Pergamon

Tetrahedron 54 (1998) 7395–7400

TETRAHEDRON

Formation of Pyrazinoisoquinoline Ring System by the Tandem Amidoalkylation and *N*-Acyliminium Ion Cyclization: An Efficient Synthesis of Praziquantel

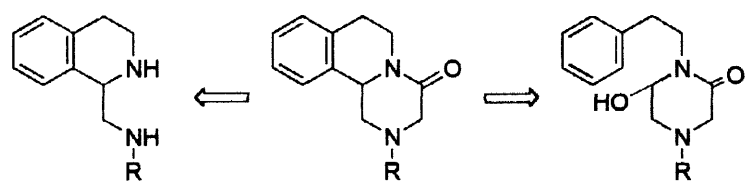
Joong Hyup Kim, Yong Sup Lee, Hokoon Park, and Choong Sup Kim*

Division of Applied Science, Korea Institute of Science & Technology, P.O. Box 131 Cheongryang, Seoul 130-650, Korea

Received 23 March 1998; accepted 20 April 1998

Abstracts: An efficient synthesis of pyrazinoisoquinoline derivatives including Praziquantel has been accomplished by the tandem amidoalkylaion and *N*-acyliminium ion cyclization of amido-acetals.

Pyrazinoisoquinolines constitute an important class of heterocycles because of their remarkable biological activity. For example, 2-cyclohexanecarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-*a*]isoquinoline (Praziquantel) is a well known anthelmintic compound.[1] Since the introduction of Praziquantel,[2] much efforts have been devoted in order to afford new pyrazinoisoquinoline derivatives exhibiting stronger antischistosomal activity.[3] However, Praziquantel is still the drug of choice for the treatment of cestodiasis disease. Current estimates suggest that 150 million humans are infected with schistosomes,[4] and it is expected that Praziquantel will play the key role in controlling those infections. Although several approaches for the production of Praziquantel have appeared in the literatures[2,5] and in patents,[7] more efficient synthetic route needs to be developed in respect to the relatively expensive cost and obvious importance of Praziquantel in global health care.



2 **1** **3**

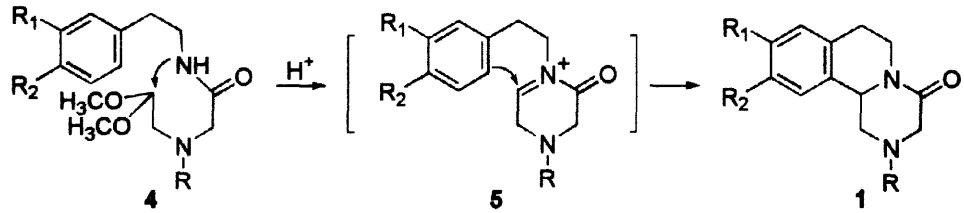
Original synthesis of Praziquantel has been accomplished by the formation of piperazine ring from 1-aminomethyl-tetrahydroisoquinoline ring **2**. This synthetic pathway has some disadvantages since it required a catalytic hydrogenation step with high pressure (ca. 100 atm.) to produce the tetrahydroisoquinoline **2** from isoquinoline.[2,7] Another approach utilizes hydroxypiperazinones **3**, which were prepared by the partial reduction of piperazine-2,6-dione, to form an isoquinoline ring system.[5] However, this approach requires multistep sequence or vigorous reaction condition for the construction of piperazine-2,6-dione and afforded Praziquantel in moderate overall 19~35% yields in 5 steps starting from *N*-benzyliminodiacetic acid or

0040-4020/98/$19.00
PII: S0040-4020(98)00401-3

iminodiacetonitrile. In this paper, we wish to report our results on the efficient synthesis of pyrazinoisoquinoline derivatives including Praziquantel.

