SYNTHESES OF IMIDAZO[1,2-*c*]PYRIMIDINES AND 1,3,5-TRIAZEPINES FROM 2-AZABUTA-1,3-DIENES AND 1,2-DIAMINES

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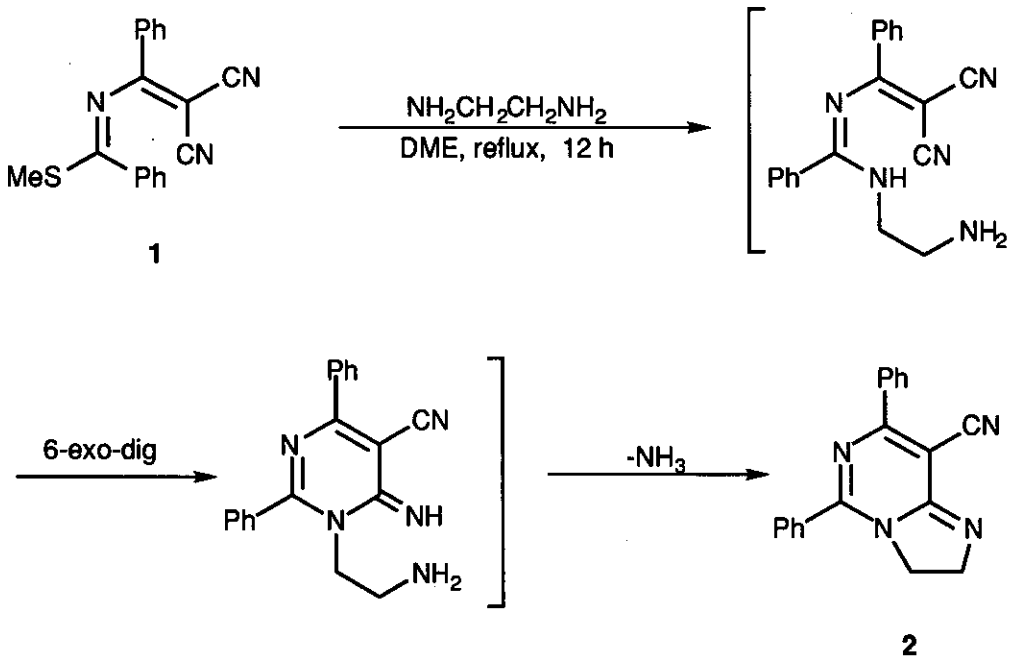
Abstract - Syntheses of imidazo[1,2-*c*]pyrimidines and 1,3,5-triazepines from 2-azabuta-1,3-dienes and 1,2-diamines are reported.

The most versatile procedure for the synthesis of imidazo[1,2-*c*]pyrimidines involves the condensation of a 4-aminopyrimidine with an α-halocarbonyl compound. [1-6] A similar intermediate must be involved in the reaction of a 4-halopyrimidine with aminoacetaldehyde diethylacetal which cyclizes to an imidazo[1,2-*c*]pyrimidine by treatment with acid. [5,7] Cytidine and some derivatives produce imidazo[1,2-*c*]pyrimidines when reacted with β-acetylvinyltriphenylphosphonium bromide. [8,9] Another useful procedure is the treatment of a 4-halopyrimidine with 2-chloroethylamine to afford a 4-(2-chloroethyl)amino derivative which can be cyclized readily. [10,11] The chemistry of the 1,3,5-triazepines has been scarcely studied. Fully unsaturated monocyclic 1,3,5-triazepines were obtained from photolysis of azidopyrimidines [12,13] or azidopyrazines.[12] A useful method for the synthesis of condensed 1,3,5-triazepines involves the reaction of 2-amino-1-(2-aminoethyl)benzimidazoles or 1-(2-aminoaryl)-2-iminoimidazolidines with C1 reagents such as phosgene, thiocarbonyl chloride or cyanogen bromide.[14,15] A similar procedure for the synthesis of this class of compounds by the reaction of a formamidine or a formimidate with an aldehyde or ketone was reported.[16] An interesting synthesis of the imidazo[1,2-*e*]1,3,5-triazepine ring system has been described involving the reaction of 2-chloromethylimidazole and primary amines in dichloromethane. [17]

