PRAZIQUANTEL ANALOGUES. II.[1] SYNTHESIS OF 4-OXO-OCTAHYDRO-PYRAZINO[1′,2′:1,2]PYRIDO[3,4-*b*]- AND -[4,3-*b*]INDOLES

Nativitat Valls*, Víctor M. Segarra, Xavier López, and Joan Bosch

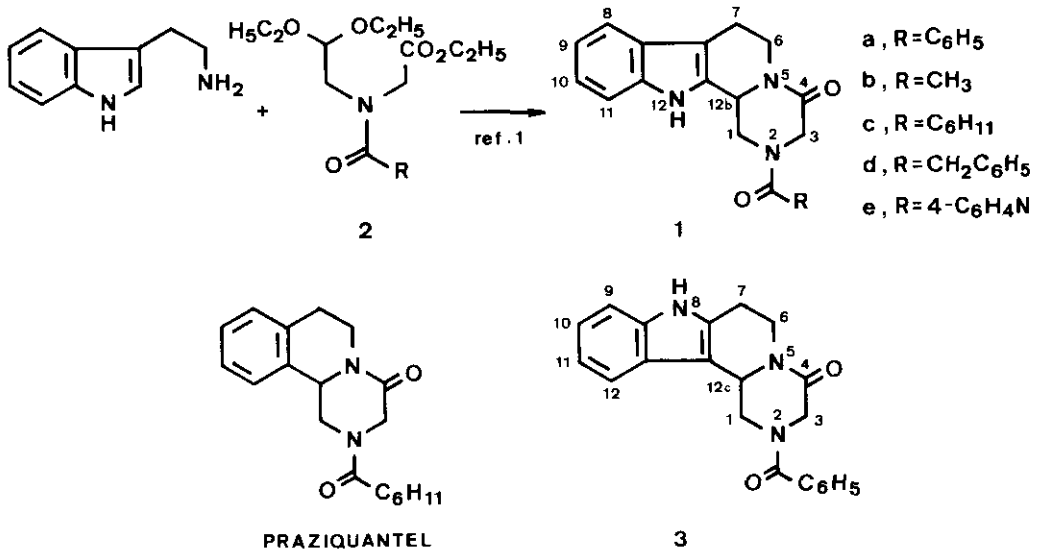
Laboratory of Organic Chemistry, Faculty of Pharmacy,

University of Barcelona, 08028-Barcelona, Spain

Abstract- The title compounds **1a** and **3** have been synthesized by cyclization of the *N*-acyliminium ion generated from 1-(3-indolylethyl)piperazinedione **7** and by Pictet-Spengler condensation between isotryptamine and ester acetal **2a**, respectively.

In a previous paper[1] we reported the synthesis of a series of 1,2,3,4,6,7,12,12b-octahydropyrazino-[1′,2′:1,2]pyrido[3,4-*b*]indoles **1** by Pictet-Spengler reaction between tryptamine and ester acetal **2** with simultaneous lactamization (Scheme 1).

Continuing our interest in preparing analogues of the anthelmintic agent praziquantel,[2] we proposed (i) to explore an alternative synthetic route to the tetracyclic system **1** based on the cyclization of *N*-acyl-

