

SYNTHESIS OF NEW DISUBSTITUTED AZOLIUM YLIDES

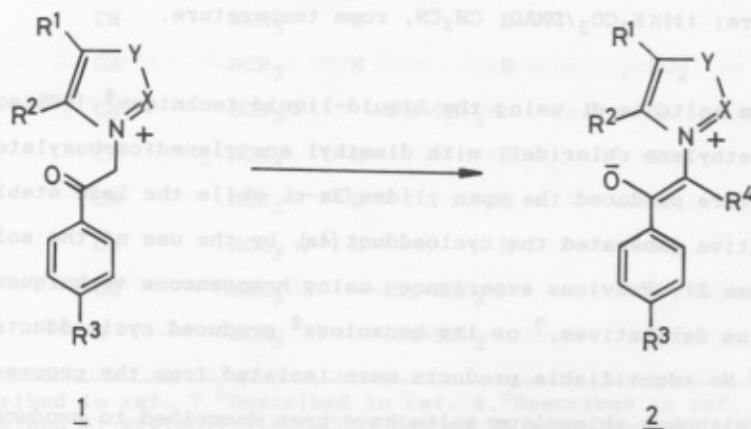
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Abstract- A series of several azolium methylides have been obtained by reaction of 1-phenacylazolium salts with the corresponding dipolarophiles in a two-phase system. Only by the reaction of a benzimidazolium derivative with dimethyl acetylenedicarboxylate 1,3-dipolar cycloaddition was observed.

Cycloimmonium ylides are highly interesting compounds for their reactivity, biological properties and applications.¹ Although azinium derivatives have been extensively studied,² those bearing azolium moieties have attracted much less attention, and the experience concerning their synthesis and reactivity is comparatively scarce.

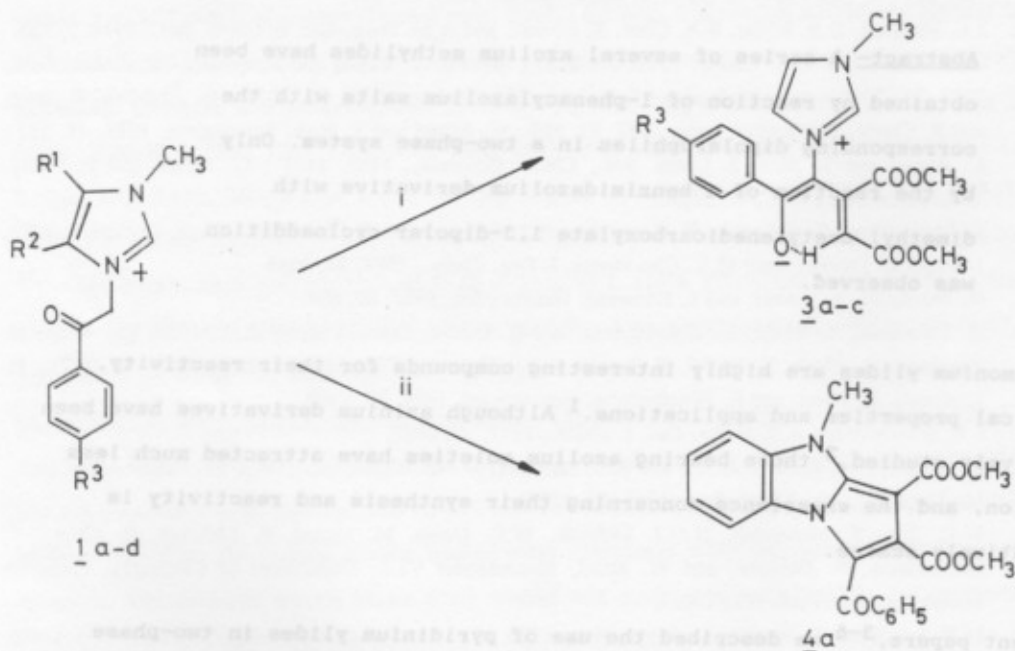
In recent papers,³⁻⁶ we described the use of pyridinium ylides in two-phase



Scheme 1.

systems, either solid-liquid or liquid-liquid, which in some examples favored the formation of disubstituted ylides instead of 1,3-cycloaddition products. In the present paper we report the application of the same technique to several azolium derivatives(1), reacting them with usual dipolarophiles.

