ARTICLE

OBC
www.rsc.org/obc

Benzoindolizine derivatives of *N*-acylphenothiazine. Synthesis and characterization

Elena Bâcu,[a] Dalila Samson-Belei,[a] Guy Nowogrocki,[b] Axel Couture[c] and Pierre Grandclaudon*[c]

[a] *Catedra de Chimie Organica, Facultatea de Chimie, Universitatea "Al. I. Cuza", 11 Bd Carol I, RO-6600 Iasi, Roumanie*

[b] *Laboratoire de Cristallochimie et Physicochimie du Solide, UMR 8012, ENSC Lille, BP 108, F-59652 Villeneuve d'Ascq Cedex, France*

[c] *Laboratoire de Chimie Organique Physique, associé à l'ENSCL, UMR 8009, Université des Sciences et Technologies de Lille 1, F-59655 Villeneuve d'Ascq Cedex, France*

Received 7th March 2003, Accepted 7th May 2003
First published as an Advance Article on the web 22nd May 2003

A variety of unsaturated or partly and differentially saturated benzoindolizine derivatives of *N*-acylphenothiazine **1**–**3** has been efficiently synthesized by cyclocondensation of acetylenic or olefinic dipolarophiles with azomethine ylide **4** derived from *N*-acetylisoquinolinium salt **5** flanking a phenothiazine unit.

Introduction

During the past five decades studies devoted to the phenothiazine class of compounds[1–4] have been stimulated by the discovery of the pharmacodynamic properties of a number of derivatives in which a variety of aminoalkyl side chains are connected to the nitrogen atom of the heterocyclic unit. Consequently, drugs incorporating a phenothiazine ring system[5–7] have played a crucial role in medicinal chemistry and have occupied a place of choice in the arsenal of pharmaceutical drugs, owing namely to their antibacterial,[8] antihistamine, tranquillizing and spasmolitic activities[9,10] and more recently to their promising antitumor properties.[11–13]

In the context of our research projects aimed at the synthesis of new phenothiazine compounds for subsequent biological evaluation, we were recently interested in the elaboration of different models comprising the phenothiazine unit linked to a variety of nitrogen containing heterocycles through alkyl chains of different lengths.[14–18] Curiously, to the best of our knowledge, compounds in which such aromatic ring systems are connected to an *N*-acylphenothiazine unit have been very rarely studied even though *N*-acylated models equipped with 1,4-benzodioxan,[19] furan[20] or benzofuran[21] aromatic units have displayed interesting neurotropic properties. Recently, two patents emphasizing serine hydrolase modulating activities of structurally related models connected to a pyridone moiety have appeared in print.[22,23] These rare examples encouraged us to develop a synthetic strategy for the construction of compounds incorporating totally or partially unsaturated benzoindolizine units which led us to embark on the synthesis of models **1**–**3**.

Results and discussion

Quaternary salts obtained by condensation of pyridine systems with halogenoalkylacetamide derivatives have been rarely used for the generation of azomethine ylides.[24–26] However it was assumed that 1,3-dipolar cycloaddition between ylides generated in this way and an array of acetylenic and olefinic dipolarophiles[27–30] could undoubtedly represent a conceptually interesting synthetic approach to the target compounds **1**–**3**. It has been widely demonstrated that such cycloadditions are highly regioselective[28,31,32] but the initial reaction products are rarely isolated. Instead, isomerization or aromatization often occurs,[28–30] depending mainly on the nature of the reagents involved in the cyclocondensation and/or the experimental conditions used.

Initially ylide **4** was generated from the isoquinolinium salt **5** resulting from the condensation of isoquinoline with *N*-(2-chloroacetyl)phenothiazine[33] **6**. It was subsequently exposed to an array of acetylenic and olefinic dipolarophiles (Scheme 1). In these studies we were mainly concerned with the influence of the unsaturated character of the dipolarophile, the nature of the solvent and the degree of unsaturation of the cyclocondensed product. For this purpose, the ylide **4** was generated by deprotonation of the isoquinolinium salt **5** with triethylamine (TEA) in the presence of the appropriate dipolarophile, in different mixed solvents and at temperatures varying from room temperature to solvent reflux. Two representative protocols were primarily selected and examined, *i.e.* reactions carried out in refluxing dichloromethane (CH_2Cl_2) and those performed in a mixture of benzene (C_6H_6)–dimethyl sulfoxide (DMSO) at reflux.

