

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

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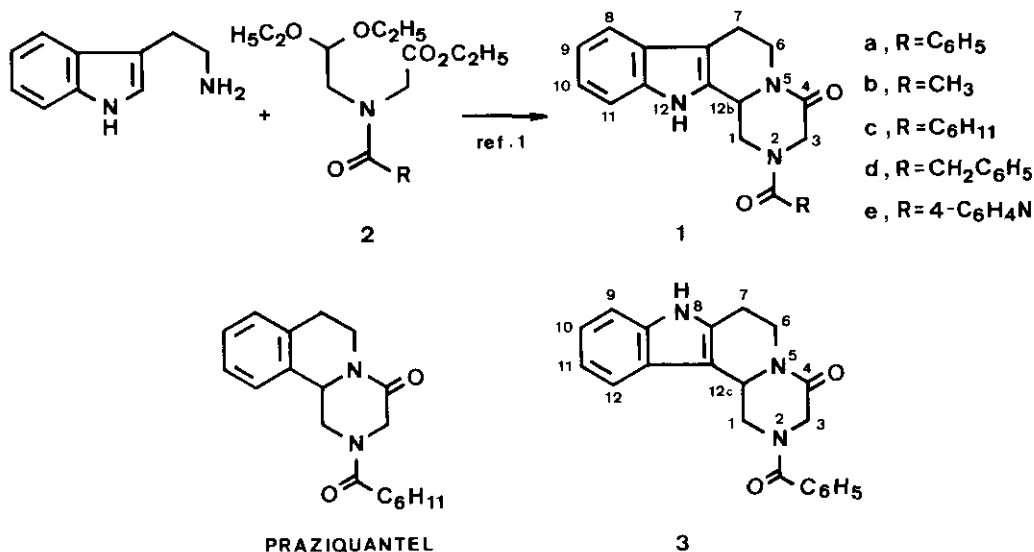
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Abstract- The title compounds **1a** and **3** have been synthesized by cyclization of the *N*-acyliminium ion generated from 1-(3-indolyylethyl)piperazinedione **7** and by Pictet-Spengler condensation between isoptryptamine and ester acetal **2a**,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

In a previous paper¹ 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-

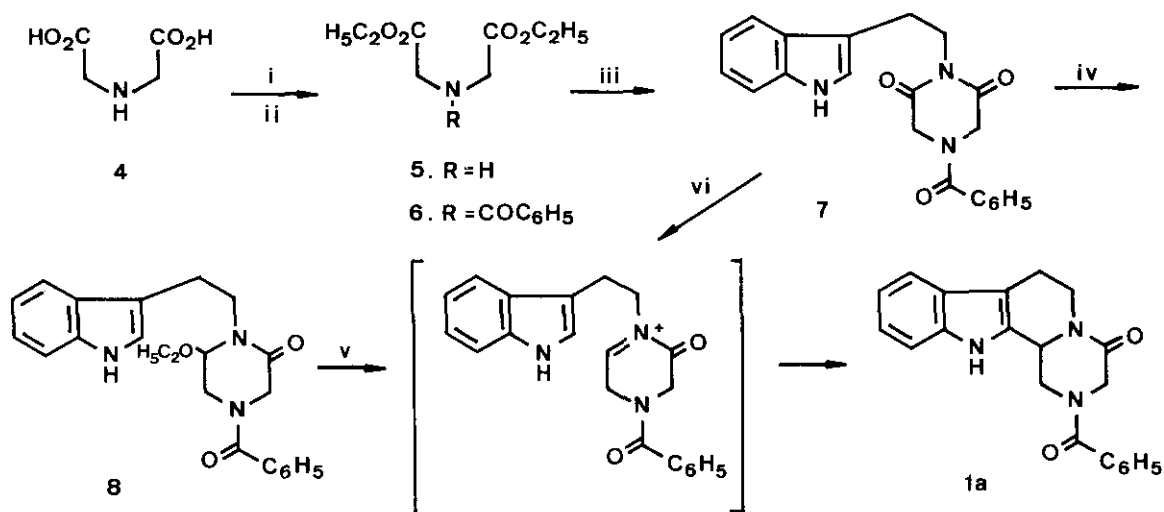


Scheme 1

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. However, this compound could only be obtained in 31% yield^{3,4} by reaction between tryptamine and amido diester 6⁶ which, in turn, was prepared in 71% yield from iminodiacetic acid (4) by esterification followed by benzoylation. The most significant signals in the ¹H-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-ethanol⁷. Formation of the intermediate ethoxylactam 8 was evident from the ¹H-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 1a¹⁰ in 56% yield. However, the



