One-Pot Synthesis of Novel Spiro-Annelated Pyrrole-Containing Heterocyclic Systems from Suitable Synthons

M. Artico*, S. Massa, A. Mai and R. Silvestri

Dipartimento di Studi Farmaceutici,
Università degli studi di Roma
"La Sapienza", P. le A. Moro 5,
00185 Roma, Italy

G. Stefancich

Dipartimento di Scienze Farmaceutiche,
Università di Trieste, P. le Europa 1,
34127 Trieste, Italy

Received September 12, 1991

New tetracyclic systems containing a pyrrolobenzodiazepine **5** or a pyrrolobenzotriazepine **6** moiety bounded by a spiro linkage to the piperidine nucleus are described. They have been synthesized by a simple reaction involving the interaction between proper aromatic amines and 4-oxopiperidines substituted or not at the 1-position in the presence of maleic acid as a catalyst. The synthesis of spiropyrrolo[1,2-*a*]quinoxaline-2,4'-piperidine **7** and its 1'-acyl derivatives by the same procedure is also reported.

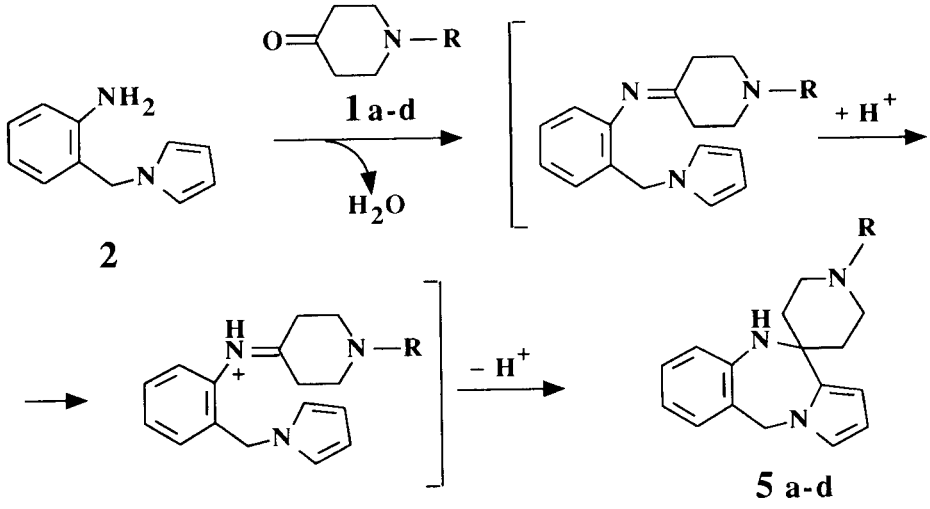
J. Heterocyclic Chem., **29**, 241 (1992).

The discovery of buspirone and related psychotropic agents, some of which are non-benzodiazepine anxiolytic drugs that have revolutionized the drug therapy of anxiety, has renewed the efforts in the synthetic chemical field with the aim to obtain new spiro derivatives active on the central nervous system. Buspirone and spiroxatrine were found to act as anxiolytic agents and tiospirone was showing good antipsychotic effects [1-4].

Although the pharmacological profile of buspirone analogues is largely determined by the dominant influence of the heteroarylpiperazine moiety, it is also evident that the spirobicyclic system of such compounds plays a fundamental role as a pharmacophoric group for displaying promising biological activities.

Our continuing interest in the chemistry of pyrrolobenzodiazepines and related systems prompted us to synthe-