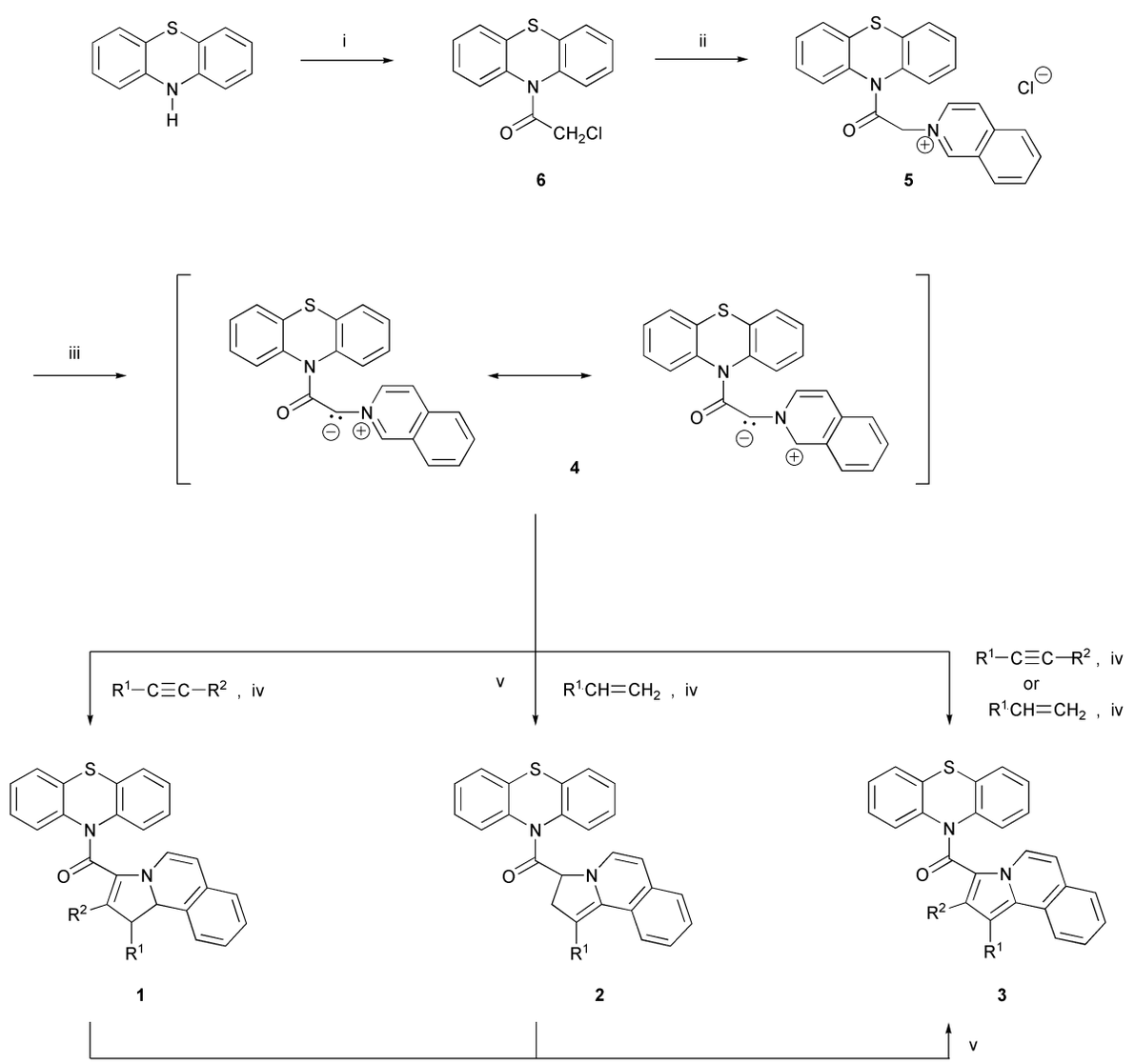
From Table 1, it can be seen that the chemical behaviour of the primary adduct, obtained by condensation of the ylide **4** in the presence of acetylenic dipolarophiles, is strongly affected by the degree of substitution of the parent alkyne.

For example, the primary adduct derived from the reaction with the disubstituted acetylenic dipolarophile dimethyl acetylenedicarboxylate (DMAD) is easily isomerized to the partly unsaturated system **1a**, characterized by a bright yellow colour. This may tentatively be explained by the highly conjugated character of the adduct attributable to the combined presence of the carboxylate group of the dipolarophile associated with the carboxamide moiety of the ylide. This particular behaviour is not affected by experimental conditions (Table 1, entries 1, 2). The structure of **1a** was readily assigned from ^{1}H and ^{13}C NMR spectra. Thus the ^{1}H NMR spectrum exhibited an AB double-doublet at δ 4.47 and 4.71 ppm with a high coupling constant (^3J = 13.2 Hz) characteristic of the aliphatic dihydropyrrole ring system protons. The dihydropyridine unit was unambiguously identified by the presence of two doublet signals at δ 5.54 and 6.51 ppm with a coupling constant of 7.6 Hz. In the ^{13}C NMR spectrum the two tertiary carbons embedded in the dihydropyrrole skeleton displayed signals at δ 53.6 and 65.2 ppm and these different assignments were further corroborated by two-dimensional correlation studies (^{13}C–^{1}H CORR). Finally, the structure was ultimately established by X-ray diffraction (Fig. 1; Table 2). The structural resolution was accurate enough to locate all the hydrogen atoms and refine their position and

DOI: 10.1039/b302662k

Table 1 Condensation of ylide **4** with acetylenic and olefinic dipolarophiles

Entry	Dipolarophile	R^1	R^2	Experimental conditions	Cycloadduct (yield)
1	R^1–C≡C–R^2	COOMe	COOMe	CH_2Cl_2, reflux, 3 h	**1a** (64%)
2				C_6H_6–DMSO (3 : 1; v/v), reflux, 3 h	**1a** (60%)
3				C_6H_6–DMF, $CoPy_4(HCRO_4)_2$, reflux, 3 h	**3a** (49%)
4		COOMe	H	CH_2Cl_2, reflux, 2 h	**3b** (71%)
5				C_6H_6–DMSO (3 : 1; v/v), reflux, 3 h	**3b** (67%)
6		COOEt	H	CH_2Cl_2, reflux, 2 h	**3c** (73%)
7				C_6H_6–DMSO (3 : 1; v/v), reflux, 3 h	**3c** (70%)
8	R^1–CH=CH–R^2	–CO–N(Ph)–CO–		CH_2Cl_2, rt, 36 h	**7e** (78%)
9		COOEt	H	CH_2Cl_2, reflux, 2 h	**2c** (70%)
10				C_6H_6, reflux, 3 h	**2c** (66%)
11				C_6H_6–DMSO (3 : 1; v/v), reflux, 3 h	**2c** + **3c** (65 : 35)
12				C_6H_6–DMSO (3 : 1; v/v), reflux, 10 h	**3c** (56%)
13		CN	H	CH_2Cl_2, reflux, 2 h	**2d** (65%)
14				C_6H_6–DMSO (3 : 12; v/v), reflux, 3 h	**3d** (67%)



