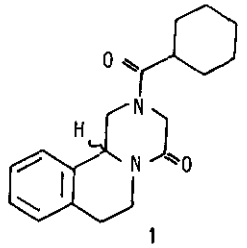
SYNTESIS OF THE NEW TRICYCLIC SYSTEM THIENO [3',2' : 3,4] PYRIDO [1,2-a] PYRAZIN-4-ONE

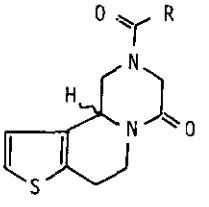
Daniel Fréhel* and Jean-Pierre Maffrand
Sanofi Recherche, Ligne Hémobiologie
195 route d'Espagne, 31036 Toulouse, France

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] piperazin-2-one. Those hydroxyimides result from selective reduction of corresponding piperazine-2,6-diones.

In a recent paper[1], 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 synthesis[2] 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).



1



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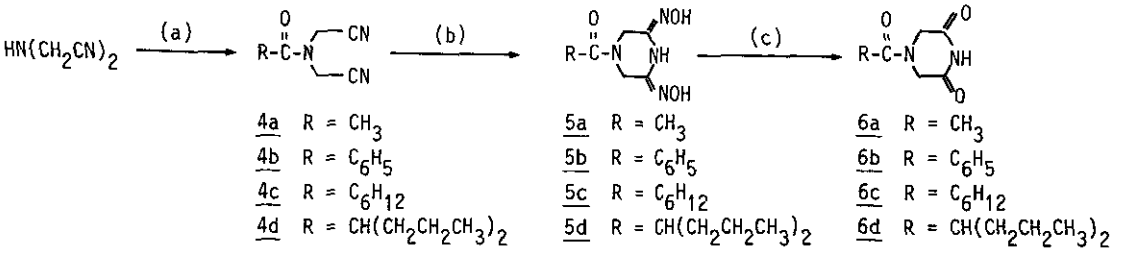
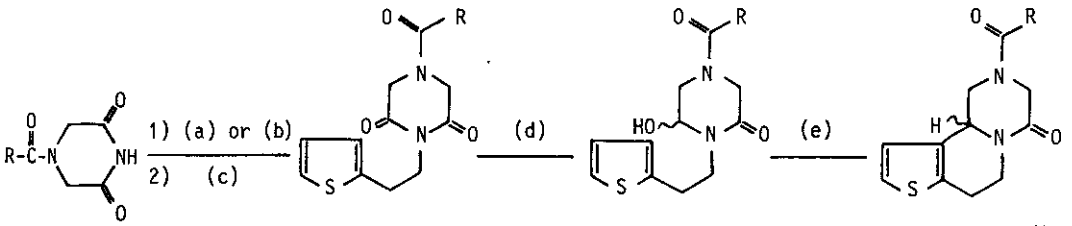
Intermediate 4-acylpiperazine-2,6-diones 6a-6d were prepared according to the slightly modified[1] Elvidge method[3] (scheme 1).

Scheme 1



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

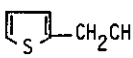
Scheme 2



6a	R = CH_3	8a	R = CH_3	9a	R = CH_3	10a	R = CH_3
6b	R = C_6H_5	8b	R = C_6H_5	9b	R = C_6H_5	10b	R = C_6H_5
6c	R = C_6H_{12}	8c	R = C_6H_{12}	9c	R = C_6H_{12}	10c	R = C_6H_{12}
6d	R = $CH(CH_2CH_2CH_3)_2$	8d	R = $CH(CH_2CH_2CH_3)_2$	9d	R = $CH(CH_2CH_2CH_3)_2$	10d	R = $CH(CH_2CH_2CH_3)_2$

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

(b) CH_3ONa (1.05 eq.), dimethylformamide, r.t., 2 h.

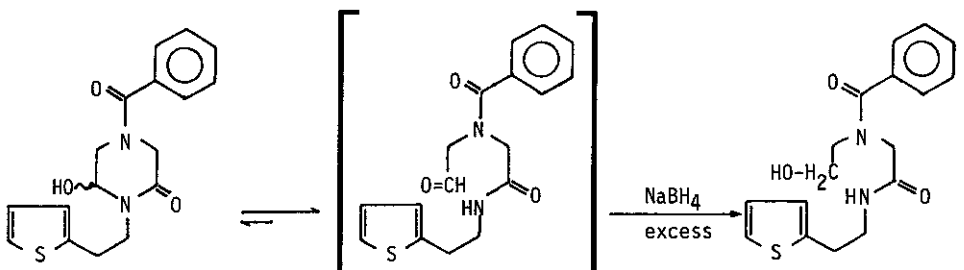
(c)  , dimethylformamide, reflux, 2 h.

