SYNTHESIS OF PRAZIQUANTEL *VIA N*-ACYLIMINIUM ION CYCLIZATION OF AMIDO ACETALS THROUGH SEVERAL SYNTHETIC ROUTES

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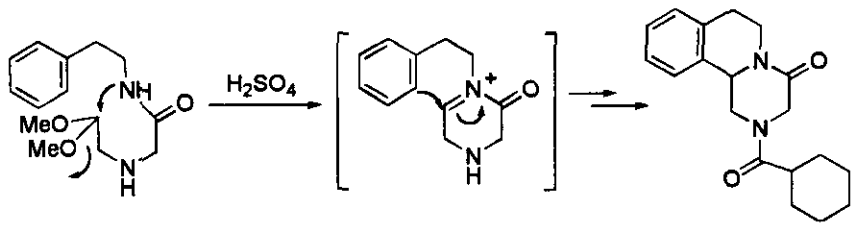
Abstract- Syntheses of praziquantel have been accomplished *via* an *N*-acyliminium ion by several routes including the tandem nucleophilic addition-cyclization sequence from amido acetal (**8**) or (**10**) and a stepwise cyclization of enamide (**9**) generated from the nucleophilic addition reaction of amido acetal (**8**) or (**10**).

The discovery of praziquantel (**1**) represented as a synthetic drug of pyrazinoisoquinoline derivatives has played an important role in the treatment of cestodiasis disease.[1] Accordingly, many research groups have extensively investigated on structure-activity relationships of this class of compounds[2] and attempted to develop a more efficient synthetic route to praziquantel and its derivatives.[3~5]

Most of the known synthetic methods involve successive constructions of piperazine ring and isoquinoline ring in pyrazinoisoquinoline ring system, which require multistep sequence or vigorous reaction conditions.[3,4] On the other hand, we have recently reported an efficient synthesis of praziquantel by a tandem nucleophilic addition followed by *N*-acyliminium ion cyclization of amido acetal (**2**) (Scheme 1).[6]

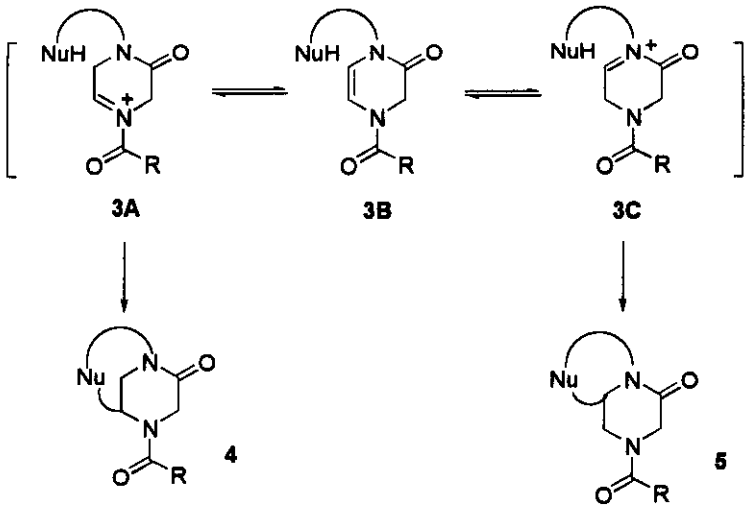


2 **1**

Scheme 1

This strategy features the concomitant construction of piperazine ring and isoquinoline ring in one-pot procedure leading to a shortened synthetic pathway for praziquantel. The aim of exploring the scope of this tandem cyclization reaction prompted us to investigate a more efficient synthetic method for praziquantel and its derivatives in connection with our interest in the synthesis of several heterocyclic systems.[7]

N-Acyliminium ions, generated *in situ* as intermediates can be readily captured by a variety of nucleophiles in reversible[8] or irreversible[9] processes to produce polyheterocyclic systems. On the other hand, the formation of enamides such as **3B** from *N*-acyliminium ion precursor (**3A**) *via* loss of a proton was reported by our laboratory[10] (Scheme 2).