Scheme 1 *Reagents and conditions*: (i) $ClCH_2COCl$, C_6H_6, reflux; (ii) isoquinoline, CH_2Cl_2, rt; (iii) NEt_3; (iv) dipolarophile, CH_2Cl_2 or C_6H_6–DMSO, reflux; (v) $CoPy_4(HCrO_4)_2$, DMF, reflux.

clearly confirmed the presence of two sp3 carbon atoms bearing two hydrogen atoms in an *anti* configuration in the five membered ring. Compound **1a** was easily converted into **3a** by oxidation with tetrakis(pyridino)cobalt(II) dichromate[34] [TPCD; $CoPy_4(HCrO_4)_2$] in refluxing dimethylformamide (DMF). The totally unsaturated fused compound **3a**, obtained as white crystals, was also straightforwardly accessible by performing the cyclocondensation in a refluxing mixture of C_6H_6–DMF in the presence of the oxidizing agent (Table 1, entry 3).[35]

Interestingly, whatever reaction conditions were used, monosubstituted acetylenic dipolarophiles, as exemplified by propiolates (Table 1, entries 4–7), gave rise to the unsaturated models **3b** and **3c** after isomerization and oxidation following formation of the initial adduct. One can reasonably assume that the absence of a stabilizing group R^2 accounts for the instability of the partly unsaturated transient system and consequently for its spontaneous oxidation into a model possessing a marked degree of conjugation.

Table 2 Crystallographic data for compounds **1a** and **2c**

	1a	**2c**
Empirical formula	$C_{29}H_{22}N_2O_5S$	$C_{28}H_{22}N_2O_3S$
MW/g mol^{-1}	510.55	466.54
Temperature/K	100(1)	293(2)
Crystal system	Monoclinic	Monoclinic
Space group	*C*2/*c*	*C*2/*c*
a/Å	37.608(6)	20.180(4)
b/Å	8.6937(14)	18.259(4)
c/Å	15.053(3)	14.878(3)
α/°	90	90
β/°	99.163(3)	125.498(3)
γ/°	90	90
Volume/Å^3	4858.8(14)	4463.0(15)
Z	8	8
Absorption coefficient/mm^{-1}	0.178	0.180
Reflections measured	14845	13018
Independent reflections	4155 [*R*(int) = 0.0430]	3713 [*R*(int) = 0.0406]
Final R indices [$I>2\sigma(I)$]	*R*1 = 0.0459, w*R*2 = 0.1219	*R*1 = 0.0501, w*R*2 = 0.1291
R indices (all data)	*R*1 = 0.0611, w*R*2 = 0.1295	*R*1 = 0.0705, w*R*2 = 0.1394

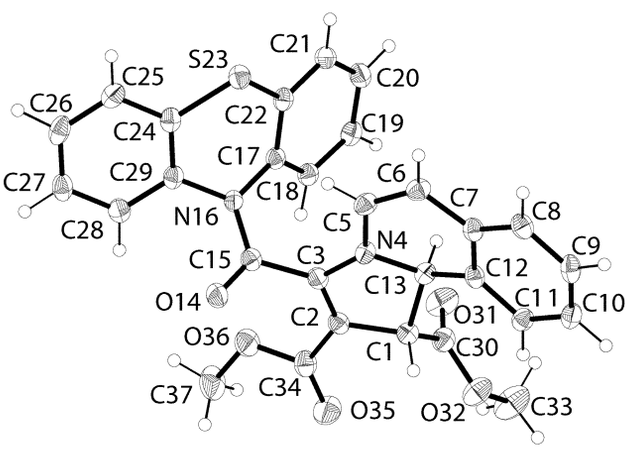
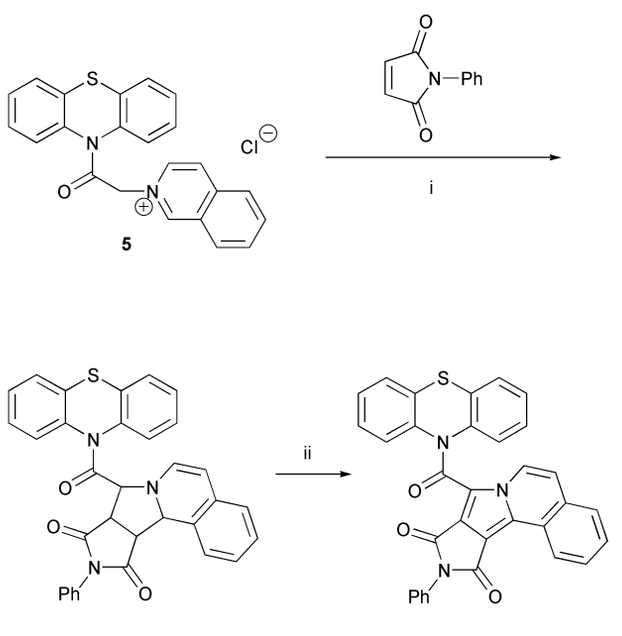


Fig. 1 X-Ray crystal structure of **1a**.

