SYNTHESIS AND STRUCTURE DETERMINATION OF *N,N*-DIETHYL-3-[3-ARYL-1,2,4- OXADIAZOL-5-YL]PROPIONAMIDES

Rajendra Mohan Srivastava,[*a] Maria da Conceição Pereira,[a] Fernando Hallwass,[a] and Carlos R. N. Pacheco[b]

[a]Departamento de Química Fundamental, Universidade Federal de Pernambuco, 50.670-901 Recife, PE, Brazil
[b]Centro de Pesquisas da Petrobrás, Ilha do Fundão, Quadra 7, Cidade Universitária, 21949-900 Rio de Janeiro, RJ, Brazil

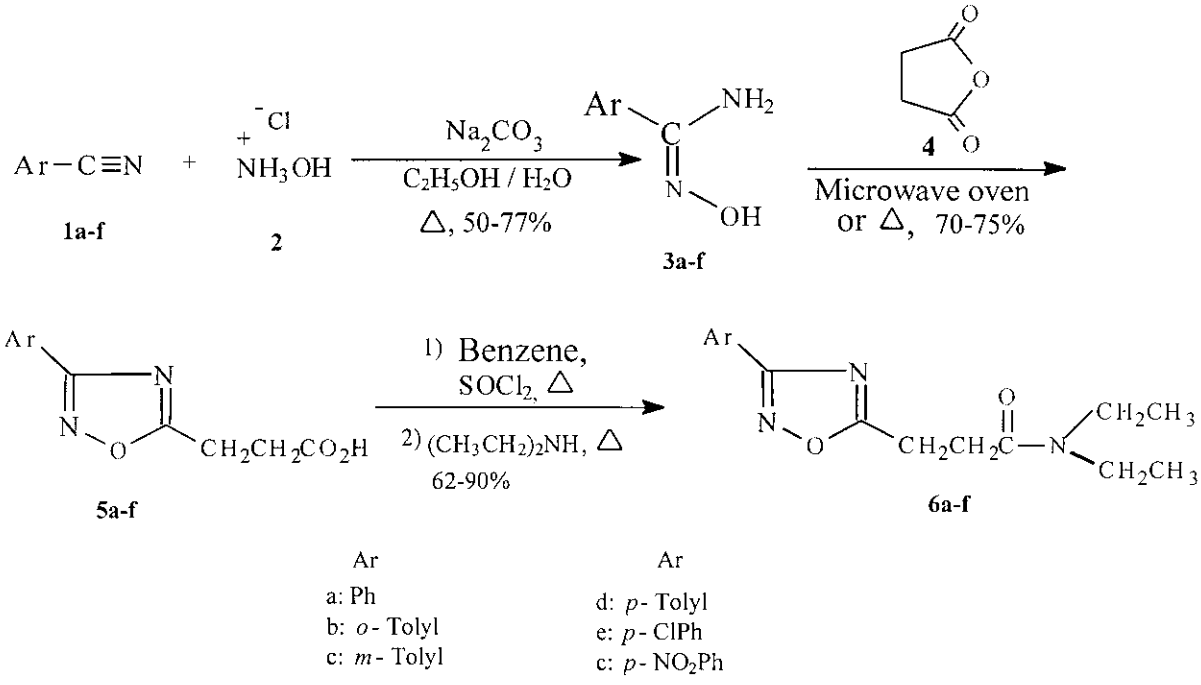
Abstract – *An efficient and facile synthesis of six new 1,2,4-oxadiazoles **(6a-f)** with a tertiary amide group attached on the side-chain, in high yield, is described. Correct assignments of side-chain methylene, methyl protons, and carbon signals have been made with the assistance of COSY, NOESY and HETCOR NMR experiments.*

For the last one hundred years, 1,2,4-oxadiazoles have been the subject of interest for a large number of researchers, and this topic has been reviewed twice by Clapp.[1,2] As reported in these reviews, many 1,2,4-oxadiazoles are biologically active and some of them are available commercially. For example, Oxolamine[3,4] and Libexin[5] have been used as antitussive (cough) agents, and Irrigor[4,6] as coronary vasodilator and local anaesthetic. We found that 3-[3-phenyl-1,2,4-oxadiazol-5-yl]propionic acid is analgesic as well as antiinflammatory.[7] The analgesic and antiinflammatory activities of one of the oxadiazoles, 5-methyl-3-phenyl-1,2,4-oxadiazole, have been reported in 1972.[8] Recently, we found that 3-aryl-5-isopropyl-1,2,4-oxadiazoles are also antiinflammatory.[9] A recent publication discusses the importance of these molecules.[10]