The starting azolium salts 1 were prepared by heating the corresponding heterocycles with phenacyl bromides, as indicated in Table 1.



Scheme 2. Reagents and conditions: i) 50% aq. K₂CO₃/DMAD, CH₂Cl₂, room temperature; ii) K₂CO₃/DMAD, CH₃CN, room temperature.

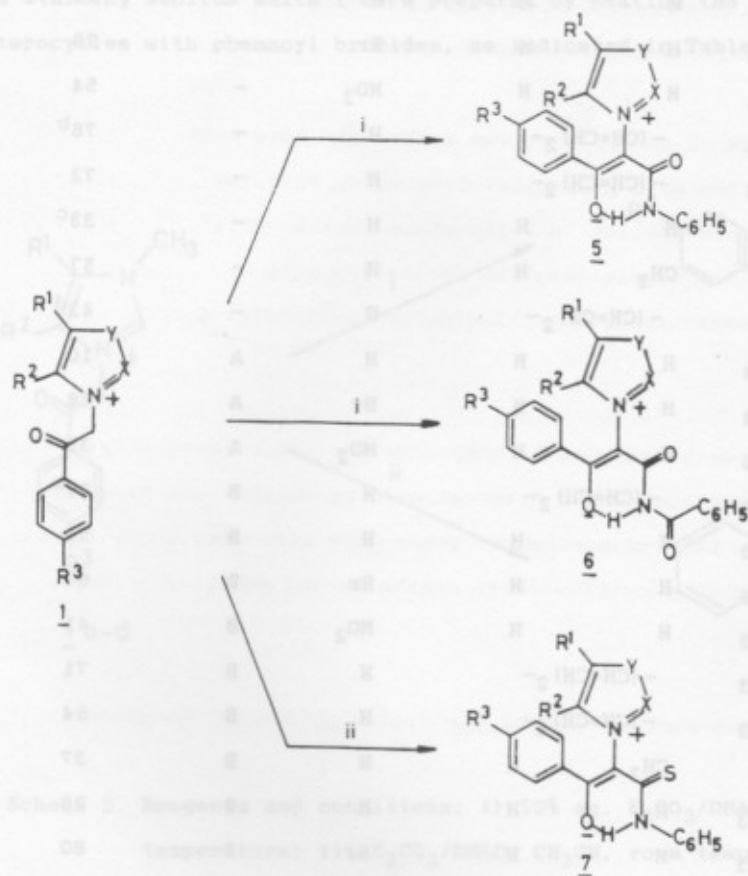
Reaction of imidazolium salts (1a-d), using the liquid-liquid technique⁴ (50% aq. potassium carbonate/ methylene chloride), with dimethyl acetylenedicarboxylate (DMAD) at room temperature produced the open ylides (3a-c), while the less stable benzimidazolium derivative generated the cycloadduct (4a), by the use of the solid-liquid technique (Scheme 2). Previous experience, using homogeneous techniques, with similar imidazolium derivatives,⁷ or its benzologs⁸ produced cycloadducts or derived compounds.^{9,10} No identifiable products were isolated from the processes using the salts (1e-h), although thiazolium salts have been described to produce cycloadducts which rearrange on isolation.¹¹

Table 1. Azolium derivatives 1, 3-7 prepared.

Comp.No.	X	Y	R ¹	R ²	R ³	Method	Yield (%)
1a	CH	NCH ₃	H	H	H	-	46 ^a
1b	CH	NCH ₃	H	H	Br	-	78
1c	CH	NCH ₃	H	H	NO ₂	-	54
1d	CH	NCH ₃	-(CH=CH) ₂ ⁻	H	H	-	78 ^b
1e	N	NCH ₃	-(CH=CH) ₂ ⁻	H	H	-	72
1f	CH	S	H	H	H	-	33 ^c
1g	CH	S	CH ₃	H	H	-	57
1h	CH	S	-(CH=CH) ₂ ⁻	H	H	-	43 ^d
3a	CH	NCH ₃	H	H	H	A	10
3b	CH	NCH ₃	H	H	Br	A	38
3c	CH	NCH ₃	H	H	NO ₂	A	35
4a	CH	NCH ₃	-(CH=CH) ₂ ⁻	H	H	B	17 ^b
5a	CH	NCH ₃	H	H	H	B	51
5b	CH	NCH ₃	H	H	Br	B	60
5c	CH	NCH ₃	H	H	NO ₂	B	41
5d	CH	NCH ₃	-(CH=CH) ₂ ⁻	H	H	B	71
5e	N	NCH ₃	-(CH=CH) ₂ ⁻	H	H	B	54
5f	CH	S	CH ₃	H	H	B	37
6a	CH	NCH ₃	H	H	H	B	23
6b	CH	NCH ₃	H	H	Br	B	80
6c	CH	NCH ₃	H	H	NO ₂	B	71
6d	CH	NCH ₃	-(CH=CH) ₂ ⁻	H	H	B	20
7a	CH	NCH ₃	H	H	H	A	50
7b	CH	NCH ₃	H	H	Br	A	76
7c	CH	NCH ₃	H	H	NO ₂	A	72
7d	CH	NCH ₃	-(CH=CH) ₂ ⁻	H	H	A	66
7e	N	NCH ₃	-(CH=CH) ₂ ⁻	H	H	A	81