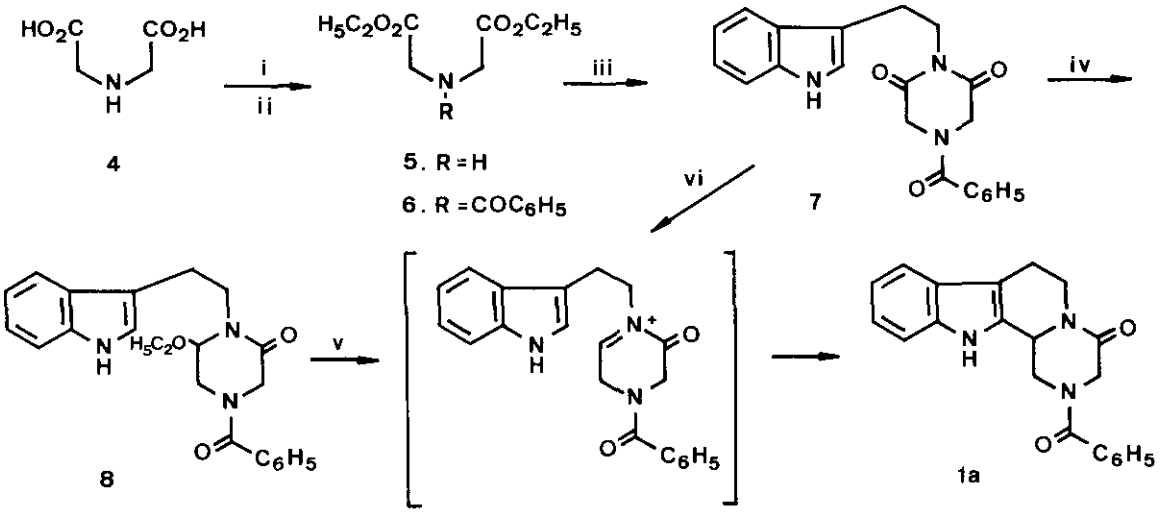


Scheme 1

iminium ions generated from appropriate cyclic imides, and (ii) to develop an efficient route for the synthesis of the regioisomeric 1,2,3,4,6,7,8,12c-octahydropyrazino[1',2':1,2]pyrido[4,3-*b*]indole system **3**.

The new reaction sequence that we have investigated for the synthesis of **1a** is depicted in Scheme 2. The key intermediate was piperazinedione **7**. Howewer, this compound could only be obtained in 31% yield[3,4] by reaction between tryptamine and amido diester **6**[6] which, in turn, was prepared in 71% yield from iminodiacetic acid (**4**) by esterification followed by benzoylation. The most significant signals in the ^{1}H-nmr spectrum of piperazinedione **7** were a singlet at δ 4.32 due to the ring methylene protons and two triplets (δ 2.83, *J*=7.8 Hz, and δ 3.87, *J*=7.8 Hz) attributable to the tryptamine chain.

The partial reduction of the imide group of **7** was accomplished in 52% yield with sodium borohydride in the presence of hydrogen chloride-ethanol[7]. Formation of the intermediate ethoxylactam **8** was evident from the ^{1}H-nmr spectrum, in which two triplets (δ 1.07, *J*=8.1 Hz, and δ 4.60, *J*=6.5 Hz) due to the methyl group and the C-6 methine proton, respectively, were observed. As expected, acid cyclization of **8** with *p*-toluenesulfonic acid[8,9] afforded pyrazinopyridoindole **1a**[10] in 56% yield. Howewer, the



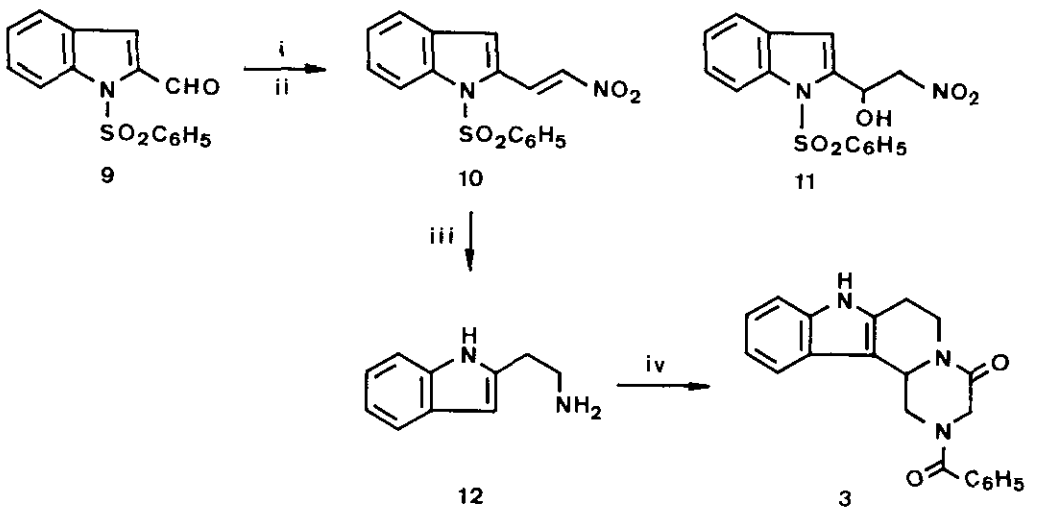
Reagents and conditions: (i) 2.5N HCl-EtOH, reflux, 2 h, 98%; (ii) C_6H_5COCl (1 eq.), 1N aq. K_2CO_3 (excess), CH_2Cl_2, rt, overnight, 71%.; (iii) tryptamine (1 eq.), 175°C, overnight; (iv) $NaBH_4$, EtOH, 2.5N HCl-EtOH (4 drops each 15 min), -5°C, 4 h, 52%; (v) HOTs (1 eq.), C_6H_6, reflux, 3 h, 56%; (vi) $NaBH_4$ (excess), EtOH, 2N HOMs-EtOH (4 drops each 15 min), -5°C, 4 h, 67%

