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Preparation, structural analysis and anticonvulsant activity of 3- and 5-aminopyrazole *N*-benzoyl derivatives

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Summary — Some unsymmetrical *N*-exocyclic and *N*-endocyclic derivatives from benzoylation of 3- and 5-aminopyrazole were prepared with the aim of comparing their anticonvulsant activity towards the MES and scMET tests. Unambiguous proof of their structure was obtained from heteronuclear long-range correlation spectroscopy and NOE difference spectra. Only the *N-exo*-pyrazole benzamides showed good protection with respect to these tests.

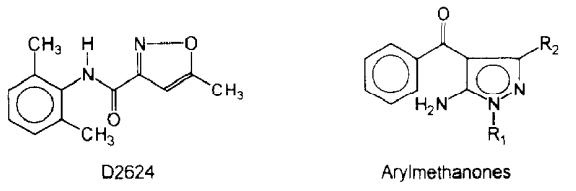
benzamide / aminopyrazole / anticonvulsant activity / NMR / selective long-range heteronuclear correlations / steady-state nuclear Overhauser effect

Introduction

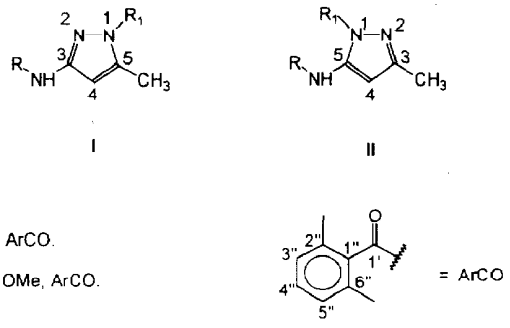
In a previous study we reported the anticonvulsant activity of a series of *N*-aryl isoxazole carboxamide derivatives [1]. Some of them reveal considerable potency especially with respect to the maximal electroshock seizure (MES) test. We started preclinical investigations with the most promising of them, D2624 (scheme 1). This compound has been shown to possess a phenytoin-like profile [2].

These results prompted us to synthesize a variety of analogues of *N*-heterocycle benzamides like isoxazole, pyrazole, thiazole and thiadiazole derivatives. As a first step in elucidating the structure–activity relationship of the *N*-pyrazole series, we carried out the present study in order to ascertain which basic structure displays the better activity. Indeed, it is known that the toluenesulfonylation of aminopyrazole affords a mixture of *N*-exocyclic and *N*-endocyclic derivatives [3]. We therefore anticipated that the benzoylation of these same aminopyrazoles would also give a mixture of condensed compounds with structures **I** (exocyclic amino group) or **II** (endocyclic amino group) (scheme 2). With the free amino group compounds **II** may be related to a novel series of (1,3-dialkyl-5-amino-1*H*-pyrazol-4-yl)arylmethanones (scheme 1), which demonstrated potential anticonvulsant properties and a low order of acute toxicity [4].

In the course of this work, we encountered some difficulties in structural determination particularly for the N_1-unsubstituted compounds for which tautomerism may occur. The tautomerism of *N*-unsubstituted aminopyrazoles has been the subject of several studies with controversial results [5, 6] but to date it is generally agreed that the 3-amino derivative should be more stable than the 5-amino isomer [7, 8].



Scheme 1.



Scheme 2.

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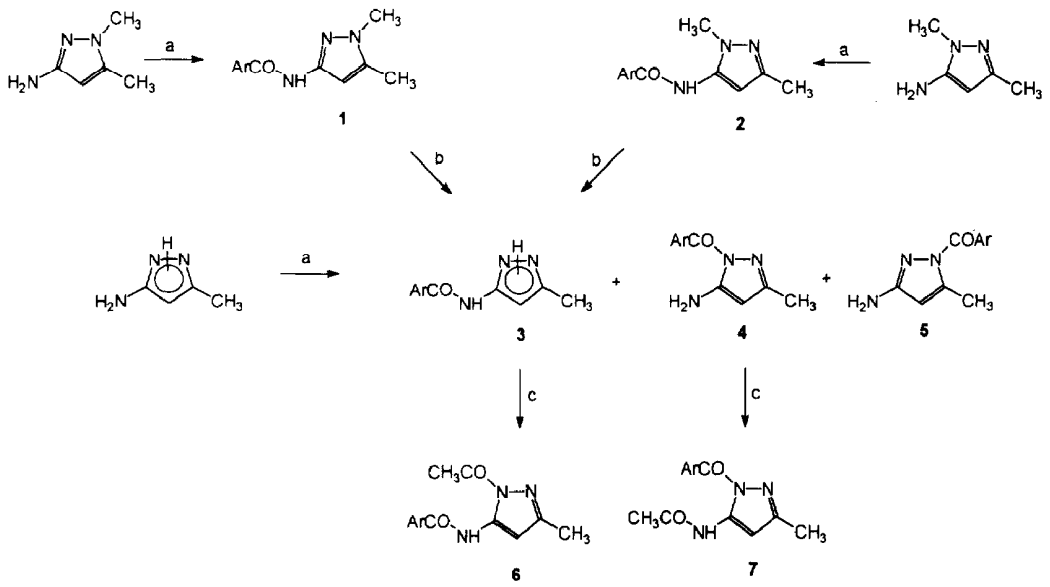

a : ArCOCl. b : pyridine.HCl; 220°C. c : CH_3COCl.

