An Easy Preparation of 11-Membered Ring Compounds *via* Enamine From Diethylenetriamine and DMAD

Tadashi Okawara, Shuji Ehara, Shigenori Matsumoto, Yoshinari Okamoto, Tetsuo Yamasaki, and Mitsuru Furukawa
Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-hon-machi, Kumamoto 862, Japan

Diethylenetriamine (**1**) reacts with dimethyl acetylenedicarboxylate (**2**) to give the tetrahydropyrazinodiazepinedione (**3**). On hydrolysis this gives the triazacycloundecanetrione (**4**).

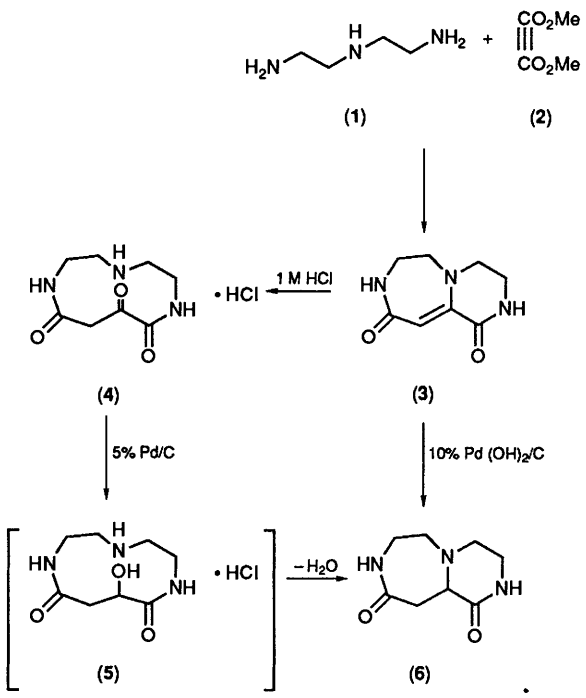
Cyclic polyamines with medium sized rings have been the focus of much attention because of their ability to chelate with various metals and their enzymatic function. Although there are several methods for the preparation of such compounds[1,2] their formation from diethylenetriamine (**1**) and dimethyl acetylenedicarboxylate (DMAD) (**2**) has not before been reported.

In connection with our work on saturated fused heterocycles using polyfunctionalized acyclic compounds,[3] we allowed the

triamine (**1**) to react with DMAD (**2**) to give the tetrahydropyrazino[1,2-*d*]diazepinedione (**3**); this, upon hydrolysis with 1M HCl, gave the triazacycloundecanetrione (**4**) (Scheme).

The structure of the dione (**3**), readily formed upon addition of DMAD (**2**) to an ethanolic solution of the triamine (**1**), was elucidated upon the basis of spectral evidence and elemental analyses. Thus, the mass spectrum showed a parent ion at *m/z* 181 [loss of 2 MeOH from the sum of (**1**) and (**2**)] and the ^{1}H NMR spectrum, a characteristic signal for a β-methine hydrogen of an enamine at δ 5.56. The ^{13}C NMR spectrum using the DEPT technique indicated two carbonyl carbons at δ 160.8 and 169.2 ppm, a quaternary α-carbon and a β-methine carbon for an enamine at δ 141.5 and 96.5 ppm, and four methylene carbons. These results confirm that the product has structure (**3**).

The dione (**3**) was readily hydrolysed with 1M HCl to give (**4**), the structure of which was confirmed by the evidence of the ^{13}C NMR spectrum (3 carbonyl carbons at 151.9, 163.9, and 172.6 ppm and 4 methylene carbons at 40.8, 45.8, 52.4, and 58.9 ppm, respectively). Catalytic hydrogenation of (**4**) over 5% Pd/C gave the intermediate, hydroxy compound (**5**), which was immediately dehydrogenated to give (**6**). The latter was also produced by hydrogenation of (**3**) with 10% $Pd(OH)_2/C$. Recently Cantatore[4] reported the preparation of derivatives of (**6**) from dimethyl fumarate and triamine.



Scheme.