Scheme 2

desired tetracyclic lactam **1a** was more efficiently (67% yield) obtained in a one-pot reaction, without isolating the intermediate ethoxylactam, by direct reduction-cyclization of imide **7** with sodium borohydride in the presence of methanolic methanesulfonic acid.[11]

Although this key cyclization reaction takes place in satisfactory yield, the overall yield of the reaction sequence here developed is clearly lower than that obtained by the Pictet-Spengler route.[1]

For this reason, the synthesis of the regioisomeric tetracyclic lactam **3**[12] was undertaken by the route depicted in Scheme 3, which involves a Pictet-Spengler cyclization as the key step. The required starting material, isotryptamine (**12**), was prepared in five steps from indole (57% overall yield), by a modification of the method reported by Harley-Mason.[13,14] Thus, condensation of indolecarbaldehyde **9**[15] with nitromethane under alkaline conditions[13] afforded a nearly equimolecular mixture of nitrovinylindole **10**[18] and alcohol **11**[19] that could be separated from each other. Howewer, this separation is unnecessary because when the above mixture was heated *in vacuo* in the presence of *p*-toluenesulfonic acid[20] the nitrovinylindole **10** was obtained as the sole product in 93% yield. Subsequent reduction of **10** with lithium aluminum hydride occurred with concomitant elimination of the sulfonyl group to give isotryptamine (**12**)[21] in 83% yield.



Reagents and conditions: (i) CH_3NO_2 (3.5 eq.), MeOH, 50% aq. NaOH, 0°C, 1 h, 79%; (ii) HOTs (0.04 eq.), 90°C, 12 mm Hg, 2 h, 93%; (iii) LAH, Et_2O, reflux, 7 h, 83%; (iv) **2a** (0.8 eq.), 50% aq. HOAc, reflux, 3 h, 73%.

Scheme 3

Finally, as expected, treatment of isotryptamine (12) with ester acetal **2a**[1] under Pictet-Spengler reaction conditions brought about closure of rings C and D, the latter by lactamization, in a single synthetic step to give pyrazinopyridoindole **3**[22] in 73% yield.

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2. J. Seubert, R. Pohlke, and J. Loebich, *Experientia*, 1977, **33**, 1036.
3. Compound **7**; mp 155-156°C (methanol); ms: *m/z* 36(M^+); ir (KBr):3200 (NH), 1735 and 1675 (imide C=O), 1620 (amide C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.83 (t, *J*=7.8 Hz, 2H, CH_2-In), 3.87 (t, *J*=7.8 Hz, 2H, CON-CH_2), 4.32 (s, 4H, CH_2CO), 6.7-7.5 (m, 11H, ArH and NH); ^{13}C-nmr (DMSO-d_6): 22.7 (β-C), 39.1 (α-C), 42.3-48.7 (br, 3-C and 5-C), 110.3 (3'-C), 111.1 (7'-C), 117.7 (4'-C), 118.1 (5'-C), 120.7 (6'-C), 122.5 (2'-C), 127.0 (3a'-C), 135.9 (7a'-C), 167.7 (imide C=O), 168.8 (lactam C=O).
4. Attempts to prepare **7** by heating tryptamine with *N*-benzoyliminodiacetic acid[5] were unsuccessful.
5. A. T. Fields, D. W. Porter, P. S. Callery, E. B. Harvey, and M. D. Loberg, *J. Label. Comp. Radiopharm*, 1978, **15**, 387.
6. Compound **6** was isolated as an oil and purified by "flash" chromatography (silica gel, 65:35 ether-hexane); ir (NaCl): 1740 (ester C=O), 1645 (amide C=O), 1200 (C-O) cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.20 (t, *J*=7.0 Hz, 6H, CH_3), 3.97 and 4.10 (2 s, 4H, NCH_2), 4.05 (q, *J*=7.0 Hz, 4H, CH_2), 7.17 (s, 5H, phenyl).

7. (a) J. C. Hubert, W. Steege, W. N. Speckamp, and H. O. Huisman, *Synth. Commun.*, 1971, **1**, 103; (b) J. C. Hubert, J. B. P. A. Wijnberg, and W. N. Speckamp, *Tetrahedron*, 1975, **31**, 1437.

