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In this paper we report the synthesis of an isosteric series of new heterotricyclic derivatives, corresponding to pyrazolo[3,4-*b*]thieno[2,3-d]pyridine (**1**), pyrazolo[3,4-*b*]furano[2,3-*d*]pyridine (**2**) and pyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine (**3**). These functionalized compounds were obtained, in high overall yield, by an 'one-pot' reaction of the chloroester intermediate **4**, possessing the pyrazolo[3,4-*b*]pyridine system, with an adequate α-hetero-acetyl ester derivative, in SNAr/Dieckman cyclization type consecutive reactions.

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Introduction.

In the scope of a research program aiming at the design, synthesis and pharmacological evaluation of new compounds active at the arachidonic acid cascade (AAC) enzymes level [1-6], we have previously described the synthesis and the antinociceptive profile of the 5-acylarylhydrazone-1-*H*-pyrazolo[3,4-*b*]pyridine derivatives **5** [7], exploring the chloro-ester derivative **4** as an advantageous precursor.

In this paper we describe the utilization of compound **4** as the key intermediate in the synthesis of three new isosteric condensed heterotricyclic compounds, corresponding to pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridine (**1**), pyrazolo-[3,4-*b*]furano[2,3-*d*]pyridine (**2**) and pyrazolo[3,4-*b*]-pyrrolo[2,3-*d*]pyridine (**3**), which represent important synthons to a new class of heterocyclic potentially bioactive compounds [8] (Figure 1).

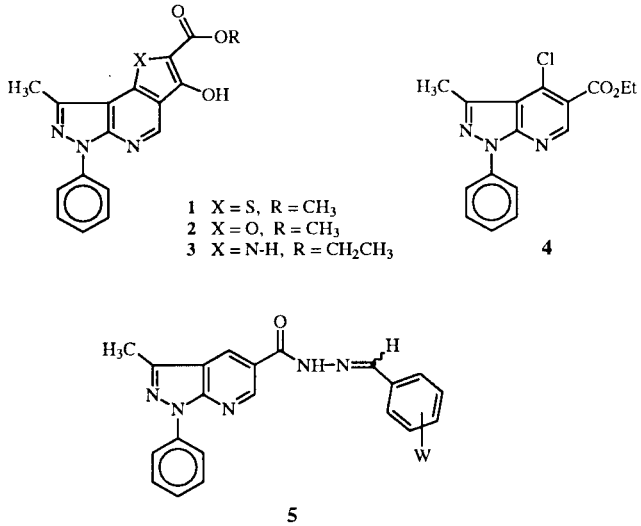


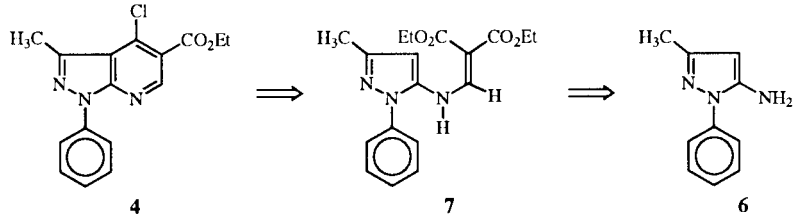
Figure 1

Chemistry.

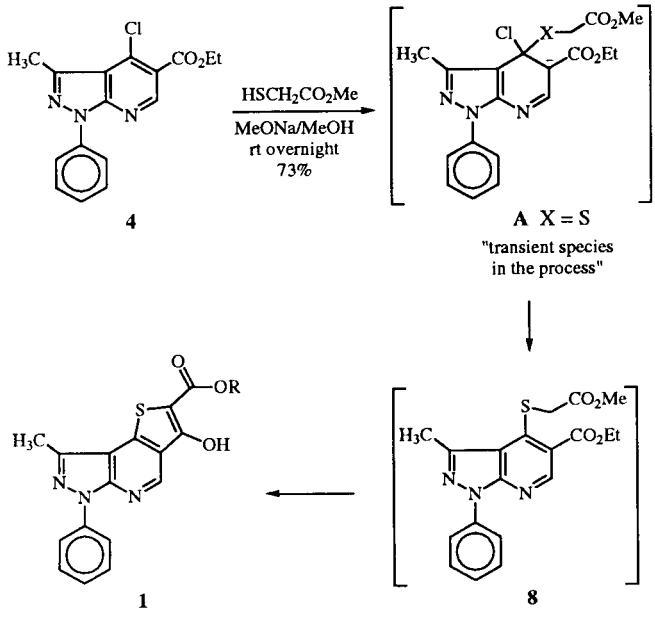
Preparation of 1-phenyl-3-methyl-4-chloro-5-carbethoxypyrazolo[3,4-*b*] pyridine (**4**) was accomplished, as previously described, in 60% overall yield, by exploring the Michael addition reaction between diethyl ethoxymethylenemalonate and 1-phenyl-3-methyl-5-aminopyrazole (**6**), followed by '*in situ*' treatment of the enamine intermediate **7** with phosphorus oxychloride at reflux, to furnish directly the desired chloroester **4**, in a thermal intramolecular condensation process [7] (Scheme 1).