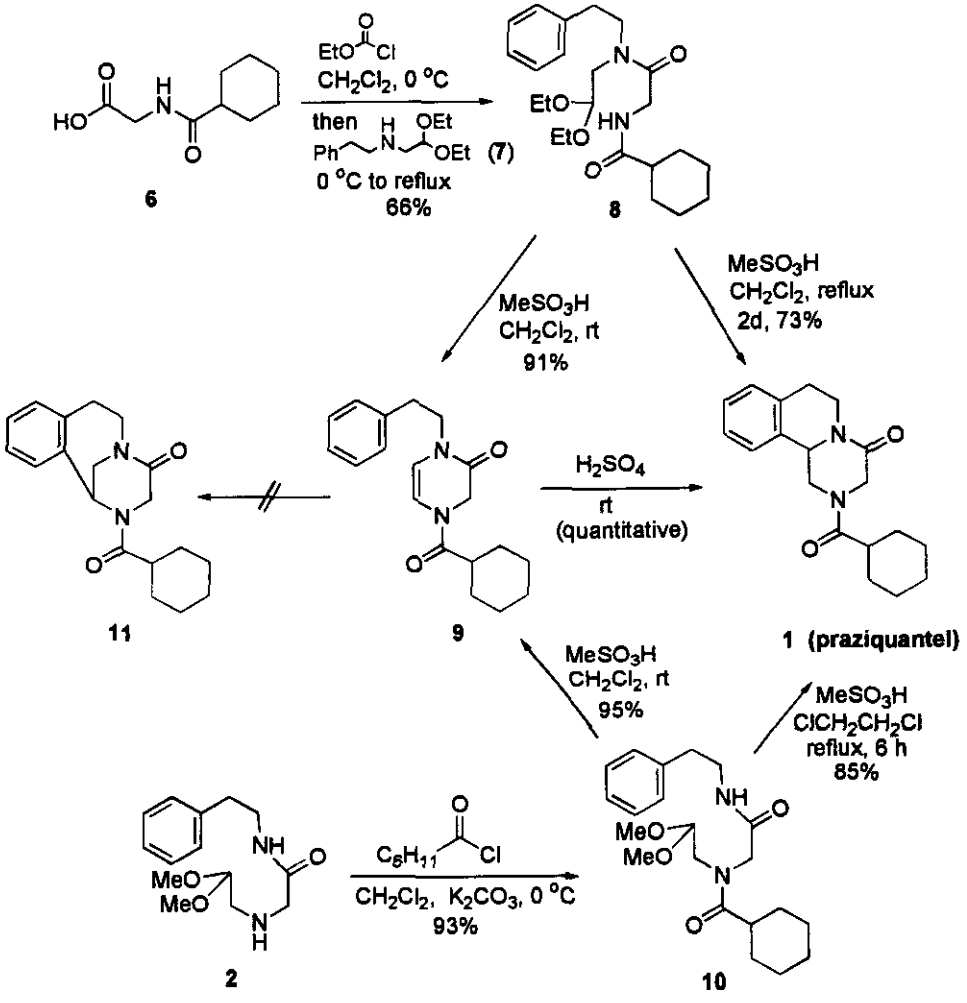


Scheme 2

Enamides also have been extensively used as *N*-acyliminium ion precursors for the synthesis of several alkaloids due to their ready conversion to *N*-acyliminium ion.[11,12b] At this point, we imagined that *N*-acyliminium ion (**3A**) would be in equilibrium state with **3C** through an isolable intermediate (**2B**) in acidic media; then **3A** or **3C** may react intramolecularly with a tethered nucleophile to furnish cyclized product (**4**) and/or (**5**). Although the synthesis of several bridged cyclic compound (**4**) through *N*-acyliminium ion cyclization has been reported in literatures,[12] we expected that pyrazinoisoquinoline ring system (**5**) could be derived selectively from a precursor of *N*-acyliminium ion (**3A**) or (**3C**) by the tandem intramolecular nucleophilic addition followed by cyclization or stepwise cyclization reaction *via* intermediate (**3B**). In order to prove this assumption and develop a more efficient synthetic route to praziquantel, we attempted the synthesis and cyclization reaction of amido acetals (**8**, **10**) and enamide (**9**)

by using readily available starting materials as shown in Scheme 3.

The starting compound (**6**), readily prepared from the reaction of glycinamide with cyclohexanecarbonyl chloride in quantitative yield by the known procedure,[13] was treated with ethyl chloroformate in dichloromethane at 0 °C followed by amino acetal (**7**) to afford amido acetal (**8**) in 66% yield. The another starting amido acetal (**10**) was prepared by acylation of the amine compound (**2**) as reported in our previous work.[6]



Scheme 3

With the desired amido acetals (**8**) and (**10**) in hand, their *N*-acyliminium ion cyclization was studied. Upon treatment of amido acetal (**8**) and (**10**) with methanesulfonic acid in dichloromethane or dichloroethane at reflux temperature, praziquantel (**1**), a cyclized product through the *N*-acyliminium ion (**3C**) (Scheme 2), indeed was obtained in 73% and 85% yields, respectively. When the cyclization of amido acetals (**8**) and