In previous papers we described the synthesis [18] and synthetic applications [19] of 1-methylthio-2-azabuta-1,3-diene-4-carbonitriles. In this paper we report a synthetic procedure of imidazo[1,2-*c*]pyrimidines and 1,3,5-triazepines from 2-azabuta-1,3-diene-4-carbonitriles and 1,2-diamines. Thus the reaction of the (*E*)-1-methylthio-1,3-diphenyl-2-azabuta-1,3-diene-4,4-dicarbonitrile (**1**) with ethylenediamine affords 8-cyano-5,7-diphenyl-2,3-dihydroimidazo[1,2-*c*]pyrimidine (**2**) (*6-exo-dig cyclization process*). The process can be depicted as follows:

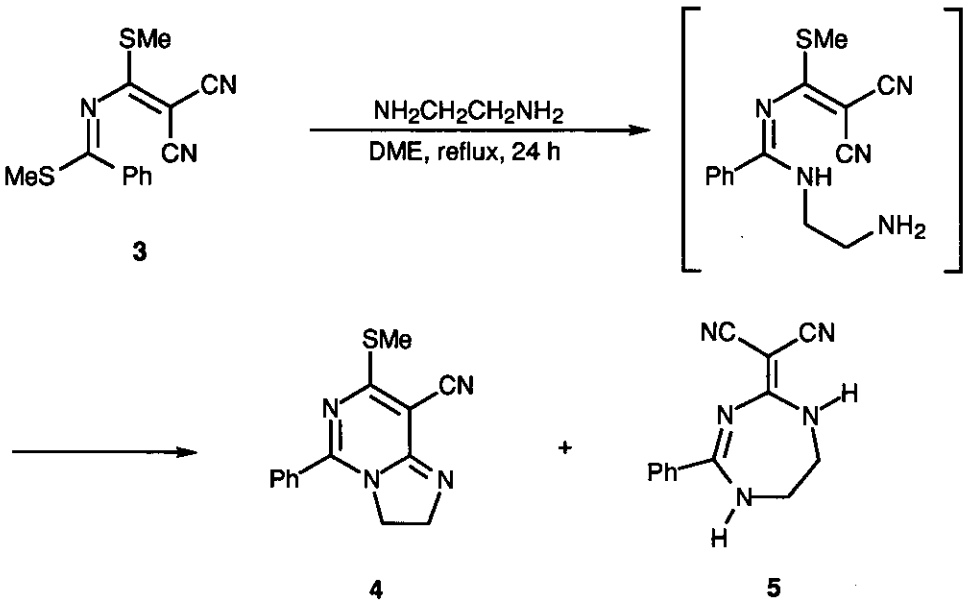
Scheme 1



1 2

We have also studied the reactivity of the (*E*)-1,3-dimethylthio-1-phenyl-2-azabuta-1,3-diene-4,4-dicarbonitrile (**3**) with ethylenediamine which affords a mixture of 8-cyano-7-methylthio-5-phenyl-2,3-dihydroimidazo[1,2-*c*]pyrimidine (**4**) (*6-exo-dig* cyclization process) and the 4-dicyanomethylidene-2-phenyl-4,5,6,7-tetrahydro-1,3,5-triazepine (**5**) (*7-exo-trig* cyclization process).

Scheme 2

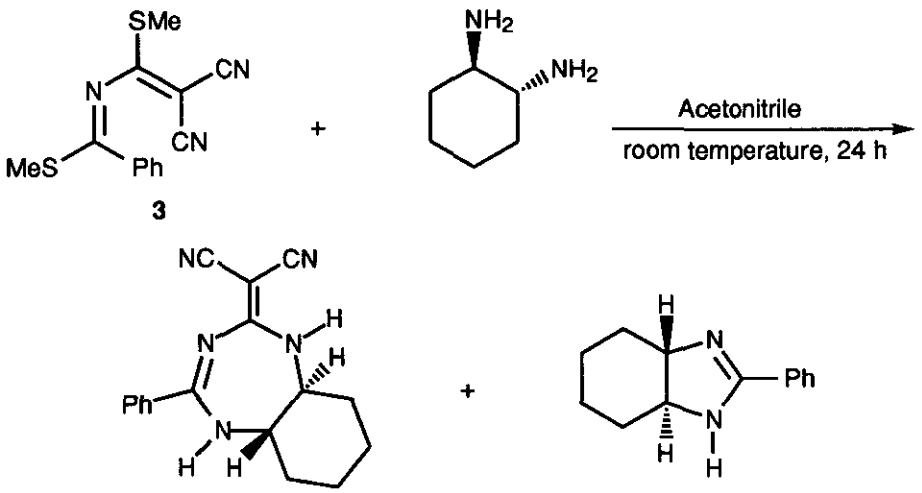


3 4 5

Regioselective displacement of one methylthio group of **3** results from the activation induced by the carbon-nitrogen double bond.