The initial approach towards the preparation of the pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridine nucleus present in **1** consisted in an heteroaromatic nucleophilic displacement of chlorine atom at C-4 of **4** using the sodium salt of methyl thioglycolate [9] in a protic environment [10] as nucleophilic species (Condition A), followed by the intramolecular Dieckman condensation of the aryl thioether intermediate **8**, promoted by an excess of sodium methoxide present in the medium (Scheme 2). The reactivity of the

Scheme 1



Scheme 2

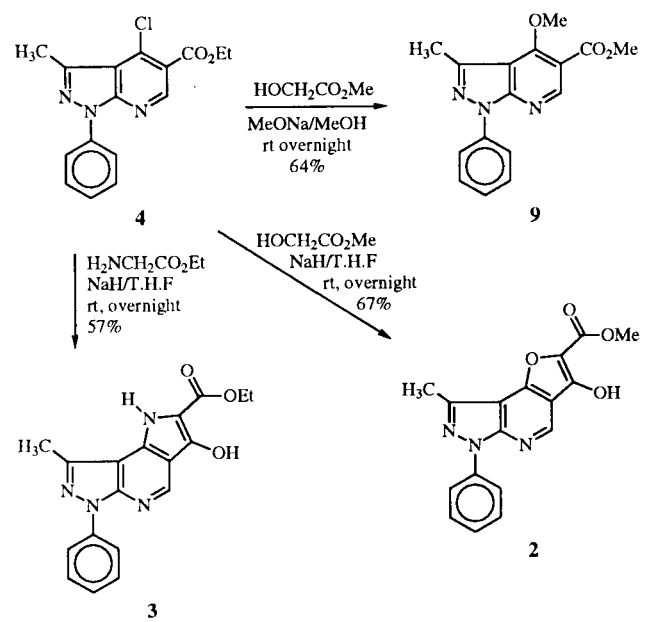


chlorine atom at C-4 of compound **4** under nucleophilic conditions is due to the activation promoted by the ester neighboring-group, that delocalize the negative charge of the transient sigma complex initially formed (species A). This successful 'one pot' procedure led to the desired compound **1**, in 73% yield, obtained as a pale yellow solid which displayed a purple color in ferric chloride test [11] characteristic of the β-hydroxycarbonyl moiety.

In the planned synthetic route to the *oxa*-isoster compound **2**, we intended to submit the key-intermediate chloroester **4** to the same experimental conditions described above, replacing the nucleophilic sodium methyl thioglycolate species by sodium methyl glycolate [9]. Nevertheless, we were able to obtain the corresponding 4-methoxy-1-phenyl-3-methyl-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid methyl ester (**9**) as a single product, in 64% yield (Scheme 3). These results can be rationalized as a competition between two nucleophilic species generated in the process, *i.e.* methoxy and methyl glycolate anions. The preferential nucleophilic attack of the methoxy anion is probably due to the high reactivity over the methyl glycolate anion, which is stabilized by the carbonyl inductive effect, producing a less nucleophilic entity.

