Synthesis, Characterization and *In Vitro* Anthelmintic Activity against *Nippostrongylus brasiliensis* of New 5-Aryl-2-phenyl-6,7-dihydro-pyrazolo[1,5-*a*]pyrimidines

Jairo Quiroga* and Braulio Insuasty

Department of Chemistry, Universidad del Valle, A. A. 25360, Cali, Colombia

Angelina Hormaza

Department of Chemistry, Universidad Nacional, A. A. 3840, Medellín, Colombia

Daniela Gamenara [a], Laura Dominguez [b]† and Jenny Saldaña [b]

[a] Cátedra de Química Orgánica, [b] Cátedra de Farmacología y Biofarmacia, Facultad de Química, Universidad de la República, Av. Gral. Flores 2124, Montevideo, Uruguay

Received July 21, 1998

Several new pyrazolo[1,5-*a*]pyrimidines were obtained from the reaction of 1*H*-5-amino-3-phenylpyrazole (**1**) with β-dimethylaminopropiophenones **2** in pyridine. The structure elucidation of 6,7-dihydropyrazolo[1,5-*a*]pyrimidines **3** is based on nmr measurements. These compounds showed moderate anthelmintic *in vitro* activity against the *Nipposirongylus brasiliensis* model.

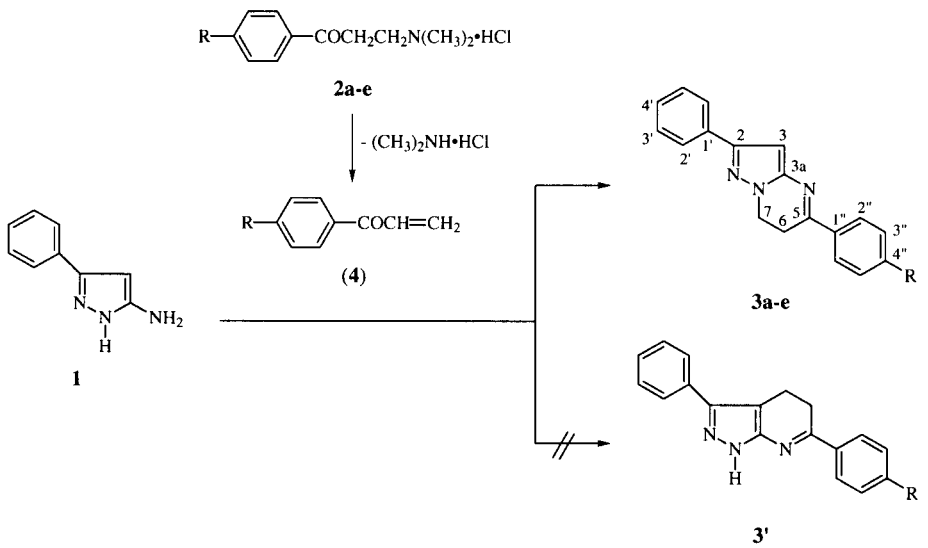
J. Heterocyclic Chem., **36**, 11 (1999).

Synthesis and study of the pyrazolo[1,5-*a*]pyrimidines have been of interest due to their physiological and biological activities [1-5]. Pyrazolopyrimidines are purines analogues and as such they have useful properties as antimetabolites in purine biochemical reactions [6,7]. Moreover, these compounds have marked antitumor and antileukemic activity [8].

In previous work we have reported some procedures for the synthesis of aromatic derivatives of pyrazolo[1,5-*a*]-pyrimidines [9-11]. In this work, the reaction of 1*H*-5-amino-3-phenylpyrazole (**1**) with β-dimethylaminopropiophenones **2a-e** was investigated: the aminopyrazole **1** reacts with equimolecular amounts of β-dimethylaminopropiophenone **2a** in pyridine to afford the 2,5-diphenyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine **3a** (Scheme 1).

