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SYNTHESIS OF NEW *N*-ALKYL- AND *N*-ACYLDIOXINO-PHENOTHIAZINE AND ACRIDINONE DERIVATIVES

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Abstract - The synthesis of new substituted dioxino[*b*]- and [*c*]phenothiazines or acridinones is reported. *N*-Arylation of [1,4]benzodioxin-6-amine with organolead or organobismuth reagents gave *N*-aryl-2,3-dihydro-1,4-benzodioxin-6-amine; subsequent Bernthsen thionation led to phenothiazine ring formation, followed by *N*-acylation. On the other hand [1,4]benzodioxin-6-amine was first *N*-alkylated and the resulting alkylamines were *N*-phenylated before Bernthsen thionation to provide the tetracyclic phenothiazines. Alternative arylation with chlorobenzoic acid followed by cyclization under acidic conditions afforded the dioxinoacridinones, which were successfully alkylated.

INTRODUCTION

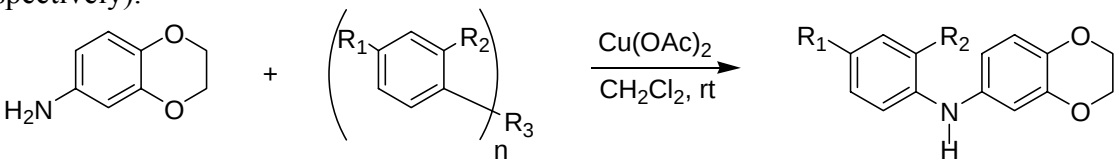
Acridine derivatives are well known therapeutic agents because of their wide range of pharmacological and biological activities, and many derivatives have been reported as being neuroleptics[1] or anticancer agents.[2] The interest in tetracyclic derivatives has increased in the last few years;[3] we previously reported the preparation of new compounds bearing a pyrazole,[4] a cyclopentane,[5] or a dioxole fourth ring fused to a phenothiazine or acridine moiety. Herein we report the preparation of *N*-substituted tetracycles bearing a dioxane ring.

RESULTS AND DISCUSSION

To our knowledge there have been few syntheses of linear dioxino[2,3-*b*]acridines, but without *N*-substitution.[6] Our approach is based on the *N*-arylation of commercial [1,4]benzodioxin-6-amine (**1**) with organolead and organobismuth reagents,[7] in the presence of copper catalyst, followed by cyclization by Bernthsen thionation of the corresponding *N*-aryl[1,4]benzodioxin-6-amines (**3**). In the same way, coupling of benzoic acid with **1**, followed by cyclization in acidic media led to the dioxinoacridinones

(**4-5**).

The first key step is the synthesis of diarylamines (**3a-e**) by copper catalysis. For this purpose we used the Ullmann conditions but yields of desired products were low;[8] on the other hand, a modified procedure using organolead or organobismuth derivatives led us to significantly improve the yield of this *N*-arylation step.[9] With *p*-tolyllead triacetate (**2a**) and 4-methoxyphenyllead triacetate (**2b**), we obtained the corresponding coupling products *N*-4-methylphenyl-[1,4]benzodioxin-6-amine (**3a**) and *N*-4-methoxyphenyl-[1,4]benzodioxin-6-amine (**3b**) (43-51 % yield) (Scheme 1). The *N*aryl[1,4]benzodioxin-6-amine (**3c-d**) were prepared in the same manner using the arylbismuth reagents (**2c-d**) (62 and 32 % yields respectively).



1 **2a-e** **3a-e**

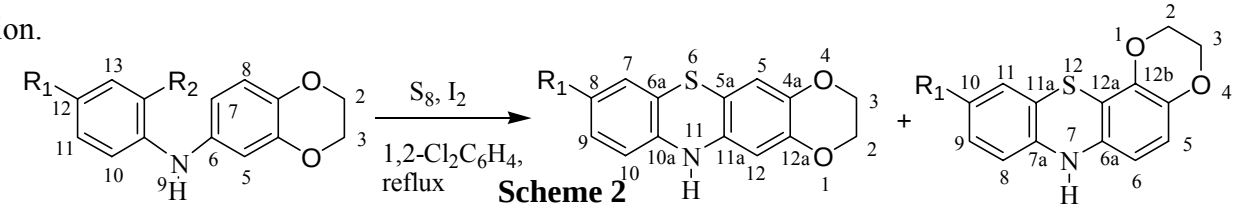
Scheme 1

Table 1: Synthesis of *N*-arylamine derivatives (**3a-e**)

Compound No	R_1	R_2	R_3	n	Products obtained
2a	CH_3	H	$Pb(OAc)_3$	1	**3a**
2b	OCH_3	H	$Pb(OAc)_3$	1	**3b**
2c	H	H	$Bi(OAc)_2$	3	**3c**
2d	Cl	H	$Bi(OAc)_2$	3	**3d**
2e	H	COOH	Cl	1	**3e***

* Cu, 1-pentanol, 110°C

The cyclization of **3a-d** was performed by Bernthsen thionation in refluxing *o*-dichlorobenzene with sulfur and iodine. Usually a mixture of two isomers can be obtained owing to two possible cyclization sites in the [1,4]benzodioxol moiety; thus, cyclization of derivatives (**3**) would lead to a linear [*b*]fused phenothiazine isomer (cyclization at position 7) and to an angular [*a*]fused isomer (cyclization at position 5) (Scheme 2). Indeed, cyclization of **3a** and **3b** turned out to be regioselective and led to a single isomer, the linear 8-methyl-11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (**4a**) and 8-methoxy-11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (**4b**) (47 and 29 % respectively); in contrast, with **2c**, a mixture of both angular and linear isomers (**4c**) and (**5c**), which could not be separated, was obtained (43 % crude yield, isomeric ratio 60/40). Cyclization of the chloroaryl amine (**3d**) was unsuccessful, leading to many side products of degradation.



3a-d **4a-c** **5c**

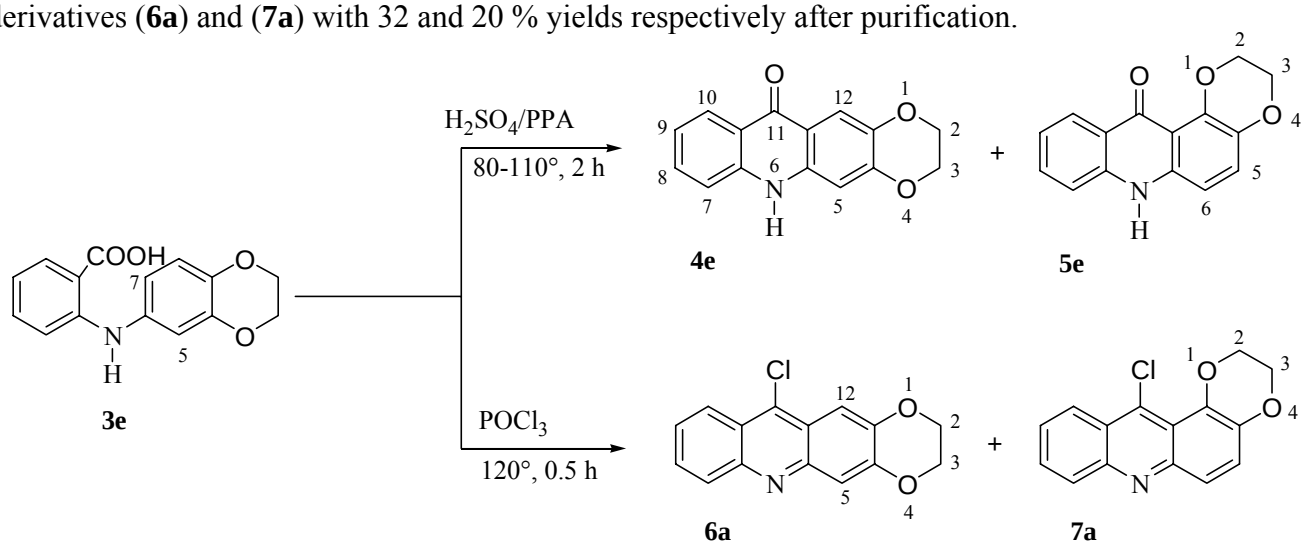
Scheme 2

Table 2: Synthesis of phenothiazine derivatives (**4a-c**, **5c**).

