

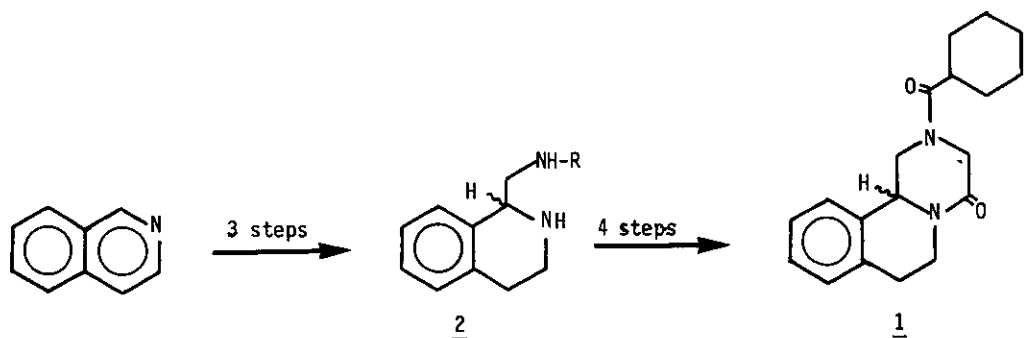
NEW SYNTHESIS OF PRAZIQUANTEL : 2-(CYCLOHEXYLCARBONYL)-1,2,3,6,7,11b-HEXAHYDRO-4H-PYRAZINO[2,1-a]ISOQUINOLIN-4-ONE

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Abstract - This paper describes two different synthetic pathways for praziquantel, a new broad spectrum schistosomicide and cestocide. Easy to apply on an industrial scale, they involve a selective reduction of 4-acyl-1-phenethylpiperazine-2,6-dione in 4-acyl-6-hydroxy-1-phenethylpiperazin-2-one, the cyclisation of which in acidic medium gives tricyclic compounds 2-acyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one.