In order to circumvent this unexpected behavior in the 'one-pot' procedure our attention turned to modify the basic entity to a less nucleophilic species using sodium hydride in a polar aprotic medium to generate the methyl glycolate anion (Condition B). Under these conditions we

Scheme 3



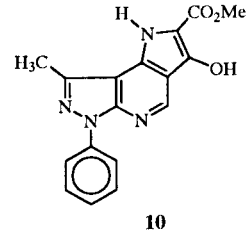


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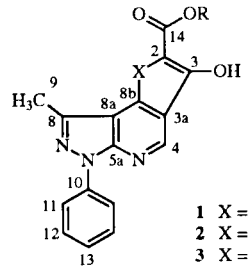
Figure 2

Table 1

CMR Shifts of Compounds **1**, **2** and **3** (200 MHz, DMSO-d_6 (TMS), at 40 mg/ml)



1 X = S, R = CH_3
2 X = O, R = CH_3
3 X = NH, R = CH_2CH_3

Carbon	δ (ppm) 1	2	3
8*	103.5	201.6	110.6
8a*	106.3	104.0	112.7
5a*	163.0	165.9	162.4
4	151.5	151.9	153.6
3a*	120.7	120.4	120.5
8b*	163.5	167.9	166.2
2*	129.1	128.9	129.1
3*	138.6	138.6	138.7
9	14.0	18.1	15.5
10*	143.5	142.0	143.3
11	120.8	121.3	120.5
12	128.9	128.7	127.5
13	126.0	125.8	125.9
14*	168.9	170.7	168.8

* Quaternary carbons.