Compound No	R_1	R_2	Products obtained
3a	CH_3	H	**4a**
3b	OCH_3	H	**4b**
3c	H	H	**4c/5c**
3d	Cl	H	-

The assignment of the linear and angular structures of the fused tetracycles was determined unambiguously by the ^{1}H-NMR spectra, in particular by the evaluation of the multiplet pattern of the C-ring proton signals: In the case of [*b*] fusion, 5-H and 12-H are expected to resonate as singlets, whereas two doublets (AB quartet, J = 8 Hz) would be expected in the case of [*a*] fusion (5-H and 6-H) (Scheme 2). In fact, this former pattern was observed, for example with two singlets at δ 6.25 and 6.47 ppm (12-H and 5-H) for 8-methyl-11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (**4a**); in contrast two doublets at δ 6.16 and 6.48 ppm prove the angular fused structure of 7*H*-[1,4]dioxino[2,3-*c*]phenothiazine (**5c**).

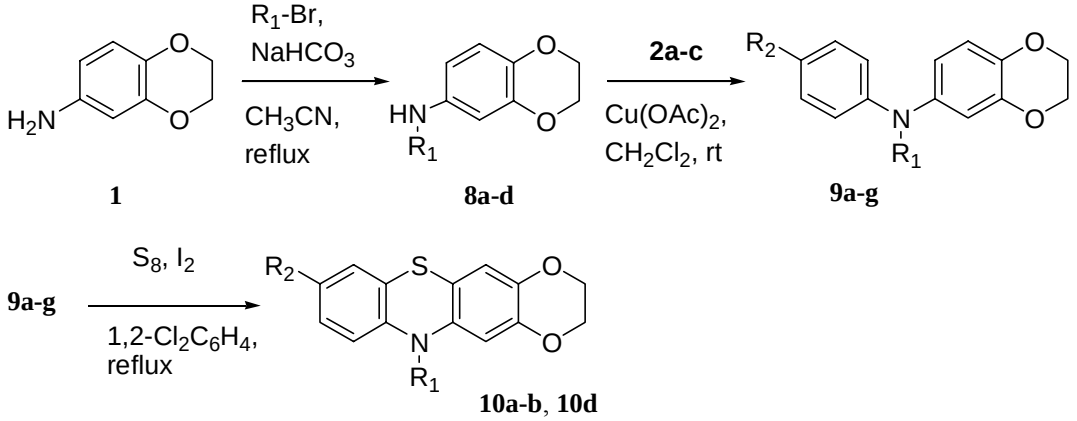
The tetracyclic acridinones (**4-7**) were also obtained by cyclization but with Friedel-Crafts acylation of the anthranilic acid (**3e**) under acidic conditions (Scheme 3). A mixture of both isomers was obtained with a reversed isomeric ratio depending on the solvent. Effectively, performing the reaction in polyphosphoric acid (PPA) or sulfuric acid led, after chromatography separation, to the angular *7H*-[1,4]dioxino[2,3-*a*]acridin-12-one (**5e**) (43 % yield), and the linear *6H*-[1,4]dioxino[2,3-*b*]acridin-11-one (**4e**) (28 % yield). On the other hand, cyclization with phosphorous oxychloride led to the chloro derivatives (**6a**) and (**7a**) with 32 and 20 % yields respectively after purification.



Scheme 3

The next step involved the conversion of the phenothiazines (**4**) and (**5**) into *N*-alkylaminoalkyl and *N*-acyl derivatives. Previously described preparative procedures for direct *N*-aminoalkylation of similar dioxolophenothiazines[10] with sodium amide in xylene or sodium hydride and *N*,*N*-dimethylaminoalkyl

halides in DMSO, or phase transfer catalysis[11] were unsuccessful. Direct *N*-alkylation of the *N*-aryl[1,4]benzodioxin-6-amines (**3a-d**) before cyclization was also attempted but the desired products were not obtained. We therefore decided to monoalkylate the aromatic amine (**1**) with different alkyl halides in the presence of sodium hydrogen carbonate in acetonitrile.[12] 1-Bromobutane and 1-bromo-3-methylbutane gave *N*-butyl- and *N*-isopentyl[1,4]benzodioxin-6-amines (**8a** and **8b**) (48-50 %). Compounds (**8c**) and (**8d**) were prepared in the same way (15-38 %). Next, the reaction of **8a-d** with triacetates (**2a-b**) or triphenylbismuth diacetate (**2c**) led to the corresponding *N*-alkyl-*N*-aryl[1,4]benzodioxin-6-amines (**9a-g**) (Scheme 4).



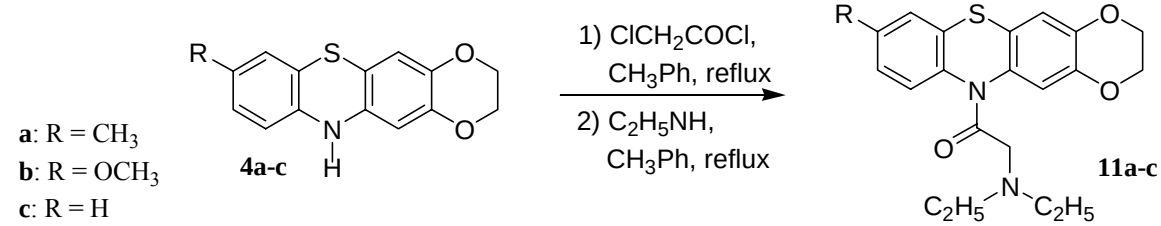
Scheme 4

Table 3: Synthesis of *N*-alkyl phenothiazine derivatives (**10a-b**, **10d**)

	8	**9**	**10**	R_1	R_2
1	**8a**	**9a**	**10a**	$(CH_2)_3CH_3$	H
	8a	**9b**	**10b**	$(CH_2)_3CH_3$	OCH_3
	8a	**9c**	-	$(CH_2)_3CH_3$	CH_3
	8b	**9d**	**10d**	$(CH_2)_2CH(CH_3)_2$	H
	8c	**9e**	-	$CH(CH_3)_2$	H
	8d	**9f**	-	$CH(CH_3)(CH_2)_2CH_3$	CH_3
	8d	**9g**	-	$CH(CH_3)(CH_2)_2CH_3$	H

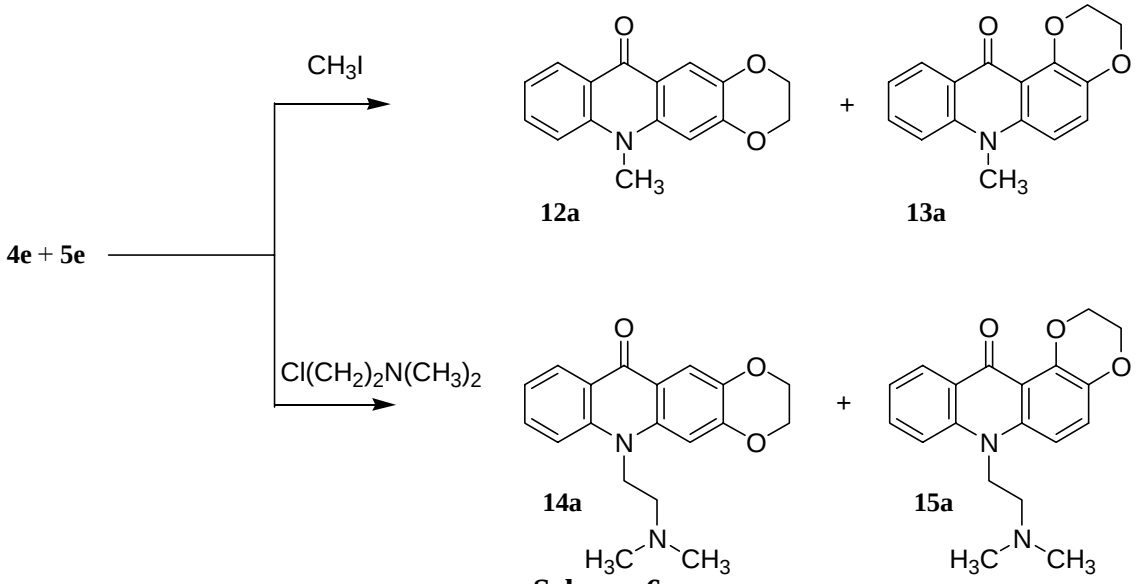
Under Bernthsen's condition, only three arylamines (**9a**, **9b** and **9d**) were cyclized to regioselective linear fused phenothiazine products (**10a, 10b** and **10d**) (11-17 %). By contrast **9c**, **9e**, **9f** and **9g** led to degradation products only.