^aDescribed in ref. 7. ^bDescribed in ref. 8. ^cDescribed in ref. 12. ^dDescribed in ref. 13. Method A: acetonitrile/K₂CO₃; Method B: methylene chloride/50% aq. K₂CO₃.

Reaction of the salts(1) with isocyanates and isothiocyanates is shown in the Scheme 3. All examples produced disubstituted ylides, all showing an intramolecular hydrogen bond, observed in the ir and nmr spectra. Isocyanate adducts (5, 6) were obtained using the solid-liquid technique, as both dipolarophiles decomposed on the contact with water. Phenylisothiocyanate,



Scheme 3. Reagents and conditions: i) $C_6H_5-N=C=O$ or $C_6H_5CO-N=C=O/K_2CO_3/CH_3CN$, room temperature; ii) $C_6H_5-N=C=S/50\%$ aq. K_2CO_3/CH_2Cl_2 , room temperature.

however, was used in the liquid-liquid method with high yields. In all examples, thiazole derivatives failed to produce any ylides or cycloadducts, except for 5f. This should be related with the easy opening of the heterocyclic ring in the presence of base.¹¹ By opposite, benzotriazolium derivatives (5e, 7e) were obtained with high yields.

Structures of all new compounds are supported by full spectroscopic data and by combustion analysis. The stability of the ylides (3, 5, 6 and 7) is associated not only with the delocalization of the negative charge but also with the presence of an intramolecular hydrogen bond, evident by the low field signals corresponding to the NH proton in the $^1\text{H-Nmr}$ of the compounds (5-7). Another distinctive signal is the low field singlet, appearing ca. $\delta = 9.0$ ppm, which corresponds to the CH of the azolium moiety, in α -position with the quaternary nitrogen.

As a conclusion, the two-phase method seems to be an easy way to generate disubstituted ylides, not only of azinium derivatives but also in the azolium field. As has been shown before, both methods solid-liquid and liquid-liquid³⁻⁵ can be alternatively applied, with the limit of the bad results generally obtained with thiazolium salts.

EXPERIMENTAL

Melting points were determined on a Büchi SMP-20 and are uncorrected. Ir spectra were recorded on Perkin Elmer 700 or 1310 spectrophotometers. $^1\text{H-Nmr}$ spectra were obtained on a Varian FT-80 (80 MHz) instrument using TMS as an internal reference.

Synthesis of Azolium Salts 1. To a solution of the corresponding 2-bromoacetophenone (50 mmol) in ethyl acetate (30 ml), the azole (50 mmol) was added in portions. The mixture was refluxed with stirring for 3 h. Then, the separated azolium salt was recrystallised from the solvent indicated in Table 2.

Reaction of Azolium Salts 1 with DMAD. Compounds 3 and 4. To a stirred mixture of the corresponding azolium salt (2 mmol) in methylene chloride (10 ml) and 50% aqueous potassium carbonate (10 ml), dimethyl acetylenedicarboxylate (DMAD) (4 mmol) was added. The process was maintained with vigorous stirring at room temperature for 8 h. Then, if precipitates appeared, it should be filtered, washed with water, and recrystallised as indicated in Table 2. If no solid had been produced in the process, the organic layer should be separated and the aqueous one is extracted with methylene chloride (3x20 ml). All the organic extracts are mixed, dried over MgSO_4 , concentrated and recrystallised as indicated.