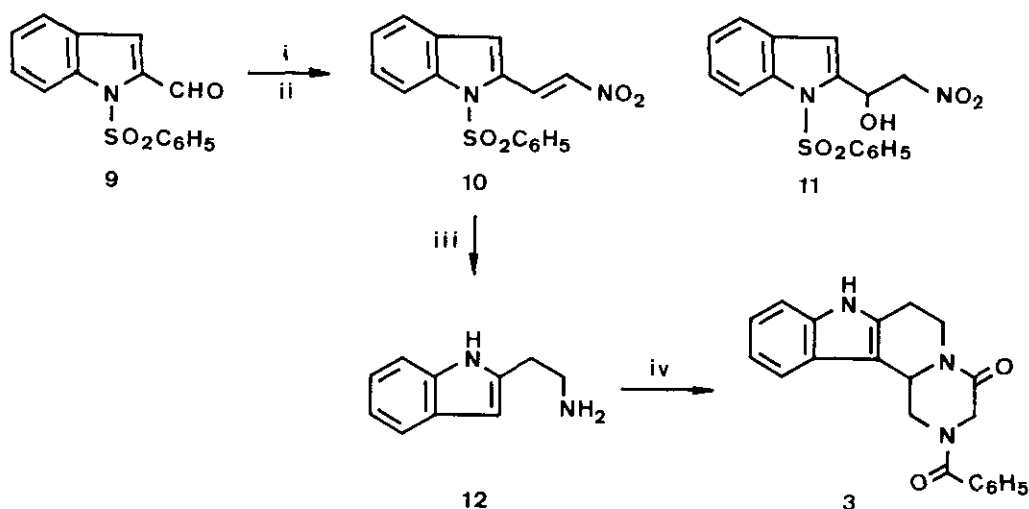
Reagents and conditions: (i) 2.5N HCl-EtOH, reflux, 2 h, 98%; (ii) C₆H₅COCl (1 eq.), 1N aq. K₂CO₃ (excess), CH₂Cl₂, rt, overnight, 71%; (iii) tryptamine (1 eq.), 175°C, overnight; (iv) NaBH₄, EtOH, 2.5N HCl-EtOH (4 drops each 15 min), -5°C, 4 h, 52%; (v) HOTs (1 eq.), C₆H₆, reflux, 3 h, 56%; (vi) NaBH₄ (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 conditions¹³ afforded a nearly equimolecular mixture of nitrovinylindole **10**¹⁸ and alcohol **11**¹⁹ that could be separated from each other. However, this separation is unnecessary because when the above mixture was heated *in vacuo* in the presence of *p*-toluenesulfonic acid²⁰ 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, Et₂O, 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.

ACKNOWLEDGEMENT

This work was supported by the "Fondo de Investigaciones Sanitarias de la Seguridad Social", Ministerio de Sanidad y Consumo, Spain (Project Number 87/1252) and by the "Comissió Interdepartamental de Recerca i Innovació Tecnològica", Generalitat de Catalunya (Project Number AR87/191).

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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; ¹H-nmr (CDCl₃): δ 2.83 (t, $J=7.8$ Hz, 2H, CH₂-In), 3.87 (t, $J=7.8$ Hz, 2H, CON-CH₂), 4.32 (s, 4H, CH₂CO), 6.7-7.5 (m, 11H, ArH and NH); ¹³C-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 acid⁵ were unsuccessful.
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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; ¹H-nmr (CDCl₃): δ 1.20 (t, $J=7.0$ Hz, 6H, CH₃), 3.97 and 4.10 (2 s, 4H, NCH₂), 4.05 (q, $J=7.0$ Hz, 4H, CH₂), 7.17 (s, 5H, phenyl).

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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.
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15. 1-(Phenylsulfonyl)indole-2-carbaldehyde (9) was prepared in two steps from indole in 75% yield according to a modification¹⁶ of the Gribble procedure¹⁷.
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18. Compound 10; mp 177-181°C (chloroform-hexane); ir(KBr): 1530 and 1340 (NO₂) cm⁻¹; ¹H-nmr (CDCl₃): 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 (NO₂) cm⁻¹; ¹H-nmr (DMSO-*d*₆): δ 4.52 (dd, *J*=12.6, 9.0 Hz, 1H, CH₂NO₂), 4.93 (dd, *J*=9.0, 3.6 Hz, 1H, CH₂NO₂), 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).
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21. Compound 12; mp 96-98°C (chloroform-hexane) (Lit.^{14c} mp 100-101°C); ir (KBr): 3320-3260 (NH) cm⁻¹; ¹H-nmr (CDCl₃): 2.83 (br s, 4H, CH₂CH₂), 3.20 (br, 2H, NH₂), 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 C₂₁H₁₉N₃O₂.1/3H₂O: 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-CH₂), 3.8-4.6 (br, 2H, 3-CH₂), 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); ¹³C-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).

Received, 3rd October, 1988