Acylation of **4a-c** performed with chloroacetyl chloride in toluene, followed by condensation with *N*,*N*-diethylamine provided the corresponding *N*-(2-diethylaminoacetyl) derivatives (**11a-c**) (52-69 %) (Scheme 5).



Scheme 5

N-Alkylacridinones (**12-15**) were obtained by direct alkylation of a mixture of both linear and angular dioxinoacridinones (**4e**) and (**5e**), followed by chromatographic separation. With dimethyl sulfate in acetone,[13] the tetracycles (**12a**) and (**13a**) were obtained (28 and 43 % yields after separation); in contrast, phase transfer catalysis in toluene with 2-dimethylaminoethyl chloride hydrochloride yielded the 6-[2-dimethylaminoethyl]-*6H*-[1,4]dioxino[2,3-*b*]acridin-11-one (**14a**) and the 7-[2-dimethylaminoethyl]-*7H*-[1,4]dioxino[2,3-*a*]acridin-12-one (**15a**) (8 % each one) (Scheme 6).



Scheme 6

CONCLUSION

We report the preparation of a new class of tetracyclic heterocycles, *N*-alkyl- and *N*-acyl-[1,4]dioxino[2,3-*b*]phenothiazines and acridinones, employing organometalic reagents and benzoic acid for *N*-arylation, followed by Bernthsen thionation or acidic condition for ring closure.

EXPERIMENTAL

Melting points were measured on a Mettler FP 61 apparatus and are uncorrected. The ^{1}H- and ^{13}C-NMR spectra were measured on a Bruker 200 spectrometer. Chemical shifts were recorded as units relative to tetramethylsilane as the internal standard. Separations by chromatography were performed on silica gel (Merck, 70-230 mesh). [1,4]Benzodioxin-6-amine (**1**) is commercially available and was used as received; triacetates (**2a**) and (**2b**) and diacetates (**2c**) and (**2d**) were prepared according to the literature.[14]

N-(4-Methylphenyl)[1,4]benzodioxin-6-amine (3a)

To a solution of [1,4]benzodioxin-6-amine (**1**) (1 g, 6.6 mmol) in dry dichloromethane (40 mL) at rt were slowly added *p*-tolyllead triacetate (**2a**) (3.5 g, 7.3 mmol) and copper(II) acetate (0.12 g, 0.66 mmol). The mixture was stirred during 3 h at rt. Next, dichloromethane was added to the solution (20 mL) and the

resulting mixture was filtered. The insoluble part was washed with dichloromethane (2 x 20 mL), and the organic layers were dried over anhydrous sodium sulphate and evaporated to give a crude reaction product which was purified by chromatography on silica gel with toluene as the eluent. A white powder was obtained, yielding 0.8 g (51 %) of **3a**; mp 54°C (from toluene). ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s, CH_3), 4.16 (2H, m, 2-H), 4.20 (2H, m, 3-H), 6.52 (1H, dd, *J* = 2.6, 8.3 Hz, 7-H), 6.54 (1H, d, *J* = 2.6 Hz, 5-H), 6.72 (1H, d, *J* = 8.3 Hz, 8-H), 6.87 (2H, d, *J* = 8.4 Hz, 10-H and 14-H), 6.99 (2H, d, *J* = 8.2 Hz, 11-H and 13-H), 7.69 (1H, s, 9-H). ^{13}C-NMR (DMSO-d_6) δ: 20.29 (CH_3), 63.90 (2-C), 64.35 (3-C), 106.06 (5-C), 110.92 (7-C), 116.23 (2C, 10-C and 14-C), 117.33 (8-C), 127.67 (12-C), 129.59 (2C, 11-C and 14-C), 137.12 (8a-C), 137.85 (6-C), 141.93 (9a-C), 143.62 (4a-C). *Anal*. Calcd for $C_{15}H_{15}NO_2$: C 74.67; H 6.27; N 5.81. Found: C, 74.82; H, 6.53; N, 6.13.

***N*-(4-Methoxyphenyl)[1,4]benzodioxin-6-amine (3b)**

As described above for **3a** but with **1** (1 g, 6.6 mmol) and 4-methoxyphenyllead triacetate (**2b**) (3.6 g, 7.3 mmol). After work up, chromatography on silica gel with dichloromethane yielded 0.7 g (43 %) of **3b** as yellow needles; mp 90°C (from dichloromethane). ^{1}H-NMR (DMSO-d_6) δ: 3.69 (3H, s, OCH_3), 4.15 (2H, m, 2-H), 4.18 (2H, m, 3-H), 6.43 (1H, dd, *J* = 2.6, 8.3 Hz, 7-H), 6.44 (1H, d, *J* = 2.6 Hz, 5-H), 6.69 (1H, d, *J* = 8.4 Hz, 8-H), 6.85 (2H, d, *J* = 8.9 Hz, 11-H and 13H), 6.91 (2H, d, *J* = 8.9 Hz, 10-H and 14H), 7.51 (1H, s, 9-H). ^{13}C-NMR (DMSO-d_6) δ: 55.16 (OCH_3), 63.79 (2-C), 64.24 (3-C), 104.65 (5-C), 109.60 (7-C), 114.50 (2C, 11-C and 13-C), 117.25 (8-C), 118.87 (2C, 10-C and 14-C), 136.68 (8a-C), 137.41 (9a-C), 139.00 (6-C), 143.58 (4a-C), 153.14 (12-C). *Anal*. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.39, H, 5.47; N, 5.81.

***N*-Phenyl[1,4]benzodioxin-6-amine (3c)**

As described above for **3a** but with **1** (1 g, 6.6 mmol) and triphenylbismuth diacetate (**2c**) (1.35 g, 2.4 mmol). Purification was performed by chromatography with hexane/ethanol (60/40) to yield 0.95 g (63 %) of **3c** as white needles; mp 91°C (from ethanol). ^{1}H-NMR (DMSO-d_6) δ: 4.18 (2H, m, 2-H), 4.21 (2H, m, 3-H), 6.56 (1H, dd, *J* = 2.6, 8.2 Hz, 7-H), 6.58 (1H, d, *J* = 2.5 Hz, 5-H), 6.72 (1H, m, 12-H), 6.75 (1H, d, *J* = 8.2 Hz, 8-H), 6.94 (2H, m, 10-H and 14-H), 7.16 (2H, m, 11-H and 13-H), 7.83 (1H, s, 9-H). ^{13}C-NMR (DMSO-d_6) δ: 63.92 (2-C), 64.33 (3-C), 107.03 (5-C), 115.44 (2C,10-C and 14-C), 117.36 (8-C), 117.79 (7-C), 118.69 (12-C), 129.17 (11-C), 137.05 (6-C), 137.61 (8a-C), 143.61 (4a-C), 144.65 (9a-C). *Anal.* Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.20; H, 5.94; N, 6.33.

***N*-(4-Chlorophenyl)[1,4]benzodioxin-6-amine (3d)**

As described above for **3a** but with **1** (1 g, 6.6 mmol) and tris(4-chlorophenyl)bismuth diacetate (**3e**)

(1.59 g, 2.4 mmol). Purification was performed by chromatography with dichloromethane to yield 0.95 g (32 %) of **3d** as brown needles; mp 77°C (from dichloromethane). ^{1}H-NMR (DMSO-d_6) δ: 4.18 (2H, m, 2-H), 4.21 (1H, m, 3-H), 6.55 (1H, dd, *J* = 2.5, 7.8 Hz, 7-H), 6.57 (1H, br s, 5-H), 6.76 (1H, d, *J* = 8.1 Hz, 8-H), 6.91 (2H, d, *J* = 8.9 Hz, 10-H and 14-H), 7.18 (2H, d, *J* = 8.9 Hz, 11-H), 8.00 (1H, br s, 9-H). ^{13}C-NMR (DMSO-d_6) δ: 63.84 (2-C), 64.42 (3-C), 107.63 (5-C), 112.30 (7-C), 116.36 (2C, 10-C and 14-C), 117.37 (8-C), 121.47 (12-C), 128.85 (11-C), 136.24 (6-C), 138.02 (8a-C), 143.57 (4a-C), 143.76 (9a-C). *Anal*. Calcd for $C_{14}H_{12}NO_2Cl$: C, 64.25; H, 4.62; N, 5.35. Found: C, 64.31; H, 4.84; N, 5.39.