For reactions carried out with ethylenic derivatives, the primary adduct could not be isolated, except in the case of *N*-phenylmaleimide as illustrated by the formation of **7e** (Scheme 2; Table 1, entry 8) and this particular behaviour has been already described and discussed.[31] Compound **7e** was oxidized with $CoPy_4(HCrO_4)_2$ in DMF to afford the fully unsaturated compound **3e** (Scheme 2). In the case of monosubstituted ethylenic dipolarophiles (ethyl acrylate and acrylonitrile) we have observed a slow and progressive oxidation of the primary adduct depending upon the reaction temperature and/or the presence of DMSO as the co-solvent (Table 1, entries 9–14). Reactions carried out in refluxing CH_2Cl_2 gave access to the partly unsaturated compounds **2c** and **2d** obtained as yellow crystals and possessing an olefinic carbon–carbon double bond linking the ester or nitrile functional group to the hydrocarbon aromatic unit. The ^{1}H NMR spectra revealed the presence of two protons in the δ 2.40–2.70 ppm region and one proton in the δ 5.00–5.50 ppm region. The structure was further confirmed by ^{13}C NMR which exhibited signals at δ 32.9 ppm (CH_2) and δ 61.4 ppm (CH) for **2c**. The structure of compound **2c** was ultimately established by X-ray diffraction (Fig. 2; Table 2). Furthermore compounds **2c** and **2d** were readily oxidized with $CoPy_4(HCrO_4)_2$ in DMF to furnish the aromatic compounds **3c** and **3d** respectively. On the other hand, compounds **3c** and **3d** could be directly obtained by performing the cyclocondensation reaction in refluxing C_6H_6–DMSO (Table 1, entries 12 and 14).



Scheme 2 *Reagents and conditions*: (i) NEt_3, CH_2Cl_2, rt; (ii) $CoPy_4(HCrO_4)_2$, DMF, reflux.

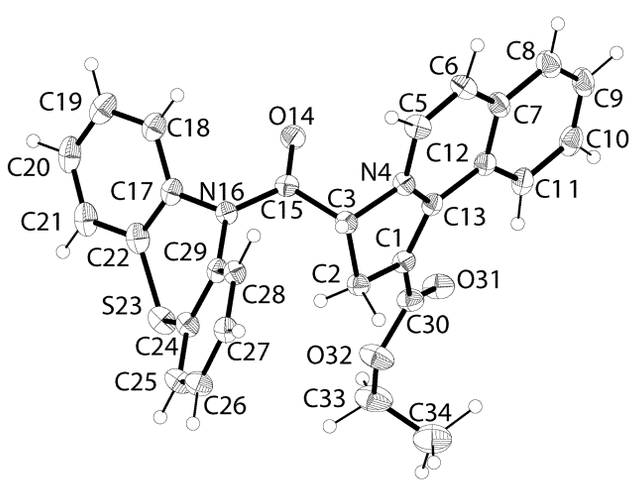


Fig. 2 X-Ray crystal structure of **2c**.

To sum up, we have developed a concise and efficient approach to a variety of unsaturated or partly saturated benzoindolizine derivatives of *N*-acylphenothiazines. The reaction can equally well be performed with acetylenic or olefinic compounds and should be undoubtedly broadened to the synthesis of other polycyclic indolizine-containing compounds. We also

believe that the procedural simplicity, the high efficiency and the easy accessibility of the reaction partners should be rewarded by giving access to a wide array of heterocyclic frameworks equipped with a pendant phenothiazine unit.

Experimental

General

Mps were determined on a Reichert-Thermopan apparatus and are uncorrected. Elemental analyses were obtained using Carlo-Erba CHNS-11110 equipment. Mass spectral analyses were performed on a Vestec 2001 spectrometer (EI 70 eV). IR spectra were recorded on a TF-IR Bomem MB 104 spectrometer. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AM 300 spectrometer; ^{1}H (400 MHz), ^{13}C NMR (100 MHz) and ^{13}C–^{1}H CORR spectra were recorded on a Bruker DRX 400 spectrometer. Chemical shifts are expressed in ppm, positive shifts being downfield from TMS; coupling constants (J) are given in Hz and rounded to the nearest 0.1 Hz.

Crystallography

Crystal data and refinement details for derivatives **1a** and **2c** are presented in Table 2. All measurements were made on a Bruker AXS Smart three-circle diffractometer using graphite-monochromatized Mo-Kα radiation (λ = 0.71073 Å), and equipped with a CCD two-dimensional detector. The structures were solved with the SHELXTL software package.[36] Direct methods revealed the positions of all non-hydrogen atoms. After anisotropic refinement, the hydrogen atoms could be located on Fourier difference maps for compound **2c**. However, for compound **1a**, the anisotropic displacement parameters were so high for the methyl groups that the hydrogen atoms could not be found. To lower the thermal agitation, another data collection was made at 100 K: in these conditions, the anisotropic parameters were more reasonable and the position of hydrogen atoms found without difficulty. The refinement (on F^2) converged to $R1$ = 0.0459, Rw = 0.1219 for compound **1a** and to $R1$ = 0.0501, Rw = 0.1291 for **2c**.†

