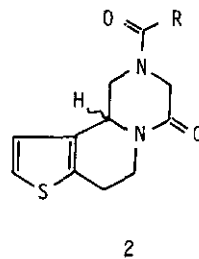
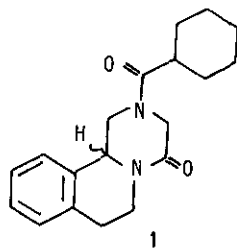


SYNTHESIS OF THE NEW TRICYCLIC SYSTEM
THIENO [3',2' : 3,4] PYRIDO [1,2-a] PYRAZIN-4-ONE

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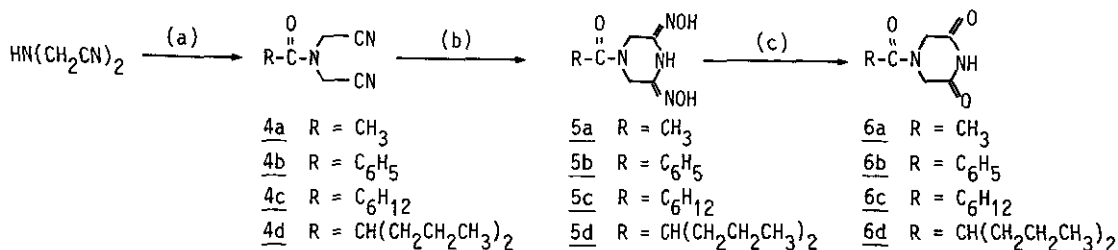
Abstract - The new tricyclic system thieno[3'2' : 3,4] pyrido(1,2-a) pyrazin-4-one, a thiophenic isostere of the heterocyclic system pyrazino-(1,2-a)isoquinolin-4-one is synthesised by cyclisation in acidic medium from 4-acyl-6-hydroxy-1-[2-(2-thienyl)ethyl] piperazine-2-one. Those hydroxyimides result from selective reduction of corresponding piperazine-2,6-diones.

In a recent paper¹, we described an original synthesis of praziquantel, a very potent schistosomicide, the structure of which points to the pyrazino(1,2-a)isoquinolin-4-one system (1). We present in this paper, the synthesis² of a thiophenic isostere of praziquantel and some analogs, the structure of which belongs to the new heterocyclic system thieno[3'2' : 3,4] pyrido(1,2-a) pyrazin-4-one (2).



Intermediate 4-acylpiperazine-2,6-diones 6a-6d were prepared according to the slightly modified¹ Elvidge method³ (scheme 1).

Scheme 1

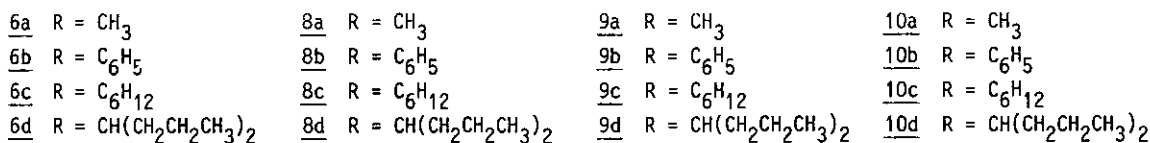
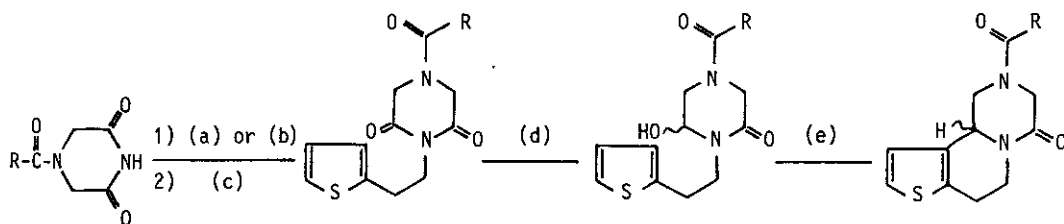


(a) : RCOCl (1.1 eq.), K₂CO₃ (1.5 eq.), water-methylene chloride, r.t., 2 h.

(b) : NH₂OH.HCl (4 eq.), K₂CO₃ (1 eq.), water-methanol, reflux, 2 h.

(c) : NaNO₂ (3 eq.), water-acetic acid, 0°C, 24 h.

Scheme 2



(a) NaH (1.05 eq.), dimethoxyethane, r.t., 2 h.

(b) CH₃ONa (1.05 eq.), dimethylformamide, r.t., 2 h.