2-([1,4]Benzodioxin-6-amino)benzoic acid (3e)

A mixture of [1,4]benzodioxin-6-amine (**1**) (1 g, 6.62 mmol), *o*-chlorobenzoic acid (**2e**) (1.5 g, 7.65 mmol), powdered copper (60 mg, 0.9 mmol) and 1-pentanol (30 mL) was heated at 110°C with stirring for 15 h. The mixture was filtered and the solvent was removed under reduced pressure. Next, ethyl acetate was added to the residue and the mixture was extracted with sodium hydroxide (100 mL, 0.1 N). The alkaline layer was acidified with 3N hydrochloric acid until pH = 3 to give 0.95 g (53 %) of **3e** as a greenish solid; mp 191°C (from ethanol). ^{1}H-NMR (DMSO-d_6) δ: 4.22 (4H, s, 2-H and 3-H), 6.67 (1H, m, 12-H), 6.72 (1H, d, *J* = 2.0 Hz, 5-H), 6.72 (1H, dd, *J* = 1.3, 8.0 Hz, 7-H), 6.84 (1H, d, *J* = 8.0 Hz, 8-H), 6.99 (1H, d, *J* = 8.0 Hz, 10-H), 7.32 (1H, dt, *J* = 1.3, 7.2 Hz, 11-H), 7.85 (1H, d, *J* = 7.9 Hz, 13-H). ^{13}C-NMR (DMSO-d_6) δ: 63.96 (2-C), 64.18 (3-C), 111.70 (13a-C), 111.94 (5-C), 113.14 (10-C), 116.51 (12-C), 116.34 (7-C), 117.59 (8-C), 131.80 (13-C), 133.71 (6-C), 134.12 (11-C), 140.10 (8a-C), 143.75 (4a-C), 148.33 (9a-C), 170.06 (COOH). ***Anal.*** Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.23; H, 5.17; N, 5.31.

8-Methyl-11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (4a)

A mixture of *N*-(4-methylphenyl)[1,4]benzodioxin-6-amine (**3a**) (0.5 g, 2.1 mmol), sulfur (0.13 g, 4.1 mmol) and one crystal of iodine was refluxed under nitrogen in dry *o*-dichlorobenzene (4 mL) for 6 h. The mixture was extracted with ether (15 mL), filtered and concentrated. The resulting oil was chromatographed on silica gel with dichloromethane to yield 0.26 g (47 %) of **4a** as a red powder; mp 153° C (from dichloromethane). ^{1}H-NMR (DMSO-d_6) δ: 2.12 (3H, s, CH_3), 4.13 (2H, m, 2-H), 4.16 (2H, m, 3-H), 6.25 (1H, s, 12-H), 6.47 (1H, s, 5-H), 6.54 (1H, d, *J* = 8.1 Hz, 10-H), 6.73 (1H, br s, 7-H), 6.78 (1H, br d, *J* = 8.0 Hz, 9-H), 8.21 (1H, s, 11-H). ^{13}C-NMR (DMSO-d_6) δ: 20.00 (CH_3), 63.93 (2-C), 64.37 (3-C), 103.03 (12-C), 108.02 (5a-C), 114.19 (5-C), 114.26 (10-C), 116.32 (6a-C), 126.49 (7-C), 127.90 (9-C), 130.25 (8-C), 136.61 (11a-C), 138.31 (4a-C), 139.98 (10a-C), 142.60 (12a-C). ***Anal.*** Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.72; H, 5.07; N, 5.31.

8-Methoxy-11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (4b)

As described above for **4a** but with *N*-(4-methoxyphenyl)[1,4]benzodioxin-6-amine (**3b**) (0.5 g, 2 mmol) and sulfur (0.12 g, 4 mmol) gave after chromatography with hexane/ether (70/30) as eluent to yield 0.32 g (29 %) of **4b** as a yellow powder; mp 152 °C (from ether). ^{1}H-NMR (DMSO-d_6) δ: 3.64 (3H, s, OCH_3), 4.13 (1H, m, 2-H), 4.16 (1H, m, 3-H), 6.26 (1H, s, 12-H), 6.49 (1H, s, 5-H), 6.58 (2H, m, 9-H and 10-H), 6.60 (1H, br s, 7-H), 8.15 (1H, s, 11-H). ^{13}C-NMR (DMSO-d_6) δ: 55.43 (OCH_3), 63.92 (2-C), 64.37 (3-C), 102.95 (12-C), 107.63 (5a-C), 111.58 (7-C), 113.11 (9-C), 114.24 (5-C), 114.96 (10-C), 117.69 (6a-C), 136.09 (10a-C), 137.12 (11a-C), 138.20 (4a-C), 142.68 (12a-C), 154.33 (8-C). *Anal.* Calcd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4,87. Found: C, 62.55; H, 4.39; N, 5.14.

11*H*-[1,4]Dioxino[2,3-*b*]phenothiazine (4c) and 7*H*-[1,4]dioxino[2,3-*c*]phenothiazine (5c)

As described above for **4a** but with *N*-phenyl[1,4]benzodioxin-6-amine (**3c**) (0.5 g, 2.2 mmol) and sulfur (0.14 g, 4.4 mmol). After chromatography with ether a mixture (0.32 g, 43 %) of **4c** and **5c** (60/40) was obtained.

4c, ^{1}H-NMR (DMSO-d_6) δ: 4.14 (H, m, 2-H), 4.17 (2H, m, 3-H), 6.28 (1H, s, 12-H), 6.49 (1H, s, 5-H), 6.65 (1H, dd, *J* = 1.0, 8.0 Hz, 10-H), 6.72 (1H, dt, *J* = 1.2, 7.4 Hz, 8-H), 6.90 (1H, dd, *J* = 1.4, 7.7 Hz, 7-H), 6.97 (1H, dt, *J* = 1.5, 7.4 Hz, 9-H), 8.37 (1H, s, 11-H). ^{13}C-NMR (DMSO-d_6) δ: 63.98 (2-C), 64.41 (3-C), 103.24 (12-C), 108.09 (5a-C), 114.32 (5-C), 114.37 (10-C), 116.47 (6a-C), 121.42 (8-C), 126.29 (7-C), 127.50 (9-C), 136.32 (11a-C), 138.58 (4a-C), 142.53 (10a-C), 142.68 (12a-C).

5c, ^{1}H-NMR (DMSO-d_6) δ: 4.17 (2H, m, 2-H), 4.23 (2H, m, 3-H), 6.16 (1H, d, *J* = 8.6 Hz, 6-H), 6.48 (1H, d, *J* = 8.6 Hz, 5-H), 6.58 (1H, dd, *J* = 1.0, 8.0 Hz, 8-H), 6.68 (1H, dt, *J* = 1.1, 7.6 Hz, 10-H), 6.86 (1H, dd, *J* = 1.1, 7.7 Hz, 11-H), 6.93 (1H, dt, *J* = 1.0, 7.8 Hz, 9-H), 8.26 (1H, s, 7-H). ^{13}C-NMR (DMSO-d_6) δ: 63.70 (3-C), 64.88 (2-C), 105.10 (12a-C), 106.64 (6-C), 114.18 (8-C), 114.91 (5-C), 114.99 (11a-C), 121.28 (10-C), 126.43 (11-C), 127.65 (9-C), 135.67 (6a-C), 138.27 (4a-C), 139.24 (12b-C), 142.32 (7a-C).

***6H*-[1,4]Dioxino[2,3-*b*]acridin-11-one (4e) and *7H*-[1,4]dioxino[2,3-*a*]acridin-12-one (5e)**

Polyphosphoric acid procedure: To well stirred polyphosphoric acid (4 g, 1.9 mL), heated to 90 °C, was added 2-([1,4]benzodioxin-6-amino)benzoic acid (**3e**) (0.33 g, 1.22 mmol); the mixture was stirred at 110 °C for 2 h and poured onto ice. The precipitate was collected by filtration, washed with a saturated solution of sodium hydrogen carbonate and dried to yield a mixture of **4e** and **5e** (0.22 g, 72 %).