1-[2-Oxo-2-(10*H*-phenothiazin-10-yl)ethyl]isoquinolinium chloride 5

A solution of *N*-(2-chloroacetyl)phenothiazine[33] **6** (2.75 g, 10 mmol) and isoquinoline (1.55 g, 12 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 24 h. The crude precipitate was filtered and then recrystallized from EtOH to afford the salt **5** as white crystals (3.24 g, 80%), mp 256–258 °C (Found: C, 68.0; H, 4.2; N, 6.95. $C_{23}H_{17}ClN_2OS$ requires C, 68.2; H, 4.2; N, 6.9%); ν_{max} (KBr)/cm^{-1} 1676, 1640 (NCO); δ_H (DMSO-d$_6$–D$_2$O, 1 : 1) 5.52 and 6.38 (2 H, two br. s, CH_2), 7.25–7.75 (8 H, m, H_{pheno}), 8.01 (1 H, dt, J 1.2, 8.1, $H_{7,iso}$), 8.21 (1 H, dt, J 1.0, 8.0, $H_{6,iso}$), 8.27 (1 H, d, J 8.0, $H_{5,iso}$), 8.43 (1 H, d, J 8.3, $H_{8,iso}$), 8.48 (1 H, d, J 6.9, $H_{4,iso}$), 8.60 (1 H, d, $H_{3,iso}$), 9.90 (1 H, s, $H_{1,iso}$); δ_C (DMSO-d$_6$–D$_2$O, 1 : 1) 63.2 (CH_2), 125.9, 127.4, 128.0, 126.0–130.0 (m, 4 C_{pheno} and 8 CH_{pheno}), 131.2, 132.1, 136.9, 137.9, 138.4 (C_1), 162.2 (CO).

General procedure for the synthesis of the benzoindolizine derivatives of *N*-acylphenothiazine

Method A (reaction in CH_2Cl_2). A solution of TEA (0.6 g, 6 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 15 min to a stirred suspension of the salt **5** (2 g, 5 mmol) in a solution of the appropriate dipolarophile (6 mmol) in CH_2Cl_2 (25 mL). The resulting orange mixture containing the ylide **4** was stirred for 1 hour at room temperature and then refluxed for 2 h. Then the reaction mixture was cooled, filtered, and concentrated in vacuum. The oily residue was washed with water and the crude solidified residue was crystallised from acetone–EtOH or ethyl acetate.

Method B (reaction in C_6H_6–DMSO). A solution of TEA (0.6 g, 6 mmol) in C_6H_6 (5 mL) was added dropwise over 15 min to a stirred suspension of the salt **5** (2 g, 5 mmol) in a mixture of C_6H_6 (20 mL) and DMSO (10 mL). Then the appropriate dipolarophile (6 mmol) in C_6H_6 (5 mL) was added to the resulting orange mixture which was refluxed for 3–10 h and treated as described in Method A.

{1,2-Bis(methoxycarbonyl)-1,10b-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl}(10*H*-phenothiazin-10-yl)methanone 1a. From ylide **4** and DMAD. Yellow crystals (1.63 g, 64%), mp 186–187 °C (Found: C, 68.0; H, 4.2; N, 5.8. $C_{29}H_{22}N_2O_5S$ requires C, 68.2; H, 4.3; N, 5.5%); m/z (EI) 510 (M$^+$, 6%), 312 (100), 284 (42), 252 (32), 198 (25), 166 (22); ν_{max} (KBr)/cm^{-1} 1740 (CO), 1680 (CO); δ_H (400 MHz, $CDCl_3$) 3.89 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 4.47 (1 H, d, J 13.2, H-1), 4.71 (1 H, d, J 13.2, H-10b), 5.64 (1 H, d, J 7.6, H-6), 6.51 (1 H, d, J 7.6, H-5), 6.93 (1 H, d, J 6.4, aromatic H), 7.16 (2 H, dd, J 7.6, 8.4, aromatic H), 7.22–7.32 (3 H, m, aromatic H), 7.35–7.50 (4 H, m, aromatic H), 7.80 (2H, dd, J 8.0, 8.4, aromatic H); δ_C (100 MHz, $CDCl_3$) 51.7 (CH_3), 52.8 (CH_3), 53.6 (CH-1), 65.2 (CH-10b), 105.5 (C-2), 108.5 (CH-6), 123.2 (CH-5), 123.6, 124.5, 126.0, 127.0, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.2, 129.5, 131.2, 131.4, 132.6, 136.0, 136.5, 148.6, 159.5 (CO), 164.9 (CO), 174.1 (CO).

{1-Ethoxycarbonyl-2,3-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl}(10*H*-phenothiazin-10-yl)methanone 2c. From ylide **4** and ethyl acrylate. Yellow crystals (1.66 g, 71%), mp 203–204 °C (Found: C, 72.3; H, 4.5; N, 6.2. $C_{28}H_{22}N_2O_3S$ requires C, 72.1; H, 4.75; N, 6.0%); m/z (EI) 466 (M$^+$, 10%), 268 (100), 240 (22), 198 (24), 166 (32); ν_{max} (KBr)/cm^{-1} 1690 (CO), 1650 (CO); δ_H (DMSO-d$_6$) 1.13 (3 H, t, J 7.0, CH_3), 2.68 (2 H, br. s, CH_2), 3.87–4.07 (2 H, m, OCH_2), 5.59 (1 H, br. s, H-3), 6.30 (1 H, d, J 7.0 aromatic H), 7.29 (2 H, q, J 7.0, aromatic H), 7.35–7.70 (9 H, m, aromatic H), 8.00 (1 H, br. s, H_{arom}), 9.69 (1 H, d, J 8.3, aromatic H); δ_C (DMSO-d$_6$) 15.5 (CH_3), 34.4 (CH_2), 59.0 (CH_3), 62.3 (CH-3), 90.2 (C-1), 106.4, 124.1, 126.2, 126.7, 128.1, 128.9, 129.2, 131.2, 134.5, 136.9, 138.2, 138.6, 151.9, 165.4 (CO), 170.7 (CO).