As illustrated in Scheme 1, the basic strategy of our synthesis involves the tandem amidoalkylation and *N*-acyliminium ion cyclization of amido-acetals **4**. We anticipated that the construction of piperazine ring and isoquinoline ring could be accomplished in an one-pot procedure in acidic medium by the consecutive intramolecular amidoalkylation of acetal with amide followed by cyclization of the resultant *N*-acyliminium ion in **5** with aromatic π-nucleophile. Although the synthesis of Praziquantel by the concomitant construction of piperazine and isoquinoline ring has been appeared in the literature,[6] this procedure required high temperature (400 °C) during the imino-Diels-Alder reaction of benzocyclobutene, which is impractical for large scale production.

N-Acyliminium ion cyclization is a versatile tool in the synthesis of several types of alkaloids.[8] *N*-Acyliminium ion precursors can be prepared by the intramolecular reaction of amides with acetals. In this regard, we have recently reported the synthesis of several heterocyclic systems by the amidoalkylation reaction of amido-ureido-acetals.[9] In our continuing interest in the synthesis of isoquinoline derivatives[10] we tried to establish a general synthetic route to pyrazinoisoquinoline system by the extension of our synthetic strategy. Our objective was also to develop a short and efficient synthesis of Praziquantel.

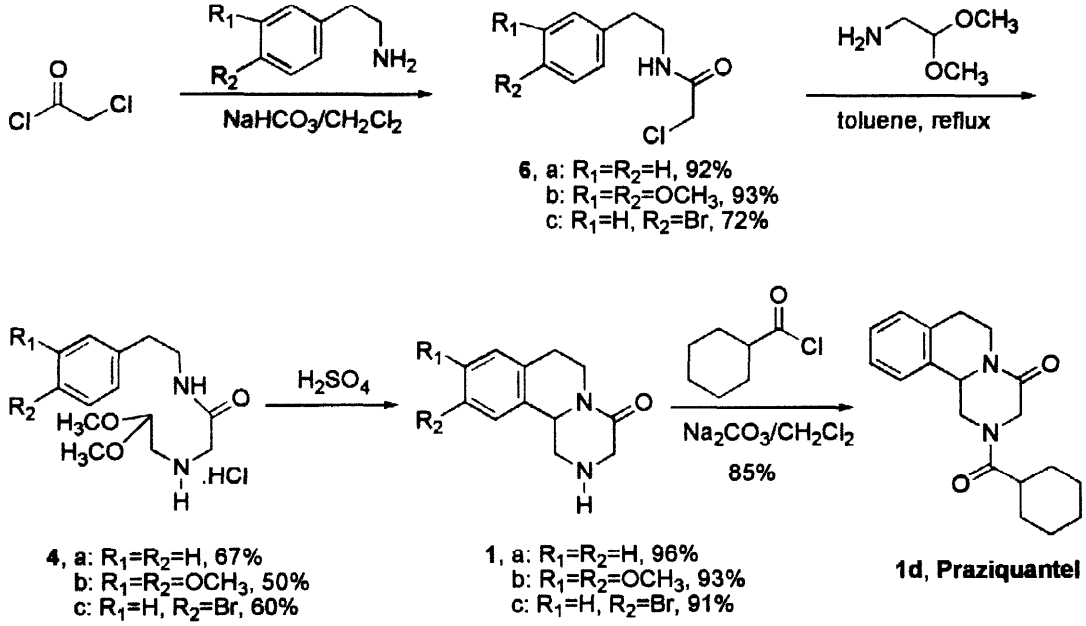


Scheme 1.

We started our synthetic work by preparing the key intermediate, the amido acetals **4**, from readily available and inexpensive chloroacetyl chloride and arylethylamines as shown in Scheme 2. In order to test the generality of our synthetic route to pyrazinoisoquinoline derivatives, we used phenethylamine, 3,4-dimethoxyphenethylamine, and 4-bromophenethylamine as arylethylamine.

Treatment of chloroacetyl chloride with several arylethylamines afforded chloroactamides **6a~c** in 72~93% yields. Aminoalkylation reaction of **6a~c** to form **4a~c** was carried out using 2.1 equivalents of aminoacetaldehyde dimethyl acetal as both reagent and base to trap hydrochloride which was generated during the reaction. For the purification of products without using column chromatography and easy treatment, **4a~c** was isolated as hydrochloride salts in 50~67% yields. The resulting aminoacetaldehyde dimethyl acetal hydrochloride was recovered for recycling.