Sulfuric acid procedure: A mixture of 2-([1,4]benzodioxin-6-amino)benzoic acid (**3e**) (0.33 g, 1.22 mmol) and sulfuric acid (3 mL, 95%) was heated at 80 °C with vigorous stirring for 2 h. Then, ice was added carefully into the flask. The resulting solution was neutralized with 2N aqueous ammonia. The

precipitate was collected by filtration. The precipitate was washed with water, dried and evaporated to yield a mixture of **4e** and **5e** (0.19 g, 62 %). In all cases, the crude reaction product was purified by chromatography on silica gel. First compound (**5e**) was eluted with ether and next compound (**4e**) with ethanol.

5e was obtained as a yellow powder 0.133 g (43 %); mp > 300 °C (from ether). ^{1}H-NMR (DMSO-d_6) δ: 4.26 (2H, m, 3-H), 4.33 (2H, m, 2-H), 7.11 (1H, d, *J* = 8.9 Hz, 6-H), 7.14 (1H, dt, *J* = 1.4, 7.6 Hz, 10-H), 7.25 (1H, d, *J* = 9.1 Hz, 5-H), 7.53 (1H, d, *J* = 7.0 Hz, 8-H), 7.61 (1H, dt, *J* = 1.3, 7.0 Hz, 9-H), 8.11 (1H, dd, *J* = 1.4, 7.9 Hz, 11-H), 11.99 (1H, s, 7-H). ^{13}C-NMR (DMSO-d_6) δ: 64.37 (2-C), 63.40 (3-C), 109.11 (6-C), 111.82 (12a-C), 116.76 (8-C), 120.46 (10-C), 121.16 (11a-C), 123.90 (5-C), 125.99 (11-C), 132.74 (9-C), 136.09 (4a-C), 137.71 (6a-C), 140.12 (7a-C), 142.82 (12b-C), 176.18 (12-C). *Anal.* Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.42; H, 4.68; N, 5.34.

4e was obtained as a yellow powder 0.086 g (28 %); mp > 300 °C (from ethanol). ^{1}H-NMR (DMSO-d_6) δ: 4.30 (2H, m, 3-H), 4.37 (2H, m, 2-H), 6.93 (1H, s, 12-H), 7.18 (1H, t, *J* = 7.4 Hz, 8-H), 7.44 (1H, d, *J* = 8.2 Hz, 10-H), 7.59 (1H, s, 5-H), 7.65 (1H, dt, *J* = 1.4, 7.6 Hz, 9-H), 8.17 (1H, dd, *J* = 8.0 Hz, 7-H), 11.46 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 63.91 (3-C), 64.95 (2-C), 102.95 (12-C), 111.78 (5-C), 115.61 (5a-C), 119.58 (5a-C), 120.53 (8-C), 125.98 (7-C), 132.91 (9-C), 136.87 (11a-C), 139.81 (4a-C), 140.91 (10a-C), 149.46 (12a-C), 176.18 (11-C). *Anal.* Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.38; H, 4.62; N, 5.29.

11-Chloro[1,4]dioxino[2,3-*b*]acridine (6a) and 12-chloro[1,4]dioxino[2,3-*a*]acridine (7a)

A mixture of 2-([1,4]benzodioxin-6-amino)benzoic acid (**3e**) (0.5 g, 1.85 mmol) and phosphorus oxychloride (5 mL, 54.6 mmol) was heated at 120°C for 30 min. After cooling, the excess of phosphorus oxychloride was extracted with petroleum ether (20 mL). The sticky residue was neutralized with 10 % ammonia. After filtration, the green precipitate was washed with water and dried to yield 0.31 g of **6a** and **7a** (62 % yield). The crude reaction product was purified by chromatography on silica gel with petroleum ether/ether (4/1) to yield two separated fractions. Compound (**7a**) was obtained from the first fraction and compound (**6a**) from the second fraction.

7a was obtained as a yellow powder (0.1 g, 20 %); mp 183 °C (from ether). ^{1}H-NMR ($CDCl_3$) δ: 4.45 (2H, m, 2-H), 4.45 (2H, m, 3-H), 7.41 (1H, d, *J* = 9.4 Hz, 6-H), 7.58 (1H, td, *J* = 1.3, 6.6 Hz, 10-H), 7.72 (1H, td, *J* = 1.4, 7.1 Hz, 9-H), 7.76 (1H, d, *J* = 9.4 Hz, 5-H), 8.12 (1H, dd, *J* = 0.7, 7.9 Hz 8-H), 8.50 (1H, dd, *J* = 1.3, 8.1 Hz, 11-H). ^{13}C-NMR ($CDCl_3$) δ: 64.02 (3-C), 64.25 (2-C), 118.03 (12a-C), 123.47 (6-C), 124.50 (5-C), 124.71 (11-C), 125.33 (11a-C), 126.91 (10-C), 129.48 (9-C), 129.73 (8-C), 136.12 (12b-C), 137.39 (12-C), 139.29 (4a-C), 146.60 (6a-C), 147.15 (7a-C). *Anal.* Calcd for $C_{15}H_{10}NO_2Cl$: C, 66.31; H,

3.71; N, 5.16. Found: C, 66.55; H, 3.98; N, 4.86.

6a was obtained as a yellow powder 0.160 g (32 %); mp 132°C (from ether). ^{1}H-NMR ($CDCl_3$) δ: 4.42 (2H, m, 2-H), 4.42 (2H, m, 3-H), 7.53 (1H, td, *J* = 1.1, 8.0 Hz, 9-H), 7.60 (1H, s, 5-H), 7.70 (1H, td, *J* = 1.4, 8.1 Hz, 8-H), 7.77 (1H, s, 12-H), 8.09 (1H, d, *J* = 8.6 Hz, 7-H), 8.32 (1H, d, *J* = 8.5 Hz 10-H). ^{13}C-NMR ($CDCl_3$) δ: 64.43 (3-C), 64.49 (2-C), 107.64 (12-C), 112.74 (5-C), 121.43 (11a-C), 123.34 (10a-C), 124.23 (10-C), 125.96 (9-C), 129.15 (7-C), 129.60 (8-C), 136.45 (11-C), 145.61 (12a-C), 146.29 (4a-C), 147.99 (5a-C), 148.61 (6a-C). *Anal.* Calcd for $C_{15}H_{10}NO_2Cl$: C, 66.31; H, 3.71; N, 5.16. Found: C, 66.60; H, 3.96; N, 5.41.

***N*-Butyl[1,4]benzodioxin-6-amine (8a)**

To a solution of [1,4]benzodioxin-6-amine (**1**) (2g, 13.2 mmol) in dry acetonitrile (30 mL) was added 1-bromobutane (2 g, 14.6 mmol) and sodium hydrogen carbonate (1.23 g, 14.6 mmol). The mixture was refluxed under stirring for 8 h, neutralized with 2N hydrochloric acid (7 mL), and then dichloromethane (20 mL) was added. The organic phase was separated, washed twice with water (40 mL), and evaporated. The residue was dissolved in methanol (20 mL), acidified with sulfuric acid (3 mL), filtrated, and the filtrate was concentrated to 5 mL volume. The mixture was neutralized with sodium hydrogen carbonate (1.5 g, 17.9 mmol) and dissolved in dichloromethane (20 mL). The organic phase was separated, washed twice with water (20 mL) and dried over anhydrous sodium to give a crude reaction product. Purification by chromatography on silica gel with toluene as the eluent gave a yellow oil (**8a**) (1.4 g, 50 %). ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, *J* = 7.3 Hz, δ-H), 1.35 (2H, m, γ-H), 1.47 (2H, m, β-H), 2.88 (2H, t, *J* = 7.0 Hz, α-H), 4.08 (2H, m, 2-H), 4.14 (2H, m, 3-H), 5.05 (1H, br s, 9-H), 6.03 (1H, d, *J* = 2.5 Hz, 5-H), 6.06 (1H, dd, *J* = 2.6, 8.5 Hz, 7-H), 6.56 (1H, d, *J* = 8.5 Hz, 8-H). ^{13}C-NMR (DMSO-d_6) δ: 13.95 (δ-C), 19.95 (γ-C), 31.03 (β-C), 43.30 (α-C), 63.78 (2-C), 64.23 (3-C), 100.23 (5-C), 105.72 (7-C), 117.18 (8-C), 134.15 (8a-C), 143.77 (4a-C), 144.21 (6-C). *Anal.* Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H: 8.27; N, 6.76. Found: C, 69.87; H: 8.03; N, 6.34.