Ar = 2,6-dimethylphenyl

Scheme 3.

Identification of tautomeric *N*-substituted amino pyrazoles is based on either spectral analysis or chemical reactivity. G Ege *et al* [3] distinguished between the 3- and 5-amino isomers using the variation in the ^1H chemical shift of H-4 (see scheme 2 for the atom labels) caused by *exo*-*N*-tosylation. J Elguero *et al* [6] relied on the ^{13}C chemical shift of C-4. Hecht *et al* [9] used the difference in chemical reactivity due to the steric hindrance of the amino group. Finally, Y Kurasawa *et al* [10] conducted intramolecular cyclization which can only occur through the formation of the 5-amino intermediate.

None of the previous methods could be used for the identification of our structures. In this communication we present a complete ^1H- and ^{13}C-NMR study of a series of *N*-(3- and 5-pyrazolyl) benzamides. This structural analysis is based on both long-range heteronuclear proton–carbon coupling constants and NOE enhancements.

Chemistry

Synthesis

Two synthetic approaches were explored. In the first, benzamides *N*-(1,5-dimethyl-3-pyrazolyl) **1** and *N*-(1,3-dimethyl-5-pyrazolyl) **2** were prepared from 2,6-dimethylbenzoyl chloride and, respectively, 3-amino-1,5-dimethylpyrazole [11] or 5-amino-1,3-dimethylpyrazole [12] *(vide infra)*. *N*-Demethylation by heating with pyridine hydrochloride led to the same demethylated compound **3** regardless of the starting *N*-methyl derivative **1** or **2** (scheme 3).

In the second approach, the classical condensation of 2,6-dimethylbenzoyl chloride with 3-amino-5-methylpyrazole led to a mixture of three compounds, **3**, **4** and **5** (scheme 3). The proportion of these products did not vary with the reaction conditions (*eg*, temperature, hydrogen scavenger). Finally, **3** and **4** were acetylated with acetyl chloride to afford **6** and **7**, respectively (scheme 3).

Structural analysis

The molecular formulae calculated for pyrazoles **1–7** from chemical ionization mass spectra are collected in table I. That of **1** (**2**) corresponds to *N*-methyl-3(5)-amino-5(3)-methylpyrazole derivatives carrying a 2,6-dimethylbenzoyl substituent. The *m/z* values for molecules **3–5** corroborate the addition of a 2,6-dimethylbenzoyl moiety to the 3- or 5-methylpyrazole ring. Finally, the molecular weights of compounds **6**

and **7** indicate that further substitution by an acetyl group has occurred.

^{1}H- and ^{13}C-NMR chemical shifts are collected in tables II and III, respectively. The phenyl proton shifts (6.98–7.45 ppm) were identified from the COSY [13] (COSYLR [14]) spectra. The low-field signals between 5.45 and 6.93 ppm were attributed to H-4 of the pyrazole ring. A similar value of 6.42 ppm has been described for H-4 of unsubstituted pyrazole [15]. As regards the methyl resonances, those of substituents attached to both the phenyl and pyrazole rings were identified by long-range scalar coupling with H-3"/H-5" and H-4 respectively through COSY or COSYLR spectra. The remaining methyl signal was assigned to the R^1 group in the case of **1** (δ 2.97 ppm) and **2** (δ 3.65 ppm). An analogous value of 3.55 ppm has been reported for the *N*-methyl group of 1-methyl-3-aminopyrazole [16]. As regards the pyrazoles **6** and **7**, the methyl of the acetyl moiety was identified by long-range coupling to the carbonyl carbon. The chemical shifts of the signals appearing at lowest field (7.70–12.24 ppm) lie within the range of values typical of amido protons and protons α to nitrogen in unsaturated heterocyclic compounds [17]. The assignment of the amido protons was corroborated by long-range coupling to the carbonyl carbon. The high-field shift of the amido signal in **2** (7.7 ppm) is striking. In contrast, the values of 12.24 ppm for NH-1 in **3**, and 6.93 and 5.71 ppm for NH_2 in **4** and **5** are typical of *N*-unsubstituted [18] and aminopyrazole derivatives [19], respectively.

