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]

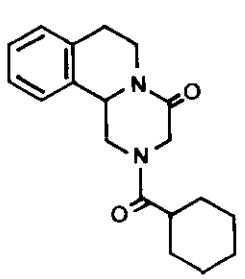
Nativitat Valls, Víctor M. Segarra, and Joan Bosch

Department of Organic Chemistry, Faculty of Pharmacy,
University of Barcelona, 08028-Barcelona, Spain

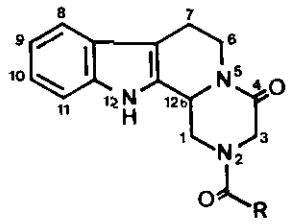
Abstract- A series of potential anthelmintic 2-acyl-4-oxo-1,2,3,4,6,7,12,12b-*octahydropyrazino*[1',2':1,2]*pyrido*[3,4-*b*]*indoles* has been synthesized in high yield by Pictet-Spengler reaction between tryptamine and the appropriate *N*-acyl-*N*-(2,2-diethoxyethyl)glycine ethyl ester.

Diseases caused by helmintic infections are of great importance in human and veterinary medicine.[2] Praziquantel[3-5] is a pyrazino[2,1-*a*]isoquinoline derivative[6] 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



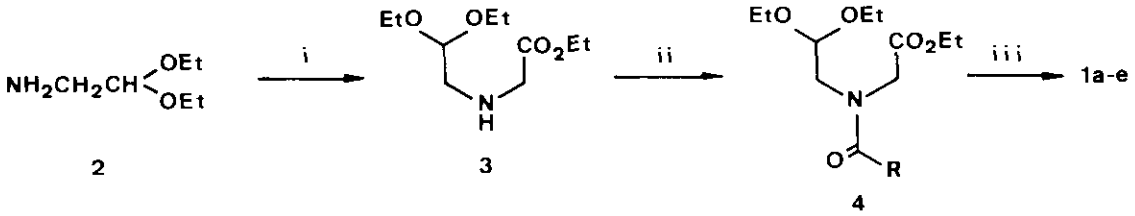
1

a. R = CH_3
b. R = C_6H_5
c. R = C_6H_{11}
d. R = 4-C_5H_4N
e. R = $C_6H_5CH_2$

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] Howewer, 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. R = CH_3; **b.** R = C_6H_5; **c.** R = C_6H_{11}; **d.** 4-C_5H_4N; **e.** $C_6H_5CH_2$

(i) $BrCH_2CO_2Et$ (0.2 eq), *N*,*N*-dimethylformamide, r. t., overnight; (ii) acyl chloride (1eq): CH_3COCl, C_6H_5COCl, $C_6H_{11}COCl$, $C_6H_5CH_2COCl$, 1N K_2CO_3 (excess), water-methylene chloride, r. t., overnight or $(4\text{-}C_5H_4NCO)_2O$ (2 eq), triethylamine-chloroform, r. t., overnight; (iii) tryptamine (1.3 eq), 50% water acetic acid, reflux, 2-3 h.

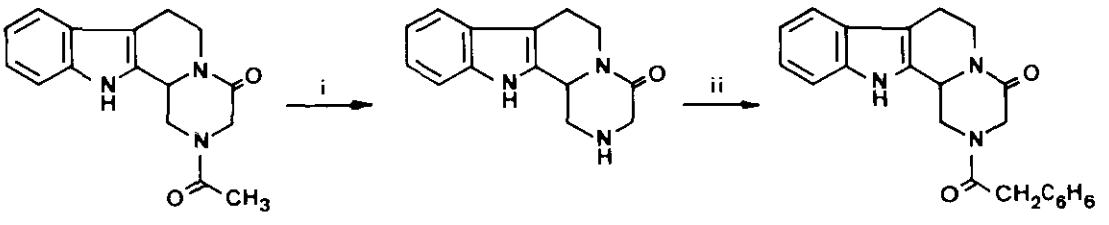
and 3300 cm^{-1} (Table 1) and the presence of two amido carbonyl groups between 1610 and 1660 cm^{-1}.

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)

[a]Compounds 1a-e were crystallized from absolute methanol and compound 5 from absolute ethanol.
[b]Elementary analysis of compound 1e was calculated for $C_{22}H_{21}N_3O_2.H_2O$.

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.



1a 5 1e

(i) 2N HCl, reflux, 3h; (ii) $C_6H_5CH_2COCl$ (1.1 eq), 1N K_2CO_3 (excess), water-chloroform, r.t., overnight.

ACKNOWLEDGEMENT

We are grateful to the "Direcció General d'Ensenyament Universitari, Generalitat de Catalunya", for financial support of this work.

REFERENCES

1. This work was presented in a preliminary form at the IV Congreso Nacional de la Sociedad Española de Química Terapéutica, Sitges (Spain), 1985.
2. a) P. J. Islip, Progress in Drug Research, 1973, 17, 241. b) R. B. Burrows, Progress in Drug Research, 1973, 17, 108.
3. J. Seubert, R. Pohlke, and F. Loebich, Experientia, 1977, 33, 1036.
4. D. Frehel and J. P. Maffrand, Heterocycles, 1983, 20, 1731.
5. a) J. Seubert, H. Thomas, and P. Andrews, Ger. Offen., 1975, 2,362,539. Chem. Abstr., 1976, 84, 5007b. b) R. Pohlke, F. Loebich, J. Seubert, H. Thomas, and P. Andrews, Ger. Offen., 1973, 2,331,713; Chem. Abstr., 1975, 82, 156369f. c) J. Seubert, Ger. Offen., 1974, 2,457,971; Chem. Abstr., 1976, 85, 160160k. d) J. Seubert, Ger. Offen., 1975, 2,504,250; Chem. Abstr., 1976, 85, 142999m. e) J. Seubert, R. Pohlke, H. Thomas, and P. Andrews, Ger. Offen., 1974, 2,441,261; Chem. Abstr., 1976, 85, 5687u.
6. For a review on isoquinoline drugs, see: A. Brossi, Heterocycles, 1978, 11, 521.
7. "Biltricide Symposium on African Schistosomiasis", Nairobi, 1980, Arzneim. Forsch. (Drug Res.), 1981, 31, 535.
8. S. Archer, U.S., 1969, 3,468,890; Chem. Abstr., 1969, 71, P112977w.
9. G. de Stevens and H. M. Blatter, U.S., 1964, 3,151,116; Chem. Abstr., 1964, 61, 16080e.
10. G. de Stevens and M. Sklar, J. Org. Chem., 1963, 28, 3210.
11. a) W. M. Whaley and T. R. Govidanchari, Org. React., 1951, 6, 151. b) F. Ungemach and J. M. Cook, Heterocycles, 1978, 9, 1089. c) F. Ungemach, M. Di Pierro, R. Weber, and J. M. Cook, J. Org. Chem., 1981, 46, 164.
12. Atta-ur-Rahman, J. A. Beisler, and J. Harley-Mason, Tetrahedron, 1980, 36, 1063.
13. G. Lowe and B. S. Sproat, J. Biol. Chem., 1980, 255, 3944.

Received, 25th November, 1985