Synthesis of 1-Phenyl-Substituted 3-Methyl-1*H*-pyrazolo[3,4-*b*]pyrazine-5,6-dicarboxylic Acid Diethyl Esters

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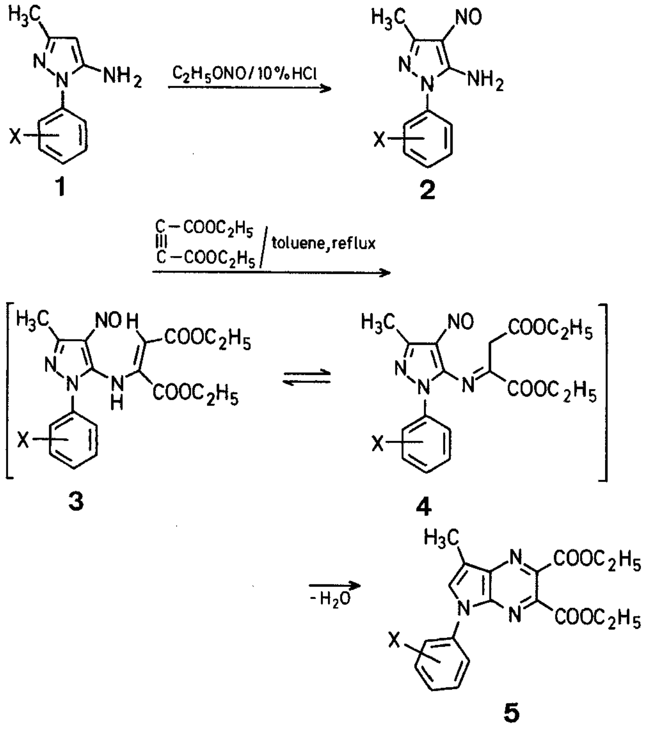
In connection with studies on possible structure-activity relationships of condensed heterocyclic compounds containing the pyrazole nucleus, we decided to investigate the pyrazolo[3,4-*b*]pyrazine system whose chemical and pharmacological properties are scarcely known. The most common approaches employed to synthesize this nucleus are either the condensation of 4,5-diaminopyrazoles with a 1,2-dicarbonyl compounds[1] or the condensation-cyclization sequence of 4-nitroso-5-aminopyrazoles with several carbon sources, such as malonates[2], carboxylic anhydrides[3], and phenylacetonitriles[4].

In the present paper, we report another utilization of 4-nitroso-5-aminopyrazoles (**2a–e**), readily available through nitrosation[5] with ethyl nitrite of the corresponding 5-aminopyrazoles (**1a–e**)[5,6,7], as the direct starting material for the construction of pyrazolo[3,4-*b*]pyrazines. This route consists of the reaction of 4-nitroso-5-aminopyrazoles (**2a–e**) with diethyl acetylenedicarboxylate in refluxing toluene for 12 h to give 1-phenyl-substituted 3-methyl-1*H*-pyrazolo[3,4-*b*]pyrazine-5,6-dicarboxylic acid diethyl esters (**5a–e**) in good yields (Table). The structures of (**5a–e**) were established by elemental analysis, I.R. and N.M.R. spectral data.



A possible mechanism for this reaction presumably involves the initial formation of the adducts **3**, followed by intramolecular dehydration of the tautomeric nitroso compounds **4**.

Compounds **2a–d** are prepared as described in the literature[5].

1-(4-Methylphenyl)-3-methyl-4-nitroso-5-amino-pyrazole (2e):
Through a solution of 1-*p*-tolyl-3-methyl-5-aminopyrazole (**1e**; 4 g, 0.021 mol) in ethanol (40 ml) is bubbled a stream of ethyl nitrite for 10 min. To the cooled solution is added 10% aqueous hydrochloric acid (0.5 ml) and the bubbling of ethyl nitrite is continued until the separation of a red precipitate (30 min) is complete. The crystals are collected by filtration, washed with diethyl ether, and recrystallized from ethanol affording the pure compound; yield: 3 g (65%); m.p. 202–203 °C.

$C_{11}H_{12}N_4O$	calc.	C 61.09	H 5.59	N 25.91
(216.2)	found	60.91	5.59	25.73

I.R. (KBr): $\nu = 1550, 1640, 3260, 3320\ cm^{-1}$.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 2.4$ (s, 3 H); 2.8 (s, 3 H); 7.5–7.7 (m, 4 H); 8.0 ppm (br. s, 2 H).