Scheme 1

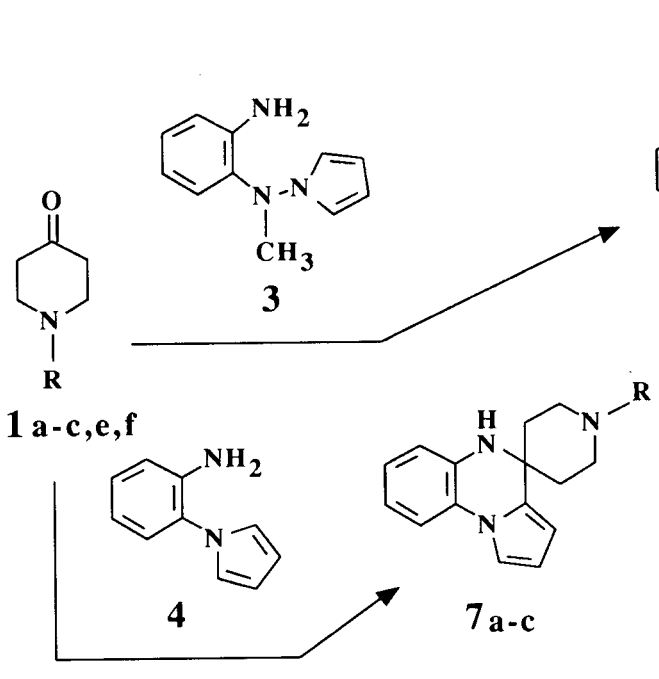


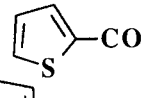
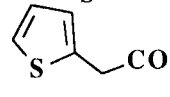
1,5	R
a	H
b	CH_3
c	$C_6H_5CH_2$
d	$4\text{-}NO_2C_6H_4$

size some spiro annelated compounds containing a buspirone-like piperidine moiety bounded by the spiro linkage to the pyrrolobenzodiazepine nucleus. The new spiro derivatives could create great interest as modulating agents of the psychotropic effects because of their potential ability to interact with the active sites of both benzodiazepines and buspirone-like congeners.

Intramolecular cyclization (Bischler-Napieralski, Pictet-Spengler and other reactions) as a method of choice to build tricyclic pyrrolobenzodiazepines and related systems is well documented in the literature [5-10]. We therefore used the Pictet-Spengler method for the synthesis of new spiro annelated heterocyclic systems containing a pyrrole moiety using as synthons 1-substituted 4-oxopiperidines **1**

