), 259 (4.44), 280 (4.36), 298sh (4.13) ; Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.26. Found: C, 74.01; H, 4.81; N, 15.37.

Compound **4c** (R=OEt,R'=Me,R"=H) gave compound **9c** (R'=Me,R"=H) which was recrystallized from ethanol, (yield 93%), mp 340°C; ir cm^{-1} : 3185 (NH), 1665 (C=O); uv nm λ_{max} (log ε) : 246(4.53),253sh(4.46),268sh(4.15), 295(4.00); Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.26. Found: C, 74.25; H, 4.80; N, 15.18.

Compound **4d** (R=OEt,R'=R"=Me) gave compound **9d** (R'=R"=Me) which was recrystallized from ethanol, (yield 82%), mp 210°C; ir cm^{-1} : 1665 (C=O); uv nm λ_{max} (log ε) : 248(4.54),255sh(4.46),272sh(4.14),299(3.94); Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.53. Found: C, 75.05; H, 5.21; N, 14.63.

Compound **4e** (R=OEt,R'=Ph,R"=H) gave compound **9e** (R'=Ph,R"=H) which was recrystallized from ethanol, (yield 81%), mp > 350°C; ir cm^{-1} : 3185 (NH), 1665 (C=O); uv nm λ_{max} (log ε) : 247(4.41),256sh(4.38),270sh(4.24), 300(4.04); Anal. Calcd. for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.46. Found: C, 78.50; H, 4.43; N, 12.51.

Compound **4f** (R=R'=Me,R"=H) gave **10a** (R'=Me) as hydrochloride salt (yield 90%) which was transformed into the free base by treatment with triethylamine in chloroform, purified by chromatography on column of silica gel (eluant cyclohexane : ethyl acetate 1:1) and recrystallized from cyclohexane (yield 63%), mp 170°C; ir cm^{-1} : 1600 (C=N); uv nm λ_{max} (log ε) : 235sh(4.49), 242sh(4.56),247(4.59),263(4.44),298sh(3.95),322sh(3.70),337sh (3.54); ^1H nmr ($CDCl_3$) δ : 2.84(3H,s,1-CH_3),2.95(3H,s,4-CH_3), 7.55(5H, s,C_6H_5), 7.10-7.80(2H,m,7-H and 8-H),8.07(2H,m,6-H and 9-H); Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53; N, 15.38. Found: C, 78.81; H, 5.42; N, 15.60.

Compound **4g** (R=Me,R'=Ph,R"=H) gave **10b** (R'=Ph) as hydrochloride salt (yield 95%) which was transformed into the free base as described above (yield 70%), mp 218°C; ir cm^{-1} : 1597 (C=N); uv nm λ_{max} (log ε) : 231(4.48),269(4.49), 299sh(4.06),322sh(3.84),338sh(3.62); ^1H nmr ($CDCl_3$) δ : 3.02(3H,s,4-CH_3),7.35 and 7.45(10H,2s,2xC_6H_5),7.16-7.70(2H,m,7-H and 8-H), 7.71(1H, m, 9-H), 8.05(1H,m,6H); Anal. Calcd. for $C_{23}H_{17}N_3$: C, 82.36; H, 5.11; N, 12.53. Found: C, 82.39; H, 5.08; N, 12.43.

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