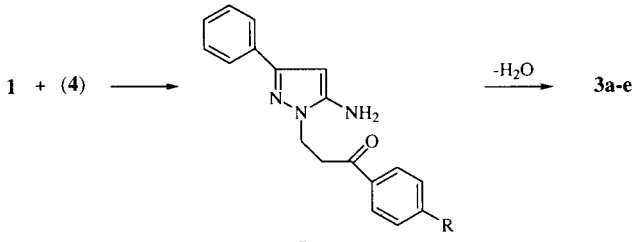
β-Aminopropiophenones are relatively unstable in basic medium and easily lose the amino group forming aryl vinyl ketones [12-15]. Addition of the aryl vinyl ketone, resulting from elimination of dimethylamine hydrochloride from **2**, to the nitrogen atom of the pyrazole ring and subsequent cyclization with elimination of water gives **3**. On the other hand, addition of the nucleophilic carbon atom at position 4 of amine **1** to the β-C atom of aryl vinyl ketone followed by cyclization can afford **3'**. The

Scheme 1



formation of **3** is assumed to proceed by a Michael type addition of the most basic ring nitrogen atom in aminopyrazoles [2] to the activated double bond of the aryl vinyl ketone (**4**). The Michael adduct intermediate **5** cyclizes by elimination of water to give the 6,7-dihydropyrazolo-[1,5-*a*]pyrimidines **3a-e** (Scheme 2).

Scheme 2



5

Structural assignment of **3a** was made on spectroscopic grounds. The presence of molecular ion at m/z 273 (M^+) in the mass spectrum was consistent with structure **3a**. The ^{1}H nmr spectrum of **3a** showed typical signals for the CH_2-CH_2 skeleton: two triplets (one proton each) at δ 3.29 and 4.39 ppm for the protons attached to C6 and C7, whereas a multiplet among δ 7.11-8.34 ppm was assigned to the aromatic protons and one singlet at δ 6.69 ppm corresponding to the =C3-H proton (Table 1). This last evidence mentioned above is to determine the reaction route **1** + **2(4)** → **5** → **3a-e**, eliminating the formation of isomeric compounds **3'**.

Table 1

^{1}H-NMR Data of **3a-e** (δ values, Tetramethylsilane as the Internal Standard, in Deuteriochloroform, 400 MHz)

Compound	3-H s	6-H t	7-H t	3-Aryl m	5-Aryl dd
3a	6.69	3.29	4.39	7.28-7.83	7.81-7.99
3b	6.63	3.24	4.36	7.28-7.82	6.96-7.98
3c	6.63	3.25	4.38	7.11-7.81	7.42-7.99
3d	6.67	3.28	4.35	7.12-7.81	7.58-7.88
3e	6.99	3.33	4.42	7.31-7.81	7.96-8.34

The general reaction was employed with the 1*H*-5-amino-3-phenylpyrazole and β-dimethylamino-4-R-propiophenones **2b-e** (R = CH_3O, Cl, Br, NO_2) that were treated as was compound **3a;** they afforded **3b-e** as the only products. The ^{1}H-nmr data for compounds **3a-e** are summarized in Table 1. The ^{13}C-nmr spectra of compounds **3b-e** were similar to that shown by compound **3a,** therefore they are not discussed in detail. The mass spectra of these compounds showed the molecular ion and their fragmentation corresponds to the assigned structure.

Compounds **3a-c** were evaluated using the *N. brasiliensis* nematode (L4 parasitant stage) *in vitro* model, according to the protocol described in [16]. The model was calibrated using Albendazole, Fenbendazole, Levamisole as standards with known anthelmintic activity, and the EC_{50} of every drug determined (Table 3). The EC_{50} of compounds **3a-c** corresponding to an EC_{50} more than one

Table 2

^{13}C-NMR Data of **3a-e** (δ values, Tetramethylsilane as the Internal Standard, in Deuteriochloroform, 400 MHz)

