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

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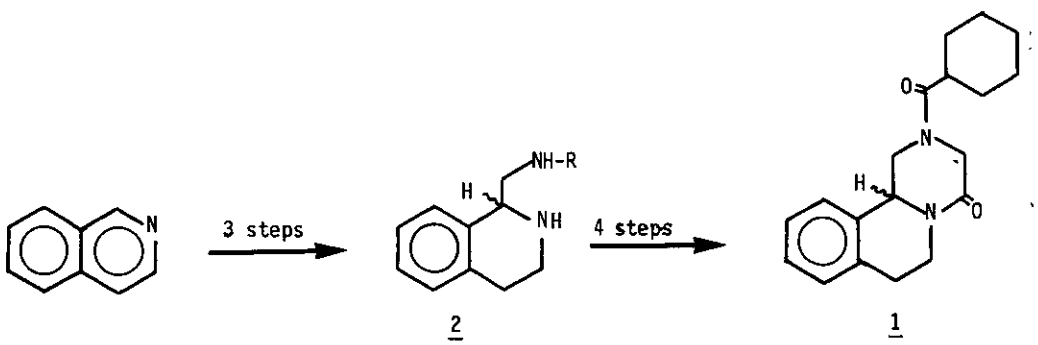
Abstract - This paper describes two different synthetic pathways for praziquantel, a new broad spectrum schistosomicide and cestocide. Easy to apply on an industrial scale, they involve a selective reduction of 4-acyl-1-phenethylpiperazine-2,6-dione in 4-acyl-6-hydroxy-1-phenethylpiperazin-2-one, the cyclisation of which in acidic medium gives tricyclic compounds 2-acyl-1,2,3,6,7,11b-hexahydro-4H-pyrazin [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 WHO[1]. Praziquantel[2] (1), a well-known anticestodal compound exhibits remarkable activity against all three species of schistosomas affecting man. Its pharmacological profile[3] allows praziquantel to be considered as an exceptional chemotherapeutic agent for eradication of bilharziasis. In spite of the short treatment[4], 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 literature[5] and in patents[6-11] (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).