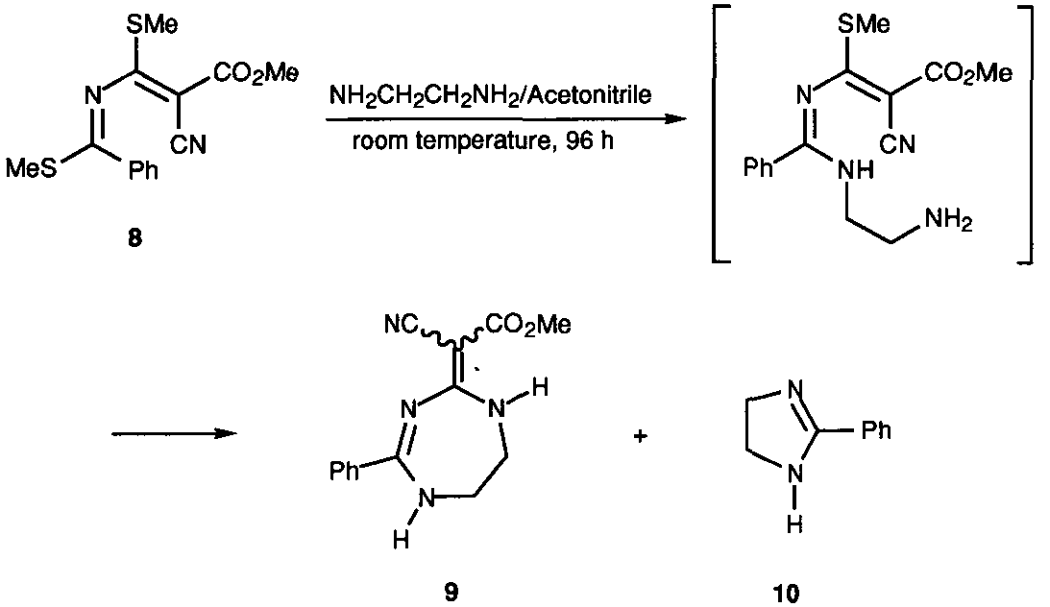
In a similar fashion, the reaction of **3** with (±)-*trans*-1,2-diaminocyclohexane gave a mixture of the 1,3,5-triazepine (**6**) (*7-exo-trig* cyclization process) and the hexahydro-1*H*-benzimidazole (**7**) (*5-exo-trig* cyclization process).

Scheme 3



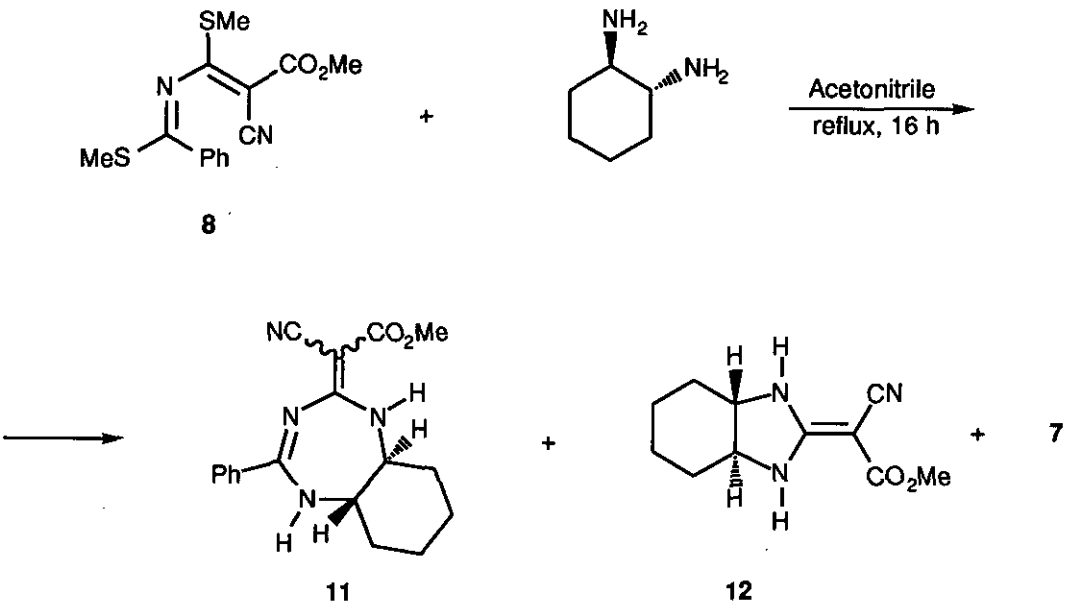
The reaction of the 2-azabuta-1,3-diene (**8**) with ethylenediamine was also studied and afforded the 1,3,5-triazepine (**9**) (*7-exo-trig* cyclization process) and the dihydroimidazole (**10**) (*5-exo-trig* cyclization process).