The ^{13}C chemical shifts (table III) were assigned from heteronuclear long-range coupling ($^2J_{C,H}$, $^3J_{C,H}$, $^4J_{C,H}$ and $^5J_{C,H}$) to the pyrazole ring substituents. These long-range correlations (table IV) were obtained from INAPT [20] spectra which were generally acquired with a 5 Hz filter which optimizes three-bond correlations with respect to two-, four- and five-bond transfer. However, in some cases a 2.5 Hz filter was used to optimize the latter type of correlation. The long-range INAPT [20] experiments generally led to the assignments of virtually all of the quaternary carbons.

In the case of compound **1**, a 2D heteronuclear correlation spectrum led to the assignment of all the protonated carbons. Long-range coupling between the methyl protons of R^1 and 5(3)-CH_3 in **1** (**2**) and the pyrazole carbon C-5 (C-5 and C-3) established the position of the latter methyl substituent. Chemical shifts, which were calculated for these pyrazoles according to Begtrup *et al* [21], are also given in table III (values in brackets) and the agreement with the experimental values is reasonable. These variations, 0.3–2.0 ppm, may be due to the fact that the increments used for the theoretical values were those of substituted benzene and thus not strictly appropriate.

Table I. Molecular formulae of pyrazoles **1–7**.

Pyrazole	C_x	H_y	N_3	O_z
1, 2	C_{14}	H_{17}	N_3	O
3	C_{13}	H_{15}	N_3	O
4	C_{13}	H_{15}	N_3	O
5	C_{13}	H_{15}	N_3	O
6	C_{15}	H_{17}	N_3	O_2
7	C_{15}	H_{17}	N_3	O_2

Table II. 400 MHz ^{1}H-NMR chemical shifts[a] (ppm) of pyrazoles **1–7**.

Pyrazole	*N-H*	*R^1*	*H-4*	*CH_3*[b]	*Me-2", 6"*[c]	*H-3", H-5"*	*H-4"*
1	10.06	2.97	6.65	2.16	2.28	6.98	7.16
2	7.70	3.65	6.12	2.20	2.35	7.05	7.21
3	10.77	12.24	6.62	2.435	2.44	7.27	7.39
4[d]	6.93		5.45	2.14	2.31	7.29	7.45
5[e]	5.71		6.01	2.75	2.29	7.25	7.39
6	10.46	2.67	6.93	2.31	2.35	7.07	7.22
7[f]	10.58		6.77	2.17	2.21	7.09	7.28

With the exception of the resonances of the aromatic protons, all signals are singlets. [a]**1**, **2**, **6** and **7** in $CDCl_3$ (δ_H 7.27 ppm), **3–5** in DMSO-d_6 (δ_H 2.72 ppm). [b]Assigned from COSY (**7**) and COSYLR (**1**, **6**) spectra through three-bond coupling with H-4. [c]Assigned from correlation spectra through three-bond coupling with H-3" and H-5". [d]Signal at 6.93 ppm integrates for 2 protons. [e]Signal at 5.71 ppm integrates for 2 protons. [f]Signal of the Me α to the carbonyl appears at 2.29 ppm.

Table III. Experimental[a] (calculated in italics[b]) 100 MHz ^{13}C-NMR chemical shifts of pyrazoles **1–7**.

Carbon (3-Amino) (5-Amino)	*1* (1)	*2* (2)	*3* (3) (3)	*4* (4)	*5* (5)	*6* (6) (6)	*7* (7) (7)
C_α-1	34.28[c]	35.39		171.83	169.30	174.51	174.14
C_β-1						23.39	
C-3	145.93 *(145.40)*	147.48 *(147.80)*	147.30 *(144.30)* *(145.40)*	154.57 *(154.32)*	153.09 *(159.32)*	154.17 *(148.90)* *(149.50)*	155.48 *(149.30)* *(151.01)*
C-4	97.52[c] *(99.40)*	99.79 *(100.60)*	96.46 *(97.60)* *(99.10)*	87.99 *(92.63)*	103.47 *(96.73)*	99.25 *(102.10)* *(98.70)*	99.09 *(101.80)* *(101.80)*
C-5	139.52 *(138.00)*	135.05 *(136.90)*	138.70 *(139.10)* *(135.50)*	151.66 *(147.22)*	143.87 *(138.42)*	140.73 *(134.50)* *(133.50)*	141.31 *(136.70)* *(134.80)*
CH_3	11.17[c]	13.74	10.92	14.00	14.62	14.25	14.38
C-1'	167.81	168.76	167.47			167.02	166.99
C_α-1							24.36
C-1"	137.59	136.40	138.40	136.57	137.67	136.34	135.04
C-2", C-6"	134.61	134.22	133.89	133.41	133.40	134.52	134.31
C-3", C-5"	127.32[c]	127.66	127.30	127.12	127.19	127.84	127.35
C-4"	128.71[c]	129.34	128.48	128.95	128.64	129.52	129.73
Me-2", Me-6"	19.09	19.24	19.14	18.92	19.09	19.39	19.38