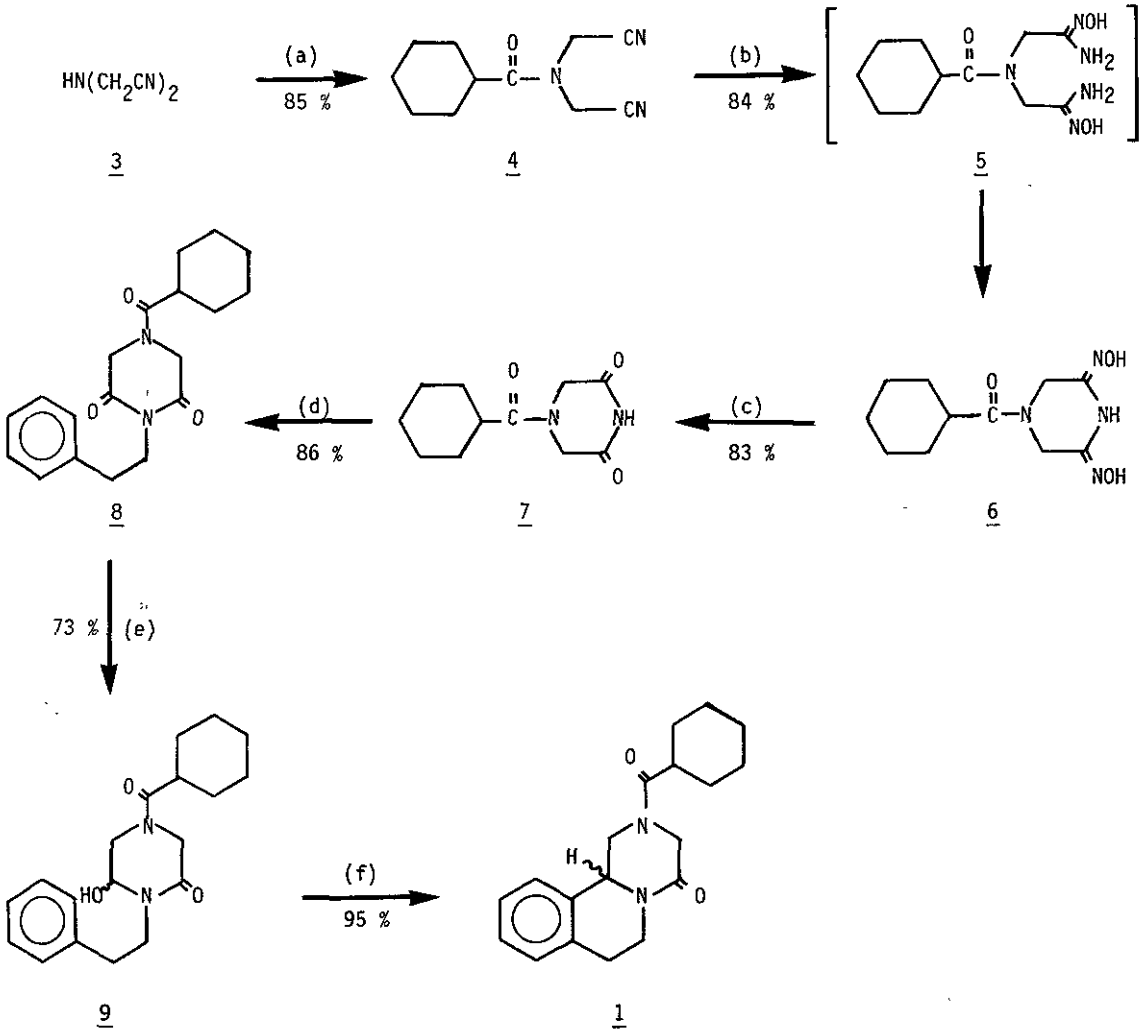
Scheme 1



2 1

We present here a different approach, easier to apply on an industrial scale[12]. 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

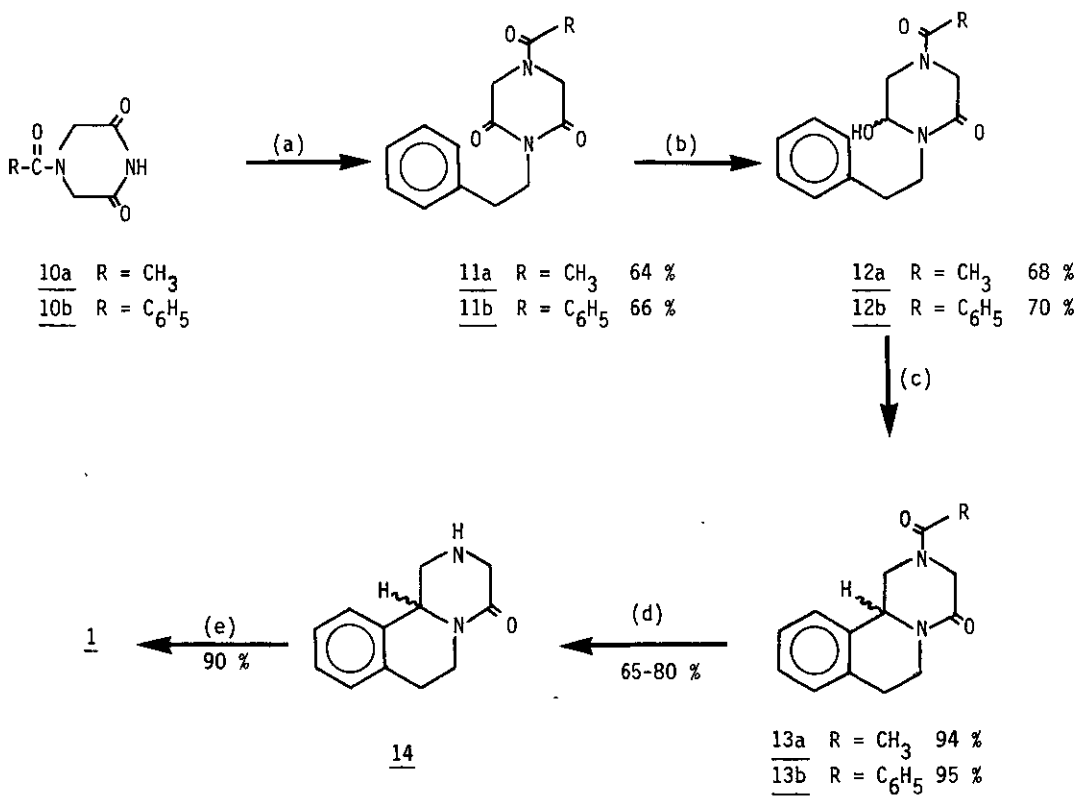


(a) : $C_6H_{11}COCl$(1.1 eq.), K_2CO_3(1.5 eq.) , water-methylene chloride, R.T., 2 h.
(b) : NH_2OH, HCl(4 eq.), K_2CO_3(1 eq.), water-methanol, reflux, 2.5 h.
(c) : $NaNO_2$ (3 eq.), water-acetic acid, 0°C, 24 h.
(d) : CH_3ONa(1.1 eq.), dimethylformamide, R.T., 1 h ; $C_6H_5CH_2CH_2I$ (1 eq.), 80°C, 5 h.
(e) : $CuCl_2$, $2H_2O$ (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 method[13]: 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 reduction[14] of the imide function in 8, according to the Atta-ur-Rahman method[15], 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