Since the literature does not record any 1,2,4-oxadiazole with a tertiary amide group attached in its side-chain, it was decided to introduce such a function with a view to evaluate its effect on the biological activity of these compounds. The importance of an amide group in a molecule is known. For example, D-lysergic acid is not active, but its diethylamide derivative (LSD)[11] profoundly alters human behavior, eliciting psychic alterations and hallucinations at doses as low as 1 μg/kg. Another compound is zolpidem (ambien), having a dimethylamido group in the side-chain, is a nonbenzodiazepine sedative hypnotic drug that became available in the United States in 1993.[12] This drug is as effective as benzodiazepines in shortening sleep latency and prolonging total sleep time in patients with insomnia. Nonsteroidal antiinflammatory carboxylic amides have been found to possess antioxidant and

antiproliferative activity.[13] Considering a wide-range of known pharmacological properties[1-10] of these compounds, 1,2,4-oxadiazoles with amide function in their side-chain appear as potential candidates for diverse biological activity tests. The present work therefore reports the synthesis of the compounds **(6a-f)** from **1a-f** (**Scheme**).

Scheme



RESULTS AND DISCUSSION

3-[3-Aryl-1,2,4-oxadiazol-5-yl]propionic acids **(5a-f)**[14] were transformed to their acyl chloride derivatives. The crude acyl chlorides thus obtained, on treatment with diethylamine, yielded the diethylamide derivatives **(6a-f)** (62-90%).

The IR spectrum (KBr) of **6a-f** exhibited a strong absorption around 1642 cm^{-1} due to the carbonyl group of a tertiary amide. The C=N bond of the heterocyclic ring also absorbed in this region. The N-O stretching motion was observed between 890-905 cm^{-1}. The C=C bond of the aromatic ring showed four weak to moderate absorptions between 1485-1600 cm^{-1}. These results are consistent with the oxadiazole system observed earlier.[15]

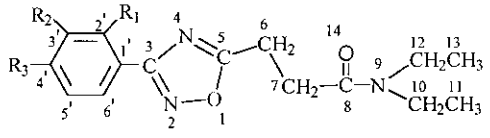
The ^1H NMR spectrum of **6a** exhibited two triplets - one at δ 1.05 and the other at 1.17 ppm due to two magnetically nonequivalent methyl groups. The former and the latter are due to H-13s and H-11s respectively (*vide infra*). Initially, difficulties were encountered in distinguishing the methylene protons

of C-6 and C-7, but the homonuclear NOESY helped to solve this problem. This technique also established the interaction of N-CH_2 protons with H-7, but not with H-6.

Since NOESY helped to locate the correct position of H-10 at δ 3.30 ppm, the location of H-12 became obvious at δ 3.33. The COSY technique confirmed the couplings of each methylene group with the methyl function, thus establishing the location of each methyl group. The absortion of H-13s at higher field is in accordance with the stable molecular conformation where these protons fall in the magnetic anisotropic region of the carbonyl group. H-10s and H-12s are assigned at higher and lower fields.

The ^{13}C NMR spectra of the compounds **(6a-f)** have been examined (Table 1) and assignments of all

Table 1. ^{13}C NMR chemical shift assignments of *N,N*-diethyl-3-[3-aryl-1,2,4-oxadiazol-5-yl]-propionamides **(6a-f)**.