Compound	**3a**	**3b**	**3c**	**3d**	**3e**
C-2	151.8	151.7	151.5	150.4	152.1
C-3	100.0	99.3	100.2	100.5	101.3
C-3a	146.0	146.4	146.2	146.4	146.6
C-5	163.3	162.7	161.8	162.2	163.5
C-6	26.5	26.2	26.4	26.2	26.6
C-7	42.7	42.7	42.6	42.8	43.2
CH-aromatic	125.8, 127.3, 129.0, 129.1, 129.2, 131.7	114.7, 125.7, 128.9, 129.3, 131.3	126.6, 128.8, 128.9, 129.1, 131.2	125.6, 127.9, 128.5, 128.8, 132.0	123.8, 125.4, 127.7, 128.2, 128.7
C_q	137.6, 140.6	135.0, 140.7, 155.4	132.3, 137.2, 141.0	129.0, 138.8, 143.2	130.9, 138.7, 143.2

The ^{13}C-nmr spectrum showed 14 signals and a DEPT experiment indicated that seven of them correspond to CH, two to CH_2 and five to Cq. The ^{1}H-^{13}C correlation (HETCOR) allowed us to identify signals: δ 26.5 (C-6), 42.7 (C-7), 100.0 (C-3), 125.8 (C-2'), 127.3 (C-2"), 129.0 (C-3"), 129.1 (C-3'), 129.2 (C-4'), 131.7 (C-4"), 146.0 (C-3a), 151.8 (C-2) and 163.3 (C-5) ppm. All the above data agree with the structure 2,5-diphenyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine **3a**.

Table 3

In vitro Anthelmintic Activity against *N. brasiliensis* of Standard Drugs and Compounds **3a-c**

Compound	PM	EC_{50} μg/ml	EC_{50} m*M*
Albendazol	265	0.091	$3.4.10^{-4}$
Fenbendazol	299	0.036	$1.2.10^{-4}$
Levamisole	204	0.044	$2.1.10^{-4}$
3a	273	10.91	$4.0.10^{-2}$
3b	303	17.4	$5.7.10^{-2}$
3c	307.5	15.6	$4.4.10^{-2}$

hundredfold higher than the EC_{50} of the standard used to calibrate the model.

EXPERIMENTAL

Melting points were taken on a Buchi melting point apparatus and are uncorrected. The ^1H- and ^{13}C nmr spectra were run on a Bruker DPX 400 in acetone-d_6 and dimethyl-d_6 sulfoxide. Chemical shifts are related to tetramethylsilane as the internal standard. The mass spectra were recorded on a Shimadzu GC-MS QP 1100 EX spectrometer, operating at 70 eV. Elemental analyses were obtained using LECO CHNS-900 equipment. The culture medium and the experimental protocol used for the preparation of parasites for culture, have already been described by Jenkins *et al.* [17,18]. All the reagents used to prepare culture media were analytical quality (DIFCO, MERCK).

Synthesis of 5-Aryl-2-phenyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine **3**.

General Procedure.

A solution of 1*H*-5-amino-3-phenylpyrazole (**1**) (0.5 mmole) and the corresponding β-dimethylaminopropiophenone hydrochloride **2** (0.5 mmole) in 2 ml of pyridine was heated to reflux for 15-20 minutes. The cyclized products **3** were isolated by cooling, followed by filtration, washing with ethanol, drying and recrystallization from ethanol.

2,5-Diphenyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine **3a**.

This compound was obtained according to general procedure described above as pale yellow crystals; ms: m/z 274 (21), 273 (100, M^+), 272 (37), 271 (10), 114 (20), 103 (16), 77 (15).

Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.22; H, 5.20; N, 15.23.

5-(*p*-Methoxyphenyl)-2-phenyl-4,5-dihydropyrazolo[1,5-*a*]-pyrimidine **3b**.

This compound was obtained by the general procedure described above as pale yellow crystals; ms: m/z 304 (22) 303 (100, M^+), 302 (34), 301 (10), 133 (14), 114 (18), 77 (10).

Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.32; H, 5.50; N, 13.93.

5-(*p*-Chlorophenyl)-2-phenyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine **3c**.

This compound was obtained by the general procedure described above as pale yellow crystals; ms: m/z 308 (28), 309/307 (31/100, M^+), 306 (35), 305 (25), 304 (13), 137 (11), 114 (23), 77 (10).

Anal. Calcd. for $C_{18}H_{14}N_3Cl$: C, 70.24; H, 4.58; N, 13.65. Found: C, 70.31; H, 4.67; N, 13.56.

