A facile synthesis of 1-ethyl-3-methyl-11-phenyl-1,4-dihydro-5*H*-pyrazolo[3,4-*c*][1,5]benzodiazocin-5-ones. A new ring system

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Dedicated to Professor Alain Krief on the occasion of his 65th anniversary

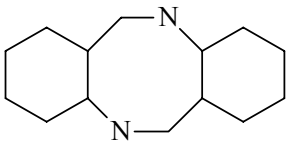
Abstract
The new ring system pyrazolo[3,4-*c*][1,5]benzodiazocine was obtained through cyclization of the key intermediate of type **6a-d** and **9**, in refluxing toluene in presence of a catalytic amount of *p*-toluensulfonic acid, from moderate to high yields (45-85%).

Keywords: Pyrazole, 1,5-benzodiazocine, pyrazolo-1,5-benzodiazocine, antitumor activity

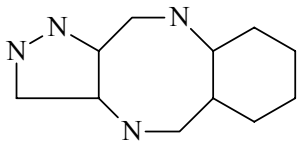
Introduction

1,5-Diazocine system have received great attention because of their broad spectrum of biological properties. Also annelated 1,5-benzodiazocine have shown interesting activity. In particular Troger's base and analogues, containing a dibenzo-1,5-diazocine skeleton **1**, posses intercalating capability between DNA base pairs.[1-4] Due to the interesting biological activities, different analogues bearing heterocyclic rings have been prepared.[5-7]

In our effort to search for novel antitumor compounds, we became interested in the synthesis of the new ring system pyrazolo[3,4-*c*][1,5]benzodiazocine of type **2** with the aim of evaluating their antiproliferative activity.