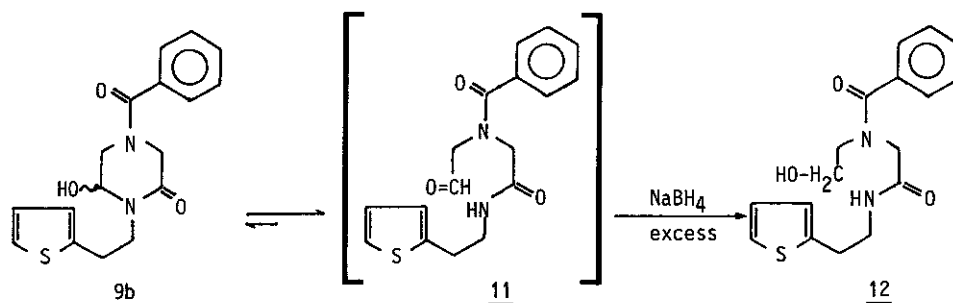
(c) -CH₂CH₂OSO₂C₆H₅, dimethylformamide, reflux, 2 h.

(d) CuCl₂·2H₂O (1.05 eq.), ethanol, 0°C, 1 h; NaBH₄ (5-fold molar excess), 0°C, 0.5 h.

(e) 12N HCl, 0°C, overnight.

During our first experiments of selective reduction of the imide 8b, we obtained the reduction product 12 from the aldehyde 11 which results from the cleavage of the hydroxyimide 9b (scheme 3).

Scheme 3



We have reduced this secondary reaction by maintaining rigorously the temperature of the reaction medium between 0° and -5°C (it is advisable to add the reducing agent slowly) and by destroying immediately the excess of reducing agent by acetone as soon as the starting imide has completely disappeared from the reaction medium.

The spectral characteristics of alcohol 12 are presented in the table II.

Compounds 4a-4c, 5a-5c, 6a-6c were described previously^{1,2}. Compounds 4d, 5d, 6d are described in the table I.

Table I

Compound	mp°C (solvent)	Yield %	IR (KBr, film) ν max (cm ⁻¹)	H ¹ NMR 60 MHz (solvent); δ ppm; J(Hz); s: singlet; t: triplet; m: multiplet
<u>4d</u>	oil	86	1670, 2240 (weak)	CDCl ₃ : 1.30 (m, 14H, $\text{CH}_2\text{CH}_2\text{CH}_3$) ₂ ; 2.67 (m, 1H, $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)$) ₂ ; 4.40 (s, 4H, NCH_2CN)
<u>5d</u>	240 (EtOH-MeOH)	54	1630, 1670, 3140, 3260, 3420	DMSO-d ₆ : 1.14 (m, 14H, $\text{CH}_2\text{CH}_2\text{CH}_3$) ₂ ; 2.73 (m, 1H, $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)$) ₂ ; 4.43 (s, 4H, NCH_2CN)
<u>6d</u>	90 (Et ₂ O-C ₆ H ₁₂)	93	1640, 1700, 1740, 3100, 3220	CDCl ₃ : 1.20 (m, 14H, $\text{CH}_2\text{CH}_2\text{CH}_3$) ₂ ; 2.67 (m, 1H, $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)$) ₂ ; 4.40 (s, 4H, NCH_2CN)

N-alkylation of 4-acylpiperazine-2,6-diones by [2-(2-thienyl) ethyl] benzenesulfonate⁴, in strongly basic medium gives 4-acyl-1-[2-(2-thienyl) ethyl] piperazine-2,6-diones 8a-8d (scheme 2). Selective reduction of the imide function in hydroxyimide, by 5-fold molar excess sodium borohydride in presence of metallic catalyst (CuCl₂ · 2H₂O), involves complexation of imidic nitrogen and/or oxygen from one of carbonyl groups with metallic ions which renders carbonyl groups more electrophilic for the attack by hydride ions⁶. Thus 4-acyl-1-[2-(2-thienyl) ethyl] piperazine-2,6-diones 8a-8d give 4-acyl-6-hydroxy-1-[2-(2-thienyl) ethyl] piperazin-2-ones 9a-9d. Cyclisation in acidic medium of these hydroxyimides gives tricyclic compounds 10a-10d (scheme 2).