{1-Cyano-2,3-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl}(10*H*-phenothiazin-10-yl)methanone 2d. From ylide **4** and acrylonitrile. Yellow crystals (1.66 g, 71%), mp 223–225 °C (Found: C, 74.2; H, 3.8; N, 9.9. $C_{26}H_{17}N_3OS$ requires C, 74.4; H, 4.1; N, 10.0%); m/z (EI) 419 (M$^+$, 9%), 221 (100), 198 (35), 193 (34); ν_{max} (KBr)/cm^{-1} 2168 (CN), 1680 (CO); δ_H (DMSO-d$_6$) 2.57 (2 H, br. s, CH_2), 6.21 (1 H, br. s, aromatic H), 7.25–7.70 (11 H, m, aromatic H), 7.98 (1 H, br. s, aromatic H), 8.24 (1 H, d, J 6.6, aromatic H); δ_C (DMSO-d$_6$) 34.1 (CH_2), 63.4 (CH-3), 105.0, 108.0, 112.6, 115.6, 122.2, 123.3, 124.0, 126.0, 127.7, 128.3, 129.0, 132.5, 133.0, 136.1, 139.6, 141.0, 153.4, 170.1 (CO).

8-(10*H*-Phenothiazin-10-ylcarbonyl)-10-phenyl-8a,9,10,11,11a,11b-hexahydro-8*H*-pyrrolo[3′,4′:3,4]pyrrolo[2,1-*a*]isoquinoline-9,11-dione 7e. From ylide **4** and *N*-phenylmaleimide (2.11 g, 78%), mp 201–203 °C (Found: C, 73.0; H, 4.2; N, 7.95. $C_{33}H_{23}N_3O_3S$ requires C, 73.2; H, 4.3; N, 7.8%); m/z (EI) 541 (M$^+$, 2%), 312 (100), 284 (37), 252 (84), 166 (30); ν_{max} (KBr)/cm^{-1} 1705 (CO), 1675 (CO); δ_H (400 MHz, DMSO-d$_6$) 3.60 (1 H, t, J 8.0, CH), 4.04 (1 H, br. s, CH), 5.00 (1 H, d, J 7.6, CH), 5.09 (1 H, d, J 7.5, CH), 5.24 (1 H, s, CH), 5.42 (1 H, br. s, CH), 6.81 (1 H, d, J 7.0, aromatic H), 6.94–7.10 (8 H, m, aromatic H), 7.20 (1 H, d, J 7.6, aromatic H), 7.27–7.45 (5 H, m,

† CCDC reference numbers 205735 and 205736. See http://www.rsc.org/suppdata/ob/b3/b302662k/ for crystallographic data in .cif or other electronic format.

aromatic H), 7.52 (2 H, br. d, *J* 8.0, aromatic H); δ_C (100 MHz, DMSO-d_6) 47.3, 52.7, 61.9, 70.0, 100.7, 124.3, 125.8, 126.8, 127.7, 128.2, 128.4, 128.6, 129.2, 131.6, 133.1, 135.4, 139.0, 167.7 (CO), 174.3 (CO), 176.8 (CO).

General Procedure for the oxidation of cycloadducts with TPCD $[CoPy_4(HCrO_4)_2]$

A solution of the partly unsaturated cycloadduct **1a**, **2c**, **d** or **7e** (1 mmol) and TPCD (0.4 g, 0.66 mmol) in DMF (10 mL) was refluxed for 5 h. The solution which turned green, was filtered hot, concentrated in vacuum and then diluted with water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuum to afford **3a**, **c**, **d**, **e** as a white solid which was recrystallized in acetone (**3a**–**d**) or in acetone–EtOH (**3e**).

{1,2-Bis(methoxycarbonyl)pyrrolo[2,1-*a*]isoquinolin-3-yl}-(10*H*-phenothiazin-10-yl)methanone 3a. White crystals (oxidation of **1a**: 422 mg, 83%), mp 215–217 °C (Found: C, 68.7; H, 4.1; N, 5.9. $C_{29}H_{20}N_2O_5S$ requires C, 68.5; H, 4.0; N, 5.5%); *m*/*z* (EI) 508 (M^+, 3%), 310 (100), 282 (23), 198 (30), 166 (21); ν_{max} (KBr)/cm^{-1} 1745 (CO), 1689 (CO); δ_H (DMSO-d_6) 3.79 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 7.20–7.26 (4 H, m, aromatic H), 7.28 (1 H, d, *J* 7.2, H-5), 7.45–7.61 (6 H, m, aromatic H), 7.80–7.82 (1 H, m, H-6), 8.15–8.22 (1 H, br. d, *J* 7.2, H-4), 8.31–8.33 (1 H, m, H-9); δ_C (DMSO-d_6) 52.2 (CH_3), 53.3 (CH_3), 110.0 (C-1), 118.9, 123.0, 123.4, 123.6, 124.5, 124.9, 126.8, 127.2, 128.2, 128.4, 128.7, 129.0, 129.7, 129.9, 132.6, 137.8, 160.5 (CO), 163.8 (CO), 167.0 (CO).