1-Phenyl-Substituted 3-Methyl-1*H*-pyrazolo[3,4-*b*]pyrazine-5,6-dicarboxylic Acid Diethyl Esters (5a–e); General Procedure:
A mixture of the appropriate 4-nitroso-5-aminopyrazole (**2a–e**; 0.01 mol) and diethyl acetylenedicarboxylate (3.4 g, 0.02 mol) in dry toluene (50 ml) is refluxed for 12 h in a Dean-Stark apparatus. The mixture is evaporated in vacuo and the dark oily residue is treated with a small amount of methanol to cause the separation of crystals, which are collected by filtration and dried. Recrystallization from methanol gives yellow needles (Table).

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[1] I. Grandberg, G. V. Klyuchko, *Zh. Obshch. Khim.* **32**, 1898 (1962); *C. A.* **58**, 4537 (1963).

[2] H. Hoehn, *U. S. Patent* 3957782 (1976); *C. A.* **85**, 123472 (1976).

[3] M. Guarneri, P. Giori, *Gazz. Chim. Ital.* **99**, 463 (1969).

[4] G. Y. Paris, M. D. Perlin, A. G. Pernet, N. L. Shipkowitz, *U. S. Patent* 4303658 (1981); *C. A.* **96**, 85590 (1982).

[5] P. Giori, D. Mazzotta, G. Vertuani, M. Guarneri, D. Pancaldi, A. Brunelli, *Farmaco Ed. Sci.* **36**, 1021 (1981); *C. A.* **96**, 142748 (1982).

[6] A. Michaelis, *Liebigs Ann. Chem.* **339**, 138 (1905).

[7] C. Alberti, C. Tironi, *Farmaco Ed. Sci.* **19**, 618 (1964); *C. A.* **61**, 13299 (1964).

Table. Compounds **5a–e** prepared

Product	X	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	I.R. (KBr)[c] ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$)[d] δ [ppm]
5a	H	65	113–114°	$C_{18}H_{18}N_4O_4$ (354.4)	1740, 1720, 1600	1.45 (m, 6 H); 2.8 (s, 3 H); 4.55 (m, 4 H); 7.3–7.6 (m, 3 H); 7.65–7.8 (m, 2 H)
5b	2-Cl	61	97–98°	$C_{18}H_{17}ClN_4O_4$ (388.8)	1750, 1730, 1610	1.45 (m, 6 H); 2.8 (s, 3 H); 4.5 (m, 4 H); 7.4–7.7 (m, 5 H)
5c	3-Cl	70	126–127°	$C_{18}H_{17}ClN_4O_4$ (388.8)	1740, 1725, 1600	1.45 (m, 6 H); 2.8 (s, 3 H); 4.55 (m, 4 H); 7.2–7.5 (m, 3 H); 8.2–8.4 (m, 2 H)
5d	4-Cl	68	140–141°	$C_{18}H_{17}ClN_4O_4$ (388.8)	1750, 1720, 1600	1.45 (m, 6 H); 2.8 (s, 3 H); 4.55 (m, 4 H); 7.5 (m, 2 H); 8.2 (m, 2 H)
5e	4-CH$_3$	73	145–146°	$C_{19}H_{20}N_4O_4$ (368.4)	1740, 1720, 1610, 1590	1.45 (m, 6 H); 2.4 (s, 3 H); 2.8 (s, 3 H); 4.5 (m, 4 H); 7.3 (m, 2 H); 8.1 (m, 2 H)

[a] Yield of products recrystallized from methanol.

[b] Satisfactory microanalyses obtained: C ±0.35, H ±0.30, N ±0.31, Cl ±0.27.

[c] I.R. spectra were recorded on a Perkin-Elmer 297 spectrometer.

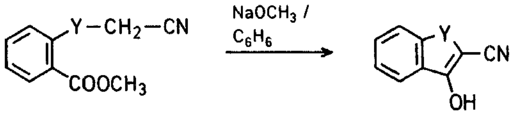
[d] ^{1}H-N.M.R. spectra were measured with a Perkin-Elmer R32 spectrometer using TMS as internal standard.

Errata and Addenda 1984

M. H. Elnagdi, M. R. H. Elmoghayar, G. E. H. Elgemeie, *Synthesis* **1984** (1), 1–26:

The second paragraph on page 2 should read:
Cyclic 3-oxoalkanenitriles **11** are obtained via cyclisation of methyl *N*-acetyl-*N*-cyanomethylanthranilate **(10a)**[61a], methyl 2-(cyanomethoxy)-benzoate **(10b)**[61b], or methyl 2-(cyanomethylthio)-benzoate **(10c)**[61] under basic conditions.