(6a): R_1=R_2=R_3=H **(6d):** R_1=R_2=H; R_3=CH_3

(6b): R_1=CH_3; R_2=R_3=H **(6e):** R_1=R_2=H; R_3=Cl

(6c): R_1=R_3=H; R_2=CH_3 **(6f):** R_1=R_2=H; R_3=NO_2

Compound	Carbons															
	3	5	6	7	8	10	11	12	13	1'	2'	3'	4'	5'	6'	$ArCH_3$
6a	169.1	179.3	22.4	29.3	168.1	41.8	14.1	40.3	12.9	126.8	127.3	128.7	130.9	128.7	127.3	–
6b	169.1	178.2	22.2	29.2	168.1	41.7	14.0	40.3	12.9	126.0	138.0	129.8	131.1	125.7	130.3	21.9
calcd[a]										127.0	136.2	129.4	130.8	125.8	127.2	
6c	169.0	179.2	22.3	29.3	167.3	41.7	14.1	40.2	13.0	126.6	127.8	138.4	131.7	128.5	–	21.2
calcd[a]										126.7	128.0	137.6	131.6	128.6		
6d	169.1	179.1	22.4	29.3	168.1	41.8	14.1	40.3	13.0	124.0	127.2	129.4	141.2	129.4	127.2	21.4
calcd[a]										123.9	127.2	129.4	139.8	129.4	127.2	
6e	169.0	179.6	22.4	29.3	167.3	41.8	14.1	40.3	13.0	125.4	128.6	129.0	137.0	129.0	128.6	–
calcd[a]										124.9	128.6	129.1	137.1	129.1	128.6	
6f	168.9	180.3	22.4	29.2	166.6	41.8	14.2	40.4	13.0	132.9	128.3	124.0	149.3	124.0	128.3	–
calcd[a]										132.6	128.2	123.9	150.9	123.9	128.2	

[a] The value for each substituent has been obtained from ref. 18, and added to C-1', C-2', C-3', C-4', C-5' and C-6' of the compounds **(6a)** to give the calculated values.

carbon atoms have been made. It is interesting to see that each methyl group of *N*-ethyl function produces a separate signal. The one, which is on the carbonyl oxygen side is presumed to be at higher field. This is based on the fact that *N,N*-dimethylformamide gives two methyl signals[16] – one at δ 35.0 and the other at δ 38.0 ppm. Methylene carbon signals have been attributed similary. We encountered problems in assigning the chemical shifts of C-6 and C-7. Initially it was thought that C-6 should absorb at lower field and C-7 at higher field, but this is not true. HETCOR spectrum of **6b** (^{1}H-^{13}C) clearly shows that C-6 absorbs at δ 22.2 and C-7 at δ 29.2 ppm respectively. Next, we concentrated to study the substituent effect on the benzene ring. It has been found that the additivity holds well for *meta* and *para* substituents, but the *ortho* substituent gives deviation for C-2' and C-6'. This kind of deviation due to *ortho* substituent has been observed earlier.[14,17] The calculated and observed chemical shifts of all carbon atoms are given in Table 1 for comparison.

The spectroscopic results in conjunction with the semi-empirical molecular orbital calculations (AM1 method)[19,20] helped to elucidate the structure and conformation[21] of the title compounds.

CONCLUSION

We have been able to synthesize the six new 1,2,4-oxadiazoles **(6a-f)**. Spectroscopic data fully support their structures. The COSY, HETCOR and NOESY techniques established the exact chemical shifts of ^{1}H and ^{13}C atoms of methylene and methyl groups respectively.

EXPERIMENTAL

IR spectra were recorded on a Bruker IFS 66 apparatus, and ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were measured on a Varian Unity plus instrument using $CDCl_3$ as solvent and TMS as an internal standard. TLC were carried out on precoated Kieselgel 60 F_{254} plates (Merck) using solvent system $CHCl_3/AcOC_2H_5$ (8.0:2.0) followed by reveletion of spots under ultraviolet light. The elemental analyses of the compounds **(6b,c,f)** were done in the Microanalytical laboratory, Instituto de Química, Universidade de São Paulo, SP. The molecular weights ($M^{+\bullet}$ ions) of all compounds were also determined on a low resolution Finnigan GCQ-MAT mass spectrometer.

General procedure for the preparation of *N,N*-diethyl-3-[3-aryl-1,2,4-oxadiazol-5-yl]propionamides:

To an appropriate 3-[3-aryl-1,2,4-oxadiazol-5-yl]propionic acid **(5a-f)** (2.3 mmol) in a round-bottom flask and benzene (~20 mL) was added an excess of thionyl chloride (0.58 g, 7.0 mmol). The contents were refluxed for 1.0-1.5 h under nitrogen atmosphere and then cooled to rt. Removal of the solvent and

thionyl chloride with a current of dry nitrogen provided the crude acyl chloride, which was used for the next step without purification.