10a R = CH_3
10b R = C_6H_5

11a R = CH_3 64 %
11b R = C_6H_5 66 %

12a R = CH_3 68 %
12b R = C_6H_5 70 %

13a R = CH_3 94 %
13b R = C_6H_5 95 %

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(a) : CH_3ONa (1.1 eq.), dimethylformamide, R.T., 1 h ; $C_6H_5CH_2CH_2I$, 120°C, 5 h.
(b) : $CuCl_2$, $2H_2O$ (1.1 eq.), ethanol, 0°C, 1 h ; $NaBH_4$ (5-fold molar excess), 0°C, 45 min.
(c) : 12N HCl, 0°C, overnight.
(d) : N HCl,reflux, 3 h or 70 % aq. H_3PO_4, reflux, 3 h.
(e) : $C_6H_{11}COCl$ (1.1 eq.), NEt_3 (1.1 eq.), dimethoxyethane, R.T., 15 h.

Table I

* Compound	mp (°C) Solvent	IR(KBr) ν max (cm^{-1})	H^1 NMR (Solvent) ; δ(ppm) ; J (Hz) s : singlet ; t : triplet ; m : multiplet
8	90 (C_6H_{12})	1645,1680,1735	($CDCl_3$) : 1.53(m,10H,$(CH_2)_5$); 2.40(m,1H,CH_2CHCO);2.76(t,J=7,2H,$CH_2C_6H_5$); 4.00(t,J=7,2H,N-CH_2); 4.33(s,4H,NCH_2CO); 7.20(s,5H arom.)
9	134 (C_6H_{12})	1620,1650,3250	($CDCl_3$) : 1.46(m,10H,$(CH_2)_5$); 2.40(m,1H,CH_2CHCO);2.86(t,J=7,2H,$CH_2C_6H_5$); 3.06-4.80(m,7H,NCH_2CONCH_2, NCH_2CHOH); 7.20(m,5H arom.)
4	82 (C_6H_{12} - AcOEt)	1650,2240	($CDCl_3$) : 1.46(m,10H,$(CH_2)_5$) ; 2.46(m,1H,CH_2CHCO) ; 4.40(s,4H,NCH_2CN)
6	>260 (EtOH - H_2O)	1620,1660,3260,3400	($DMSOd_6$): 1.48(m,10H,$(CH_2)_5$) ; 2.62(m,1H,CH_2CHCO) ; 4.30(s,4H,NCH_2)
7	186 (EtOH)	1650,1685,1730,1740, 3100,3200	($DMSOd_6$): 1.47(m,10H,$(CH_2)_5$); 2.59(m,1H,CH_2CHCO) ; 4.26(s,4H,NCH_2CO)
11a	130 (iPr_2O - AcOEt)	1630,1690,1740	($CDCl_3$) : 2.06(s,3H,$COCH_3$);2.76(t,J=7,2H,$CH_2C_6H_5$);3.94(t,J=7,2H;NCH_2CO); 4.34(s,4H,NCH_2CO);7.02(s,5H arom.)
11b	102 (C_6H_{12} - AcOEt)	1650,1680,1735	($CDCl_3$) : 2.83(t,J=7,2H,$CH_2C_6H_5$);4.00(t,J=7,2H,NCH_2CO);4.40(s,4H, NCH_2CO);7.20(s,5H arom.);7.37(s,5H arom.)
12a	oil	1625,1660,3300	($CDCl_3$) : 2.03(s,3H,$COCH_3$);2.83-4.93(m,9H,NCH_2CHOH,$NCH_2CONHCH_2CH_2C_6H_5$) ; 7.18(s,5H arom.)
12b	oil	1630,1660,3200	($CDCl_3$) : 2.86-4.77(m,9H,$NCH_2CONHCH_2CH_2C_6H_5$, NCH_2CHOH) ; 7.14(s,5H arom.) ; 7.32(s,5H arom.)

* Satisfactory elementary analyses for the synthetised 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 synthetised products in our laboratories.

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