Table 2. Physical and Spectroscopic Data of Compounds 1 to 7.

Compd. No	mp (°C)	Molecular Formula	Ir (KBr) (cm ⁻¹)	¹ H-Nmr ^a δ (ppm)
1a	108-110 ^b (iPrOH)	C ₁₂ H ₁₃ N ₂ OBr	1700, 1600, 1450	9.13 (s, 1H); 8.09-7.58 (m, 7H); 6.13 (s, 2H); 3.96 (s, 3H)
1b	217-220 (iPrOH)	C ₁₂ H ₁₂ N ₂ O ₂ Br ₂	1700, 1590, 1400	9.04 (s, 1H); 8.00-7.66 (m, 6H); 6.04 (s, 2H); 3.92 (s, 3H)
1c	186-189 (iPrOH)	C ₁₂ H ₁₂ N ₃ O ₃ Br	1710, 1600, 1520	9.06 (s, 1H); 8.31 (c, J=9.0 4H); 7.73 (d, J=5.2, 2H); 6.14 (s, 2H); 3.95 (s, 3H)
1d	209-212 ^c (EtOH/ Ether)	C ₁₆ H ₁₅ N ₂ OBr	1700, 1590, 1550	9.72 (s, 1H); 8.16-8.01 (m, 4H); 7.70-7.54 (m, 5H); 6.49 (s, 2H); 4.19 (s, 3H)
1e	148-150 (EtOH/ Ether)	C ₁₅ H ₁₄ N ₃ OBr	1700, 1605, 1460	8.54-8.38 (m, 2H); 8.24-7.66 (m, 7H); 7.15 (s, 2H); 4.75 (s, 3H)
1f	220-222 ^d (EtOH)	C ₁₁ H ₁₀ NOBrS	1700, 1600, 1580, 1450	10.18 (s, 1H); 8.52-8.33 (m, 2H); 8.07-7.95 (m, 2H); 7.76-7.58 (m, 3H); 6.45 (s, 2H)
1g	242-244 (MeOH/ Water)	C ₁₂ H ₁₂ NOBrS	1680, 1600, 1580, 1450, 1230	10.20 (d, J=2.7, 1H); 8.12 8.00 (m, 3H); 7.77-7.60 (m, 3H); 6.54 (s, 2H); 2.46 (s, 3H)
1h	232-234 ^e (MeOH/ Water)	C ₁₅ H ₁₂ NOBrS	1680, 1600, 1580, 1510	10.63 (s, 1H); 8.62-7.54 (m, 9H); 6.79 (s, 2H)
3a	226-227 (MeOH)	C ₁₈ H ₁₈ N ₂ O ₅	1740, 1660, 1560, 1400	8.92 (s, 1H); 7.54 (s, 2H); 7.11 (s, 5H); 3.70 (s, 6H); 3.39 (s, 3H)
3b	208-210 (MeCN/ EtOH)	C ₁₈ H ₁₇ N ₂ O ₅ Br	1740, 1690, 1560, 1500, 1420, 1370	8.94 (s, 1H); 7.56 (s, 2H); 7.33 (d, J=8.2, 2H); 7.00 (d, J=8.2, 2H); 3.72 (s, 3H); 3.63 (s, 3H); 3.39 (s, 3H)
3c	220-222 (MeCN/ EtOH)	C ₁₈ H ₁₇ N ₃ O ₇	1740, 1680, 1570, 1520, 1500, 1350	9.00 (s, 1H); 8.00 (d, J=8.5 2H); 7.57 (s, 2H); 7.32 (d, J=8.5, 2H); 3.71 (s, 3H); 3.68 (s, 3H); 3.45 (s, 3H)
4a	210-212 ^f (EtOH)	C ₂₂ H ₁₈ N ₂ O ₅	1730, 1700, 1610 1460, 1210	8.66 (d, J=7.2, 1H); 7.99-7.42 (m, 8H); 4.41 (s, 3H); 3.90 (s, 3H); 3.45 (s, 3H)
5a	260-261 (MeCN)	C ₁₉ H ₁₇ N ₃ O ₂	1640, 1590, 1540, 1490, 1420, 1210	12.65 (s, 1H); 8.81 (s, 1H); 7.58-7.18 (m, 7H); 7.13 (s, 5H); 3.70 (s, 3H)
5b	230-232 (EtOH)	C ₁₉ H ₁₆ N ₃ O ₂ Br	1630, 1590, 1530, 1430, 1210	12.36 (s, 1H); 8.84 (s, 1H); 7.55-6.84 (m, 11H); 3.73 (s, 3H)

^a In DMSO-d₆, chemical shifts in ppm and coupling constants in Hz. ^b 103-105 in ref. 7. ^c 205 in ref. 8. ^d 227-229 in ref. 12. ^e 235-236 in ref. 13. ^f 130-131 in ref. 8.