The above acyl chloride was treated with an excess of diethylamine (0.51 g, 7.0 mmol) in dichloromethane (~10 mL), and the solution was refluxed 40 min. After cooling and solvent removal, the contents were transferred to a separatory funnel with the help of dichloromethane, washed with a saturated solution of sodium bicarbonate (3x3 mL), water (3x3 mL), dried over anhydrous sodium sulfate, filtered and solvent removed to give a thick mass. Thin layer chromatography using chloroform/ethyl acetate (4:1) showed mainly one spot (R_f value ≈ 0.50). There also appeared a very faint spot having R_f value of 0.6. The crude material was chromatographed on a silica gel column using initially *n*-hexane and later gradually increasing the polarity by adding chloroform in hexane. The compound with $R_f \approx 0.5$ eluted when the column was flushed with chloroform-*n*-hexane: the fractions containing the desired compound were combined, solvent evaporated to provide **6a-f**.

***N,N*-Diethyl-3-[3-phenyl-1,2,4-oxadiazol-5-yl]propionamide (6a)**: colorless viscous liquid; 90% yield; $R_f = 0.45$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, J = 7.5, 3H, H-13), 1.17 (t, J = 7.2, 3H, H-11), 2.85 (t, J = 6.4, 2H, H-7), 3.25 (t, J = 6.3, 2H, H-6), 3.30 (q, J = 7.2, 2H, H-10), 3.33 (q, J = 7.2, 2H, H-12), 7.35-7.50 (m, 3H arom), 7.95-8.03 (m, 2H arom); ^{13}C NMR δ 12.9 (C-13), 14.1 (C-11), 22.4 (C-6), 29.3 (C-7), 40.3 (C-12), 41.8 (C-10), 126.8 (C-1'), 127.3 (C-2'and C-6'), 128.7 (C-3' and C-5'), 130.9 (C-4'), 168.1 (C-8), 169.1 (C-3), 179.3 (C-5). *Anal.* Calcd for $C_{15}H_{19}N_3O_2.1/4\ H_2O$: C, 64.84; H, 7.07; N,15.12. Found: C, 64.83; H, 6.94; N, 14.93.

***N,N*-Diethyl-3-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl]propionamide (6b)**: colorless viscous liquid; 68% yield; $R_f = 0.47$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J = 7.2, 3H, H-13), 1.25 (t, J = 6.9, 3H, H-11), 2.62 (s, 3H, Ar-CH_3), 2.90 (t, J = 6.6, 2H, H-7), 3.32 (t, J = 6.6, 2H, H-6), 3.29 (q, J = 6.9, 2H, H-10), 3.36 (q, J = 7.2, 2H, H-12), 7.27-7.43 (m, 3H arom), 7.94-8.01 (m, 1H arom); ^{13}C NMR δ 12.9 (C-13), 14.0 (C-11), 21.9 (Ar- CH_3), 22.2 (C-6), 29.2 (C-7), 40.3 (C-12), 41.7 (C-10), 125.7 (C-5'), 126.0 (C-1'), 129.8 (C-3'), 130.3 (C-6'), 131.1 (C-4'), 138.0 (C-2'), 168.1 (C-8), 169.1 (C-3), 178.2 (C-5). *Anal.* Calcd for $C_{16}H_{21}N_3O_2.1/4\ H_2O$: C, 65.85; H, 7.43; N,14.39. Found: C, 66.33; H, 7.51; N, 14.15.

***N,N*-Diethyl-3-[3-(*m*-tolyl)-1,2,4-oxadiazol-5-yl]propionamide (6c)**: colorless viscous liquid; 89% yield; $R_f = 0.47$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J = 7.1, 3H, H-13), 1.20 (t, J = 7.2, 3H, H-11), 2.37 (s, 3H, Ar-CH_3), 2.88 (t, J = 7.0, 2H, H-7), 3.28 (t, J = 7.0, 2H, H-6), 3.30 (q, J = 7.2, 2H, H-10), 3.36 (q, J = 7.1, 2H, H-12), 7.22-7.36 (m, 2H arom), 7.78-7.88 (m, 2H arom); ^{13}C NMR δ 13.0 (C-13), 14.1 (C-11), 21.2 (Ar-CH_3), 22.3 (C-6), 29.3 (C-7), 40.2 (C-12), 41.7 (C-10), 126.6 (C-1'), 127.8 (C-2'),

128.5 (C-5'), 131.7 (C-4'), 138.4 (C-3'), 167.3 (C-8), 169.0 (C-3), 179.2 (C-5). *Anal.* Calcd for $C_{16}H_{21}N_3O_2$: C, 66.87; H, 7.37; N, 14.62. Found: C, 66.50; H, 7.54; N, 14.46.