[a]Assigned from INAPT spectra. **1**, **2**, **6** and **7** in $CDCl_3$ (δ_C 77.00 ppm) and **3–5** in DMSO-d_6 (δ_C 39.50 ppm). [b]The basic chemical shifts of the following pyrazoles were used in the calculations: 1,5-dimethylpyrazole (CD_2Cl_2) [22] for **1**, 1,3-dimethylpyrazole (CD_2Cl_2) [22] for **2**, 1-*H*-pyrazole (DMSO-d_6) [23] for 3- and 5-amido isomers of **3**, 1-benzoylpyrazole (DMSO-d_6) [22] for **4** and **5**, 1-acetylpyrazole ($CDCl_3$) [24] for 3- and 5-derivatives of **6**, and 1-benzoylpyrazole ($CDCl_3$) [22] for 3- and 5-isomers of **7**. As recommended in ref [21], the SCS were those reported for substituted benzenes [25]. [c]From a heteronuclear COSY[^{1}H-^{13}C] spectrum.

As regards compound **3**, correlations between C-1' and both N-H and H-1 were weak which is compatible with $^2J_{C,H}$ and $^4J_{C,H}$ or $^5J_{C,H}$ transfer respectively. Thus, the tautomeric structure could not be attributed from this data. However, the observation of broad signals for C-3 and C-5 clearly indicates that the sample contains an exchanging tautomeric mixture [21]. Comparison of the experimental chemical shifts with those calculated for 3- or 5-amino forms of **3** suggests that the former tautomer is the major one under these experimental conditions. The sum of the chemical shift variations between theoretical and experimental values are 4.54 and 7.70 ppm for the 3- and 5-amino derivatives, respectively.

The chemical shifts of the ring carbons of aminopyrazoles **4** and **5** were also obtained from INAPT spectra. The comparison between the experimental data and those calculated for **4** and **5** suggests that they are the 5-amino and 3-amino isomers, respectively. However, the fit ($\Delta\delta$ 8.42 and 9.33 ppm) between the calculated and experimental values here is much less satisfactory. The reference structures used for the theoretical chemical shift calculations are given in the footnote to table III. As expected, poorer fits are observed as the number of substituents increases.

In the case of compound **6**, the fit between the chemical shifts calculated for either 3- or 5-isomer

Table IV. 100 MHz long-range heteronuclear correlations for pyrazoles **1–7**.

Compound		*Chemical shifts of correlated[a] carbons*			
1	NH	167.61 (C-1')			
	R^1	139.38 (C-5)			
	H-4	139.38 (C-5)	145.80 (C-3)		
	Me-5	139.38 (C-5)	97.50 (C-4)		
	H-3", H-5"	134.46 (C-2", C-6")	137.45 (C-1")	167.68 (C-1')	
	Me-2", 6"	127.10 (C-3", C-5")	134.46 (C-2", C-6")	137.45 (C-1")	
2	N-H	168.83 (C-1')	135.10 (C-5)		
	R^1	135.10 (C-5)			
	H-4	135.10 (C-5)	147.54 (C-3)		
	Me-3	147.54 (C-3)	99.79 (C-4)		
	Me-2", 6"	127.71 (C-3", C-5")	134.27 (C-2", C-6")	136.46 (C-1")	
3	N-H	167.47 (C-1')			
	H-1	167.47 (C-1')			
	Me-3(5), 2", 6"	167.47 (C-1')	138.40 (C-1")	133.35 (C-2", C-6")	127.50 (C-3", C-5")
4	H-4	151.66 (C-5)	154.57 (C-3)		
	Me-3	154.57 (C-3)			
5	H-4	153.09 (C-3)	143.87 (C-5)		
	Me-5	143.87 (C-5)			
6	N-H	140.73 (C-5)	167.02 (C-1')		
	R^1	174.51 (C_α-1)			
	H-4	140.73 (C-5)	154.17 (C-3)		
	Me-3	99.25 (C-4)	154.17 (C-3)		
	Me-2", 6"	127.84 (C-3", C-5")	134.52 (C-2", C-6")	136.33 (C-1")	
7[b]	Me_α-1'[c]	141.31 (C-5)	166.99 (C-1')		
	H-4	141.31 (C-5)	155.48 (C-3)		
	Me-3	99.08 (C-4)	155.48 (C-3)		
	Me-2", 6"[c]	127.35 (C-3", C-5")	134.31 (C-2", C-6")	135.04 (C-1")	174.10 (Me_α-1')