Scheme 2



1,6,7	R
1b,6a	CH_3
1c,6b	$C_6H_5CH_2$
1a,7a	H
1e,7b	
1f,7c	

Scheme 3

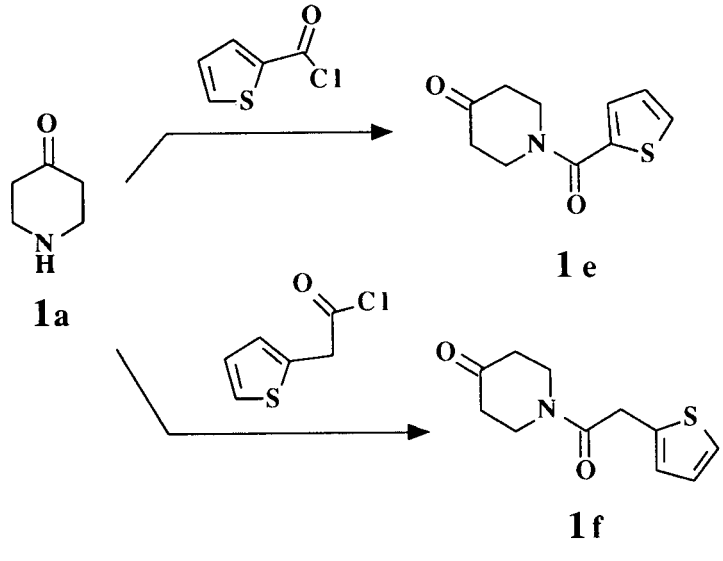


Table 1

Chemical and Physical Data of Spiro Derivatives **5**, **6** and **7**

Product	Reaction time (hours)	Yield (%)	Formula (mol weight)	Mp (°C) (solvent)	Elemental Analyses % Calcd./Found C	H	N	Cl	S
5a	3	64	$C_{16}H_{35}Cl_4N_3O_6$ [a]	194-197	50.53	7.16	11.05	18.65	–
			(380.3)	(ethanol)	50.27	7.15	11.09	18.79	–
5b	3	79	$C_{17}H_{25}Cl_4N_3$[b]	183-185	60.00	6.81	12.35	20.84	–
			(340.3)	(ethanol)	60.13	6.80	12.17	20.90	–
5c	3	73	$C_{23}H_{25}N_3$	135-136	80.43	7.34	12.23	–	–
			(343.5)	(cyclohexane)	80.18	7.47	12.35	–	–
5d	3	55	$C_{22}H_{22}N_4O_2$	199-200	70.57	5.92	14.96	–	–
			(374.5)	(choloroform)	70.69	5.87	15.09	–	–
6a	4	42	$C_{17}H_{22}N_4$	137-140	72.30	7.85	19.84	–	–
			(282.4)	(ligroin)	72.27	7.84	19.73	–	–
6b [c]	4	63	$C_{25}H_{28}N_4O_4$	196-198	66.94	6.29	12.49	–	–
			(448.5)	(absolute ethanol)	67.15	6.23	12.29	–	–
7a [d]	1	100	$C_{15}H_{17}N_3$	295-297 dec	75.28	7.16	17.56	–	–
			(239.3)	(ethanol)	75.43	7.14	17.43	–	–
7b	1	89	$C_{20}H_{19}N_3OS$	187-189	68.54	5.75	11.99	–	9.15
			(350.4)	(ethyl acetate)	68.70	5.82	11.72	–	8.99
7c	1	100	$C_{21}H_{21}N_3OS$	95-97	69.39	5.82	11.56	–	8.82
			(363.5)	(benzene/cyclohexane)	69.52	5.77	11.48	–	8.78

[a] As dihydrochloride trihydrate. [b] As dihydrochloride. [c] As oxalate. [d] Lit [16].