5-(*p*-Bromophenyl)-2-phenyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine **3d**.

This compound was obtained by the general procedure described above as pale yellow crystals; ms: m/z 353/351 (84/100, M^+), 349 (42), 270 (12), 135 (26), 134 (14), 114 (34), 102 (19), 77 (25).

Anal. Calcd. for $C_{18}H_{14}N_3Br$: C, 61.38; H, 4.01; N, 11.93. Found: C, 61.26; H, 4.12; N, 11.82.

5-(*p*-Nitrophenyl)-2-phenyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine **3e**.

This compound was obtained by the general procedure described above as yellow crystals; ms: m/z 319 (21), 318 (100, M^+), 317 (14), 316 (21), 271 (16), 114 (12), 77 (11).

Anal. Calcd. for $C_{18}H_{14}N_4O_2$: C, 67.92; H, 4.43; N, 17.60. Found: C, 67.84; H, 4.16; N, 17.73.

Acknowledgment.

We are grateful to COLCIENCIAS and Universidad del Valle for financial support.

REFERENCES AND NOTES

† Author to whom correspondence regarding biological assays should be addressed.

[1] J. V. Greenhill in Comprehensive Heterocyclic Chemistry, Vol **5**, A. R. Katritzky and C. W. Rees, eds, 1984, p 305.

[2] M. H. Elnagdi, M. R. H. Elmoghayar and G. E. H. Elgemeie, *Adv. Heterocyclic Chem.*, **41**, 320 (1987).

[3] M. H. Elnagdi, S. M. Fahmy, E. M. Zayed and M. A. M. Ilias, *Z. Naturforsch.*, **31b**, 795 (1976) and references cited therein.

[4] K. Senga, T. Novison, and H. R. Wilson, *J. Med. Chem.*, **24**, 610 (1981).

[5] R. K. Robins, D. E. O'Brien, T. Novinson and H. Springer, German Offen. 2,257,547; *Chem. Abstr.*, **79**, 78840 (1973).

[6] R. A. Earl, R. J. Pugmire, G. R. Revamker and L. B. Townsend, *J. Org. Chem.*, **40**, 1822 (1975).

[7] B. G. Hildick and G. Show, *J. Chem. Soc. (C)*, 1610 (1971).

[8] Y. Makamizawa, Japan Patent 1364063 (1960); *Chem. Abstr.*, **60**, 531 (1964).

[9] V. D. Orlov, J. Quiroga, N. N. Kolos and S. M. Desenko, *Khim. Geterosikl Soedin.*, 962 (1988).

[10] J. Quiroga, B. Insuasty, R. Rincón, M. Larrahondo, N. Hanold and H. Meier, *J. Heterocyclic Chem.*, **31**, 1333 (1994).

[11] J. Quiroga, A. Hormaza, B. Insuasty, C. Saitz, C. Jullian and A. Cañete, *J. Heterocyclic Chem.*, **35**, 61 (1998).

[12] H. Hellmann and G. Opitz, *Alpha*-aminoalkylurung, Verlag Chemie, Weinheim, 1960, p 246.

[13] S. Piroelle and P. Rollin, *Bull. Soc. Chim. France*, 2543 (1973).

[14] J. Quiroga, B. Insuasty, P. Hernández, R. Moreno, Regina H. de Almeida and H. Meier, *Eur. J. Org. Chem.*, **6**, 1201 (1998).

[15] J. Quiroga, B. Insuasty, S. Cruz, P. Hernández, A. Bolaños, R. Moreno, A. Hormaza and Regina H. de Almeida, *J. Heterocyclic Chem.*, **35**, 333 (1998).

[16] S. Gordon, L. Costa, M. Incerti, E. Manta, J. Saldaña, L. Domínguez, R. Mariezcurrena and L. Suescún, *Il Farmaco*, **52**, 10, 603 (1997).

[17] D. C. Jenkins, R. Armitage, and T. S. Carrington, *Z Parasitenkd*, **63**, 261 (1980).

[18] D. C. Jenkins, E. B. Rapson and P. Topley, *Parasitology*, **93**, 531 (1986).