1



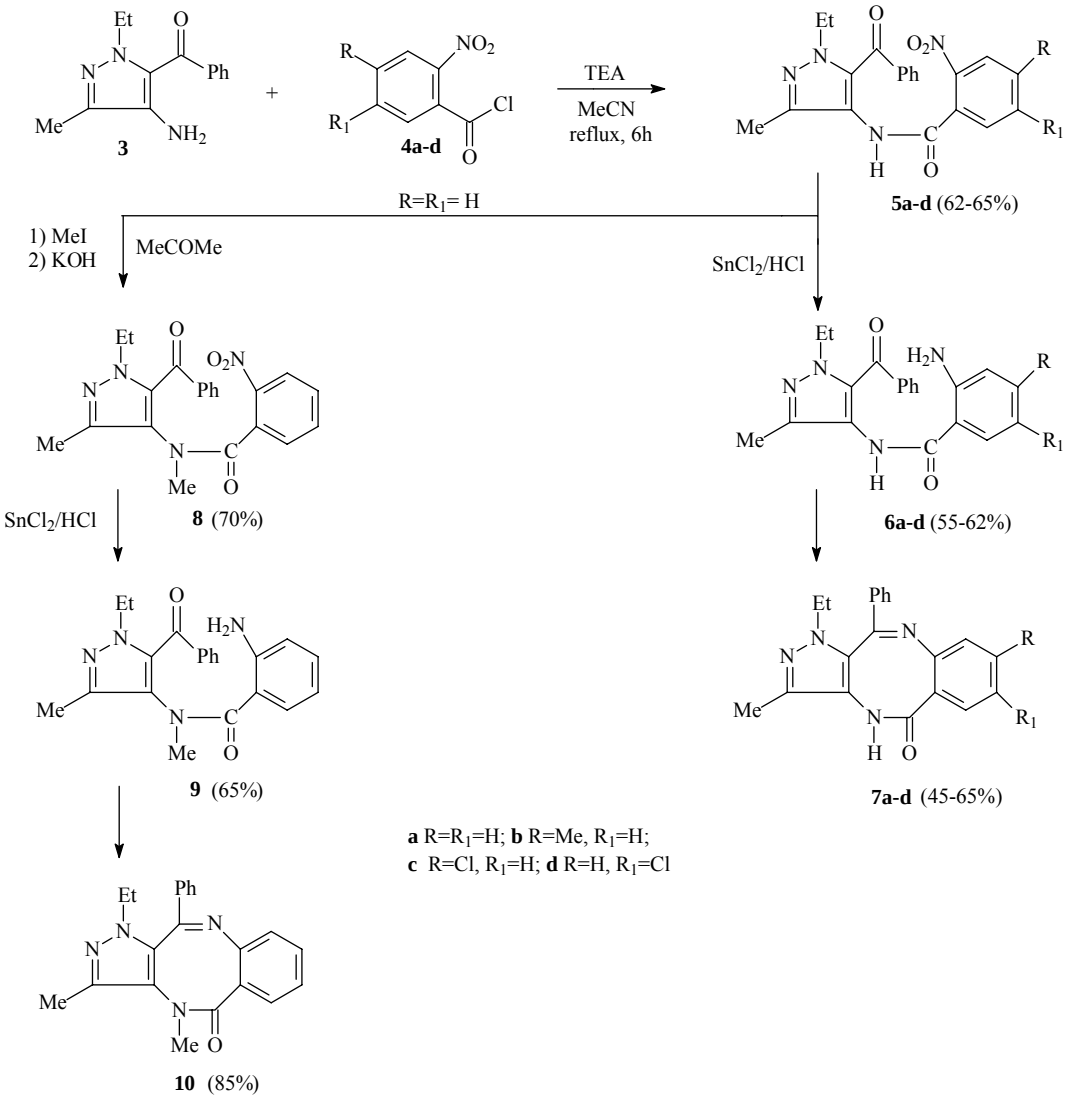
2

Figure1

In this paper we report the synthesis of pyrazolo[3,4-*c*][1,5]benzodiazocine derivatives of type **2**, in which the benzene moiety was replaced by a pyrazole ring.

Results and Discussion

2-Amino-*N*-(5-benzoyl-1-ethyl-3-methyl-1*H*-pyrazol-4-yl)benzamide derivatives **6a-d** appeared valuable and versatile intermediates for the synthesis of the new ring system pyrazolo[3,4-*c*][1,5]benzodiazocine. We started our synthesis reacting 4-aminopyrazole **3**[8] with the substituted 2-nitrobenzoyl chlorides **4a-d** to give nitro derivatives **5a-d** in good yields (62-65%). Reduction of these latter with stannous chloride in hydrochloric acid led to the corresponding amines **6a-d** in satisfactory yields (55-62%).



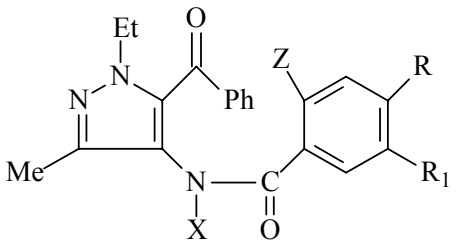
Refluxing of amines **6a-d** in presence of a catalytic amount of *p*-toluenesulfonic acid in toluene, using a Dean Stark apparatus, provided the expected new tricyclic system pyrazolo[3,4-*c*][1,5]benzodiazocines **7a-d** in reasonable yields (45-65%). The treatment of the derivative **5a** with potassium hydroxide and methyl iodide in acetone yielded the corresponding N-methyl derivative **8** (70% yield). Reduction of this latter afforded the amine **9** (65%) which upon refluxing with a catalytic amount of *p*-toluenesulfonic acid in toluene led to the *N*-methylpyrazolo[3,4-*c*][1,5]benzodiazocine **10** in high yield (85%). The structure of all compounds synthesized was confirmed by their analytical and spectral data (IR, ^{1}H and ^{13}C NMR). Pyrazolo[1,5]benzodiazocines **7a-c** and **10** undergo partial ring opening to give **6a-c** and **9** respectively at room temperature upon standing silica gel for 5 days acid catalysis or by refluxing in aqueous ethanol and acid catalysis.

In conclusion, we have provided a very simple way for the synthesis of the novel heterocycle ring system, pyrazolo[3,4 -*c*][1,5]benzodiazocine, in good yields.

Experimental Section

General Procedures. All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected; IR spectra were determined in bromoform with a Perkin-Elmer Infracord 137 spectrophotometer as nujol mulls.; ^{1}H and ^{13}C NMR spectra were measured at 200 and 50.3 MHz respectively, using a Bruker AC series 200 MHz spectrometer (TMS as internal reference). Column chromatography was performed with Merck silica gel 230-400 Mesh ASTM. Mass spectra were recorded on a JEOL JMS-OI-SG-2 spectrometer at 75 eV (100μA). Elemental analyses were within ±0.4% of the theoretical values.