Table II

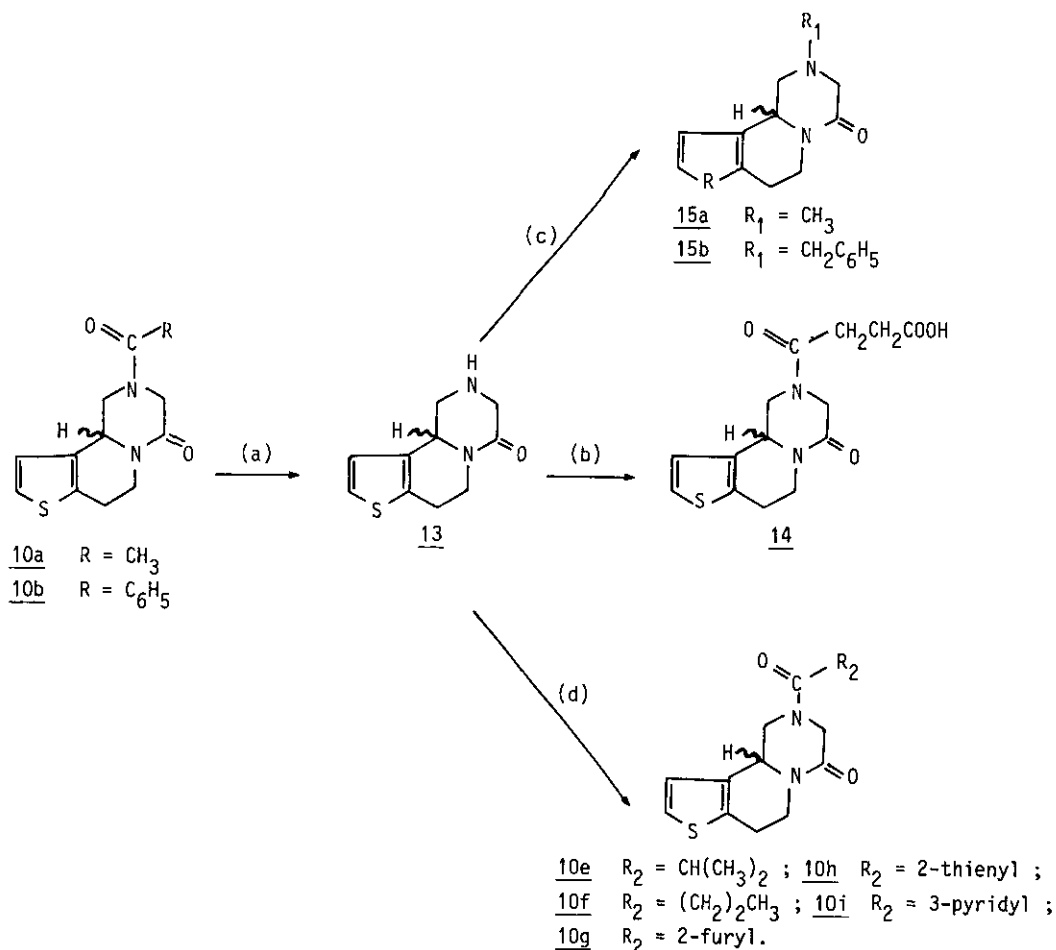
Compound	mp °C solvent	Yield %	IR (KBr) $\nu_{\max}$ (cm ⁻¹)	¹ H NMR (60 MHz) ; thiophen protons system (3) ; δ ppm ; d : doublet ; m : multiplet
<u>10a</u>	178 (CH ₃ CN)	87	1640, 1660	7.10 (m) ; 7.37 (d)
<u>10b</u>	120 (ACOEt)	81	1630, 1650	6.73 (m) ; 7.10 (d)
<u>10c</u>	160 (ACOEt)	85	1640, 1650	6.80 (d) ; 7.13 (d)
<u>10d</u>	82 (ACOEt)	76	1640, 1650	6.90 (d) ; 7.20 (d)
<u>10e</u>	184 (CH ₃ CN)	91	1640, 1655	6.77 (d) ; 7.07 (d)
<u>10f</u>	160 (CH ₃ CN)	80	1630, 1650	6.83 (d) ; 7.17 (d)
<u>10g</u>	114 (ACOEt)	91	1620, 1640	6.80 (d) ; 7.13 (d)
<u>10h</u>	136 (CH ₃ CN)	94	1605, 1640	6.80 (d) ; 7.13 (d)
<u>10i</u>	128 (CH ₃ CN)	75	1625, 1650	6.73 (m) ; 7.13 (d)
<u>13*</u>	236 (EtOH)	61 (1) 74 (2)	1645	6.60 (d) ; 7.01 (d)
<u>14</u>	184 (EtOH)	91	1610, 1655, 1665	7.00 (m) ; 7.26 (d)
<u>15a**</u>	148 (EtOH)	91	1660	6.86 (d) ; 7.27 (d)
<u>15b*</u>	170 (EtOH)	78	1660	6.90 (d) ; 7.33 (d)

• Hydrochloride ** Maleate (1) 10a hydrolysis (2) 10b hydrolysis (3) J = 5.5 Hz for doublets

Satisfactory elementary analyses for the synthesised compounds are obtained.