Scheme 4



Finally, by reacting **8** with (±)-*trans*-1,2-diaminocyclohexane the 1,3,5-triazepine (**11**) (*7-exo-trig* cyclization process) and the hexahydro-1*H*-benzimidazoles (**7**) and (**12**) [20] were obtained as side products.

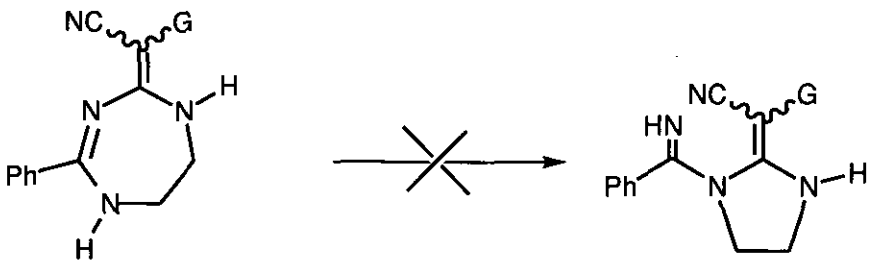
Scheme 5



Formation of **12** can be explained by addition of the diamine to the C(3)-C(4) double bond of **8** and subsequent cyclization.

All new compounds had analytical and spectral properties in agreement with the assigned structures. Thus, 500 MHz ^{1}H nmr spectra of the triazepines (**5**) and (**9**) ruled out alternative structures resulting from ring contraction:

Scheme 6



5: G = CN
9: G = CO_2Me

EXPERIMENTAL

All melting points were determined with a Electrothermal IA 9100 and are uncorrected. Ir spectra were recorded on a Perkin Elmer 883 spectrophotometer. Nmr spectra were measured on Varian UNITY 300 and 500 spectrometers. Mass spectra were obtained with a Hewlett Packard HP-5988 at 70 eV. Microanalyses were performed in a Heraeus CHN. Flash column chromatographies were carried out on silica gel SDS 230-400 mesh. 2-Azabuta-1,3-dienes (**1**, **3** and **8**) were synthesized according reported procedures.[18]

8-Cyano-5,7-diphenyl-2,3-dihydroimidazo[1,2-*c*]pyrimidine (2): To a solution of **1** (303 mg, 1 mmol) in dry 1,2-dimethoxyethane (40 ml) ethylenediamine (120 mg, 2 mmol) was added. The reaction mixture was heated at reflux for 12 h and then the precipitate was collected. The mother liquors were concentrated *in vacuo* and the resulting residue was purified by flash column (diameter: 2 cm) chromatography (silica gel, hexane/AcOEt 1:1 and then hexane/AcOEt/triethylamine 1:1:1) affording an additional amount of product. The resulting solid was recrystallized from 2-propanol to obtain **2** (155 mg, 52%); mp 198-199 °C (lit., [21] mp 199-200 °C).