***N,N*-Diethyl-3-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]propionamide (6d)**: colorless semi-solid; 71% yield; R_f = 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.2, 3H, H-13), 1.23 (t, *J* = 7.2, 3H, H-11), 2.40 (s, 3H, Ar-CH_3), 2.91 (t, *J* = 6.6, 2H, H-7), 3.30 (t, *J* = 6.6, 2H, H-6), 3.37 (q, *J* = 7.2, 2H, H-10), 3.39 (q, *J* = 7.2, 2H, H-12), 7.26 (d, *J* = 8.3, 2H, H-3' and H-5'), 7.94 (d, *J* = 8.3, 2H, H-2'and H-6'); ^{13}C NMR δ 13.0 (C-13), 14.1 (C-11), 21.4 (Ar- CH_3), 22.4 (C-6), 29.3 (C-7), 40.3 (C-12), 41.8 (C-10), 124.0 (C-1'), 127.2 (C-2' and C-6'), 129.4 (C-3' and C-5'), 141.2 (C-4'), 168.1 (C-8), 169.1 (C-3), 179.1 (C-5). *Anal.* Calcd for $C_{16}H_{21}N_3O_2$: C, 66.87; H, 7.37; N,14.62. Found: C, 66.75; H, 7.31; N, 14.42.

***N,N*-Diethyl-3-[3-(*p*-chlorophenyl)-1,2,4-oxadiazol-5-yl]propionamide (6e)**: colorless crystals, mp 63 °C (EtOH/H_2O); 90% yield; R_f = 0.45; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, *J* = 7.3, 3H, H-13), 1.16 (t, *J* = 7.2, 3H, H-11), 2.84 (t, *J* = 7.4, 2H, H-7), 3.23 (t, *J* = 7.4, 2H, H-6), 3.29 (q, *J* = 7.2, 2H, H-10), 3.32 (q, *J* = 7.3, 2H, H-12), 7.36 (d, *J* = 8.4, 2H, H-3' and H-5'), 7.91 (d, *J* = 8.4, 2H, H-2'and H-6'); ^{13}C NMR δ 13.0 (C-13), 14.1 (C-11), 22.4 (C-6), 29.3 (C-7), 40.3 (C-12), 41.8 (C-10), 125.4 (C-1'), 128.6 (C-2' and C-6'), 129.0 (C-3' and C-5'), 137.0 (C-4'), 167.3 (C-8), 169.0 (C-3), 179.6 (C-5). *Anal.* Calcd for $C_{15}H_{18}N_3O_2Cl$: C, 58.52; H, 5.90; N, 13.66. Found: C, 58.44; H, 6.36; N, 13.58.

***N,N*-Diethyl-3-[3-(*p*-nitrophenyl)-1,2,4-oxadiazol-5-yl]propionamide (6f)**: colorless crystals, mp 95 °C (EtOH/H_2O); 62% yield; R_f = 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.1, 3H, H-13), 1.26 (t, *J* = 6.9, 3H, H-11), 2.94 (t, *J* = 7.2, 2H, H-7), 3.33 (t, *J* = 7.2, 2H, H-6), 3.37 (q, *J* = 6.9, 2H, H-10), 3.38 (q, *J* = 7.1, 2H, H-12), 8.26 (d, *J* = 9.0, 2H, H-2'and H-6'), 8.34 (d, *J* = 9.0, 2H, H-3' and H-5'); ^{13}C NMR δ 13.0 (C-13), 14.2 (C-11), 22.4 (C-6), 29.2 (C-7), 40.4 (C-12), 41.8 (C-10), 124.0 (C-3' and C-5'), 128.3 (C-2' and C-6'), 132.9 (C-1'), 149.3 (C-4'), 166.6 (C-8), 168.9 (C-3), 180.3 (C-5). *Anal.* Calcd for $C_{15}H_{18}N_4O_4$: C, 56.62; H, 5.70; N, 17.51. Found: C, 57.21; H, 5.39; N, 17.30.

ACKNOWLEDGMENT

The authors express their gratitude to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Ciência e Tecnologia (FACEPE) for financial help. Our thanks are due to Maria Luisa Aleixo Gonçalves of CENPES, Petrobras, Rio de Janeiro, for doing the microanalyses of the compounds **(6a,d,e)**. We are grateful to Sonia M.C. de Menezes of CENPES, Petrobras, Rio de Janeiro, for helping us at various occasions.