[a]From INAPT spectra. In all cases partial inversion of the aromatic methyl protons was observed when the offset frequency for the selective proton pulse was set to that of the Me-3(5) group and *vice versa*. [b]Correlations between the MeCO protons and C-3 (141.31) and C-1' (166.99) were also observed. [c]A 2.5 Hz filter was used.

and the experimental ones is mediocre. However, the theoretical C-3 (δ 150 ppm) and C-5 (δ 134 ppm) values are very different and from the assignment of the C-5 (δ 140.73 ppm) and C-3 (δ 154.17 ppm) carbons, which is obtained through long-range coupling with the N-H and 3-CH_3 protons, respectively, it can be concluded that this derivative is related to pyrazoles **II**. Correlations were also observed between the acetyl methyl protons and the carbonyl signal at 174.51 ppm and between the N-H proton and the carbonyl resonance at 167.02 ppm. The electronegativity of the amido nitrogen (δ_H 5.71–10.77 ppm) is expected to be lower than that of the pyrazole sp_3 nitrogen (δ_H 12.24 ppm) based on the deshielding of protons α to these two types of nitrogen. The chemical shift variation between the amido carbonyl (δ_H 167.02 ppm) and the one attached to sp_3 pyrazole nitrogen (δ 174.51 ppm) is also likely to be related to the electronegativity of the heteroatom. In contrast, as regards the pyrazole **7**, correlations to the carbonyls suggest that the 2",6"-dimethylbenzoyl substituent is attached to the ring nitrogen (Me-2"/6" is coupled to the carbonyl that resonates at 174.14 ppm) whereas the acetyl moiety is attached to the exocyclic nitrogen (the acetyl methyl is correlated to the carbonyl at 166.99 ppm).

Spatial proximity can also be probed with NOE difference spectra [26]. In the case of compounds **1** and **2**, noticeable effects are only observed between N-H and R^1 for the latter pyrazole in agreement with the proposed 3D structures [27] (see *Molecular mechanics* in the *Experimental protocols*). It is to be noted that strong effects (5.3%) are observed between the amido proton and the aromatic methyl groups for both **1** and **2**.

Table V. 400 MHz steady-state NOEs[a] (%) for pyrazoles **1–7**.

Compound	*Saturated protons*	*N-H*	*R¹*	*H-4*	*Me (3 or 5)*	*Me-2", 6"*	*H-3", H-5"*	*H-4"*
1	N-H			1.3		5.3		
	R^1				2.1			
	H-4				3.2	1.6		
	Me-5		2.2	2.7			1.0	
	Me-2", 6"						4.0	
2	N-H		5.3	4.0		5.3		
	R^1	1.4						
	H-4	1.8			4.4	1.1		
	Me-3			2.8				
	Me-2", 6"						5.5	
3	H-1			1.1	12.5			
	N-H			2.8	6.5	1.8		
	H-4				8.2			
	Me-3(5), 2", 6"	1.4		3			11.7	
	H-3", H-5"			−1.2		9.8		5.6
	H-4"			−1.7			15.4	
4	NH_2			6.7		1.5		
	H-4	2.5			6.6			
	Me-3			3.1				
	H-3", H-5"					9.2		11.5
	H-4"						21.8	
	Me-2", 6"						5.3	
5	NH_2			6.0				
	H-4	1.0			4.0			
	Me-5			3.1				
	H-3", H-5"					8.0		
	H-4"						2.7	
	Me-2", 6"						5.0	
6	N-H		1.4	2.4		8.7		
	H-4[b]	1.3	1.4		5.7	3.7		
	Me-3[c]			7.0			1.7	
	Me-2", 6"						4.0	
7[c]	N-H[d]			2.5	1.0	2.1		
	Me_α-1'	4.0						
	H-4	1.0			5.0			
	Me-5			4.2			1.2	
	Me-2", 6"						6.2	

[a]At 296 K, approximately 0.12 M. Only NOE effects larger than 1% are indicated. In the case of all of the compounds except **5** partial saturation of the aromatic methyls upon irradiation of Me-3(5) was observed. [b]Partial saturation of H-3". [c]Partial saturation of the three methyl groups was observed upon saturation of any one of these moieties. [d]13.6% with the MeCO-group.

The strong effect between H-1 and 5(3)-CH_3 in **3** (12.5%) suggests a strong preference for the 3-amido tautomer but, as previously stated, the observation of broad signals for C-3 and C-5 clearly indicates that both tautomers are present [21]. In the case of compounds **4** and **5**, the absence of strong effects between the exocyclic amino protons and the aromatic methyl groups confirms that the aromatic acyl moieties are attached to a ring nitrogen. The small effect observed for **4** (1.5%) is compatible with the 5-amino structure.