The next remaining step is the concomitant construction of piperazine and isoquinoline ring. When amido-acetals **4a~c** hydrochloride were treated with concentrated H_2SO_4, pyrazinoisoquinoline derivatives **1a~c** were obtained in 91~96% yields. Particularly, amido-acetal **4c**, which has 4-bromophenyl ring as a π-nucleophile, cyclized smoothly to provide **1c** in good yield.[10a] Therefore, the possibility of using various aromatic rings as π-nucleophile enhances the versatility of this strategy. Finally, **1a** was converted to Praziquantel (**1d**) by the acylation with cyclohexanecarbonyl chloride in 85% yield.



Scheme 2.

In summary, we realized an efficient synthesis of pyrazinoisoquinoline derivatives **1a~d**. The synthetic pathway was shortened by the concomitant formation of piperazine ring and isoquinoline ring in an one-pot procedure. The whole synthesis of Praziquantel comprises only 4 steps from phenethylamine and proceeds in ca. 50% yield without any chromatographic purification. To our best knowledge, our synthetic pathway to Praziquantel is the shortest known to date. Furthermore, compound **1a~c** could serve as good intermediates for the study of structure-activity relationship to find potent antischistosomal compounds by the simple acylation of amine function with several acid chloride or isocyanate compounds.

EXPERIMENTAL

Melting points (mp) were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Gemini Varian-300 (300MHz) spectrometer or JEOL PMX-60 (60MHz) spectrometer. ^{13}C NMR spectra were recorded on a Gemini Varian-300 (75MHz) spectrometer. Infrared (IR) spectra were recorded on Perkin Elmer 16F-PC FT-IR using a potassium bromide pellet. Low (EI) resolution mass spectra were determined on HP GC 5972 and HP MS 5988A system at 70eV and High (EI) resolution mass spectra were determined on VG70 - VSEQ (VG ANALITICAL, UK) at 70eV.

***N*-(2-Phenyl)ethyl chloroacetamide (6a).** Chloroacetamides **6a~c** were obtained by the slight modification of the known procedure[11] as follows: To a solution of phenethylamine (121 g, 1.0 mol) and $NaHCO_3$ (106 g, 1 mol) in dichloromethane (1000 ml) was added dropwise chloroacetyl chloride (136 g, 1.2 mol) at 0 °C over 1 hr. After stirring at 10 °C for 2 h, the reaction mixture was quenched by slow addition of water (500 ml) at 0 °C. The organic layer was separated, and washed successively with 10% aqueous HCl solution and brine. After evaporation of solvent, the resulting solid was recrystallized with CH_3OH (300 ml) and water (200 ml) to afford **6a** (160 g, 92%) as a needle: mp 60-63 °C (CH_3OH/H_2O), lit.[10] mp 67 °C; ^{1}H NMR ($CDCl_3$) δ 2.85 (2H,

t, J = 7.0 Hz, PhCH_2), 3.55 (2H, q, J = 6.7 Hz, PhCH$_2$$CH_2$NH), 3.99 (2H, s, CH_2Cl), 6.73 (1H, br s, *NH*), 7.19-7.34 (5H, m, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 35.51, 41.03, 42.68, 126.72, 128.75, 138.75, 165.91; IR (KBr) 3350, 1650 cm^{-1}.

***N*-2-(3,4-Dimethoxyphenyl)ethyl chloroacetamide (6b).** By the use of the procedure described above for **6a**, compound **6b** was obtained from 3,4-dimethoxyphenethylamine (50.8 g, 0.28 mol) and chloroacetyl chloride (38 g, 0.34 mol) as a white needle (66.8 g, 93 %): mp 94-95 °C (EtOAc/*n*-hexane), lit.[10] mp 96 °C; ^{1}H NMR ($CDCl_3$) δ 2.82 (2H, t, J = 6.0 Hz, PhCH_2), 3.59 (2H, t, J = 6.0 Hz, PhCH$_2$$CH_2$NH), 3.90 (6H, s, O$CH_3$), 4.01 (2H, s, CH_2Cl), 6.79 (3H, m, aromatic protons); IR (KBr) 3350, 1655 cm^{-1}.