Table 2

Spectroscopic Data of Spiro Derivatives **5**, **6** and **7**

Product	IR ν cm^{-1}	Solvent	^{1}H-NMR δ (ppm)
5a	3320 (NH)	deuteriochloroform	1.83 (s, 1H, NH piperidine, exchangeable with deuterium oxide), 1.97-2.12 (m, 4H, H-3,5 piperidine), 2.39-3.03 (m, 4H, H-2,6 piperidine), 4.12 (s, 1H, NH diazepine, exchangeable with deuterium oxide), 5.10 (s, 2H, CH_2), 5.98 (m, 2H, H-3,4 pyrrole), 6.53 (m, 1H, H-5 pyrrole), 6.68-7.15 (m, 4H, benzene protons)
5b	3360 (NH)	deuteriochloroform	2.05-2.83 (m, 11H, piperidine and CH_3 protons), 4.05 (s, 1H, NH diazepine, exchangeable with deuterium oxide), 5.08 (s, 2H, CH_2), 6.00 (m, 2H, H-3,4 pyrrole), 6.55 (m, 1H, H-5 pyrrole), 6.73-7.17 (m, 4H, benzene protons)
5c	3340 (NH)	carbon tetrachloride	1.97-2.77 (m, 8H, piperidine protons), 3.50 (s, 2H, CH_2-C_6H_5), 3.97 (s, 1H, NH diazepine, exchangeable with deuterium oxide), 4.98 (s, 2H, CH_2 diazepine), 5.83 (m, 2H, H-3,4 pyrrole), 6.35 (m, 1H, H5 pyrrole), 6.70-7.23 (m, 9H, benzene protons)
5d	3340 (NH)	DMF-d_7	2.17-2.28 (m, 4H, H-3,5 piperidine), 3.72-3.85 (m, 4H, H-2,6 piperidine), 5.28 (s, 2H, CH_2), 5.60 (s, 1H, NH diazepine, exchangeable with deuterium oxide), 5.93 (m, 2H, H-3,4 pyrrole), 6.75 (m, 2H, H-2,6 of 4-$NO_2C_6H_4$), 7.07-7.23 (m, 5H, H-5 pyrrole and benzene protons), 8.13 (m, 2H, H-3,5 of 4-$NO_2C_6H_4$)
6a	3380 (NH)	deuteriochloroform	2.10-2.83 (m, 11H, CH_2 and NCH_3 piperidine), 3.33 (s, 3H, NCH_3 triazepine), 3.93 (s, 1H, NH triazepine, exchangeable with deuterium oxide), 5.83 (m, 1H, pyrrole proton), 6.03 (m, 1H, pyrrole proton), 6.43-7.10 (m, 5H, pyrrole and benzene protons)
6b	3360 (NH)	deuteriochloroform	2.13-2.86 (m, 8H, piperidine), 3.31 (s, 3H, CH_3), 3.52 (s, 2H, CH_2 benzyl), 3.90 (s broad, 1H, NH triazepine, exchangeable with deuterium oxide), 5.85 (m, 1H, pyrrole proton), 6.03 (m, 1H, pyrrole proton), 6.40-7.08 (m, 5H, aromatic and pyrrole protons), 7.21-7.53 (m, 5H, $CH_2C_6H_5$)
7a	3320 (NH)	deuteriochloroform	1.65-1.97 (m, 4H, H-3,5 piperidine), 2.10 (m, 1H, NH piperidine, exchangeable with deuterium oxide), 2.97-3.00 (m, 4H, H-2,6 piperidine), 4.35 (s, 1H, NH piperazine, exchangeable with deuterium oxide), 6.03 (m, 1H, pyrrole proton), 6.27 (m, 1H, pyrrole proton), 6.73-7.33 (m, 5H, pyrrole and benzene protons)
7b	3310 (NH), 1590 (CO)	DMF-d_7	1.90-2.05 (m, 4H, H-3,5 piperidine), 3.63-4.23 (m, 4H, H-2,6 piperidine), 6.12-6.28 (m, 2H, H-3,4 pyrrole), 6.43 (s, 1H, NH piperazine, exchangeable with deuterium oxide), 6.75-7.73 (m, 8H, H-5 pyrrole, thiophene and benzene protons)
7c	3330 (NH), 1620 (CO)	carbon tetrachloride	1.67-1.93 (m, 4H, H-3,5 piperidine), 3.37-4.20 (m, 4H, H-2,6 piperidine), 3.38 (s, 2H, CH_2 superimposed signals), 4.60 (s, 1H, NH piperazine, exchangeable with deuterium oxide), 5.87 (m, 1H, pyrrole proton), 6.17 (m, 1H, pyrrole proton), 6.77-7.27 (m, 8H, H-5 pyrrole, thiophene and benzene protons)

and the proper aromatic amines, namely 1-(2'-aminobenzyl)-1*H*-pyrrole **2** [11], *N*-(2'-aminophenyl)-*N*-methyl-1*H*-pyrrol-1-amine **3** [12], and 1-(2'-aminophenyl)-1*H*-pyrrole **4** [13]. Interaction between the above synthons and subsequent intramolecular cyclization of their intermediates furnished directly the spiro derivatives **5** (Scheme 1), **6** and **7** (Scheme 2). The presence of maleic acid as a catalyst was required in this one-pot reaction.

We used piperidones **1e** and **1f** in the synthesis of **7b** and **7c**. Compounds **1e** and **1f** were prepared by acylation of 4-oxopiperidine (Scheme 3) with thien-2-oyl chloride and thien-2-ylacetyl chloride, respectively.

Derivatives **1** already known were purchased or were prepared following standard procedures according to the literature [14].

Chemical and physical data of spiro derivatives **5**, **6** and **7** are reported in Tables 1 and 2. Pharmacological assays of these compounds to test their effects on the central nervous system are in progress.