The NOE effects between the amido proton and the aromatic methyl groups in **6** and **7** are very different, 8.7 and 2.1% respectively. This confirms that the aromatic acyl group is attached to the exocyclic nitrogen in **6** and to N-1 in **7**, compatible with both 5-

Table VI. Quantitative anticonvulsant activity of some benzamide *N-exo* and *N-endo* pyrazole derivatives, intraperitoneal administration in the mice and the effective dose (ED_{50}).

Compounds[a]	*N-Benzoyl P2 position*	*MES*[b] ED_{50}[d] *(mg/kg)*	*MMS*[c] ED_{50} *(mg/kg)*
3	*N-exo*	25 (16–39)	38 (25–58)
1	*N-exo*	39 (28–54)	27 (16–46)
2	*N-exo*	43 (37–50)	100
6	*N-exo* + N1-Ac	> 100	> 100
5	*N-endo*	> 60	> 60
4	*N-endo*	> 60	> 60
7	*N-endo*	> 100	> 100
Carbamazepine[e]		8.8 (5.5–14.1)	> 100
Phenytoin[e]		9.5 (8.1–10.4)	> 300
Valproate[e]		272 (247–338)	149 (123–177)

[a]The compounds were administered intraperitoneally. [b]MES = maximal electroshock seizure test. [c]MMS = maximal metrazol seizure test. [d]Numbers in parentheses are 95% confidence intervals. [e]Reference [31].

amido structures. Finally, the NOEs observed between the acetyl and amide protons in **7** are compatible with both **6** and **7** structures (scheme 3).

Pharmacological results

The pharmacological testing of the compounds is listed in table VI. These properties were evaluated in mice using the MES test and the maximal metrazol seizure (MMS) test.

Only the *N-exo* compounds, **1**, **2** and **3**, displayed noticeable activity. They antagonized electroconvulsive shock and, interestingly enough, chemically induced seizures, with ED_{50}s of 25 and 38 mg/kg respectively for the best compound **3**. Moreover, no neuromotor impairment evaluated according to the Irwin procedure was produced in mice up to 100 mg/ kg by those compounds.

Thus, this anticonvulsant profile is qualitatively different to that seen with carbamazepine and phenytoin. These prototype anticonvulsants are three orders of magnitude more potent against the MES test, but failed to prevent seizures chemically induced by pentylenetetrazol. In this respect our compounds compare favorably with valproate being active in both tests.

Moreover, the *N*-unsubstituted tautomer compound **3** and the two *N*-CH_3 isomers **1** and **2** showed a similar activity against the MES test, whereas the *N*-5 benzamide derivative was much less active than its *N*-3 isomer with respect to the scMET test (100 *versus* 27 mg/kg). Compound **6**, which was also an *N-exo*-benzoylpyrazole, was found to be inactive. This lack of activity might be due to the spacial proximity of the adjacent *N*1-acetyl group which could interact with the amidic hydrogen. An NOE effect was observed between this proton and the acetyl methyl resonance during the spectroscopy study.

The drastic difference in activity between these inactive *N-endo* derivatives and the active aminopyrazolaryl methanone described by Butler *et al* [4] is somewhat surprising considering the structural similarity of these two compounds.

Conclusions

As a result of this study, it is now possible to define the structure of compounds **3**, **4** and **5** (scheme 3).

Evidence for the tautomeric structures of the pyrazoles reported in this paper has been obtained from long-range heteronuclear coupling (**1**, **2** and **6**) and/or steady-state NOE effects (**1**, **2**, **4** and **5**). The position of the aromatic acyl group (exocyclic or ring nitrogen) was also determined from the NOE data. Comparison of theoretical and experimental carbon chemical shifts has been helpful but the fit between such data is often mediocre ($\Delta\delta \pm 5$ ppm). Considering the numerous isomers compatible with the molecular formulae of these compounds, it appears necessary to record both heteronuclear long-range correlation spectra and NOE difference spectra in order to obtain unambiguous proof of structure. A similar approach has been used to establish the structures of dinitrobenzimidazoles [28]. As a result of this brief but decisive structure–activity relationship study, it will be of interest to explore *N*-heterocyclic benzamides related to the *N-exo* structure.

Experimental protocols

Chemistry

Mass spectroscopy
Mass spectra were obtained by chemical ionization (NH_3) leading to molecular peaks of $[M + 18]^+$. Analyses led to corrected values of 243, 229 and 259 mass units for **1/2**, **3–5** and **6/7** respectively in agreement with the molecular formulae collected in table I.

NMR spectroscopy
Spectra of pyrazoles were recorded at 296 K in the following solvents: $CDCl_3$ (δ_H = 7.27 ppm, δ_C = 77.00 ppm) for **1**, **2**, **6** and **7**; DMSO-d_6 for **3–5** (δ_H = 2.72 ppm, δ_C = 39.50 ppm). The digital resolution of the ^1H spectra was 0.5 Hz/point for an acquisition time of 2 s. COSY [$^1H - ^1H$] [13] experiments were acquired with the standard Bruker program (90° – t_1 – 90° – FID), and for the COSYLR [$^1H - ^1H$] [14] experiments a delay of 0.1 s was introduced after the second 90° pulse.