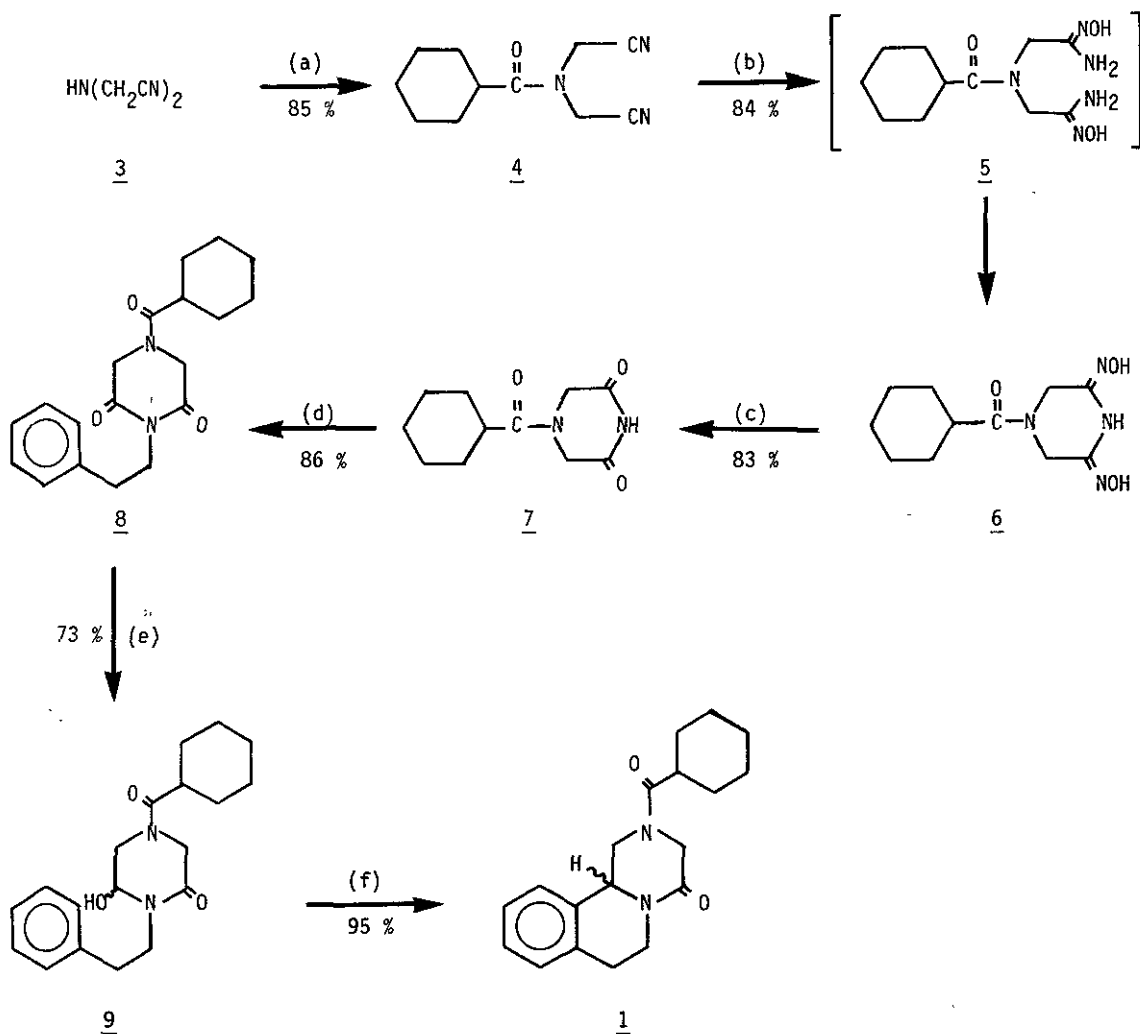
Bilharziasis, a serious parasitic disease, very widespread in many tropical and subtropical countries of Africa, China and Brazil, infects more than 200 million people according to WHO¹. Praziquantel² (1), a well-known anticestodal compound exhibits remarkable activity against all three species of schistosomes affecting man. Its pharmacological profile³ allows praziquantel to be considered as an exceptional chemotherapeutic agent for eradication of bilharziasis. In spite of the short treatment⁴, it would still be too expensive for mass eradication of endemic schistosomiasis. Consequently, it seemed desirable to consider a less expensive mode of synthesis for praziquantel. Several pathways are described in the literature⁵ and in patents⁶⁻¹¹ (Merck of Darmstadt and Bayer of Leverkusen). The synthetic pathway, which seems to us to be the best published method for production on an industrial scale, uses isoquinoline as the raw material. It uses the formation of the piperazine cycle from 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline 2 (Scheme 1).

Scheme 1



We present here a different approach, easier to apply on an industrial scale¹². The key step of this synthesis consists in selectively reducing the imide function of piperazine-2,6-dione 8 in hydroxyimide 9, followed by cyclisation in acidic medium (Scheme 2).

Scheme 2



(a) : $\text{C}_6\text{H}_{11}\text{COCl}$ (1.1 eq.), K_2CO_3 (1.5 eq.), water-methylene chloride, R.T., 2 h.

(b) : NH_2OH , HCl (4 eq.), K_2CO_3 (1 eq.), water-methanol, reflux, 2.5 h.

(c) : NaNO_2 (3 eq.), water-acetic acid, 0°C , 24 h.

(d) : CH_3ONa (1.1 eq.), dimethylformamide, R.T., 1 h ; $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{I}$ (1 eq.), 80°C , 5 h.