(**10**) was carried out at room temperature, enamide (**9**) was isolated in almost quantitative yield. The identity of enamide (**9**) was firmly established by the appearance in the ^{1}H NMR spectra of the characteristic methine signals of the enamide double bond. This enamide (**9**) was also alternatively prepared by alkylation of 4-cyclohexylcarbonyl-3,4-dihydropyrazin-2-one[14] with phenethyl bromide in the presence of benzyltributylammonium chloride. Exposure of enamide (**9**) to sulfuric acid effected rapid and clean cyclization to praziquantel (**1**) in quantitative yield. The transformation of enamide (**9**) to **1** confirms again that the *N*-acyliminium ion (**3C**) mainly participated in the cyclization. As expected, the formation of a bridged bicyclic compound (**11**) was not observed during the acid promoted cylization reaction of amido acetals (**8**, **10**) or enamide (**9**). This finding indicates that the capture of *N*-acyliminium ion (**3A**), which can be possibly generated from the compound (**8**) or (**10**), by the phenyl ring to form bridged 9-memberd ring system seems less favorable than the formation of praziquantel ring structure.

In conclusion, we have shown that praziquantel could be synthesized from two different amido acetals (**8**) or (**10**) *via* the tandem neucleophilic addition followed by *N*-acyliminium ion cyclization or a stepwise cyclization through the enamide intermediate (**9**) in one-pot procedure demonstrating the ready conversion of an *N*-acyliminium ion (**3A**) into another *N*-acyliminium ion (**3C**) through the enamide intermediate (**3B**). By using these strategies, the synthesis of praziquantel has been flexibly accomplished in *ca.* 48-53% overall yields depending on the synthetic route and availability of starting compounds *via* 3 or 5 step sequence of reactions.

EXPERIMENTAL

Melting points (mp) were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL PMX-60 (60 MHz) spectrometer. Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane. IR spectra were recorded on Perkin-Elmer 781 spectrophotometer or Perkin-Elmer 16F-PC FT-IR. Elemental analysis was performed by a Perkin-Elmer 240 DS analyzer. All chemicals used for synthetic procedure were of reagent grade.

***N*-2-Phenylethylaminoacetaldehyde diethyl acetal (7).** To a solution of NaOH (4.3 g, 0.11 mol) in DMF (80 mL) was added phenethylamine (24.2 g, 0.20 mol) and chloroacetaldehyde diethyl acetal (15.2 g, 0.10 mol), and the solution was heated at reflux for 18 h. The mixture was poured into 10% aqueous NaCl (150 mL) and extracted with CH_2Cl_2 (60 mL x 3). The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated, and purified by vacuum distillation to afford **7** (21.8 g, 92%) as an oil: bp 140-145 °C/*ca.* 3 mmHg; IR (NaCl, film) 3250, 2970, 2900, 1450, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05

(6H, t, J=6.6 Hz, CH_2CH_3), 1.40 (1H, br s, NH), 2.50-2.80 (6H, m, $PhCH_2CH_2NCH_2$), 3.47 (4H, q, J=6.6 Hz, CH_2CH_3), 4.47 (1H, t, J=5.6 Hz, $CH_2CH(OEt)_2$), 7.15 (5H, s, phenyl); *Anal.* Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.79; H, 9.81; N, 5.91.

***N*-(2,2-Diethoxy)ethyl-*N*-2-phenylethyl 2-*N*-cyclohexylcarbonylaminoacetamide (8).** To a solution of *N*-cyclohexylcarbonylglycine amide[13] (**6**, 12.95 g, 0.07 mol) and NEt_3 (10.60 g, 0.11 mol) in CH_2Cl_2 (100 mL) was added dropwise methyl chloroformate (7.28 g, 0.08 mmol) over 30 min at 0 °C. After stirring for 1 h, the mixture was treated dropwise a solution of *N*-2-phenylethylaminoacetaldehyde diethyl acetal (**7**, 16.59 g, 0.07 mol) in CH_2Cl_2 (50 mL) at the same temperature and brought up to refluxing condition for 7 h. The mixture was cooled to rt and washed with 0.7% aqueous HCl (20 mL x 2), dried ($MgSO_4$), and concentrated to afford **8** (18.51 g, 66%) as an oil, which was used at next step without further purification: IR (NaCl, film) 3320, 2940, 1640, 1450, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (6H, t, J=6.6 Hz, CH_2CH_3), 1.70-1.90 (10H, m, cyclohexyl protons), 2.50 (1H, m, $CHCONH$), 2.88 (2H, t, J=7.0 Hz, $PhCH_2$), 3.55 (4H, q, J=6.6 Hz, CH_2CH_3), 3.20-4.40 (6H, m, $PhCH_2CH_2$, NCH_2CO, NCH_2CH), 4.60 (1H, t, J=5.4 Hz, $CH_2CH(OEt)_2$), 7.25 (5H, s, phenyl).