Experimental

3,4,7,8-*Tetrahydro*-2H,6H-*pyrazino*[1,2-d][1,4]*diazepine*-1,9-*dione* (**3**).—To a solution of the triamine (**1**) (1.08 ml, 10 mmol) in EtOH (30 ml) was gradually added a solution of DMAD (**2**) (1.22 ml, 10 mmol) in EtOH (30 ml) with ice–water cooling. The reaction mixture was stirred for 5 h after which the resulting crystals were collected and recrystallized from EtOH to give the title compound (**3**) (0.40 g, 22%), m.p. 280 °C (decomp.) (Found: C, 53.3; H, 6.05; N, 23.1. $C_8H_{11}O_2N_3$ requires C, 53.03; H, 6.12; N, 23.19%); ν_{max}(KBr) 3 250, 1 650, and 1 620 cm^{-1}; $\delta_H(CDCl_3)$ 3.10–3.62 (8 H, m, CH_2 × 4), 5.56 (1 H, s, CH), 7.83 (1 H, s, NH), and 8.30 (1 H, s, NH); δ([$^2H_6$]-DMSO) 38.71, 41.01, 48.70, 56.38, 96.05, 141.50, 160.81, and 169.22; *m/z* 181 (M^+), 152, 149, and 112.

1,4,7-*Triazacycloundecane*-8,10,11-*trione* (**4**).—A solution of the dione (**3**) (0.91 g, 5 mmol) in 1M HCl (2 ml) was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to give (**5**) (1.0 g, 85%, m.p. 230–231 °C) (Found: C, 40.75; H, 6.1; N, 17.74. $C_8H_{14}ClN_3O_3$ requires C, 40.77; H, 6.0; N, 17.85); ν_{max}(KBr) 3 150, 3 050, 1 685, and 1 640 cm^{-1}; δ_C([$^2H_6$]-DMSO) 40.83, 45.84, 52.40, 56.98, 58.90, 151.82, 163.93, and 172.65; *m/z* 199 (M^+), 181, and 152.

Conversion of the Triene (**4**) *into Hexahydropyrazino*[1,2-d][1,4]*diazepine*-1,9-*dione* (**6**)·HCl.—A solution of the trione (**4**) (0.24 g, 1 mmol) was hydrogenated with 5% Pd/C (100 mg) for 4 h. After removal of the catalyst, the solution was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to afford (**6**)·HCl (0.19 g, 79%), m.p. 245–246 °C (Found: C, 43.75; H, 6.55; N, 19.25. $C_8H_{13}O_2N_3$·HCl requires C, 43.74; H, 6.42; N, 19.13); ν_{max}(KBr) 3 320, 3 250, 1 670, and 1 650 cm^{-1}; $\delta_H(D_2O)$ 3.23 (1 H, dd, CHHCO, *J* 10,17 Hz), 3.33 (1 H, d, CH*H*CO, *J* 17 Hz), 3.52–3.58 (8 H, m, CH_2 × 4), 4.44 (1 H, d, CH, *J* 10 Hz); $\delta_C(D_2O)$ 37.07, 39.57, 40.62, 52.91, 60.00, 62.75, 167.37, 178.02; *m/z* 183 (M^+), 155, and 113.

Hydrogenation of (**3**) *to* (**6**).—A solution of the dione (**3**) (0.36 g, 2 mmol) in water 20 ml was hydrogenated over 10% $Pd(OH)_2/C$ for 12 h. The reaction mixture was filtered off and evaporated under reduced pressure. The residue was recrystallized from EtOH to give (**6**) (0.33 g, 90%), m.p. 259–260 °C), which was identical with the compound produced by treatment of (**6**)·HCl with a basic ion exchange resin, Duolite 161 (OH^- from).

References

1 G. W. Gokel, D. M. Dishong, R. A. Schultz, and V. J. Gatto, *Synthesis*, 1982, 997, and refs cited therein.
2 T. J. Atkins, J. E. Richman, and W. F. Oettle, *Org. Synthesis*, 1978, **58**, 86.
3 T. Okawara, K. Uchiyama, Y. Okamoto, T. Yamasaki, and M. Furukawa, *Chem. Pharm. Bull.*, submitted.
4 G. Cantatore and V. Borzatta, European Patent EP 294 329 (*Chem. Abstr.*, 1989, **111**, 116 279).

Paper 0/01807D
Received 23*rd April* 1990
Accepted 18*th June* 1990