Table 2 (Cont). Physical and Spectroscopic Data of Compounds 1 to 7.

Compd. No	mp (°C)	Molecular Formula	Ir (KBr) (cm ⁻¹)	¹ H-Nmr ^a δ (ppm)
5c	226-227 (AcOEt)	C ₁₉ H ₁₆ N ₄ O ₄	1640, 1590, 1520 1450, 1420, 1200	12.45 (s, 1H); 8.90 (s, 1H); 8.02 (d, J=8.6, 2H); 7.58- 6.87 (m, 9H); 3.72 (s, 3H).
5d	250-252 (MeCN)	C ₂₃ H ₁₉ N ₃ O ₂	1620, 1585, 1520 1495, 1440, 1410	12.84 (s, 1H); 9.61 (s, 1H); 7.93-7.00 (m, 14H); 4.03 (s, 3H).
5e	238-240 (MeCN)	C ₂₂ H ₁₈ N ₄ O ₂	1640, 1510, 1420, 1390, 1220	12.51 (s, 1H); 8.24-7.11 (m, 9H); 7.03 (s, 5H); 4.51 (s, 3H).
5f	184-186 (AcOEt/ Ether)	C ₁₉ H ₁₆ N ₂ O ₂ S	1630, 1590, 1530, 1500, 1450, 1400	12.52 (s, 1H); 9.87 (d, J=2.7, 1H); 7.83-7.79 (m, 1H); 7.55 (d, J=7.5, 2H) 7.31-6.89 (m, 3H); 7.14 (s, 5H); 2.33 (s, 3H).
6a	222-224 (AcOEt)	C ₂₀ H ₁₇ N ₃ O ₃	1700, 1650, 1530, 1500, 1490, 1410	14.21 (s, 1H); 8.88 (s, 1H); 7.94-7.89 (m, 2H); 7.57- 7.35 (m, 5H); 7.17 (s, 5H); 3.72 (s, 3H).
6b	198-200 (MeOH/ Water)	C ₂₀ H ₁₆ N ₃ O ₃ Br	1695, 1650, 1620, 1480, 1425, 1290	14.21 (s, 1H); 8.97 (s, 1H); 8.04-7.94 (m, 2H); 7.62- 7.10 (m, 9H); 3.78 (s, 3H).
6c	228-229 (MeCN)	C ₂₀ H ₁₆ N ₄ O ₅	1700, 1540, 1480, 1420, 1410	13.99 (s, 1H); 8.95 (s, 1H); 8.14-7.74 (m, 4H); 7.57- 7.39 (m, 7H); 3.74 (s, 3H).
6d	227-229 (MeOH)	C ₂₄ H ₁₉ N ₃ O ₃	1695, 1640, 1500, 1470	14.73 (s, 1H); 9.65 (s, 1H); 8.10-7.82 (m, 4H); 7.57 (s, 5H); 7.11 (s, 5H); 4.03 (s, 3H).
7a	193-194 (AcOEt/ CH ₂ Cl ₂)	C ₁₉ H ₁₇ N ₃ OS	1600, 1560, 1500, 1390, 1200	14.58 (s, 1H); 8.96 (s, 1H); 7.78 (d, J=7.2, 2H); 7.37- 7.27 (m, 5H); 7.16 (s, 5H); 3.69 (s, 3H).
7b	196-197 (AcOEt)	C ₁₉ H ₁₆ N ₃ OBrS	1660, 1550, 1500, 1390, 1200	14.52 (s, 1H); 8.99 (s, 1H); 7.79 (d, J=7.4, 2H); 7.39- 7.09 (m, 9H); 3.74 (s, 3H).
7c	196-197 (CH ₂ Cl ₂)	C ₁₉ H ₁₆ N ₄ O ₃ S	1600, 1550, 1500, 1410, 1390, 1350 1200	14.53 (s, 1H); 9.15 (s, 1H); 8.18 (d, J=8.4, 2H); 7.90- 7.18 (m, 4H); 7.50 (s, 5H); 3.85 (s, 3H).
7d	230-232 (MeCN)	C ₂₃ H ₁₉ N ₃ OS	1600, 1560, 1500 1410, 1390	14.83 (s, 1H); 9.80 (s, 1H); 7.93-7.00 (m, 14H); 4.03 (s, 3H).
7e	188-189 (MeOH)	C ₂₂ H ₁₈ N ₄ OS	1595, 1560, 1500, 1415, 1390, 1370 1300	14.51 (s, 1H); 7.92-7.74 (m, 5H); 7.55-7.16 (m, 4H); 7.06 (s, 5H); 4.57 (s, 3H).