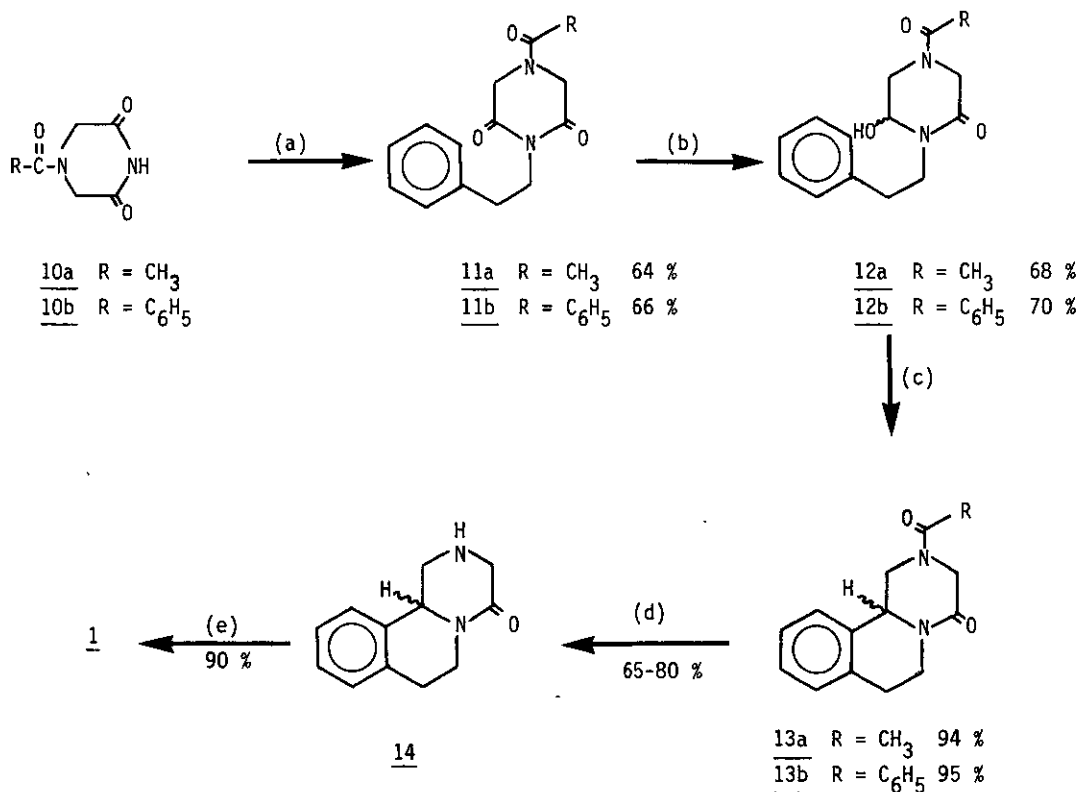
(e) : $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (1.1 eq.), ethanol, 0°C , 1 h. ; NaBH_4 (5-fold molar excess), 0°C , 45 mn.

(f) : 12N HCl , 0°C , overnight.

4-(Cyclohexylcarbonyl)-piperazine-2,6-dione (7) was prepared according to a slightly modified Elvidge method¹³: acylation of iminodiacetonitrile (3) with cyclohexylcarbonyl chloride gives compound 4. Cyclocondensation of 4 with hydroxylamine produces 4-(cyclohexylcarbonyl)-2,6-dihydroxyiminopiperazine (6) via the diamidoxime 5. Diazotation of 6 gives 4-(cyclohexylcarbonyl)-piperazine-2,6-dione (7). Alkylation of 7 with phenethyl iodide leads to 4-(cyclohexylcarbonyl)-1-phenethylpiperazine-2,6-dione (8). The selective reduction¹⁴ of the imide function in 8, according to the Atta-ur-Rahman method¹⁵, gives 4-(cyclohexylcarbonyl)-6-hydroxy-1-phenethylpiperazin-2-one (9). Cyclisation of 9 in acidic medium produces praziquantel(1)(Scheme 2).

A different access way to praziquantel consists in preparing tricyclic compounds 13a and 13b from 4-acetyl-piperazine-2,6-dione(10a) or 4-benzoylpiperazine-2,6-dione (10b)¹³, according to scheme 3.

Scheme 3



(a) : CH₃ONa (1.1 eq.), dimethylformamide, R.T., 1 h ; C₆H₅CH₂CH₂I, 120°C, 5 h.

(b) : CuCl₂, 2H₂O (1.1 eq.), ethanol, 0°C, 1 h ; NaBH₄ (5-fold molar excess), 0°C, 45 min.