Table 1. ^{1}H NMR chemical shifts of compounds **5-9**: δ_H [ppm]



Comp.	Et	Me	X	Z	R	Aryl-H
5						
X=H, Z=NO_2						
a R=R_1=H	1.35, 4.26	2.18	10.09			7.51-8.03 (9H)
b R=Me, R_1=H	1.35, 4.26	2.18	10.01		2.37	7.36-7.83 (8H)
c R=Cl, R_1=H	1.36, 4.27	2.19	10.02			7.51-8.15 (8H)
d R=H R_1= Cl	1.37, 4.28	2.19	10.18			7.55-8.09 (8H)

6						
X=H, Z=NH_2						
a R=R_1=H	1.35, 4.27	2.17	9.44	6.08		6.33-7.77 (9H)
b R=Me, R_1=H	1.32, 4.29	2.10	9.30	6.07	2.14	6.19-7.73 (8H)
c R=Cl, R_1=H	1.34, 4.25	2.18	9.49	6.35		6.39-7.73 (8H)
d R=H R_1= Cl	1.35, 4.26	2.15	9.53	6.18		6.60-7.73 (8H)
8						
X=Me, Z=NO_2						
R=R_1=H	1.32, 4.20	2.24	3.22			7.49-8.00 (9H)
9						
X=Me, Z=NH_2						
R=R_1=H	1.30, 4.19	2.22	3.20	6.10		6.30-7.73 (9H)

General procedure for the synthesis of 4 or 5 substituted *N*-(5-benzoyl-1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-2-nitrobenzamides (5a-d)

A solution of 4-aminopyrazole **3** (4 mmol), appropriate 2-nitrobenzoyl chloride derivative **4a-d** (4 mmol), and triethylamime (4 mmol) in acetonitrile (50 mL) was refluxed for 6h. The solvent was then evaporated under reduced pressure and the residue was taken up with water, filtered and recrystallized from ethanol.

Compound 5a. (R=R_1=H) Yield 65%; mp 185-186°C (white crystals); IR: 3258 (NH), 1660 (CO) cm^{-1}. Anal. Calcd. for $C_{20}H_{18}N_4O_4$: C, 63.49; H, 4.79; N, 14.81. Found: C, 63.35; H, 4.63; N, 14.68 %.

Compound 5b. (R=Me, R_1=H) Yield 63%; mp 212-213°C (white needles); IR: 3255 (NH), 1649 (CO) cm^{-1}. Anal. Calcd. for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5,14; N, 14.28. Found: C, 64.35; H, 5.32; N, 14.30 %.

Compound 5c. (R=Cl, R_1=H) Yield 62%; mp 194-195 °C (white needles); IR: 3253 (NH), 1651 (CO) cm^{-1}. Anal. Calcd. for $C_{20}H_{17}ClN_4O_4$: C, 58.19; H, 4.15; N, 13.57. Found: C, 58.24; H, 4.26; N, 13.60 %.

Compound 5d. (R=H R_1= Cl) Yield 65%; mp 215-216 °C (white needles); IR: 3360 (NH), 1670 (CO) cm^{-1}. Anal. Calcd. for $C_{20}H_{17}ClN_4O_4$: C, 58.19; H, 4.15; N, 13.57. Found: C, 58.20; H, 4.28; N, 13.45 %.

General procedure for the synthesis of 4 or 5 substituted 2-amino-*N*-(5-benzoyl-1-ethyl-3-methyl-1*H*-pyrazol-4-yl)benzamides (6a-d)

To a suspension of stannous chloride (3 mmol) in hydrochloric acid (36%, 3 mL) a suitable 2-nitrobenzamide derivative **5a-d** (3 mmol) was added dropwise with stirring at -5°C. The reaction mixture was stirred then for 20 h at room temperature.

The reaction mixture was poured into ice water and an aqueous solution of sodium hydroxide (40%) was added until the tin salts was dissolved. The resulting solution was extracted with ethyl

acetate (3x30mL). The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure to give a white solid which was recrystallized from ethanol.

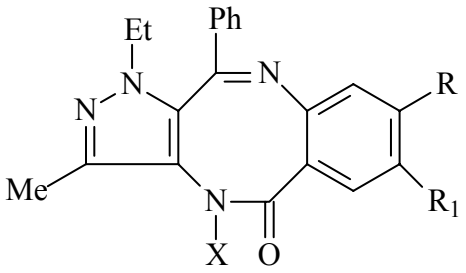
Compound 6a. (R=R_1=H) Yield 55%; mp 200-201°C (crystals); IR: 3487, 3383 (NH_2), 3220 (NH), 1642 (CO) cm^{-1}. Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.78; H, 5.82; N, 16.18 %.

Compound 6b. (R=Me, R_1=H) Yield 58%; mp 180-181°C (needles); IR: 3486, 3385 (NH_2), 3224 (NH), 1643 (CO) cm^{-1}. Anal. Calcd. for $C_{21}H_{22}N_4O_2$: C, 69.59; H, 6.12; N, 15.46. Found: C, 69.48; H, 6.21; N, 15.29 %.