8. T. Kametani, H. Terasawa, and M. Ihara, *J. Chem. Soc., Perkin Trans. I*, 1976, 2547.

9. Other reagents used in related cyclizations (EtOH-HCl, rt or HOAc, reflux) were ineffective.

10. This compound was found identical to that described in reference 1.

11. B. E. Maryanoff, D. F. McComsey, and B. A. Duhl-Emswiler, *J. Org. Chem.*, 1983, **48**, 5062.

12. The tetracyclic ring system present in **3** has been previously synthesized by Pictet-Spengler condensation of isotryptamine with glyoxalic acid followed by esterification of the resulting acid and elaboration of the pyrazine ring with aziridine: K. Bhandari, V. A. Murti, P. C. Jain, and N. Amand, *Indian J. Chem., Sect. B*, 1979, **17**, 246.

13. J. Harley-Mason and E. H. Parri, *J. Chem. Soc.*, 1963, 2565.

14. For other syntheses of isotryptamine, see: (a) V. Snieckus and S. Bhandari, *Tetrahedron Lett.*, 1969, 3375; (b) G. J. B. Corts and W. Th. Nauta, *Rec. Trav. Chim. Pays-Bas*, 1966, **85**, 744; (c) W. Schnidler, *Helv. Chim. Acta*, 1957, **40**, 2156.

15. 1-(Phenylsulfonyl)indole-2-carbaldehyde (**9**) was prepared in two steps from indole in 75% yield according to a modification[16] of the Gribble procedure[17].

16. M.-L. Bennasar, A. Torrens, M. Rubiralta, J. Bosch, D. S. Grierson, and H.-P. Husson, *Tetrahedron*, submitted.

17. H. G. Saulnier and G. W. Gribble, *J. Org. Chem.*, 1982, **47**, 757.

18. Compound **10**; mp 177-181°C (chloroform-hexane); ir(KBr): 1530 and 1340 (NO_2) cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 6.87 (s, 1H, 3-H indole), 6.9-7.7 (m, 9H, Ar-H and β-H vinyl), 8.00 (d, *J*=7.2 Hz, 1H, 4-H indole), 8.50 (d, *J*=13.5 Hz, 1H, α-H vinyl).

19. Compound **11**; ir (KBr): 3500 (OH), 1550 and 1350 (NO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 4.52 (dd, *J*=12.6, 9.0 Hz, 1H, CH_2NO_2), 4.93 (dd, *J*=9.0, 3.6 Hz, 1H, CH_2NO_2), 5.96 (dd, *J*=9.0, 3.6 Hz, 1H, CH), 6.58 (s, 1H, 3-H indole), 6.9-8.1 (m, 9H, Ar-H).

20. R. J. Sundberg and J. D. Bloom, *J. Org. Chem.*, 1980, **45**, 3382.

21. Compound 12; mp 96-98°C (chloroform-hexane) (Lit.[14c] mp 100-101°C); ir (KBr): 3320-3260 (NH) cm^{-1}; ^1H-nmr ($CDCl_3$): 2.83 (br s, 4H, CH_2CH_2), 3.20 (br, 2H, NH_2), 6.03 (s, 1H, 3-H indole), 6.7-7.4 (m, 5H, indole).

22. Compound 3; mp 265-270°C (methanol); Anal. Calcd for $C_{21}H_{19}N_3O_2.1/3H_2O$: C, 71.79 ; H, 5.60 ; N, 11.96 . Found: C, 71.85 ; H, 5.54 ; N, 11.92 ; ms: *m/z* 345 (M^+, 57%); ir (KBr): 3200 cm^{-1} (indole NH), 1660 and 1620 cm^{-1} (lactam and amide C=O). ^1H-nmr (200 MHz, DMSO-d_6): 2.7-3.2 (m, 4H, 1-Ha, 6-Ha, 7-CH_2), 3.8-4.6 (br, 2H, 3-CH_2), 4.6-5.0 (br, 2H, 6-He and 1-He), 5.0-5.2 (br, 1H, 12c-H), 6.5-7.4 (m, 4H, indole), 7.57 (s, 5H, phenyl), 11.15 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6): 22.9 (7-C), 37.7 (6-C), 46.4 (1-C), 49.5 (3-C), 52.6 (12c-C), 105.0 (12b-C), 111.8 (9-C), 116.8 (12-C), 118.8 (11-C), 120.7 (10-C), 124.1 (12a-C), 127.1 (3'-C i 5'-C), 128.6 (2'-C i 6'-C), 130.1 (4'-C), 133.8 (7a-C), 135.0 (1'-C), 136.0 (8a-C), 164.0 (lactam C=O), 168.9 (amide C=O).

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