J-modulated ^{13}C spectra were recorded with complete proton decoupling, an acquisition time of 1.11 s, digital resolution of 0.9 Hz/point and a recycle time of 3 s. Heteronuclear INAPT [20] spectra were acquired under similar conditions by using either 2.5 or 5 Hz filters (see table IV) for polarization transfer.

Proton T_1s were measured with the inversion-recovery (180° – τ – 90° – FID) sequence. Steady-state NOE experiments were performed by applying low-power irradiation at the offset frequency for 5 x T_1s with a 5 x T_1s recycle delay between successive scans. A total of 512 difference spectra were recorded and Fourier transformed with an exponential line-broadening factor of 1 Hz in order to reduce noise.

Melting points
These were measured with a kofler apparatus and are uncorrected.

Molecular mechanics
Pyrazoles **1** and **2** were studied with the molecular mechanics program CHARMm [27] using parameters (bond lengths and bond angles) [29] optimized for the pyrazole ring. In the case of **1**, systematic mapping indicated restricted rotation about the amido-nitrogen pyrazole-carbon bond (this torsion angle adopts values of 0 and 180°). The average distance between the amido-proton and the methyl group protons for these two minima are 5.65 and 5.07 Å, respectively. A much greater proportion of conformational space is accessible in the case of **2**. The average distance between the amido-proton and the methyl group protons varies from 3.27 to 4.43 Å and a Boltzmann-weighted value would be less than 4 Å.

N-(1,5-Dimethylpyrazol-3-yl)-2,6-dimethylbenzamide ***1***
A methylene chloride (100 ml) solution of the 2,6-dimethylbenzoyl chloride (23.6 g; 0.14 mol) was added to a cooled (0–5°C) solution of 3-amino-1,5-dimethylpyrazole [11] (32.7 g; 0.28 mol) in anhydrous methylene chloride (200 ml). The reaction mixture was warmed to room temperature and stirred for 18 h. The solvent was evaporated and the oily residue was partitioned between ethyl acetate and saturated $NaHCO_3$. The organic layer was separated, washed with water, dried (sodium sulfate) and concentrated. The crude material was crystallized from diisopropyloxide to give 13 g of the desired amide **1** (38%; yield based on the 2,6-dimethylbenzoyl chloride), mp 184°C. IR (KBr): ν 3205, 1669, 1583, 1486 cm^{-1}.

N-(1,3-Dimethylpyrazol-5-yl)-2,6-dimethylbenzamide ***2***
2,6-Dimethylbenzoyl chloride (16.9 g; 0.1 mol) in chloroform (20 ml) was added to a cooled (0–5°C) solution of 5-amino-1,3-dimethylpyrazole [12] (22.5 g; 0.2 mol) in anhydrous chloroform (80 ml) under a nitrogen atmosphere. The mixture was heated for 6 h and then allowed to cool to room temperature and stirred for 18 h. After filtration of the amine hydrochloride, the organic layer was poured onto cold saturated $NaHCO_3$ (100 ml) under vigorous agitation. After usual work-up, the crude material was purified by column chomatography on silica gel (60–200 microns) using CH_2Cl_2 and CH_2Cl_2/CH_3OH (98:2) as eluents to give 10.1 g of the desired amide **2** (41%, yield based on the 2,6-dimethylbenzoyl chloride), mp 190°C. IR (KBr): ν 3189, 1685, 1568, 1288 cm^{-1}.

N-(5(3)-Methylpyrazol-3(5)-yl)-2,6-dimethylbenzamide ***3***

From ***1***. A mixture of *N*-(1,5-dimethylpyrazol-3-yl)-2,6-dimethylbenzamide **1** (7.0 g; 30 mmol) and anhydrous pyridinium hydrochloride (15-fold molar excess) was heated at 220°C for 2 h. After dilution with 50 g of ice water, treatment with aqueous $NaHCO_3$ and extraction with chloroform (100 ml), the crude material was purified by column chromatography on silica gel (60–200 microns) using CH_2Cl_2 and CH_2Cl_2/CH_3OH (97.5:2.5) as eluents giving 1.5 g (22%) of the compound **3**, mp 252°C, and 3 g of the recovered amide **1**.