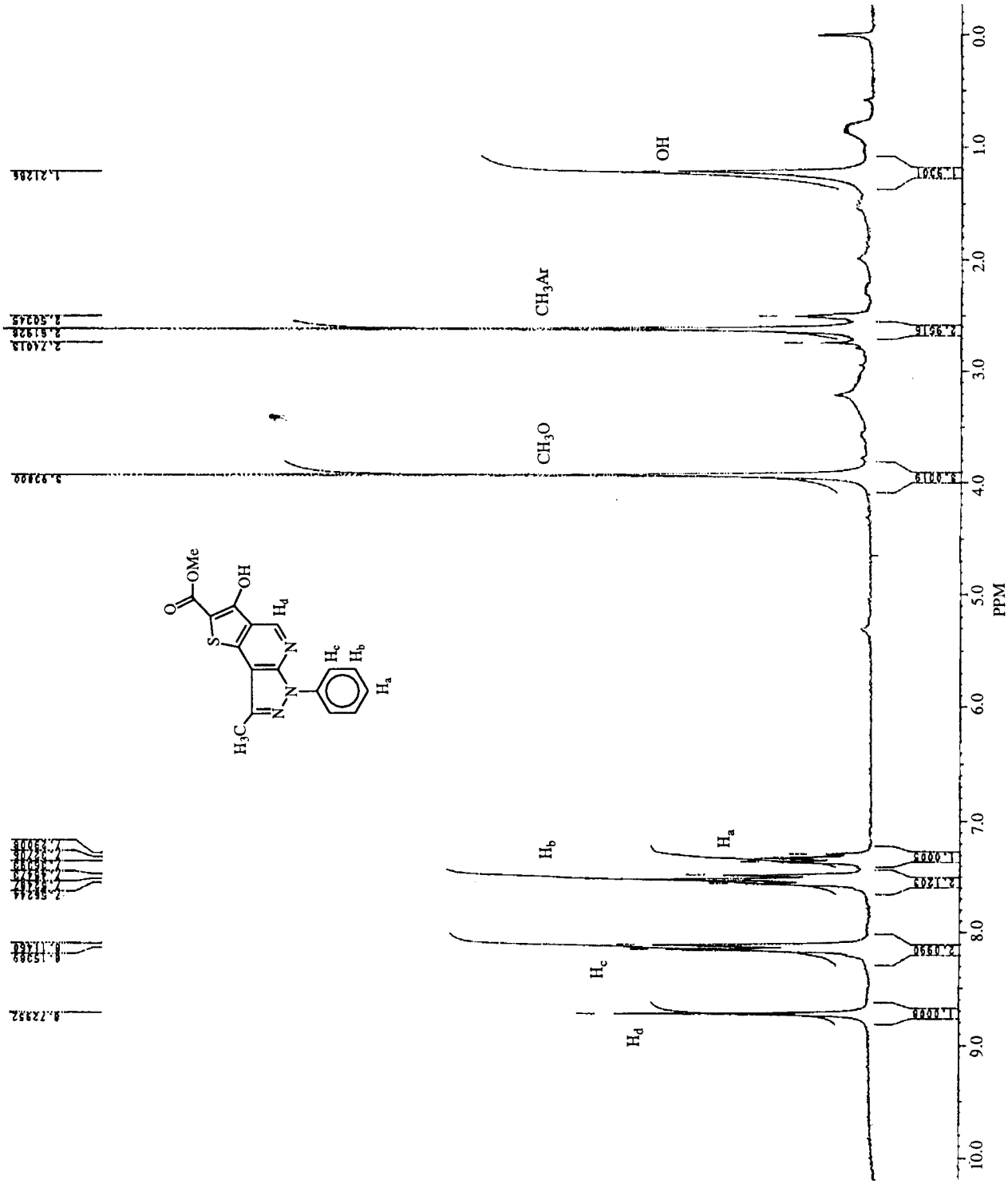


Figure 3. Pmr spectra of compound (1) (200 MHz, DMSO-d_6 (TMS), at 20 mg/ml).

were able to produce as a single product the desired isoster furan derivative **2**, in 67% yield, which also showed a purple color in the ferric chloride test [11].

Finally, this methodoloy was employed using glycine ethyl ester [12] instead of methyl glycolate, to obtain the isosteric pyrrole system present in compound **3**, in 57% yield, which gave a brown-red color with the ferric chloride test [11]. The experimental conditions B were chosen to prevent formation of possible transesterification products such as **10**, which were not detected in the final reaction product.

These derivatives **1-3** representing a new heterocyclic condensed system were fully characterized spectroscopically (pmr, cmr, ir, ms). In Table 1 are recorded the cmr chemical shifts of these new derivatives **1-3**.

In conclusion, the synthetic methodology described herein represents a high yield 'one-pot' procedure leading to these isosteric compounds, which are attractive synthons to construct new potentially bioactive compounds. We are now exploring these results in the laboratory to synthesize new chemical entities probably active at AAC.

EXPERIMENTAL

Nuclear magnetic resonance (pmr and cmr) was determined in dimethyl sulfoxide-d_6 (DMSO-d_6) containing *ca.*1% tetramethylsilane as an internal standard in a Bruker AC200 spectrometer. Splitting patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (ir) spectra were obtained in a Perkin-Elmer 1600 spectrophotometer by using potassium bromide plates. The mass spectra were obtained in a GC/VG Micromass 12 at 70 eV.

The progress of all reactions was monitored by tlc performed on 2.0 cm x 6.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under ultraviolet light. Solvents used in the reactions were dried, redistilled prior to use and stored over 3-4 Å molecular sieves. The usual work-up means that the organic extracts were treated with a saturated aqueous sodium chloride solution, referred to as brine, dried over anhydrous magnesium or sodium sulfate and filtered, before concentration under reduced pressure.

2-Methoxycarbonyl-3-hydroxy-6-phenyl-8-methylpyrazolo-[3,4-*b*]thieno[2,3-*d*]pyridine (**1**) [9].

To a solution of 0.068 g of sodium methoxide (1.26 mmoles) in 6.4 ml of dry methanol (prepared from 0.0292 g of sodium (0.00126 g-atom) was added 0.14 ml of methyl thioglycolate (0.166 g, 1.56 mmoles, 2.4 equivalents). The reaction mixture, maintained under a nitrogen atmosphere, was stirred at room temperature for 5 minutes. After this time a solution of 0.2 g of chloroester (**4**) (0.635 mmole) in 80 ml of dry methanol was quickly added and the resulting yellow mixture was stirred at room temperature overnight. The solvent was then evaporated and the residue poured into an ice-water mixture and extracted with ether (3 x 20 ml). Neutralization of the aqueous layer with 1 *M* hydrochloric acid resulted in a yellow precipitate which was filtered and dried to give 0.214 g (73%) of **1**, mp 138°; ir: ν OH 3440, ν C=O 1630, ν C=N 1627, ν C=C 1599, ν C-O-H 1375, ν C-O 1309 and 1225 cm^{-1}; pmr: δ 1.21 (s, 1H, deuterium oxide exchangeable, -OH), 2.61 (s, 3H, Ar-CH_3), 3.93 (s, 3H, O-CH_3), 7.32 (t, 1H, Ar-$H_{4'}$, J = 7.3 Hz), 7.52 (t, 2H, Ar-$H_{3'}$, J = 7.5 Hz), 8.15 (d, 2H, Ar-$H_{2'}$, J = 7.8 Hz), 8.72 (s, 1H, pyridine-*H*); ms: (m/z) 283 ($M^{+\cdot}$ -56, 100%), 251 ($M^{+\cdot}$ -88, 78%), 223 ($M^{+\cdot}$ -116, 93%), 77 ($M^{+\cdot}$ -262, 24%).