(c) : 12N HCl, 0°C, overnight.

(d) : N HCl, reflux, 3 h or 70 % aq. H₃PO₄, reflux, 3 h.

(e) : C₆H₁₁COCl (1.1 eq.), NEt₃ (1.1 eq.), dimethoxyethane, R.T., 15 h.

Table I

Compound	mp (°C) Solvent	IR(KBr) $\nu_{\max}$ (cm ⁻¹)	¹ H NMR (Solvent) ; δ (ppm) ; J (Hz) s : singlet ; t : triplet ; m : multiplet
<u>8</u>	90 (C ₆ H ₁₂)	1645,1680,1735	(CDCl ₃) : 1.53(m,10H,(CH ₂) ₅); 2.40(m,1H,CH ₂ CHCO); 2.76(t,J=7,2H,CH ₂ C ₆ H ₅); 4.00(t,J=7,2H,N-CH ₂); 4.33(s,4H,NCH ₂ CO); 7.20(s,5H arom.)
<u>9</u>	134 (C ₆ H ₁₂)	1620,1650,3250	(CDCl ₃) : 1.46(m,10H,(CH ₂) ₅); 2.40(m,1H,CH ₂ CHCO); 2.86(t,J=7,2H,CH ₂ C ₆ H ₅); 3.06-4.80(m,7H,NCH ₂ CONCH ₂ , NCH ₂ CHOH); 7.20(m,5H arom.)
<u>4</u>	82 (C ₆ H ₁₂ - AcOEt)	1650,2240	(CDCl ₃) : 1.46(m,10H,(CH ₂) ₅) ; 2.46(m,1H,CH ₂ CHCO) ; 4.40(s,4H,NCH ₂ CN)
<u>6</u>	>260 (EtOH - H ₂ O)	1620,1660,3260,3400	(DMSOd ₆) : 1.48(m,10H,(CH ₂) ₅) ; 2.62(m,1H,CH ₂ CHCO) ; 4.30(s,4H,NCH ₂)
<u>7</u>	186 (EtOH)	1650,1685,1730,1740, 3100,3200	(DMSOd ₆) : 1.47(m,10H,(CH ₂) ₅) ; 2.59(m,1H,CH ₂ CHCO) ; 4.26(s,4H,NCH ₂ CO)
<u>11a</u>	130 (iPr ₂ O - AcOEt)	1630,1690,1740	(CDCl ₃) : 2.06(s,3H,COCH ₃); 2.76(t,J=7,2H,CH ₂ C ₆ H ₅); 3.94(t,J=7,2H,NCH ₂ CO); 4.34(s,4H,NCH ₂ CO); 7.02(s,5H arom.)
<u>11b</u>	102 (C ₆ H ₁₂ - AcOEt)	1650,1680,1735	(CDCl ₃) : 2.83(t,J=7,2H,CH ₂ C ₆ H ₅); 4.00(t,J=7,2H,NCH ₂ CO); 4.40(s,4H,NCH ₂ CO); 7.20(s,5H arom.); 7.37(s,5H arom.)
<u>12a</u>	oil	1625,1660,3300	(CDCl ₃) : 2.03(s,3H,COCH ₃); 2.83-4.93(m,9H,NCH ₂ CHOH,NCH ₂ CONHCH ₂ CH ₂ C ₆ H ₅) ; 7.18(s,5H arom.)
<u>12b</u>	oil	1630,1660,3200	(CDCl ₃) : 2.86-4.77(m,9H,NCH ₂ CONHCH ₂ CH ₂ C ₆ H ₅ , NCH ₂ CHOH) ; 7.14(s,5H arom.) ; 7.32(s,5H arom.)

* Satisfactory elementary analyses for the synthesised compounds were obtained.

Deacetylation (N HCl, reflux) or debenzoylation (70 % aqueous H_3PO_4 , reflux) produces the tricyclic compound 14, easily acylated with cyclohexylcarbonyl chloride to give praziquantel(1). Table I summarises the spectral characteristics of the new synthesised products in our laboratories.

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