***N*-2-(4-Bromophenyl)ethyl chloroacetamide (6c).** By the use of the procedure described above for **6a**, compound **6c** was obtained from 4-bromophenethylamine (10 g, 0.05 mol) and chloroacetyl chloride (6.78 g, 0.06 mol) as a white needle (9.9 g, 72 %): mp 104-105 °C (CH_2Cl_2/*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 2.80 (2H, t, J = 7.0 Hz, PhCH_2), 3.51 (2H, t, J = 7.0 Hz, PhCH$_2$$CH_2$NH), 4.00 (2H, s, CH_2Cl), 7.10 (2H, d, J = 4.0 Hz, aromatic protons), 7.46 (2H, d, J = 4.0 Hz, aromatic protons); IR (KBr) 3350, 1650, 1480 cm^{-1}.

***N*-(2-Phenyl)ethyl 2-[(2,2-dimethoxyethyl)amino]acetamide (4a) hydrochloride.** To a solution of **6a** (16 g, 0.081 mol) in toluene (80 ml) was added aminoacetaldehyde dimethyl acetal (17.5 g, 0.167 mol), and the mixture was heated to reflux for 2 h. After cooling the mixture to 0 °C, the resulting solid (aminoacetaldehyde dimethyl acetal hydrochloride, 11 g, 96%) was recovered by filtration. The filtrate was washed three times with water, dried ($MgSO_4$), and concentrated to give **4a** (17.3 g, 80%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 2.41 (2H, d, J = 5.4 Hz, CH_2CH(OCH$_3$)$_2$), 2.61 (2H, t, J = 7.1 Hz, PhCH_2), 3.00 (2H, s, NHCH_2CO), 3.16 (6H, s, CH(OCH_3)$_2$), 3.31 (2H, q, J = 6.8 Hz, PhCH$_2$$CH_2$NH), 4.09 (1H, t, J = 5.4 Hz, CH$_2$*CH*(OCH$_3$)$_2$), 6.98 - 7.10 (5H, m, aromatic protons), 7.26 (1H, t, J = 1.3 Hz, *NH*CO); ^{13}C NMR ($CDCl_3$) δ 35.57, 39.93, 50.99, 52.23, 53.72 (2C), 103.42, 126.21, 128.35 (2C), 128.57 (2C), 138.92, 171.34; IR (KBr) 3340, 2975, 1670, 1530, 1460 cm^{-1}; MS (EI), m/z (relative intensity, %) 234 [(M$^+$- CH$_3$OH), 50], 191 (33), 134 (23), 118 (35), 105 (21), 86 (base peak), 75 (94); HRMS (EI) Calcd for $C_{13}H_{18}N_2O_2$ (M$^+$- CH$_3$OH): m/z 234.1368, Found: 234.1369. This product was diluted with CH_2Cl_2 (120 ml) and treated with HCl gas at 0-5 °C. The resulting solid was filtered, and dried to afford **4a** hydrochloride (16.5 g, 84%) as a white solid: mp 152-152.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.83 (2H, t, J = 7.7 Hz, PhCH_2), 3.18 (2H, d, J = 5.3 Hz, CH_2CH(OCH$_3$)$_2$), 3.38 (6H, s, OCH$_3$), 3.46 (2H, q, J = 6.5 Hz, PhCH$_2$$CH_2$NH), 4.04 (2H, s, NH$CH_2$CO), 4.84 (1H, t, J = 5.3 Hz, CH$_2$*CH*(OCH$_3$)$_2$), 7.14-7.25 (5H, m, aromatic protons), 8.62 (1H, t, J = 5.6 Hz, *NH*CO); ^{13}C NMR ($CDCl_3$) δ 35.39, 41.20, 48.45, 48.78, 54.62, 54.78, 99.64, 126.38, 128.47 (2C), 128.78 (2C), 138.72, 164.85; IR (KBr) 3500, 3330, 1635, 1560 cm^{-1}.