^a In DMSO-d₆, chemical shifts in ppm and coupling constants in Hz.

Table 3. Microanalyses of Compounds 1 to 7.

COMPOUND	Calc. (%)			Found (%)			
	C	H	N	C	H	N	
1b	38.12	3.73	7.41	37.87	3.59	7.14	(1 H ₂ O)
1c	41.88	4.10	12.21	42.12	4.12	11.81	(1 H ₂ O)
1e	54.23	4.24	12.64	53.94	4.52	12.50	
1g	48.33	4.06	4.70	48.52	4.01	4.52	
3a	63.15	5.30	8.18	63.20	5.40	8.40	
3b	51.27	3.61	6.68	51.30	3.80	6.90	
3c	55.82	4.42	10.85	56.00	4.50	11.10	
4a	67.69	4.65	7.18	67.38	4.88	6.75	
5a	71.46	5.36	13.16	71.40	5.40	13.10	
5b	57.30	4.05	10.55	57.40	4.40	10.30	
5c	62.63	4.43	15.38	62.40	4.70	15.30	
5d	74.78	5.18	11.37	75.10	5.40	11.60	
5e	71.34	4.90	15.10	71.40	5.05	15.30	
5f	67.84	4.79	8.33	67.50	4.90	8.30	
6a	69.15	4.93	12.10	69.40	5.00	12.30	
6b	56.35	3.78	9.86	56.40	4.00	10.00	
6c	61.22	4.11	14.28	61.40	4.30	14.60	
6d	72.53	4.82	10.57	72.30	4.70	10.40	
7a	68.04	5.11	12.53	68.30	5.20	12.20	
7b	55.08	3.89	10.14	54.90	4.00	10.15	
7c	59.99	4.24	14.73	60.10	4.10	15.00	
7d	71.66	4.97	10.90	72.00	5.10	11.20	
7e	68.37	4.69	14.50	68.50	4.80	14.70	

Reaction of Azolium Salts 1 with Phenyl and Benzoyl Isocyanate. Ylides 5 and 6. To a suspension of the corresponding azolium salt (2 mmol) in dry acetonitrile (20 ml) and anhydrous potassium carbonate (4 mmol), the corresponding isocyanate (2.4 mmol) was added. The mixture was vigorously stirred at room temperature for 8 h. The inorganic solid was filtered, and washed with methylene chloride until color disappearance, the organic extracts were mixed, washed with water, dried over MgSO₄ and concentrated. The residue of crude ylide was recrystallised as described

in Table 2.

Reaction of Azolium Salts 1 with Phenyl Isothiocyanate. Ylides 7. To a mixture of the corresponding azolium salt (2 mmol) in methylene chloride (10 ml) and 50% aqueous potassium carbonate (10 ml), phenyl isothiocyanate (2.4 mmol) was added. The mixture was vigorously stirred at room temperature for 8 h. Then, the organic layer was separated and the aqueous one was extracted with methylene chloride (4x20 ml). All the organic extracts were mixed, washed with water, dried over $MgSO_4$, concentrated and recrystallised as indicated in Table 2.

ACKNOWLEDGEMENTS

Authors wish to thank the Comisión Interministerial de Ciencia y Tecnología (C.I.C.Y.T.) for financial support (Project 87/0755) and to Drs. J. L. Garcia-Navio and M. L. Izquierdo for the assistance in the obtention of nmr data.

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Received, 11th June, 1990