The formula scheme **10** → **11** (p. 3) should be:



10 a Y = N–CO–CH$_3$
b Y = O
c Y = S

11 a-c

The experimental procedure for **11a** (p. 3) should read:

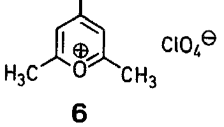
2-Cyano-3-hydroxyindole (11a; Y = NH)[61]:
A mixture of freshly prepared sodium methoxide (10 mmol) and methyl *N*-acetyl-*N*-cyanomethylanthranilate (**10a**; 10 mmol) in benzene (25 ml) is stirred for 2 h at room temperature then left for 12 h at room temperature. The mixture is poured into water. Carbon dioxide is bubbled into the resulting solution till no more solid separates. The product is collected and recrystallised; yield: 64%; m.p. 165–167 °C (dec.).

The following references should be added (p. 23):

[61] (a) D. Vorländer, *Ber. Dtsch. Chem. Ges.* **35**, 1683, 1696 (1902).
(b) R. Bryant, D. L. Haslam, *J. Chem. Soc.* **1965**, 2361.

P. Molina, A. Tárraga, E. Romero, M. L. Peña, *Synthesis* **1984** (1), 71–73:

The structure of compound **6** (p. 71) should be:



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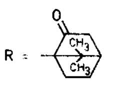
Abstract 6803, *Synthesis* **1984** (1), 82:

The substituent R should be:

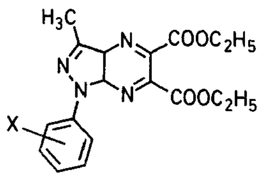


F. Pochat, *Synthesis* **1984** (2), 146–148:

Compounds **3c**, **5c**, and **5g** (p. 147 and 148) should be named as *N'*-acyl-*N'*-(methylthiomethyl)-hydrazones.

P. G. Baraldi, D. Simoni, V. Periotto, S. Manfredini, M. Guarneri, *Synthesis* **1984** (2), 148–149:

The structure of compound **5** (p. 149) should be:



5

S. C. W. Coltman, S. C. Eyley, R. A. Raphael, *Synthesis* **1984** (2), 150–152:

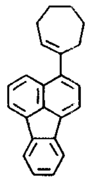
The first line of the experimental procedure for esters **4** should read:
To a solution of **2** (0.1 mol) in absolute ethanol (30 ml) is added a 1

R. Lapouyade, A. Nourmamode, *Synthesis* **1984** (2), 161–164:

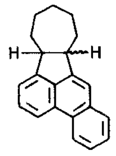
The title should read:
A New Synthesis of 6b,8,9,10,11,11a-Hexahydro-7*H*-cyclohepta[*a*]acenaphthylenes by Base-Catalyzed Photocyclization of 1-Arylcycloheptenes

The structures of products **1d**, **4b**, and **4c** in Tables 2 and 3 (p. 163) should be:

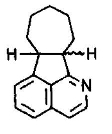
1d



4b

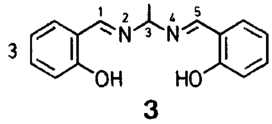


4c



T. Takajo, S. Kambe, W. Ando, *Synthesis* **1984** (3), 256–259:

The structure of product **3** (p. 257, left) should be:



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S. Podergajs, B. Stanovnik, M. Tišler, *Synthesis* **1984** (3), 263–265:

The structures of reagent **2** and products **5a–d** (p. 264) should be:

5a-d

U. Schöllkopf, U. Busse, R. Kilger, P. Lehr, *Synthesis* **1984** (3), 271–274:

The heading for the first experimental procedure (p. 274) should be: (3*S*,6*S*)-3,6-Diisobutyl-2,5-dioxohexahydropyrazine **(9)**:

J. Cabré, A. L. Palomo, *Synthesis* **1984** (5), 413–417:

The authors' address should read:
Gema S. A., Beethoven-15, Barcelona-21; Centro Marga para la Investigación, Muntaner 212, Barcelona-36, Spain
The formulae of Schemes **A** and **B** (p. 413) should be interchanged.
The following experimental procedure should be added:

Cyclohexylammonium Carboxylates (Tables 3); General Procedure:
To a solution of cyclohexylamine (1.15 ml, 10.0 mmol) in the solvent (20 ml, Table 3), the carboxylic acid is added at room temperature. The mixture is stirred for 15 min at room temperature and then cooled to 0–5 °C. The precipitate is filtered and washed with cold (0 to −5 °C) solvent (10 ml).

D. P. Stack, R. M. Coates, *Synthesis* **1984** (5), 434–436:

The structure of product **2e** (Table, p. 435) should be: