

PRAZIQUANTEL ANALOGUES. I. NEW AND SHORT SYNTHESIS OF 2-ACYL-4-
OXO-1,2,3,4,6,7,12,12b-OCTAHYDROPYRAZINO[1',2':1,2]PYRIDO[3,4-b]
INDOLES ¹

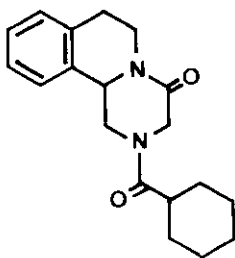
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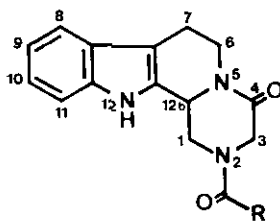
Abstract- A series of potential anthelmintic 2-acyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrazino[1',2':1,2]pyrido[3,4-b]indoles has been synthesized in high yield by Pictet-Spengler reaction between tryptamine and the appropriate *N*-acyl-*N*-(2,2-diethoxyethyl)glycine ethyl ester.

Diseases caused by helminthic infections are of great importance in human and veterinary medicine.² Praziquantel³⁻⁵ is a pyrazino[2,1-a]isoquinoline derivative⁶ which exhibits an excellent activity and tolerance in experimental animals infected with *Schistosomae* and a variety of tapeworms, as well as a remarkable activity against all species of *Schistosomae* pathogenic to man and a wide range of cestodes. It has been claimed that praziquantel seems to meet most of the requirements of an ideal antiparasitic agent for use in human and veterinary medicine.⁷ In this paper we report a short and efficient synthesis (three steps from aminoacetaldehyde diethyl acetal, in 46-63% overall yield) of a series of 2-acyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrazino[1',2':1,2]pyrido[3,4-b]indoles ¹, which can be considered as praziquantel analogues by substitution of benzene ring by indole.

In spite of the fact that the indole nucleus is present in a great number of alkaloids having the tetrahydro- β -carboline moiety, to our knowledge there are no



PRAZIQUANTEL



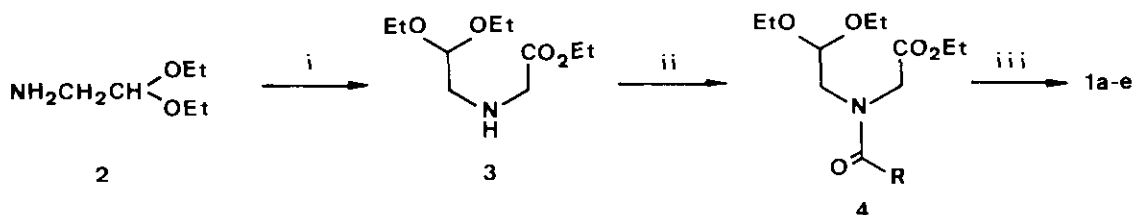
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- a. R = CH₃
- b. R = C₆H₅
- c. R = C₆H₁₁
- d. R = 4-C₅H₄N
- e. R = C₆H₅CH₂

natural products containing the octahydropyrazino[1',2':1,2]pyrido[3,4-b]indole system. Only three compounds possessing this tetracyclic ring system have been synthesized, by alternative routes that imply the construction of ring D in the last step from 1-carboxy- (or ethoxycarbonyl)-1,2,3,4-tetrahydro- β -carbolines.⁸⁻¹⁰ However, by the reported procedures it is not possible to introduce the 4-oxo substituent present in praziquantel.

The key step of our synthesis consists in the Pictet-Spengler reaction^{11,12} between tryptamine and an *N*-acyl-*N*-(2,2-diethoxyethyl)glycine ethyl ester, with simultaneous closure of ring D by lactamization.

Thus, treatment of ethyl 2-bromoacetate with aminoacetaldehyde diethyl acetal (**2**) in *N,N*-dimethylformamide at room temperature gave *N*-(2,2-diethoxyethyl)glycine ethyl ester (**3**) in 85% yield.¹³ The intermediates **4a-c** and **4e** were prepared by Schotten-Baumann acylation of the glycine derivative **3** with the appropriate acyl chloride. In turn, isonicotinoyl derivative **4d** was more conveniently obtained by treatment of the secondary amine **3** with isonicotinic anhydride in chloroform-triethylamine. All acylations were carried out overnight at room temperature in nearly quantitative yield. Carboxamides **4a-e** exhibited a characteristic ir absorption at 1645-1660 cm^{-1} and 1735-1745 cm^{-1} due to the amido and ester carbonyl groups respectively. Finally, Pictet-Spengler condensation of acetals **4a-e** with tryptamine was effected using 50% aqueous acetic acid as the solvent, at reflux for 2-3 h. The crystalline pyrazinopyridoindoles **1a-e** were obtained in 59-81% yield. The elemental analysis and the spectroscopic data were in accordance with the assigned structures. Thus, the ir spectra showed the strain of indole N-H bond between 3150