Compound 6c. (R=Cl, R_1=H) Yield 60%; mp 195-196 °C (needles); IR: 3484, 3375 (NH_2), 3233 (NH), 1643 (CO) cm^{-1}. Anal. Calcd. for $C_{20}H_{19}N_4O_2Cl$: C, 62.75; H, 5.00; N, 14.63. Found: C, 62.58; H, 5.14; N, 14.75 %.

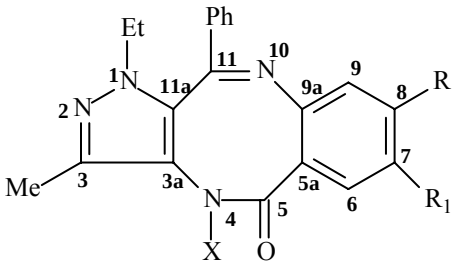
Compound 6d. (R=H R_1= Cl) Yield 62%; mp 244-245 °C (needles); IR: 3481, 3378 (NH_2), 3216 (NH), 1643 (CO) cm^{-1}. Anal. Calcd. for $C_{20}H_{19}N_4O_2Cl$: C, 62.75; H, 5.00; N, 14.63. Found: C, 62.68; H, 5.10; N, 14.69 %.

Table 2. ^{1}H NMR Chemical shifts of compounds **7,10**: δ_H [ppm]



Comp.	Et	Me	NH	NMe	Aryl-H
7					
X=H					
a R=R_1=H	0.91, 3.79	2.09	9.60		6.89-7.69 (9H)
b R=Me, R_1=H	0.93, 3.77	2.08, 2.27	9.51		6.72-7.67 (8H)
c R=Cl, R_1=H	0.94, 3.79	2.11	9.71		7.07-7.69 (8H)
d R=H R_1= Cl	0.92, 3.78	2.10	9.69		7.05-7.68 (8H)
10					
X=Me					
R=R_1=H	0.89, 3.77	2.15		3.19	6.89-7.57 (9H)

Table 3. ^{13}C NMR chemical shifts of compounds **7,10**: δ_C [ppm]



Comp.	Et	Me	Aryl-CH	C=O	N-Me
7 X=H					
a R=R_1=H	15.17, 45.57	10.60	120.65, 124.65, 128.14, 128.27, 129.21, 129.95, 132.36	170.63	
b R=Me, R_1=H	15.09, 45.54	10.60, 20.67	120.81, 125.41, 128.09, 128.33, 129,18, 132.29	170.77	
c R=Cl, R_1=H	15.09, 45.60	10.62	120.39, 124.71, 128.20, 129.22, 130.13, 132.65	169.67	
d R=H R_1= Cl	15.11, 45.59	10.60	120.32, 124.68, 128.21, 129.19, 130.10, 132.62	170.01	
10 X=Me R=R_1=H	15.06, 45.42	11.10	120.64, 124.79, 127.74, 128.14, 129.25, 129.60, 132.46	169.04	35.26

Synthesis of 7 or 8 substituted 1-ethyl-3-methyl-11-phenyl-1,4-dihydro-5*H*-pyrazolo[3,4-*c*][1,5] benzodiazocin-5-ones (7a-d)

Benzamides **6a-d** (3 mmol) were dissolved in toluene (40 mL) in presence of a catalytic amount of *p*-toluenesulfonic acid and refluxed for 21 h (5 hours in the case of **6a**). Then the mixture was maintained for further 14 h at room temperature. The resulting precipitate **7a** was collected by filtration and recrystallized from ethanol. Pyrazolo[1,5]benzodiazocin-5-ones **7b-d** were obtained after removing the solvent under reduced pressure and subsequent purification by flash *chromatography using a mixture of petroleum ether (40-70°C)/ethyl acetate 6:4 as eluent.*

Compound 7a. (R=R_1=H) Yield 60%; mp 204-205°C (pale yellow crystals from 1,4-dioxane); IR: 3140 (NH), 1658 (CO) cm^{-1}; ms: m/z 330 (M^+). Anal. Calcd. for $C_{20}H_{18}N_4O$: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.65; H, 5.36; N, 16.81 %.

Compound 7b. (R=Me, R_1=H): yield 65%; mp 190-191°C (white crystals from toluene); IR: 3136 (NH), 1655 (CO) cm^{-1}; ms: m/z 344 (M^+). Anal. Calcd. for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27: Found: C, 73.38; H, 5.66; N, 16.33 %.
Compound 7c. (R=Cl, R_1=H) Yield 52%; mp 240-241°C (white crystals from toluene); IR: 3136 (NH), 1660 (CO) cm^{-1}; ms: m/z 364 (M^+). Anal. Calcd. for $C_{20}H_{17}N_4OCl$: C, 65.84; H, 4.70; N, 15.36. Found: C, 65.77; H, 4.66; N, 15.42 %.
Compound 7d. (R=H R_1= Cl) Yield 45%; mp 255-256°C (white crystals from toluene); IR: 3138 (NH), 1659 (CO) cm^{-1}; ms: m/z 364 (M^+). Anal. Calcd. for $C_{20}H_{17}N_4OCl$: C, 65.84; H, 4.70; N, 15.36. Found: C, 65.70; H, 4.73; N, 15.34 %.