{1-Methoxycarbonylpyrrolo[2,1-*a*]isoquinolin-3-yl}(10*H*-phenothiazin-10-yl)methanone 3b. White crystals (from ylide **4** and methyl propioloate: 1.60 g, 71%), mp 254–256 °C (Found: C, 71.7; H, 4.0; N, 6.3. $C_{27}H_{18}N_2O_3S$ requires C, 72.0; H, 4.0; N, 6.2%); *m*/*z* (EI) 450 (M^+, 15%), 252 (100), 224 (37), 198 (39), 166 (41); ν_{max} (KBr)/cm^{-1} 1704 (CO), 1646 (CO); δ_H (DMSO-d_6) 3.84 (3 H, s, OCH_3), 6.58 (1 H, s, H-2), 7.28–7.38 (4 H, m, aromatic H), 7.44 (1 H, d, *J* 7.4, H-5), 7.57–7.73 (6 H, m, aromatic H), 7.80–7.84 (1 H, m, H-6), 8.93 (1 H, d, *J* 7.4, H-4), 9.44–9.48 (1 H, m, H-9); δ_C (DMSO-d_6) 52.8 (CH_3), 108.8 (C-1), 115.4, 120.3, 122.7, 125.0, 126.0, 127.6, 127.8, 128.1, 128.4, 128.8, 128.9, 130.1, 130.4, 132.7, 134.6, 139.7, 160.5 (CO), 165.4 (CO).

{1-Ethoxycarbonylpyrrolo[2,1-*a*]isoquinolin-3-yl}(10*H*-phenothiazin-10-yl)methanone 3c. White crystals (from ylide **4** and ethyl propiolate: 1.70 g, 73%; oxidation of **2c**: 377 mg, 81%), mp 218–220 °C (Found: C, 72.3; H, 4.03; N, 6.1. $C_{28}H_{20}N_2O_3S$ requires C, 72.4; H, 4.3; N, 6.0%); *m*/*z* (EI) 464 (M^+, 12%), 266 (100), 238 (28), 199 (42), 166 (35); ν_{max} (KBr)/cm^{-1} 1700 (CO), 1635 (CO); δ_H (DMSO-d_6) 1.18 (3 H, t, *J* 7.1, CH_3), 4.15 (2 H, q, *J* 7.1, CH_2), 6.54 (1 H, s, H-2), 7.25–7.35 (4 H, m, aromatic H), 7.42 (1 H, d, *J* 7.5, H-5), 7.59–7.70 (6 H, m, aromatic H), 7.80–7.84 (1 H, m, H-6), 9.03 (1 H, d, *J* 7.5, H-4), 9.56–9.60 (1 H, m, H-9); δ_C (DMSO-d_6) 14.9 (CH_3), 60.8 (CH_2), 108.8 (C-1), 115.1, 119.5, 123.3, 124.9, 127.6, 128.0, 128.2, 128.5, 128.7, 129.8, 130.2, 132.7, 134.2, 139.6, 160.0 (CO), 164.5 (CO).

{1-Cyanopyrrolo[2,1-*a*]isoquinolin-3-yl}(10*H*-phenothiazin-10-yl)methanone 3d. White crystals (from ylide **4** and acrylonitrile: 1.40 g, 67%; oxidation of **2d**: 290 mg, 70%), mp 263–265 °C (Found: C, 74.4; H, 3.5; N, 10.2. $C_{26}H_{15}N_3OS$ requires C, 74.8; H, 3.6; N, 10.1%); *m*/*z* (EI) 417 (M^+, 21%), 219 (100), 198 (25), 192 (17), 166 (22); ν_{max} (KBr)/cm^{-1} 2216 (CO), 1650 (CO); δ_H (DMSO-d_6) 6.31 (1 H, s, H-2), 7.20–7.29 (4 H, m, aromatic H), 7.32 (1 H, d, *J* 7.6, H-5), 7.52–7.63 (6 H, m, aromatic H), 7.81–7.84 (1 H, m, H-6), 8.65–8.70 (1 H, m, H-9), 8.98 (1 H, d, *J* 7.5, H-4); δ_C (DMSO-d_6) 84.5 (C-1), 115.3, 117.5, 120.5 (CN), 122.6, 123.3, 124.2, 125.4, 127.6, 127.7, 128.1, 128.5, 129.2, 129.5, 130.0, 132.8, 139.3, 159.4 (CO).

8-(10*H*-Phenothiazin-10-yl-carbonyl)-10-phenyl-8*H*-pyrrolo-[3′,4′:3,4]pyrrolo[2,1-*a*]isoquinoline-9,11-dione 3e. White crystals (oxidation of **7e**: 460 mg, 85%), mp 317–319 °C (Found: C, 74.0; H, 3.3; N, 7.5. $C_{33}H_{19}N_3O_3S$ requires C, 73.7; H, 3.6; N, 7.8%); *m*/*z* (EI) 537 (M^+, 37%), 339 (100), 295 (92), 268 (30), 198 (36), 164 (68), 77 (31); ν_{max} (KBr)/cm^{-1} 1759 (CO), 1716 (CO); δ_H (400 MHz, DMSO-d_6) 7.21–7.27 (7 H, m, aromatic H), 7.36–7.40 (1 H, m, aromatic H), 7.46–7.58 (6 H, m, aromatic H), 7.57–7.70 (2 H, m, aromatic H), 7.94–7.97 (1 H, m, H-6), 8.63 (1 H, d, *J* 7.6, H-4), 8.97–9.00 (1 H, m, H-9).

Acknowledgements

We would like to thank Dr T. G. C. Bird (Astra-Zeneca, Reims) for helpful comments on the manuscript and Dr E. Maes (UMR 8576, USTL) for some 400 MHz ^1H NMR spectra.