***N*-Isopentyl[1,4]benzodioxin-6-amine (8b)**

As described above for **8a** but with **1** and 1-bromo-3-methylbutane (2.2 g, 14.6 mmol). Work up gave an orange oil (**8b**) (1.44 g, 48 %). ^{1}H-NMR (DMSO-d_6) δ: 0.89 (6H, t, *J* = 6.6 Hz, δ-H), 1.39 (2H, dt, *J* = 6.6, 7.3 Hz, β-H), 1.66 (1H, m, γ-H), 2.89 (2H, t, *J* = 7.2 Hz, α-H), 4.08 (2H, m, 2-H), 4.14 (2H, m, 3-H), 5.04 (1H, br s, 9-H), 6.03 (1H, d, *J* = 2.6 Hz, 5-H), 6.06 (1H, dd, *J* = 2.6, 8.6 Hz, 7-H), 6.57 (1H, d, *J* = 8.5 Hz, 8-H). ^{13}C-NMR (DMSO-d_6) δ: 22.61 (δ-C), 25.46 (γ-C), 37.91 (β-C), 41.77 (α-C), 63.77 (2-C), 64.41 (3-C), 100.23 (5-C), 105.72 (7-C), 117.17 (8-C), 134.16 (8a-C), 143.75 (4a-C), 144.21 (6-C). *Anal.*

Calcd for $C_{13}H_{19}NO_2$: C,70.56; H, 8.65; N, 6.33. Found: C,70.94; H, 8.43; N, 6.56.

***N*-Isopropyl[1,4]benzodioxin-6-amine (8c)**

As described above for **8a** but with **1**, 2-bromopropane (1.8 g, 14.6 mmol) and sodium hydrogen carbonate (2 g, 23.8 mmol). Next, the solution was refluxed under stirring for 72 h. After work up a yellow oil (**8c**) was obtained (1 g, 40 %). ^{1}H-NMR (DMSO-d_6) δ: 1.07 (6H, d, *J* = 6.3 Hz, β-C), 3.38 (1H, m, α-C), 4.08 (2H, m, 2-H), 4.14 (2H, m, 3-H), 4.85 (1H, s, 9-H), 6.05 (1H, d, *J* = 2.0 Hz, 5-H), 6.06 (1H, dd, *J* = 2.0, 8.1 Hz, 7-H), 6.56 (1H, d, *J* = 7.9 Hz, 8-H). ^{13}C-NMR (DMSO-d_6) δ: 22.61 (β-C), 43.71 (α-C), 63.78 (2-C), 64.14 (3-C), 101.03 (5-C),106.38 (7-C), 117.22 (8-C), 134.13 (8a-C), 143.12 (6-C), 143.78 (4a-C). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.51; H, 7.74; N, 7.52.

***N*-(1-Methylbutyl)[1,4]benzodioxin-6-amine (8d)**

As described above for **8a** but with **1** and 2-bromopentane (2.2 g, 14.6 mmol). After work up a white oil (**8d**) was obtained (1.55 g, 53 %). ^{1}H-NMR (DMSO-d_6) δ: 0.86 (3H, t, *J* = 7.1 Hz, δ-H), 1.03 (3H, d, *J* = 6.3 Hz, α'-H), 1.32 (2H, m, γ- H), 1.44 (2H, m, β-H), 3.23 (1H, m, α-H), 4.08 (2H, m, 2-H), 4.14 (2H, m, 3-H), 4.84 (1H, s, 9-H), 6.03 (1H, d, *J* = 2.6 Hz, 5-H), 6.05 (1H, dd, *J* = 2.6, 8.3 Hz, 7-H), 6.55 (1H, d, *J* = 8.4 Hz, 8-H). ^{13}C-NMR (DMSO-d_6) δ: 14.16 (δ-C), 18.98 (γ-C), 20.49 (α'-C), 38.70 (β-C), 47.67 (α-C), 63.78 (2-C), 64.22 (3-C), 100.71 (5-C), 106.12 (7-C), 117.22 (8-C), 133.94 (8a-C), 143.42 (6-C), 143.78 (4a-C). *Anal.* Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.82; H, 8.33; N, 6.58.

***N*-Butyl-*N*-phenyl[1,4]benzodioxin-6-amine (9a)**

To a solution of *N*-butyl[1,4]benzodioxin-6-amine (**8a**) (1 g, 4.8 mmol) in dry dichloromethane (30 mL) at rt were slowly added triphenylbismuth diacetate (**2c**) (0.9 g, 1.6 mmol) and copper(II) acetate (0.09 g, 0.48 mmol). The mixture was stirred at rt for 4 h. Next, dichloromethane (20mL) was added, and the resulting mixture was filtered. The insoluble part was washed with dichloromethane (2 x 20 mL), and the organic layers were dried over anhydrous sodium sulphate and evaporated to give a crude reaction product, which was purified by chromatography on silica gel with toluene as the eluent. A yellow oil was recovered, yielding 0.20 g (15 %) of **9a**. ^{1}H-NMR (DMSO-d_6) δ: 0.86 (3H, t, *J* = 7.3 Hz, δ-H), 1.30 (2H, m, α-H), 1.50 (2H, m, β-H), 3.55 (2H, t, *J* = 7.5 Hz, γ-H), 4.22 (4H, s, 2-H and 3-H), 6.55 (1H, dd, *J* = 2.6, 8.3 Hz, 7-H), 6.57 (1H, d, *J* = 2.5 Hz, 5-H), 6.70 (1H, m, 12-H), 6.72 (2H, m, 10-H), 6.82 (1H, d, *J* = 8.3 Hz, 8-H), 7.13 (2H, m, 11-H). ^{13}C-NMR (DMSO-d_6) δ: 13.87 (δ-C), 19.68 (γ-C), 29.16 (β-C), 51.40 (α-C), 63.97 (2-C), 64.14 (3-C), 113.47 (5-C), 116.27 (2C, 10-C and 14-C), 117.69 (8-C), 117.96 (7-C), 118.23 (12-C), 128.99 (2C, 11-C and 13-C), 139.93 (8a-C), 140.88 (6-C), 143.81 (4a-C), 148.83 (9a-C).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.36; H, 7.61; N, 4.77.

_N_-Butyl-_N_-(4-methoxyphenyl)[1,4]benzodioxin-6-amine (9b)

As described above for **9a** but with *N*-butyl[1,4]benzodioxin-6-amine (**8a**) (1 g, 4.8 mmol) and 4-methoxyphenyllead triacetate (**2b**) (2.6 g, 5.3 mmol). Chromatography yielded a brown oil (0.45 g, 30 %) of **9b**. ^{1}H-NMR (DMSO-d_6) δ: 0.86 (3H, t, *J* = 7.3 Hz, δ-H), 1.30 (2H, m, γ-H), 1.47 (2H, m, β-H), 3.49 (2H, t, *J* = 7.5 Hz, α-H), 3.71 (3H, s, OCH_3), 4.16 (4H, br s, 2-H and 3-H), 6.26 (1H, d, *J* = 2.7 Hz, 5-H), 6.28 (1H, dd, *J* = 2.7, 8.2 Hz, 7-H), 6.69 (1H, d, *J* = 8.1 Hz, 8-H), 6.86 (2H, d, *J* = 8.9 Hz, 11-H and 13-H), 6.90 (2H, d, *J* = 8.9 Hz, 10-H and 14-H). ^{13}C-NMR (DMSO-d_6) δ: 13.93 (δ-C), 19.74 (γ-C), 29.33 (β-C), 51.77 (α-C), 55.30 (OCH_3), 63.92 (2-C), 64.34 (3-C), 107.38 (5-C), 112.02 (7-C), 114.76 (2C, 11-C and 13-C), 117.30 (8-C), 123.90 (2C, 10-C and 14-C), 137.10 (8a-C), 141.38 (9a-C), 143.12 (6-C), 143.59 (4a-C), 154.66 (12-C). *Anal.* Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.69; H, 7.23; N, 4.55.