Reaction of the (*E*)-1,3-dimethylthio-1-phenyl-2-azabuta-1,3-diene-4,4-dicarbonitrile (3) with ethylenediamine. Synthesis of 4 and 5: To a solution of **3** (410 mg, 1.5 mmol) in dry 1,2-dimethoxyethane (30 ml), ethylenediamine (180 mg, 3 mmol) was added. The reaction mixture was heated at reflux for 24 h and then concentrated at reduced pressure. The resulting residue was purified by flash column (diameter: 3 cm) chromatography (silica gel, acetonitrile) affording **5** which was recrystallized from 2-propanol; yield 54 mg (15 %); mp 279-280 °C; ir (KBr): υ = 3266 (N-H), 2206 and 2178 (C≡N), 1592, 1566, 1493, 1435 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.61 (br s, 4H, CH_2-CH_2), 7.43-7.58 (m, $3H_{arom}$), 7.94-7.97 (m, $2H_{arom}$), 8.51 (t, J = 4 Hz, 1H, NH), 9.44 (t, J = 4 Hz, 1H, NH); ms *m/z* : 238 (M^++1, 13%), 237 (M^+, 71), 236 (29), 209 (9), 208 (7), 135 (8), 134 (100), 133 (20), 117 (12), 105 (16), 104 (43), 77 (39). *Anal.* Calcd for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 65.92; H, 4.51; N, 29.71.

Continued elution with the same eluent afforded the imidazo[1,2-*c*]pyrimidine (**4**) (212 mg, 53 %) which was recrystallized from 2-propanol; mp 186-187 °C; ir (KBr): υ = 2204 (C≡N), 1652, 1513, 1478, 1436 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 2.53 (s, 3H, CH_3), 3.86 (part A of A_2B_2 system, $C\underline{H}_2$-CH_2, J= 7.2 Hz), 4.15 (part B of A_2B_2 system, CH_2-$C\underline{H}_2$), 7.46-7.84 (m, $3H_{arom}$), 7.44-8.14 (m, $2H_{arom}$); ms *m/z* : 269 (M^++1, 19 %), 268 (M^+, 100), 267 (77), 164 (7), 149 (19), 123 (22), 103 (25), 94 (11), 77 (24). *Anal.* Calcd for $C_{14}H_{12}N_4S$: C, 62.67; H, 4.51; N, 20.88. Found: C, 62.46; H, 4.40; N, 21.17.

2-Dicyanomethylidene-4-phenyl-(5ar-9at)-1,5,5a,6,7,8,9,9a-octahydro-benzo[*f*]-1,3,5-triazepine (**6**): A mixture of **3** (295 mg, 1.08 mmol) and (±)-*trans*-1,2-diaminocyclohexane (123 mg, 1.08 mmol) in dry acetonitrile (20 ml) was stirred at room temperature for 24 h. The reaction mixture was then concentrated at reduced pressure and the crude product purified by column (diameter: 3 cm) chromatography (silica gel, hexane/EtOAc 1:1) affording 230 mg (73 %) of **6** which was recrystallized from 2-propanol; mp 277-278 °C; ir (KBr): υ = 3251 (N-H), 2210 and 2186 (C≡N), 1571, 1473 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.18-1.44 (m, 4H, 2CH_2), 1.66 (br s, 2H, CH_2), 2.06-2.28 (m, 2H, CH_2), 3.52-3.55 (m, 2H, CH), 7.46-7.60 (m, 3H_{arom}), 7.70 (s, 1H, NH), 7.88 (d, J = 7.32 Hz, 2H_{arom}), 8.73 (s, 1H, NH); ms *m/z*: 292 (M^++1, 20 %), 291 (M^+, 100), 290 (30), 188 (32), 187 (16), 145 (11), 104 (46), 92 (10), 91 (11), 77 (22). *Anal.* Calcd for $C_{17}H_{17}N_5$: C, 70.08; H, 5.88; N, 24.04. Found: C, 70.25; H, 6.03; N, 23.90.

Continued elution with methanol afforded 33 mg (15 % yield) of the hexahydrobenzimidazole (**7**); mp 178-179 °C (lit., [22] mp 180-181 °C).

4-Cyanomethoxycarbonylmethylidene-2-phenyl-4,5,6,7-tetrahydro-1,3,5-triazepine (**9**): To a solution of **8** (223 mg, 0.73 mmol) in dry acetonitrile (30 ml), ethylenediamine (44 mg, 0.73 mmol) was added. The reaction mixture was stirred at room temperature for 96 h and then concentrated at reduced pressure. The crude product thus obtained was purified by flash column (diameter: 3 cm) chromatography (silica gel, hexane/AcOEt 1:3) affording 163 mg (83 %) of **9** which was recrystallized from ethyl acetate; mp 240-241 °C; ir (KBr): υ = 3246 (N-H), 2206 (C≡N), 1642 (C=O), 1599, 1576, 1476 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 3.61 (s, 3H, OCH_3), 3.62 (m, 2H, $C\underline{H}_2$-CH_2), 3.77 (m, 2H, CH_2-$C\underline{H}_2$) 7.47-7.56 (m, 3H_{arom}), 8.02-8.04 (m, 2H_{arom}), 9.32 (t, J = 4Hz, 1H, N-H), 9.86 (t, J = 5 Hz, 1H, N-H); ms *m/z*: 271 (M^++1, 14 %), 270 (M^+, 82), 237 (32), 211 (9), 167 (55), 136 (100), 108 (23), 104 (34), 77 (37). *Anal.* Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.43; H, 5.15; N, 20.51.