Synthesis of *N*-(5-benzoyl-1-ethyl-3-methyl -1*H*-pyrazol-4-yl)-*N*-methyl-2-nitrobenzamide (8)
To a solution of **5a** (2.27g, 6 mmol) in warm acetone (80 mL) powdered potassium hydroxide (1.68 g, 30 mmol) was added. The mixture was refluxed then methyl iodide (14 mmol) in acetone (15 mmol) was added. After 20 min the reaction mixture was filtered and the resulting solution concentrated and poured onto ice water. The solid formed was collected and recrystallized from ethanol; yield 70% (white crystals), mp 155-156 °C; IR: 1648 (CO) cm^{-1}. Anal. Calcd. for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28. Found: C, 64.35; H, 5.26; N, 14.35 %.

Synthesis of 2-amino-*N*-(5-benzoyl-1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-*N*-methylbenzamide (9)
To a suspension of stannous chloride (0.569 g, 3 mmol) in hydrochloric acid (36%, 3 mL) N-(5-benzoyl-1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-*N*-methyl-2-nitrobenzamide **8** (1.18 g, 3 mmol) was added dropwise with stirring at -5°C. The reaction mixture was stirred then for 20 h at room temperature. The solution was poured into ice water and an aqueous solution of sodium hydroxide (40%) was added until the tin salts was dissolved. The resulting solution was extracted with ethyl acetate (3x25 mL). The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure to give a white solid which was recrystallized from ethanol.
Yield 65% (crystals), mp 146-147 °C; IR: 3413, 3329 (NH_2); 1640 (CO) cm^{-1}. Anal. Calcd. for $C_{21}H_{22}N_4O_2$: C, 69.59; H, 5.14; N, 14.28. Found: C, 69.47; H, 5.22; N, 15.31 %.

Synthesis of 1-ethyl-3,4-dimethyl-11-phenyl-1,4-dihydro-5*H*-pyrazolo[3,4-c][1,5]benzo diazocin-5-one (10)
A solution of 2-amino-*N*-(5-benzoyl-1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-*N*-methylbenzamide **9** (3 mmol in toluene (40 mL) and catalytic amount of *p*-toluenesulfonic acid was refluxed for 8h. The reaction mixture was filtered and the resulting solution concentrated under reduced pressure and the solid obtained was recrystallized from ethanol. Yield 85% (pale yellow crystals), mp 165-166 °C; IR: 1639 (CO) cm^{-1}. ms: m/z 344 (M^+). Anal. Calcd. for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27. Found: C, 73.32; H, 5.68; N, 16.34 %.

Acknowledgements

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References

1. Morhle, H.; Dornbrack, S.; Novak, H. I. *Monatsh. Chem*. **1981**, *112*, 1417.
2. Ernest, R. R.; Boudenhausen, G.; Wokaun, A. *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*; Clarendon: Oxford, 1987.
3. Cavanagh, J.; Fairbrother, W. J.; Palmer, A. G.; Skelton, N. *Protein NMR Spectoscopy, Principles and Pratice*; Academic Press: San Diego, CA, 1996.
4. Baldeyron, B.; Tardy, C.; Bailly, C.; Colson, P.; Houssier, C.; Charmantray, F.; Demeunynck, M. *Eur. J. Med. Chem.* **2002**, *37*, 315.
5. Cekavicus, B.; Liepinsh, E.; Vigante, B.; Sobolevs, A.; Ozols, J.; Duburs, G. *Tetrahedron Lett*. **2001**, *42*, 4239.
6. Valik, M.; Dolensky, B.; Petrickova, H.; Vasek, P.; Kral, V. *Tetrahedron Lett*. **2003**, *44*, 2083.
7. Valik, M.; Malina, J.; Palivec, L.; Foltynova, J.; Tkadlecova, M.; Urbanova, M.; Brabec, V.; Kral, V. *Tetrahedron* **2006**, *62*, 8591.
8. DeWald, H. A.; Nordin, I. C.; L'Italien Y. J.; Parcell, R. F. *J. Med. Chem.* **1973**, *16*, 1346.