Anal. Calcd. for $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.83; N, 12.38. Found: C, 60.13; H, 3.79; N, 12.29.

4-Methoxy-1-phenyl-3-methylpyrazolo[3,4-*b*]pyridine-4-carboxylic Acid Methyl Ester (**9**) [9].

To a solution of 0.068 g of sodium methoxide (1.26 mmoles) in 6.4 ml of dry methanol (prepared from 0.0292 g of sodium (0.00126 g-atom) was added 0.12 ml of methyl glycolate (0.14 g, 1.56 mmoles, 2.4 equivalents). The reaction mixture, maintained under nitrogen atmosphere, was stirred at room temperature for 5 minutes. After this time a solution of 0.2 g of the chloroester **4** (0.635 mmole) in 80 ml of dry methanol was quickly added and the resulting yellow mixture was stirred at room temperature overnight. The solvent was evaporated and the residue poured into an ice-water mixture and extracted with ether (3 x 20 ml). After the usual work-up we obtained 0.12 g (64%) of **9** as a white solid mp 73°; ir: ν C=O 1699, ν C=N 1585, ν C=C 1555, ν C-O 1270 and 1250 cm^{-1}; pmr: δ 2.65 (s, 3H, Ar-CH_3), 3.92 (s, 3H, O=C-O-CH_3), 4.06 (s, 3H, Ar-O-CH_3), 7.32 (t, 1H, Ar-$H_{4'}$, J = 7.3 Hz), 7.50 (t, 2H, Ar-$H_{3'}$, J = 8.2 Hz), 8.18 (d, 2H, Ar-$H_{2'}$ J = 7.4 Hz), 8.75 (s, 1H- pyridine-*H*); ms: (m/z) 297 ($M^{+\cdot}$, 4%), 266 ($M^{+\cdot}$ -31, 3%), 223 ($M^{+\cdot}$ -74, 12%), 149 ($M^{+\cdot}$ -148, 100%).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.05; N, 14.14. Found: C, 64.62; H, 5.02; N, 14.12.

2-Methoxycarbonyl-3-hydroxy-6-phenyl-8-methylpyrazolo-[3,4-*b*]furano[2,3-*d*]pyridine (**2**).

An 80% suspension of sodium hydride in mineral oil (0.1 g, 3.33 mmoles) was washed with dry *n*-hexane, under a nitrogen atmosphere, until a white pale solid was obtained. This residue was suspended in 10 ml of dry THF, and 0.12 ml of methyl glycolate (0.14 g, 1.56 mmoles, 2.4 equivalents) was added to the reaction mixture, which was stirred for 5 minutes at room temperature under a nitrogen atmosphere. A solution of 0.2 g of chloroester **4** (0.6349 mmole) in 10 ml of dry THF was quickly added and the resulting mixture was stirred at room temperature overnight. The solvent was evaporated and the residue poured into an ice-water mixture and extracted with ether (3 x 20 ml). Neutralization of the aqueous layer with 1 *M* hydrochloric acid resulted in a white precipitate which was filtered and dried to give 0.136 g (67%) of **2**, mp 166°. ir: ν O-H 3400, ν C=O 1670, ν C=N 1570, ν C=C 1555, ν C-O-H 1270, ν C-O 1225 and 1195 cm^{-1}; pmr: δ 2.65 (s, 3H, Ar-CH_3), 3.94 (s, 3H, OCH_3), 7.49 (t, 1H, Ar-$H_{4'}$, J = 7.4 Hz), 7.55 (t, 2H, Ar-$H_{3'}$, J = 8.0 Hz), 8.15 (m, 2H, Ar-$H_{2'}$, J = 7.5 Hz), 8.83 (s, 1H, pyridine-H), 9.36 (br s, deuterium oxide exchangeable, 1H, -O*H*); ms: (m/z) 283 ($M^{+\cdot}$ -40, 100%), 239 ($M^{+\cdot}$ -84, 19%), 77 ($M^{+\cdot}$ -246, 13%).

Anal. Calcd. for $C_{17}H_{13}N_3O_4$: C, 63.15; H, 4.02; N, 13.0. Found: C, 63.10; H, 3.98; N, 12.98.