***N*-(2-Phenyl)ethyl 2-(*N*-cyclohexylcarbonyl-2,2-dimethoxyethylamino)acetamide (10).** To a solution of *N*-2-phenylethyl 2-*N*-(2,2-dimethoxyethylamino)acetamide hydrochloride[6] (12.8 g, 0.042 mol) and NEt_3 (14.7mL, 0.11 mol) in CH_2Cl_2 (150 mL) was added slowly cyclohexanecarbonyl chloride (6.8 g, 0.047 mol) and the mixture was stirred at rt for 30 min. The mixture was washed with water, and the organic layer was dried ($MgSO_4$), and concentrated to give **10** (14.8 g, 93%). A pure sample was obtained by recrystallization with ether: mp 128-130 °C; IR (KBr) 3350, 2970, 1670, 1560, 1465, 1140, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60-1.80 (10H, m, cyclohexyl protons), 2.48 (1H, m, $CHCONH$), 3.22 (2H, t, J=6.0 Hz, $PhCH_2$), 3.65 (2H, t, J=6.0 Hz, CH_2NH), 3.80 (6H, s, OCH_3), 4.40 (2H, s, $COCH_2N$), 4.93 (1H, m, $CH_2CH(OCH_3)_2$), 7.60 (5H, m, phenyl protons); *Anal.* Calcd for $C_{21}H_{32}N_2O_4$: C,66.99; H,8.57; N, 7.44. Found: C, 66.93; H, 8.58; N, 7.49.

Preparation of 4-Cyclohexylcarbonyl-1-2-phenylethyl-3,4-dihydropyrazin-2-one (9) from 8 or 10. To a solution of **8** (4.0 g, 9.89 mmol) in CH_2Cl_2 (10 mL) was added methanesulfonic acid (1.48 g, 15.4 mmol) and the mixture was stirred at rt for 3 h. The mixture was neutralized by 10% aqueous NaOH under vigorous stirring. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated. The residue was recrystallized from ethyl acetate-hexane to afford **9** (2.8 g, 91%) as a white solid. The compound (**9**)

was also obtained from the compound (**10**) by the same method as above in 95% yield: mp 128-130 °C; IR (KBr) 3100, 2930, 2850, 1660, 1450, 1400, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30-2.50 (10H, m, cyclohexyl protons), 2.51 (1H, m, C*H*CONH), 2.90 (2H, t, J=7.0 Hz, PhC*H*$_2$), 3.70 (2H, t, J=7.0 Hz, PhCH$_2$C*H*$_2$), 4.20 (2H, s, NC*H*$_2$CO), 5.30 (1H, d, J=6.0 Hz, C*H*=), 6.00 (1H, d, J=6.0 Hz, C*H*=), 7.10 (5H, m, phenyl); *Anal.* Calcd for $C_{19}H_{24}N_2O_2$: C,73.05; H,7.74; N, 8.97. Found: C, 72.94; H, 7.80; N, 9.02.

Alternative Preparation of 9. To a solution of 4-cyclohexylcarbonyl-3,4-dihydropyrazin-2-one[14] (1.96 g, 9.41 mmol) and phenethyl bromide (2.41g, 13.02 mmol) in CH_2Cl_2 (150 mL) was added powered anhyd. K_2CO_3 (2.80 g, 20.25 mmol) and benzyltributylammonium chloride (0.31 g, 0.99 mmol). The mixture was heated at reflux for 5 h and poured into water. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was recrystallized from ethyl acetate-hexane to afford **9** (1.52 g, 52%) as a white solid.

Preparation of 2-Cyclohexanecarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline (1, praziquantel) from 9. A solution of **9** (1.4 g, 4.48 mmol) in *conc*-H_2SO_4 (5 mL) was stirred at rt for 3 h. The mixture was quenched by addition of ice and neutralized by 10% aqueous NaOH under vigorous stirring. The mixture was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated to afford **1** (1.4 g, quantitative). The spectral data of **1** were in complete agreement with those reported in literatures.[4,6]

Preparation of 1 from 8. To a solution of **8** (2.43 g, 6.01 mmol) in CH_2Cl_2 (30 mL) was added methanesulfonic acid (7.1 g, 73.88 mmol) and heated at reflux for 2 d. After usual work-up, compound (**1**) was obtained in 73% yield (1.37 g) as a white solid.

Preparation of 1 from 10. To a solution of **10** (2.6 g, 6.91 mmol) in dichloroethane (30 mL) was added methanesulfonic acid (7.9 g, 82.21 mmol) and heated at reflux for 6 h to obtain the desired compound (**1**) in 85% yield.

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14. This compound was prepared from *N*-2,2-diethoxyethyl-2-(*N*-cyclohexylcarbonylamino)acetamide by the previously reported method.[10]

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