***N*-2-(3,4-Dimethoxyphenyl)ethyl 2-[(2,2-dimethoxyethyl)amino]acetamide (4b) hydrochloride.** To a solution of **6b**, (12.86 g, 0.05 mol) in toluene (100 ml) was added aminoacetaldehyde dimethyl acetal (11.57 g, 0.11 mol) and the mixture was heated to reflux for 1.5 h. After cooling the mixture to 0 °C, the resulting solid was recovered by filtration. The filtrate was concentrated and diluted with CH_2Cl_2 (150 ml). The CH_2Cl_2 solution was washed three times with water, dried ($MgSO_4$), and concentrated to give **4b** (16.19 g, 99%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 2.67 (2H, d, J = 6.0 Hz, CH_2CH(OCH$_3$)$_2$), 2.80 (2H, t, J = 6.6 Hz, PhCH_2),

3.30 (2H, s, NHC*H*$_2$CO), 3.40 (6H, s, CH(OC*H*$_3$)$_2$), 3.90 (6H, s, OC*H*$_3$), 4.30 (1H, t, J = 6.0 Hz, CH$_2$C*H*(OCH$_3$)$_2$), 6.75 - 6.82 (3H, m, aromatic protons), 7.50 (1H, br t, J = 2.4 Hz, *NH*CO); IR (KBr) 3300, 2930, 1650, 1510 cm^{-1}. This product (4.02 g, 12.3 mmol) was diluted with EtOAc (40 ml) and treated with HCl gas at -70 °C. The resulting solution was treated with hexane, and stored at refrigerator to afford **4b** hydrochloride (2.26 g, 51%) as a white solid: mp 98-99 °C (CH$_2$Cl$_2$/EtOAc); ^{1}H NMR (CDCl$_3$) δ 2.95 (4H, m, PhC*H*$_2$, PhCH$_2$C*H*$_2$NH), 3.24 (2H, d, J = 5.4 Hz, NHC*H*$_2$CH), 3.50 (6H, s, OC*H*$_3$), 3.95 (6H, s, CH(OC*H*$_3$)$_2$), 5.00 (1H, t, J = 5.4 Hz, CH$_2$C*H*(OCH$_3$)$_2$), 7.10-7.21 (3H, m, aromatic protons); IR (KBr) 3300-3600, 3240, 1680, 1560 cm^{-1}.

***N*-2-(4-Bromophenyl)ethyl 2-[(2,2-dimethoxyethyl)amino]acetamide (4c) hydrochloride.** By the use of the procedure described above for **4a** hydrochloride, compound **4c** hydrochloride was obtained from **6c** (8.3 g, 0.03 mol) and aminoacetaldehyde dimethyl acetal (6.62 g, 0.063 mol) in overall 60% yield (6.83 g) as a white solid: mp 164 °C (CH$_2$Cl$_2$/EtOAc); ^{1}H NMR (D$_2$O) δ 2.80 (2H, t, J = 6.2 Hz, PhC*H*$_2$), 3.10 (2H, d, J = 5.3 Hz, NHC*H*$_2$CH), 3.50 (6H, s, OC*H*$_3$), 3.84 (2H, s, COC*H*$_2$NH), 4.75 (1H, t, J = 5.3 Hz, CH$_2$C*H*(OCH$_3$)$_2$), 7.16 (2H, d, J = 8.0 Hz, aromatic protons), 7.50 (2H, d, J = 8.0 Hz, aromatic protons); IR (KBr) 3330, 2950-2630, 1670, 1570 cm^{-1}.