2-Ethoxycarbonyl-3-hydroxy-6-phenyl-8-methylpyrazolo-[3,4-*b*]pyrrolo[2,3-*d*]pyridine (**3**).

An 80% suspension of sodium hydride in mineral oil (0.1 g, 3.33 mmoles) was washed with dry *n*-hexane under a nitrogen atmosphere, until a white pale solid was obtained. This residue was suspended in 10 ml of dry THF, and 0.16 g of glycine ethyl ester [12] (1.56 mmoles) was added and stirred for 5 minutes at room temperature under nitrogen atmosphere. A solution of 0.2 g of chloroester **4** (0.6349 mmole) in 10 ml of dry THF was quickly added and the resulting mixture was stirred at room temperature overnight. The solvent was evaporated and the residue poured into an ice-water mixture and extracted with ether (3 x 20 ml). Neutralization of the aqueous layer with 1 *M*

hydrochloric acid resulted in a yellow precipitate which was filtered and dried to give 0.111 g (57%) of **3**, mp 175°; ir: ν OH 3400, ν N-H 3305, ν C=O 1670, ν C=N 1585, ν C=C 1550, ν C-O-H 1325, ν C-O 1260 and 1125 cm^{-1}; pmr: δ 1.39 (t, 3H, O-CH_2-CH_3, J = 6.9 Hz), 2.60 (s, 1H, deuterium oxide exchangeable, O-H), 2.63 (s, 3H, ArCH_3), 4.37 (q, 2H, O-CH_2-CH_3, J = 6.9 Hz), 7.41 (m, 2H, Ar-$H_{3'}$), 7.87 (d, 1H, Ar-$H_{4'}$, J = 8.0 Hz), 8.16 (d, 2H, Ar-$H_{2'}$, J = 7.9 Hz), 8.55 (s, 1H, N-*H*), 8.85 (s, 1H, pyridine-*H*); ms: (m/z) 323 ($M^{+\cdot}$ +1, 79%), 291 ($M^{+\cdot}$ -31, 92%), 77 ($M^{+\cdot}$ -245, 26%).

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.76; N, 16.66. Found: C, 64.27; H, 4.75; N, 16.65.

Acknowledgments.

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REFERENCES AND NOTES

[a] This paper represents contribution #07 from LASSBio.

[1] A. C. C. Freitas and E. J. Barreiro, *J. Heterocyclic Chem.*, **29**, 407 (1992).

[2] M. E. F. Lima and E. J. Barreiro, *J. Pharm. Sci.*, **81**, 1219 (1992).

[3] C. A. M. Fraga and E. J. Barreiro, *J. Heterocyclic Chem.*, **29**, 1667 (1992).

[4] E. F. Silva and E. J. Barreiro, *J. Braz. Chem. Soc.*, **4**, 40 (1993).

[5] A. C. C. Freitas, E. J. Barreiro, E. F. R. Pereira and N. A. Pereira, *Quim. Nova*, **18**, 147 (1995).

[6] L. M. Cabral and E. J. Barreiro, *J. Heterocyclic Chem.*, **32**, 959 (1995).

[7] L. R. S. Dias, M. J. F. Alvim, A. C. C. Freitas, E. J. Barreiro and A. L. P. Miranda, *Pharm. Acta Helv.*, **69**, 163 (1994).

[8] Abstracted in part, from MSc. Thesis of A. S. Carvalho (Instituto de Química-Universidade Federal do Rio de Janeiro), in preparation.

[9] Methyl thioglycolate and methyl glycolate were prepared by esterification of the respective carboxylic acids [13] with diazomethane in ethyl ether, and carefully distilled at reduced pressure (10 mm Hg).

[10] J. M. Barker, P. R. Huddleston and D. Holmes, *J. Chem. Res. (M)*, 2501 (1985).

[11] R. L. Shriner, R. C. Fuson, D. Y. Curtin and T. C. Morrill, Identificação Sistemática dos Compostos Orgânicos, Guanabara Dois, Rio de Janeiro, RJ, 1983, p 311.

[12] Glycine ethyl ester was prepared, in 70% yield, employing the Fisher's esterification [14] of glycine [13], and purified by distillation at reduced pressure (10 mm Hg).

[13] Purchased from Aldrich Co., Milwaukee, USA.

[14] B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, Longman Scientific & Technical, London, 1991, p 762.