a. $\text{R} = \text{CH}_3$; b. $\text{R} = \text{C}_6\text{H}_5$; c. $\text{R} = \text{C}_6\text{H}_{11}$; d. $4\text{-C}_5\text{H}_4\text{N}$; e. $\text{C}_6\text{H}_5\text{CH}_2$

(i) $\text{BrCH}_2\text{CO}_2\text{Et}$ (0.2 eq), *N,N*-dimethylformamide, r. t., overnight; (ii) acyl chloride (1eq): CH_3COCl , $\text{C}_6\text{H}_5\text{COCl}$, $\text{C}_6\text{H}_{11}\text{COCl}$, $\text{C}_6\text{H}_5\text{CH}_2\text{COCl}$, 1N K_2CO_3 (excess), water-methylene chloride, r. t., overnight or $(4\text{-C}_5\text{H}_4\text{NCO})_2\text{O}$ (2 eq), triethylamine-chloroform, r. t., overnight; (iii) tryptamine (1.3 eq), 50% water acetic acid, reflux, 2-3 h.

and 3300 cm^{-1} (Table 1) and the presence of two amido carbonyl groups between 1610 and 1660 cm^{-1} .

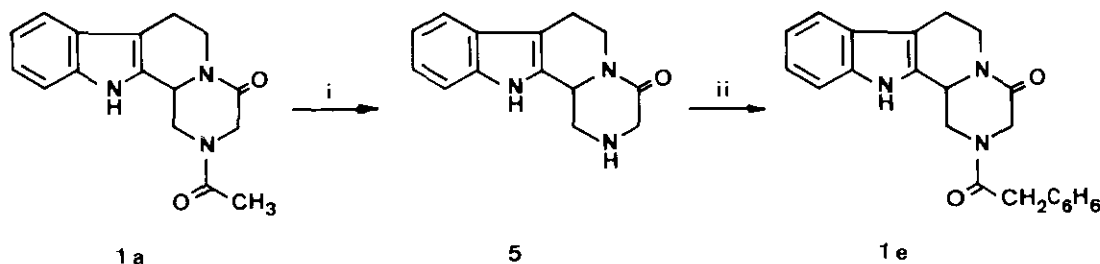
Table 1

Comp.	mp ^a (°C)	yield (%)	ir(KBr), ν max(cm^{-1})		% Analysis, Calcd. (Found)		
			NH indole	CO-NH	C	H	N
1a	260-4	59	3190	1630, 1660	67.84 (68.05)	6.01 (6.01)	14.84 (14.97)
1b	282-7	81	3190	1610, 1660	73.04 (72.94)	5.54 (5.39)	12.17 (12.16)
1c	260-7	77	3300	1620, 1640	71.79 (71.93)	7.12 (7.39)	11.96 (11.96)
1d	280-8	68	3150	1645, 1660	69.36 (69.37)	5.20 (5.20)	16.18 (16.19)
1e	128-30	71	3220	1615, 1645	70.02 (69.95)	6.10 (6.55)	11.14 (11.30) ^b
5	235-8	85	3270	1630	69.71 (69.73)	6.22 (6.33)	17.43 (17.43)

^aCompounds 1a-e were crystallized from absolute methanol and compound 5 from absolute ethanol.

^bElementary analysis of compound 1e was calculated for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2 \cdot \text{H}_2\text{O}$.

On the other hand, hydrolysis of the acetyl derivative 1a with 2N hydrochloric acid afforded the tetracyclic amine 5 in 85% yield. This secondary amine could allow the further introduction of radicals of greater pharmacological use on the nitrogen atom of the piperazine ring. As example, acylation of 5 with phenacyl chloride gave 1e in 76% yield.



(i) 2N HCl, reflux, 3h; (ii) $\text{C}_6\text{H}_5\text{CH}_2\text{COCl}$ (1.1 eq), 1N K_2CO_3 (excess), water-chloroform, r.t., overnight.

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