4-Oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-*a*]isoquinoline (1a). Compound **4a** hydrochloride (4.0 g, 12.1 mmol) was added in a small portion to a solution of *conc.* H$_2$SO$_4$ (4 ml) at 5 °C. After stirring at room temperature for 3.5 h, the reaction mixture was poured into ice-water and adjusted to pH 12 with 20% aqueous NaOH solution with cooling. The solution was extracted with CH$_2$Cl$_2$ and the CH$_2$Cl$_2$ solution was washed with brine, dried (MgSO$_4$) and concentrated. The residue was recrystallized with EtOAc and *n*-hexane to afford **1a** (2.36 g, 96%) as a white solid: mp 117-119 °C (EtOAc/ *n*-hexane), lit.[7] mp 118-119 °C, lit.[5a] oil; ^{1}H NMR (CDCl$_3$) δ 2.45-2.74 (4H, m, H-1, H-6 and 2 x H-7), 3.31 (2H, ABq, J = 17.2 Hz, 2 x H-3), 3.49 (1H, dd, J = 4.2, 12.9 Hz, H-1), 4.54-4.62 (2H, m, H-6 and H-11b), 6.89-7.01 (4H, m, aromatic protons); ^{13}C NMR (CDCl$_3$) δ 28.70, 38.59, 49.51, 49.72, 56.39, 124.68, 126.51, 126.84, 129.16, 134.22, 134.67, 166.93; IR (KBr): 3300, 2900, 1630, 1440 cm^{-1}; MS (EI), m/z (relative intensity, %) 202 (M$^+$, 40), 173 (57), 145 (base peak), 131 (67), 117 (26), 103 (13), 77 (15); HRMS (EI) Calcd for C$_{12}$H$_{14}$N$_2$O (M$^+$): m/z 202.1106, Found: 202.1107.

9,10-Dimethoxy-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-*a*]isoquinoline (1b). By the use of the procedure described above for **1a**, compound **1b** was obtained from **4b** hydrochloride (2.16 g, 5.97 mmol) and *conc.* H$_2$SO$_4$ (2 ml) in 93% yield (1.45 g): mp 136-137 °C (EtOAc); ^{1}H NMR (CDCl$_3$) δ 2.00 (1H, s, NH), 2.30-3.10 (4H, m, 4H, m, H-1, H-6 and 2 x H-7), 3.30-4.00 (3H, m, 2 x H-3 and H-1), 3.80 (6H, s, OCH$_3$), 4.40-5.00 (2H, m, H-6 and H-11b), 6.66 & 6.75 (2H, two s, aromatic protons); IR (KBr): 3240, 2950, 1640, 1510 cm^{-1}.

10-Bromo-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-*a*]isoquinoline (1c). By the use of the procedure described above for **1a**, compound **1c** was obtained from **4c** hydrochloride (6.0 g, 15.7 mmol) and *conc.* H$_2$SO$_4$ (12 ml) in 91% yield (4.03 g): mp 107-108 °C (EtOAc/ *n*-hexane); ^{1}H NMR (CDCl$_3$) δ 2.48 (1H, s, NH), 7.33 (1H, d, J = 8.0 Hz, H-8), 7.55 (1H, s, H-11), 7.64 (1H, d, J = 8.0 Hz, H-9); IR (KBr) 3270, 2860,

1620 cm^{-1}.

2-Cyclohexanecarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-*a*]isoquinoline (1d, Praziquantel). To a solution of **1a** (14.2 g, 0.07 mol) and Na_2CO_3 (13 g, 0.122 mol) in CH_2Cl_2 (40 ml) was added dropwise a solution of cyclohexanecarbonyl chloride (11.2 g, 0.076 mol) in CH_2Cl_2 (5 ml) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was treated with water (30 ml). The organic layer was separated and washed with brine, dried ($MgSO_4$) and concentrated. The residue was treated with diethyl ether and hexane to afford **1d** (praziquantel) as a slightly yellow solid (18.6 g, 85%): mp 137-138 °C (EtOAc), lit.[5a] mp 134-137 °C; ^1H NMR ($CDCl_3$) δ 1.24-1.79 (10H, m, cyclohexyl protons), 2.45 (1H, m, *CH*CON), 2.74-2.97 (4H, m, H-1, H-6, 2 x H-7), 4.06 (1H, d, J = 16.5Hz, H-3), 4.45 (1H, d, J = 16.5Hz, H-3'), 4.76-4.81 (2H, m, H-1' and H-11b), 5.15 (1H, dd, J = 13.4, 2.8Hz, H-6'), 7.16-7.27 (4H, m, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.75, 28.77, 29.04, 29.26, 39.12, 40.82, 45.21, 49.06, 54.98, 125.46, 126.98, 127.46, 129.30, 132.83, 134.79, 164.41, 174.76; IR (KBr) 2950, 2860, 1640, 1450 cm^{-1}; MS (EI), m/z (relative intensity, %) 312 (M^+, 52), 201 (96), 185 (29), 173 (18), 146 (35), 132 (base peak), 113 (15), 83 (30), 55 (46); HRMS (EI) Calcd for $C_{19}H_{24}N_2O_2$ (M^+): m/z 312.1837, Found: 312.1836.