Continued elution with methanol afforded 10 mg (10 %) of **10**; mp 100-101 °C (lit., [23] mp 101 °C).

2-Cyanomethoxycarbonylmethylidene-4-phenyl-(5ar-9at)-1,5,5a,6,7,8,9,9a-octahydro-benzo[*f*]-1,3,5-triazepine (**11**): To a solution of **8** (258 mg, 0.84 mmol) in dry acetonitrile (30 ml) (±)-*trans*-1,2-diaminocyclohexane (146 mg, 1.28 mmol) was added. The reaction mixture was heated at reflux for 16 h and then the precipitate was collected, affording 177 mg of **11**. The mother liquors were concentrated *in vacuo* and the resulting residue was purified by flash column (diameter: 3 cm) chromatography (silica gel, hexane/EtOAc 2:1), affording 30 mg (16 %) of **12** which was recrystallized from

hexane/EtOAc; mp 257-258 °C; ir (KBr): υ = 3337 and 3280 (N-H), 2190 (C≡N), 1678 (C=O), 1582, 1441 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.22-1.41 (m, 2H, CH_2), 1.45-1.60 (m, 2H, CH_2), 1.75-1.96 (m, 2H, CH_2), 2.08-2.23 (m, 2H, CH_2), 3.09-3.30 (m, 2H, CH), 3.72 (s, 3H, OCH_3), 5.73 (s, 1H, $C\underline{H}(CN)CO_2CH_3$), 8.10 (s, 1H, NH); ms *m/z* : 222 (M^++1, 14 %), 221 (M^+, 100), 191 (10), 190 (78), 189 (11), 188 (25), 165 (10), 163 (20), 161 (10), 160 (13), 147 (18), 146 (54), 138 (51), 134 (16), 133 (24), 120 (10), 119 (11), 106 (11), 105 (21), 98 (15), 94 (13), 93 (32), 82 (13), 81 (46), 80 (12), 79 (40), 77 (17). *Anal.* Calcd for $C_{11}H_{15}N_3O_2$: C, 59.70; H, 6.84; N, 19.00. Found: C, 59.93; H, 6.71; N, 19.27.

On elution with hexane/EtOAc 1:1 an additional amount (25 mg) of **11** was obtained. Combined fractions of **11** (202 mg, 74 % yield) were recrystallized from methanol; mp 273-274 °C; ir (KBr): υ = 3309 (N-H), 2184 (C≡N), 1653 (C=O), 1597, 1437 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.16-1.45 (m, 4H, $2CH_2$), 1.68 (br s, 2H, CH_2), 2.07-2.27 (m, 2H, CH_2), 3.53-3.58 (m, 2H, CH), 7.45-7.60 (m, $3H_{arom}$), 7.91 (d, J = 6.96 Hz, $2H_{arom}$), 8.67 (s, 1H, NH), 9.64 (s, 1H, NH); ms *m/z* : 325 (M^++1, 19 %), 324 (M^+, 90), 323 (79), 292 (41), 291 (100), 190 (23), 189 (28), 188 (11), 162 (45), 161 (14), 160 (10), 153 (15), 148 (21), 147 (26), 146 (34), 145 (10), 138 (11), 134 (12), 133 (11), 125 (16), 105 (13), 104 (89), 103 (11), 96 (19), 93 (18), 82 (15), 81 (47), 80 (13), 79 (29), 77 (51). *Anal.* Calcd for $C_{18}H_{20}N_4O_2$: C, 66.63; H, 6.22; N, 17.28. Found: C, 66.47; H, 6.31; N, 17.47.

Continued elution with methanol afforded 10 mg (6 % yield) of **7**.

ACKNOWLEDGMENTS

We thank the Comunidad Autónoma de Madrid for financial support (Grant C 061/91).

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Received, 17th May, 1996