_N_-Butyl-_N_-(4-methylphenyl)[1,4]benzodioxin-6-amine (9c)

As described above for **9a** but with *N*-butyl[1,4]benzodioxin-6-amine (**8a**) (1 g, 4.8 mmol) and *p*-tolyllead triacetate (**2a**) (2.5 g, 5.3 mmol). Chromatography yielded a brown oil (0.40 g, 26 %) of **9c**. ^{1}H-NMR (DMSO-d_6) δ: 0.86 (3H, t, *J* = 7.3 Hz, δ-H), 1.30 (2H, m, γ-H), 1.48 (2H, m, β-H), 2.19 (3H, s, CH_3), 3.52 (2H, t, *J* = 7.5 Hz, α-H), 4.20 (4H, br s, 2-H and 3-H), 6.44 (1H, dd, *J* = 2.7, 8.2 Hz, 7-H), 6.46 (1H, d, *J* = 2.7 Hz, 5-H), 6.71 (2H, d, *J* = 8.6 Hz, 10-H), 6.76 (1H, d, *J* = 8.2 Hz, 8-H), 6.99 (2H, d, *J* = 8.6 Hz, 11-H and 13-H). ^{13}C-NMR (DMSO-d_6) δ: 13.91 (δ-C), 19.72 (γ-C), 20.21 (CH_3), 29.26 (β-C), 51.52 (α-C), 63.96 (2-C), 64.24 (3-C), 111.24 (5-C), 115.81 (7-C), 117.51 (8-C), 118.63 (2C, 10-C and 14-C), 128.33 (12-C), 129.62 (2C, 11-C and 13-C), 138.82 (8a-C), 141.82 (6-C), 143.70 (4a-C), 146.01 (9a-C). *Anal.* Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H: 7.80; N, 4.71. Found: C, 76.41; H: 7.91; N, 5.02.

_N_-Isopentyl-_N_-phenyl[1,4]benzodioxin-6-amine (9d)

As described above for **9a** but with *N*-isopentyl[1,4]benzodioxin-6-amine (**8b**) (1 g, 4.5 mmol) and triphenylbismuth diacetate (**2c**) (0.9 g, 1.6 mmol). Chromatography yielded an orange oil (**9d**) (0.50 g, 35 %). ^{1}H-NMR (DMSO-d_6) δ: 0.87 (6H, d, *J* = 6.8 Hz, δ-H), 1.43 (2H, dt, *J* = 6.8, 7.8 Hz, β-H), 1.60 (1H, m, γ-H), 3.57 (2H, t, *J* = 7.8 Hz, α-H), 4.22 (4H, s, 2-H and 3-H), 6.55 (1H, dd, *J* = 2.0, 8.0 Hz, 7-H), 6.56 (1H, d, *J* = 2.0 Hz, 5-H), 6.70 (2H, m, 10-H and 14-H), 6.71 (1H, m, 12-H), 6.83 (1H, d, *J* = 8.0 Hz, 8-H), 7.14 (2H, m, 11-H and 13-H). ^{13}C-NMR (DMSO-d_6) δ: 22.59 (δ-C), 25.71 (α-C), 35.77 (β-C), 50.13 (α-C), 64.01 (2-C), 64.22 (3-C), 113.45 (5-C), 116.29 (2C, 10-C and 14-C), 117.76 (7-C), 117.96 (8-C), 118.31 (12-C), 129.08 (2C, 11-C and 13-C), 139.97 (8a-C), 140.91 (6-C), 143.86 (4a-C), 148.40 (9a-C).

Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.41; H, 7.97; N, 4.36.

_N_-Isopropyl-_N_-phenyl[1,4]benzodioxin-6-amine (9e)

As described above for **9a** but with *N*-isopropyl[1,4]benzodioxin-6-amine (**8c**) (1 g, 5.2 mmol) and triphenylbismuth diacetate (**2c**) (1 g, 1.8 mmol). Chromatography yielded a yellow oil (**9e**) (0.63 g, 45 %). ^{1}H-NMR (DMSO-d_6) δ: 1.05 (6H, d, *J* = 6.5 Hz, β-H), 4.23 (1H, m, α-H), 4.24 (4H, s, 2-H and 3-H), 6.48 (1H, dd, *J* = 2.5, 8.2 Hz, 7-H), 6.50 (1H, d, *J* = 2.5 Hz, 5-H), 6.55 (2H, m, 10-H and 14-H), 6.66 (1H, m, 12-H), 6.87 (1H, d, *J* = 8.1 Hz, 8-H), 7.11 (2H, m, 11-H and 13-H). ^{13}C-NMR (DMSO-d_6) δ: 20.74 (β-C), 47.06 (α-C), 64.04 (2-C), 64.12 (3-C), 115.84 (2C, 10-C and 14-C), 117.51 (8-C), 117.57 (2C, 5-C and 7-C), 121.94 (12-C), 128.92 (2C, 11-C and 13-C), 136.67 (8a-C), 141.26 (6-C), 143.72 (4a-C), 148.41 (9a-C). *Anal.* Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.03; H, 6.94; N, 5.49.

_N_-(1-Methylbutyl)-_N_-(4-methylphenyl)[1,4]benzodioxin-6-amine (9f)

As described above for **9a** but with *N*-(1-methylbutyl)[1,4]benzodioxin-6-amine (**8d**) (1 g, 4.48 mmol) and *p*-tolyllead triacetate (**2a**) (2.34 g, 4.94 mmol). Chromatography yielded a brown oil (**9f**) (0.24 g, 17 %). ^{1}H-NMR (DMSO-d_6) δ: 0.86 (3H, t, *J* = 7.3 Hz, δ-H), 1.04 (3H, d, *J* = 6.5 Hz, α'-H), 1.34 (2H, m, γ-H), 1.51 (2H, m, β-H), 2.18 (3H, s, CH_3), 3.98 (1H, m, α-H), 4.21 (4H, s, 2-H and 3-H), 6.34 (1H, d, *J* = 2.5 Hz, 5-H), 6.35 (1H, dd, *J* = 2.5, 8.2 Hz, 7-H), 6.57 (2H, d, *J* = 8.5 Hz, 10-H and 14-H), 6.76 (1H, d, *J* = 8.2 Hz, 8-H), 6.99 (2H, d, *J* = 8.5 Hz, 11-H and 13-H). ^{13}C-NMR (DMSO-d_6) δ: 14.10 (δ-C), 18.61 (γ-C), 19.70 (α'-C), 20.17 (CH_3), 37.21 (β-C), 51.99 (α-C), 63.98 (2-C), 64.18 (3-C), 113.91 (5-C), 117.34 (8-C), 118.44 (7-C), 119.56 (10-C), 128.30 (12-C), 129.53 (11-C), 139.21 (8a-C), 139.56 (6-C), 143.57 (4a-C), 145.34 (9a-C). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H: 8.09; N, 4.50. Found C, 77.55; H, 7.82; N, 4.37.

_N_-(1-Methylbutyl)-_N_-phenyl[1,4]benzodioxin-6-amine (9g)

As described above for **9a** but with *N*-(1-methylbutyl)[1,4]benzodioxin-6-amine (**8d**) (1 g, 4.48 mmol) and triphenylbismuth diacetate (**2d**) (0.9 g, 1.6 mmol). Chromatography yielded an orange oil (**9g**) (0.44 g, 33 %). ^{1}H-NMR (DMSO-d_6) δ: 0.87 (3H, t, *J* = 7.4 Hz, δ-H),1.06 (3H, d, *J* = 6.5 Hz, α-H), 1.36 (2H, m, γ-H), 1.52 (2H, m, β-H), 4.04 (1H, m, α-H), 4.24 (4H, s, 2-H and 3-H), 6.48 (1H, dd, *J* = 2.3, 8.3 Hz, 7-H), 6.50 (1H, d, *J* = 2.3 Hz, 5-H), 6.56 (2H, m, 10-H and 14-H), 6.66 (1H, m, 12-H), 7.11 (2H, m, 11-H and 13-H). ^{13}C-NMR (DMSO-d_6) δ: 13.91 (δ-C), 18.47 (γ-C), 19.53 (α'-C), 37.01 (β-C), 51.68 (α-C), 63.89 (2-C), 63.98 (3-C), 116.01 (2C, 10-C and 14-C), 116.93 (5-C), 117.38 (7-C), 117.54 (8-C), 121.41 (12-C), 128.75 (2C, 11-C and 13-C), 137.02 (8a-C), 140.93 (6-C), 143.56 (4a-C), 148.57 (9a-C). *Anal.*

Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H: 7.80; N, 4.71. Found: C, 76.92; H: 7.87; N, 4.65.