REFERENCE AND NOTES

1. L. B. Clapp, *Advances in Heterocyclic Chemistry,* Vol. 20, ed. by A. R. Katritzky, Academic Press, New York, N.Y, 1976, pp. 65-116.
2. L. B. Clapp, *Comprehensive Heterocyclic Chemistry,* Vol. 6, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, 1984, pp. 365-391.
3. B. Silvestrini, and C. Pozzatti, *Brit. J. Pharmacol.* 1961, **16**, 209 (*Chem. Abstr.*, 1962, **56**, 5356b).
4. F. Eloy and R. Lenaers, *Chim. Ther.*, 1966, 347 (*Chem. Abstr.*, 1967, **66**, 37793z).
5. K. Harsanyi, P. Kiss, D. Korbonits, and I. R. Malyata, *Arzneim. Forsch.*,1966, **16**, 615.
6. J. Sterne and C. Hirsch, *Therapie,* 1965, **20**, 89, and 95.
7. P. Afiatpour, R. M. Srivastava, M. L. de Oliveira, and E. J. Barreiro, *Braz. J. Med. Biol. Res.*, 1994, **27**, 1403 (*Chem. Abstr.*, 1994, **121**, 271857z).
8. S. E. Dahlgren and T. Dalhamn, *Acta Pharmacol et Toxicol.*, 1972, **31**, 193.
9. R. M. Srivastava, L. P. F. de Morais, M. T. J. A Catanho, G. M. L. de Souza, G. M. Seabra, A. M. Simas, and M. A. L. Rodrigues. Unpublished work.
10. S. J. de Melo, A. D. Sobral, H. de T. Lopes and R. M. Srivastava, *J. Braz. Chem. Soc.,* 1998, **9**, 465 (*Chem. Abstr.*, 1999, **130**, 139611w).
11. E. Sanders-Bush and S. E. Mayer, in "Goodman & Gilman's" *The Pharmacological Basis of Therapeutics,* ed. by J. G. Hardman, L. E. Limbird, P. B. Molinoff, and R. W. Ruddon, 9th International Edition McGraw-Hill, New York, N.Y., 1996, p. 249.
12. W. R. Hobbs, T. W. Rall, and T. A. Verdoorn (see ref. 11, p. 361).
13. M. R. Hellberg, A. Namil, P. Delgado, K. C. David, T. L. Kessler, G. Graff, K. S. Haggard, and J. C. Nixon, *J. Med. Chem.*, 1999, **42**, 267.
14. R. M. Srivastava and G. M. Seabra, *J. Braz. Chem. Soc.*, 1997, **8**, 397 (*Chem. Abstr.*, 1997, **127**, 293172y), and references cited therein.
15. R. M. Srivastava and L. M. M. e Silva, *J. Chem. Eng. data,* 1984, **29**, 221.
16. M. Hesse, H. Meier, and B. Zeeh, *Spektroskopische Methoden in der Organischen Chemie,* 5th Edition, Georg Thieme Verlag Stuttgart, New York, 1995, p. 199.
17. R. M. Srivastava, L. M. M. e Silva, and J. Bhattacharyya, *Química Nova,* 1989, **12**, 221 (*Chem. Abstr.*, 1990, **112**, 197465r).
18. R. J. Abraham and P. Loftus, "Proton and Carbon-13 NMR Spectroscopy," Heyden & Son. Ltd., London, 1978, p. 28.
19. J. J. P. Stewart, *J. Comp.- Aided Mol. Design*, 1990, 4.
20. J. J. P. Stewart, *MOPAC 93-00 Manual*, Fujitsu Limited, Tokyo, Japan, 1993.
21. The calculations show that both aryl and 1,2,4-oxadiazole rings are almost coplanar in compounds studied except in **6b** where the *o*-tolyl function is -46.66° out of the heterocyclic ring plane. The bond angles and distances of the five-membered ring are close to the values found carlier (ref. 14). The torsion angles C(10)-N(9)-C(8)-O(10) of 169.08° and C(12)-N(9)-C(8)-O(14) of 4.58° clearly demonstrate that the amide nitrogen is largely sp^2 hybridized.

Received, 6th May, 1999