References

1 S. P. Massie, *Chem. Rev.*, 1954, **54**, 797–833.
2 C. Bodea and I. Silberg, *Adv. Heterocycl. Chem.*, 1968, **9**, 321–460.
3 S. Saraf, F. Al-Omran and B. Al-Saleh, *Heterocycles*, 1987, **26**, 239–273.
4 M. Sainsbury, *1,4-Thiazines, 1,4-Benzothiazines, Phenothiazines and Related Compounds*, in *Rodd's Chemistry of Carbon Compounds*, ed. M. Sainsbury, Elsevier, Amsterdam, 2nd Edition, 1998, vol 4, Part G/Part H, pp. 575–608.
5 D. Lednicer and L. A. Mitscher, *The Organic Chemistry of Drug Synthesis*, Wiley, New York, 1976, vol 1, pp. 372–392.
6 A. A. Borbely and M. Loepfe-Hinkkanen, *Mod. Pharmacol.-Toxicol.*, 1979, **16**, 403–426.
7 A. S. Horn, in *Comprehensive Medicinal Chemistry. The Rational Design, Mechanistic Study, and Therapeutic Application of Chemical Compounds: Membranes and Receptors*, eds. C. Hansch, P. G. Sammes, J. B. Taylor and J. C. Emmett, Pergamon Press, Oxford, 1990, vol 3, p. 321.
8 J. E. Kristiansen, *Dan. Med. Bull.*, 1989, **36**, 178–185.
9 A. Lespagnol, *Bull. Soc. Chim. Fr.*, 1960, 1291–1299.
10 *Developments in Neuroscience. Phenothiazines and Structurally Related Drugs: Basic and Clinical Studies*, eds. E. Usdin, H. Eckert and I. S. Forrest, Elsevier, New York, 1980, vol 7.
11 *Bioactive Molecules. Phenothiazines and 1,4-Benzothiaiznes: Chemical and Biomedical Aspects*, ed. R. R. Gupta, Elsevier, Amsterdam, 1988, vol 4.
12 N. Motohashi, S. R. Gollapudi, J. Emrani and K. R. Bhattiprolu, *Cancer Invest.*, 1991, **9**, 305–319.
13 L. R. Morgan, A. H. Rodgers, B. W. Leblanc, S. M. Boué, Y. Yang, B. S. Jursic and R. B. Cole, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2193–2195.
14 M. Petrovanu, E. Bâcu, P. Grandclaudon and A. Couture, *Phosphorus, Sulfur, Silicon*, 1996, **108**, 231–237.
15 E. Bâcu, M. Petrovanu, C. Antohie, I. Ciocoiu and O.-C. Mungiu, *Ann. Pharm. Fr.*, 1997, **55**, 268–271.
16 E. Bâcu, M. Petrovanu, P. Grandclaudon and A. Couture, *Roum. Biotechnol. Lett.*, 1997, **2**, 383–389.
17 E. Bâcu, M. Petrovanu, A. Couture and P. Grandclaudon, *Phosphorus, Sulfur, Silicon*, 1999, **149**, 207–220.
18 E. Bâcu, A. Couture and P. Grandclaudon, *Synth. Commun.*, 2003, **33**, 143–151.
19 M. Schreibman, C. E. Miller, W. H. Shelver and J. P. Vacik, *J. Pharm. Sci.*, 1964, **53**, 985–986.
20 E. Lukevics, M. Trushule, S. Germane and I. Turovskii, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 229–233.
21 A. Prewysz-Kwinto, *Khim. Geterotsikl. Soedin.*, 1987, **6**, 756–759 (*Chem. Abstr.*, 1988, **108**, 112109).
22 S. Darvesh, D. Magee, Z. Valenta and E. Martin, PCT Int. Appl., 2001, WO 0177078(*Chem. Abstr.*, 2001, **135**, 303780).
23 S. Darvesh, D. I. Magee, R. S. Mcdonald and E. V. Martin, PCT Int. Appl., 2001, WO 0192240(*Chem. Abstr.*, 2001, **136**, 20279).
24 A. R. Katritzky, N. E. Graeskowiak and J. Alvarez-Builla, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1180–1185.
25 A. M. Shestopalov, Y. A. Sharanin, V. N. Nesterov, L. A. Rodinovskaya, V. E. Shklover, Y. T. Struchkov and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1991, **9**, 1248–1254 (*Chem. Abstr.*, 1992, **116**, 214313).
26 M. Travnicek, J. Pospisil and M. Potacek, *Collect. Czech. Chem. Commun.*, 1999, **64**, 1993–2006.

27 A. W. Johnson, *Ylide Chemistry*, Academic Press, New York, 1966.
28 I. Zugravescu and M. Petrovanu, *N-Ylide Chemistry*, McGraw Hill, New York, 1976.
29 G. Surpateanu, J. P. Catteau, P. Karafiloglou and A. Lablache-Combier, *Tetrahedron*, 1976, **32**, 2647–2663 and references cited therein.
30 G. Surpateanu and A. Lablache-Combier, *Heterocycles*, 1984, **22**, 2079–2128.
31 O. Tsuge, S. Kanemasa and S. Takenaka, *Bull. Chem. Soc. Jpn*, 1985, **58**, 3137–3157 and references cited therein.
32 O. Tsuge and S. Kanemasa, *Adv. Heterocycl. Chem.*, 1989, **45**, 231–349.
33 Y. Imakura, T. Konishi, K. Uchida, H. Sakurai, S. Kobayashi, A. Haruno, K. Tajima and S. Yamashita, *Chem. Pharm. Bull.*, 1994, **42**, 500–511.
34 Y. Hu and H. Hu, *Synth. Commun.*, 1992, **22**, 1491–1496.
35 X. Wei, Y. Hu, T. Li and H. Hu, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2487–2489.
36 G. M. Sheldrick, SHELXTL, Program for Crystal Structure Solution and Refinement, Bruker AXS Inc., Madison, WI, 1997.