(d) $CuCl_2.2H_2O$ (1.05 eq.), ethanol, 0°C, 1 h ; $NaBH_4$ (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



9b 11 12

We have reduced this secondary reaction by maintaining rigourously 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^1NMR 60 MHz (solvent) ; δ ppm ; J(Hz) ; s : singlet ; t : triplet ; m : multiplet
4d	oil	86	1670, 2240 (weak)	$CDCl_3$: 1.30 (m, 14H, $\underline{CH_2CH_2CH_3})_2$) 2.67 (m, 1H, $\underline{CH}(CH_2CH_2CH_3)_2$); 4.40 (s, 4H, $N\underline{CH_2}CN$)
5d	240 (EtOH-MeOH)	54	1630, 1670, 3140, 3260, 3420	$DMSO-d_6$: 1.14 (m, 14H, $\underline{CH_2CH_2CH_3})_2$) 2.73 (m, 1H, $\underline{CH}(CH_2CH_2CH_3)_2$ 4.43 (s, 4H, $N\underline{CH_2}CN$)
6d	90 (Et_2O-C_6H_{12})	93	1640, 1700, 1740, 3100, 3220	$CDCl_3$: 1.20 (m, 14H, $\underline{CH_2CH_2CH_3})_2$) 2.67 (m, 1H, $\underline{CH}(CH_2CH_2CH_3)_2$); 4.40 (s, 4H, $N\underline{CH_2}CN$)

N-alkylation of 4-acylpiperazine-2,6-diones by /2-(2-thienyl) ethyl/ benzenesulfonate[4], 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 ($CuCl_2 . 2H_2O$), 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 ions[6]. 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

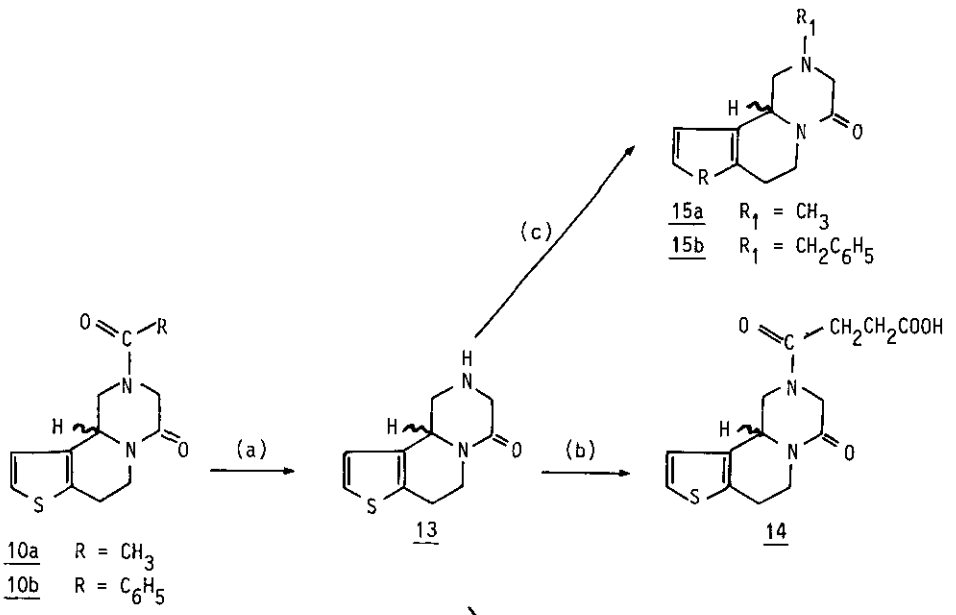
Compound	mp °C solvent	Yield %	IR (KBr) νmax (cm^{-1})	H^1NMR (60 MHz) ; thiophen protons system (3) ; δppm ; d : doublet ; m : multiplet
10a	178 (CH_3CN)	87	1640, 1660	7.10 (m) ; 7.37 (d)
10b	120 (ACOEt)	81	1630, 1650	6.73 (m) ; 7.10 (d)
10c	160 (ACOEt)	85	1640, 1650	6.80 (d) ; 7.13 (d)
10d	82 (ACOEt)	76	1640, 1650	6.90 (d) ; 7.20 (d)
10e	184 (CH_3CN)	91	1640, 1655	6.77 (d) ; 7.07 (d)
10f	160 (CH_3CN)	80	1630, 1650	6.83 (d) ; 7.17 (d)
10g	114 (ACOEt)	91	1620, 1640	6.80 (d) ; 7.13 (d)
10h	136 (CH_3CN)	94	1605, 1640	6.80 (d) ; 7.13 (d)
10i	128 (CH_3CN)	75	1625, 1650	6.73 (m) ; 7.13 (d)
13*	236 (EtOH)	61 (1) 74 (2)	1645	6.60 (d) ; 7.01 (d)
14	184 (EtOH)	91	1610, 1655, 1665	7.00 (m) ; 7.26 (d)
15a**	148 (EtOH)	91	1660	6.86 (d) ; 7.27 (d)
15b*	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



10a R = CH_3
10b R = C_6H_5

13

14

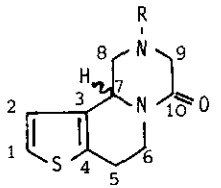
15a R_1 = CH_3
15b R_1 = $CH_2C_6H_5$

10e R_2 = $CH(CH_3)_2$; 10h R_2 = 2-thienyl ;
10f R_2 = $(CH_2)_2CH_3$; 10i R_2 = 3-pyridyl ;
10g R_2 = 2-furyl.

(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

^{13}C NMR Data : ^{13}C 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
10a	123.75	124.60	135.34	131.88	24.59	44.07	54.39	39.22	49.78	164.29	169.09 ; 21.13
10b	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
10c	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
10d	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
10e	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
10f	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
10g	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
10h	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
10i	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
13	124.19	124.86	134.93	131.35	24.00	44.03	51.37	38.20	44.27	161.33	-
14	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
15a	123.27	124.06	134.92	133.16	24.65	57.78	54.98	38.67	58.94	166.35	44.36
15b	124.07	125.41	135.42	13093	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 : deuterochloroform

* The values signed are interchangeable

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

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