EXPERIMENTAL

All reagents were commercial quality from freshly opened containers and were used without further purification. 4-Oxopiperidine, 1-methyl-4-oxopiperidine, 1-benzyl-4-oxopiperidine, thien-2-oyl chloride and thien-2-ylacetyl chloride were purchased from Fluka Chemie AG. Reactions were monitored by analytical thin layer chromatography (tlc) performed on Stratocrom SIF and Stratocrom ALF (Carlo Erba) precoated plates and products were visualized by uv light. Column chromatographies were performed using silica gel 60 Merck (70-230 mesh ASTM) and alumina 90 Merck (70-230 mesh ASTM). Melting points were taken on a Buchi 530 apparatus and are uncorrected. Infrared spectra (nujol mulls) were recorded on a Perkin-Elmer 297 instrument. The ^{1}H-nmr spectra were determined at 60 MHz on a Varian-EM 390A instrument using TMS as the internal standard. Chemical shifts are in parts per million (δ). Microanalyses were performed by Prof. A. Pietrogrande Laboratories, University of Padova, Italy.

1-(Thien-2-oyl)-4-oxopiperidine (**1e**).

A solution of thien-2-oyl chloride (5.1 g, 35 mmoles) in toluene (35 ml) and a solution of 4*N* sodium hydroxide (9.6 ml) were contemporaneously added dropwise to an ice-cooled, well stirred solution of 4-oxopiperidine hydrochloride hydrate (4.9 g, 32 mmoles) in 2*N* sodium hydroxide (19.2 ml). The mixture was vigorously stirred for 30 minutes more, then toluene was removed and the alkaline phase was extracted with chloroform (3 x 50 ml). The organic extracts were collected, washed with brine (2 x 100 ml), dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a residue which was purified by column chromatography (silica gel/ethyl acetate). Evaporation of eluates afforded **1e**, yield 2.9 g (43%), mp 85-87° (benzene/cyclohexane); ir: ν 1705 (CO ketone), 1605 (CO amide) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.45-2.58 (t, 4H, J = 6 Hz, H-3,5 piperidinone), 3.93-4.08 (t, 4H, H-2,6 piperidinone), 7.10 (m, 1H, H-4 thiophene), 7.40-7.53 ppm (m, 2H, H-3,5 thiophene).

Anal. Calcd. for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.60; H, 5.27; N, 6.43; S, 15.47.

1-(Thiophene-2-acetyl)-4-oxopiperidine (**1f**).

This compound was prepared as reported for **1e**. After chromatography pure **1f** was obtained as a colorless oil, yield 61%; ir: ν 1710 (CO ketone), 1640 (CO amide) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.28-2.47 (m, 4H, H-3,5 piperidinone), 3.77-3.98 (m, 4H, H-2,6 piperidinone), 4.00 (s, 2H, CH_2), 6.97 (m, 2H, H-3,4 thiophene), 7.25 ppm (m, 1H, H-5 thiophene).

Anal. Calcd. for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.23; H, 5.85; N, 6.40; S, 14.15.

Spiro Derivatives **5**, **6** and **7**. General Procedure.

A solution of **2**, **3** or **4** (10 mmoles), the required 4-oxopiperidine **1** (12 mmoles) and maleic acid (200 mg) in absolute ethanol (50 ml) was refluxed until the substrate **2** (**3** or **4**) disappeared (the reaction was monitored by tlc using silica gel plates and ethyl acetate as the eluent). After cooling the mixture was concentrated under reduced pressure, diluted with water (100 ml), made basic with 1*N* sodium hydroxide and extracted with chloroform (3 x 100 ml, compounds **5** and **7**) or with ethyl acetate (3 x 100 ml, compounds **6**). The organic extracts were collected, washed with brine (2 x 100 ml), dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a residue, which was chromatographed on silica gel (compounds **5c**, **5d**, **6b**, **7a** and **7b**, eluent, ethyl acetate) or on an alumina (compound **6a**, eluent, chloroform) column. Derivatives **5a** and **5b** were purified by flash chromatography according to the method of Still [15]. The first fractions were discarded and the central fractions were collected and evaporated under reduced pressure to yield the required spiro derivatives **5**, **6** or **7**, respectively (Tables 1 and 2).

Acknowledgement.

The authors are indebted to Italian MURST (60% fund) for financial aid.

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