Another access way to the final tricyclic compounds consists in acylating the amine 13 by an acyl chloride or a carboxylic acid anhydride (scheme 4). This amine 13 is obtained by deacylation in strongly acidic medium of compounds 10a (N HCl) or 10b (70 % aqueous H_3PO_4). Acylation of 13 with different acyl chlorides gives derivatives 10e-10i. Acylation with succinic anhydride gives the acid 14. Besides, N-alkylation of tricyclic amine 13 by methyl iodide or benzyl iodide gives the compounds 15a or 15b. These different transformations are summarized in the scheme 4.

Scheme 4



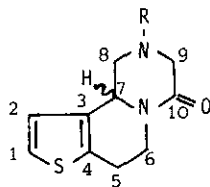
(a) N HCl, reflux, 3 h or 70 % aq. H_3PO_4 , reflux, 3h.

(b) Succinic anhydride (1.01 eq.), dimethoxyethane, reflux, 5 h.

(c) R_2COCl (1.1 eq.), NEt_3 (1.1 eq.), dimethoxyethane, r.t, overnight.

(d) R_1I (1.05 eq.), K_2CO_3 (1.05 eq.), dimethylformamide, 80°C, 3 h.

Table III
¹³C NMR Data : ¹³C Chemical shifts and assignments



Compound	C ₁	C ₂	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈	C ₉	C ₁₀	Others
<u>10a</u>	123.75	124.60	135.34	131.88	24.59	44.07	54.39	39.22	49.78	164.29	169.09 ; 21.13
<u>10b</u>	123.67	124.60	135.59	131.70	24.65	46.56	54.51	39.28	50.02	164.53	170.36 ; 134.49 ; 127.52 ; 128.85 ; 130.79
<u>10c</u>	123.69	124.60	135.40	131.95	24.65	44.25	54.57	39.22	49.05	164.72	174.79 ; 40.73 ; 29.20 ; 25.62
<u>10d</u>	123.93	124.60	155.34	132.01	24.65	44.34	54.69	39.40	49.35	164.59	175.84 ; 41.10 ; 35.09 ; 20.77 ; 14.15
<u>10e</u>	123.63	124.60	135.22	131.76	24.59	44.37	54.45	39.16	48.99	161.66	175.58 ; 30.36 ; 19.19
<u>10f</u>	123.31	124.60	135.34	131.82	24.59	44.13	54.45	39.22	49.17	164.45	171.45 ; 35.08 ; 18.28 ; 13.79
<u>10g</u>	123.63	124.60	135.53	131.64	24.59	46.38	54.39	39.16	49.29	164.72	158.59 ; 147.36 ; 117.90 ; 111.30 ; 144.63
<u>10h</u>	123.69	124.66	135.51	131.64	24.65	46.92	54.27	39.22	50.44	164.41	176.19 ; 130.19 ; 127.27
<u>10i</u>	123.57	124.34	135.58	131.46	24.65	45.89	54.45	39.35	50.38	164.11	167.37 ; 130.37 ; 148.51 ; 151.85 ; 123.69 ; 135.58
<u>13</u>	124.19	124.86	134.93	131.35	24.00	44.03	51.37	38.20	44.27	161.33	-
<u>14</u>	122.96	123.75	135.50	131.16	23.68	43.40	53.42	38.18	49.96	169.45	173.70 ; 28.28 ; 27.02
<u>15a</u>	123.27	124.06	134.92	133.16	24.65	57.78	54.98	38.67	58.94	166.35	44.36
<u>15b</u>	124.07	125.41	135.42	130.93	24.18	38.56	51.31	51.67*	51.31*	160.91	58.77 ; 129.30 ; 129.29 ; 131.84 ; 130.20

Chemical shifts in ppm downfield from TMS - Solvent : deuteriochloroform
 * The values signed are interchangeable

The physico-chemical characteristics of new compounds are summarized in the tables II and III.

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