REFERENCES

1. Sharma, S.; Dubey, S. K.; Iyer, R. N. *Progress in Drug Research*, Jacker, E., Eds, Birkhauser Verlag, Basel, **1980**, Vol 24, p 217.
2. Seubert, J.; Pohlke, R.; Loebich, F. *Experientia* **1977**, *33*, 1036.
3. (a) Abo-Ghalia, M. H.; Soliman, A. E.-M. *Arzneim.-Forsch.* **1996**, *46*, 207. (b) Hassanein, H.; El Nahal, H. M.; Gerges, F. R. *Eur. J. Med. Chem.* **1995**, *30*, 525. (c) Hu, Y.; Xia, Y.; Zhou, D.; Xiang, L.; Huang, L.; Le, W.; Mei, J. *Huaxi Yaoxue Zazhi* **1996**, *11*, 129. (d) Hu, Y.; Zhou, D.; Xiang, L.; Le, W.; Mei, Y. *Zhongguo Yaowu Huaxue Zazhi* **1997**, *7*, 37. (e) Martinez, R.; Rubio, M. F.; Toscano, R. A.; Villalobos, X.; Brito, M. A. *J. Heterocycl. Chem.* **1994**, *31*, 1521.
4. Day, T. A.; Bennett, J. L.; Pax, R. A. *Parasitol. Today* **1992**, *8*, 342.
5. (a) Yuste, F.; Pallas, Y.; Barrios, H.; Ortiz, B.; Sanchez-Obregon, R. *J. Heterocycl. Chem.* **1986**, *23*, 189. (b) Frehel, D.; Maffrand, J.-P. *Heterocycles* **1983**, *20*, 1731.
6. Berkowitz, W. F.; John, T. V. *J. Org. Chem.* **1984**, *49*, 5269.
7. (a) Pohlke, R.; Loebich, F.; Serbert, J.; Thomas, H.; Andrews, P. German Patent 2,331,713, 1975; *Chem. Abstr.* **1975**, *82*, 156369f. (b) Seubert, J.; Thomas, H.; Andrews, P. German Patent 2,362,539, 1975; *Chem. Abstr.* **1976**, *84*, 5007b. (c) Seubert, J. German Patent 2,504,250, 1975; *Chem. Abstr.* **1976**, *85*, 142999m. (d) Pohlke, R. German Patent 2,508,947, 1976; *Chem. Abstr.* **1977**, *86*, 16705v. (e) Pohlke, R. German Patent 1,795,728, 1977; *Chem. Abstr.* **1977**, *87*, 168092b.
8. (a) Hiemstra, H. and Speckamp, W. N. *Addition to N-Acyliminium Ions.* In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 1047-1082. (b) Speckamp W. N.; Hiemstra, H. *Tetrahedron* **1985**, 41, 4367.
9. Lee, Y. S.; Kim, C. S.; Park, H. *Heterocycles* **1994**, *38*, 2605.
10. (a) Lee, Y. S.; Kang, S. S.; Choi, J. H.; Park, H. *Tetrahedron* **1997**, *53*, 3045. (b) Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449. (c) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149. (d) Lee, Y. S.; Kim, S. H.; Lee, S. J.; Park, H. *Heterocycles* **1994**, *37*, 303.
11. Harwood, H. J.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55*, 2555.