From ***2***. The amide *N*-(1,3-dimethylpyrazol-5-yl)-2,6-dimethylbenzamide **2** (1.25 g; 5 mmol) was treated with pyridinium hydrochloride (20-fold molar excess) at 220°C for 1.5 h and worked-up as described above. HPLC analysis after 30 min heating gave starting material **2** (8.5%) and the *N*-demethylated compound **3** (91.5%). Crystallization from diisopropyloxide of the crude material gave 0.4 g (35%) of the compound **3**, mp 250°C. IR (KBr): ν 3414, 3183, 1678, 1601, 1489, 1302 cm^{-1}.

N-(5(3)-Methylpyrazol-3(5)-yl)-2,6-dimethylbenzamide ***3****, 5-amino-3-methyl-N1-(2,6-dimethylbenzoyl)pyrazole* ***4*** *and 3-amino-5-methyl-N1-(2,6-dimethylbenzoyl)pyrazole* ***5***
2,6-Dimethylbenzoyl chloride (17.0 g; 0.1 mol) in chloroform (25 ml) was added dropwise to a cooled (10°C) solution of 3-amino-5-methylpyrazole (9.9 g; 0.1 mol) and triethylamine (10.2 g; 0.1 mol) in anhydrous chloroform (75 ml) under a nitrogen atmosphere. The temperature rose to 20–25°C. After 3 h, the stirred mixture was heated for 2 h at 50°C, cooled to room temperature, then diluted with chloroform (200 ml) and poured onto ice-water (100 g) under vigorous agitation. The organic layer was washed with saturated $NaHCO_3$ (2 x 25 ml) and dried (magnesium sulfate).

The crude material was purified by column chromatography on silica gel (60–200 microns) using CH_2Cl_2 and CH_2Cl_2/CH_3OH (97.5:2.5) and (95.5) (v/v) as eluents. After elimination of the 2,6-dimethylbenzoyl anhydride, the three amides were separated successively to give the amides **4** (13%), mp 204°C; IR (KBr): ν 3486, 3295, 1697, 1624, 1352 cm^{-1}; **5** (6.5%), mp 128°C; IR (KBr): ν 3445, 3288, 1688, 1626, 1353 cm^{-1}; and **3** (24%), mp 252°C. Total yield 43.5%.

Using a second equivalent of 3-amino-5-methylpyrazole instead of triethylamine gave the aforementioned products with approximately the same isomer ratio and yields.

N-(1-Acetyl-3-methylpyrazol-5-yl)-2,6-dimethylbenzamide ***6***
A solution of acetyl chloride (0.8 g; 0.01 mol) in methylene chloride (10 ml) was added dropwise over 10 min to a cooled (0°C) solution of the amide **3** (2.3 g; 0.01 mol) and pyridine (0.8 g; 0.01 mol) in anhydrous methylene chloride (30 ml)

under a nitrogen atmosphere. The mixture was allowed to warm to room temperature for 1 h and poured onto ice-water and methylene chloride (50 ml), washed with saturated $NaHCO_3$ and dried (magnesium sulfate). The crude product was crystallized from pentane to give 1.7 g of the corresponding *N*1-acetyl amide **6** (63%), mp 152°C. IR (KBr): ν 3321, 1709, 1688, 1528, 1383 cm^{-1}.

N-[N1-(2,6-Dimethylbenzoyl)-3-methylpyrazol-5-yl)]acetamide **7**

Compound **7** was obtained using the same procedure as described above starting from the amide **4**. The crude mixture was crystallized from diisopropyloxide to give 0.4 g (17.4%) of recovered amide **4**. The filtrate was concentrated and then crystallized from pentane to give 0.9 g (33%) of the desired amide **7**, mp 116°C. IR (KBr): ν 3325, 1714, 1681, 1525, 1351 cm^{-1}.

Biological methods

Pharmacological tests were performed with male CD1 mice from Charles River (Saint-Aubin-les-Elbeuf, France). All compounds were suspended in 0.5% carboxymethylcellulose and administered intraperitoneally in an injection volume of 0.1 ml/10 g body weight.

MES were elicited by electrical current (50 Hz, 50 mA, 0.2 s) applied *via* corneal electrodes. Mice were tested in primary screening, 0.5 h after administration. Abolition of the hind limb tonic extension component of the seizure was defined as protection in this test.

In the MMS test, seizures were chemically induced by 70 mg/kg of pentylenetetrazol (metrazol) injected subcutaneously as a 1% solution, 30 min after injection of the test compound. Failure to observe the generalized clonic seizure was defined as protection. These are identical to the protocols used by the Antiepileptic Drug Development Program of the Epilepsy Branch of NINDS, NIH. A dose–response curve was generated with at least three doses and 10 mice per dose. The ED_{50} is the calculated dose required to protect 50% of mice in both tests. For compounds with significant anticonvulsant activity, neurotoxicity was determined 0.5, 1, 2 and 3 h after administration in the Irwin test [30] conducted with three dose levels (10, 30 and 100 mg/kg) in five mice.

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