11-Butyl-11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (10a)

A mixture of **9a** (0.20 g, 0.7 mmol), sulfur (0.05 g, 1.4 mmol), and one crystal of iodine in dry *o*-dichlorobenzene (2 mL) was refluxed under nitrogen for 8 h. The mixture was extracted with ether (10 mL), filtered and concentrated. The resulting oil was added on silicagel (5 g), and the mixture was washed with hexane (250 mL) to eliminate *o*-dichlorobenzene excess. Then the resulting silicagel/**10a** mixture was washed with ether (250 mL); the organic phase was dried over anhydrous sodium sulphate and evaporated to yield an oil. This oil was diluted with light petroleum (30 mL) and kept for one night at 4°C to afford a viscous green precipitate of **10a** after filtration (0.033 g, 15%). ^{1}H-NMR (DMSO-d_6) δ: 0.86 (3H, t, *J* = 7.4 Hz, δ-H), 1.36 (2H, m, γ-H), 1.62 (2H, m, β-H), 3.76 (2H, t, *J* = 6.8 Hz, α-H), 4.16 (2H, m, 3-H), 4.20 (2H, m, 2-H), 6.53 (1H, s, 12-H), 6.67 (1H, t, 5-H), 6.89 (1H, t, *J* = 7.4 Hz, 8-H), 6.96 (1H, d, *J* = 8.2 Hz, 10-H), 7.11 (1H, d, *J* = 7.6 Hz, 7-H), 7.16 (1H, t, *J* = 7.9 Hz, 9-H). ^{13}C-NMR (DMSO-d_6) δ: 13.67 (δ-C), 19.46 (γ-C), 28.47 (β-C), 46.25 (α-C), 63.97 (3-C), 64.32 (2-C), 105.07 (12-C), 114.98 (5-C), 115.30 (5a-C), 115.64 (10-C), 122.02 (8-C), 123.97 (6a-C), 127.05 (7-C), 127.46 (9-C), 138.86 (4a-C), 138.99 (11a-C), 142.78 (12a-C), 145.21 (10a-C). *Anal.* Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 69.05; H, 5.87; N, 4.62.

11-Butyl-8-methoxy-11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (10b)

As described above for **10a** but with *N*-butyl-*N*-(4-methoxyphenyl)[1,4]benzodioxin-6-amine (**9b**) (0.4 g, 1.3 mmol). Work up yielded 0.075 g (17 %) of **10b** as a green oil. ^{1}H-NMR (DMSO-d_6) δ: 0.85 (3H, t, *J* = 7.3 Hz, δ-H), 1.35 (2H, m, γ-H), 1.60 (2H, m, β-H), 3.71 (2H, t, *J* = 6.8 Hz, α-H), 3.68 (3H, s, OCH_3), 4.16 (2H, m, 3-H), 4.20 (2H, m, 2-H), 6.50 (1H, s, 12-H), 6.66 (1H, s, 5-H), 6.77 (1H, dd, *J* = 1.2, 8.0 Hz, 9-H), 6.80 (1H, d, *J* = 1.1 Hz, 7-H), 6.88 (1H, d, *J* = 7.5 Hz, 10-H). ^{13}C-NMR (DMSO-d_6) δ: 13.70 (δ-C), 19.48 (α-C), 28.55 (β-C), 46.39 (γ-C), 55.49 (OCH_3), 63.98 (3-C), 64.36 (2-C), 104.78 (12-C), 112.44 (7-C), 112.89 (9-C), 114.97 (5-C), 115.08 (5a-C), 116.36 (10-C), 125.54 (6a-C), 138.54 (2C, 4a and 10a-C), 138.54 (4a-C), 139.75 (11a-C), 142.82 (12a-C), 154.63 (8-C). *Anal.* Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.69; H, 6.34; N, 4.27.

11-Isopentyl-11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (10d)

As described above for **10a** but with *N*-isopentyl-*N*-phenyl[1,4]benzodioxin-6-amine (**9d**) (0.5 g, 1.7 mmol). Work up yielded a green oil (**10d**) (0.06 g, 11 %). ^{1}H-NMR (DMSO-d_6) δ: 0.87 (6H, d, *J* = 6.6 Hz, δ-H), 1.54 (2H, q, *J* = 6.9 Hz, β-H), 1.69 (1H, m, γ-H), 3.77 (1H, t, *J* = 7.0 Hz, α-H), 4.16 (2H, m, 3-H), 4.19 (2H, m, 2-H), 6.54 (1H, s, 12-H), 6.67 (1H, s, 5-H), 6.88 (1H, t, *J* = 7.5 Hz, 8-H), 6.96 (1H, d, *J* =

8.2 Hz, 10-H), 7.11 (1H, d, *J* = 7.7 Hz, 7-H), 7.16 (1H, t, *J* = 7.8 Hz, 9-H). ^{13}C-NMR (DMSO-d_6) δ: 22.41 (δ-C), 25.58 (γ-C), 35.33 (β-C), 44.97 (α-C), 63.97 (3-C), 64.33 (2-C), 105.04 (12-C), 115.01 (5-C), 115.35 (5a-C), 115.61 (10-C), 122.03 (8-C), 124.05 (6a-C), 127.06 (7-C), 127.45 (9-C), 138.87 (4a-C), 139.04 (11a-C), 142.79 (12a-C), 145.22 (10a-C). *Anal.* Calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28. Found: C, 69.21; H, 6.09; N, 4.53.

2-Diethylamino-1-(8-methyl-11*H*-[1,4]dioxino[2,3-*b*]phenothiazin-11-yl)ethan-1-one (11a)

To a solution of 8-methyl-11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (**4a**) (0.19 g, 0.7 mmol) in toluene (7 mL) was added chloroacetyl chloride (0.057 g, 0.5 mmol), and the mixture was kept at 35 °C under stirring for 45 min. The solution was concentrated, and to the residual viscous oil a solution of *N*,*N*-diethylamine (2 mL) in toluene (4 mL) was added. The solution was refluxed for 2 h under stirring and evaporated to yield a crude reaction product which was purified by chromatography on silica gel with toluene as the eluent. A red oil was obtained (**11a**) (0.14 g, 52 %). ^{1}H-NMR (DMSO-d_6) δ: 0.81 (6H, t, *J* = 7.1 Hz, δ-H), 2.45 (4H, q, *J* = 7.1 Hz, γ-H), 2.30 (3H, s, CH_3), 3.40 (2H, br s, β-H), 4.25 (4H, m, 2-H and 3-H), 6.99 (1H, s, 5-H), 7.14 (1H, s, 12-H), 7.17 (1H, br d, *J* = 8.0 Hz, 9-H), 7.31 (1H, br s, 7-H), 7.45 (1H, d, *J* = 8.0 Hz, 10-H). ^{13}C-NMR (DMSO-d_6) δ: 12.11 (δ-C), 20.45 (CH_3), 46.81 (γ-C), 54.63 (β-C), 64.23 (2-C), 64.27 (3-C), 115.26 (5-C), 115.83 (12-C), 123.77 (5a-C), 126.78 (7-C), 127.71 (10-C), 127.93 (9-C), 132.27 (6a-C), 132.35 (11a-C), 136.40 (8-C), 136.50 (10a-C), 142.10 (4a-C), 142.49 (12a-C), 169.26 (CO). *Anal.* Calcd for $C_{21}H_{24}N_2O_3S$: C, 65.60; H, 6.29; N, 7.29. Found: C, 65.41; H, 6.53; N, 7.60.

2-Diethylamino-1-(8-methoxy-11*H*-[1,4]dioxino[2,3-b]phenothiazin-11-yl)ethan-1-one (11b)

As described above for **11a** but with 8-methoxy-11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (**4b**) (0.2 g, 0.7 mmol). After work up, a green oil (**11b**) (0.17 g, 61 %) was obtained. ^{1}H-NMR (DMSO-d_6) δ: 0.80 (6H, t, *J* = 7.1 Hz, δ-H), 2.43 (4H, q, *J* = 7.1 Hz, γ-H), 3.25 (2H, s, β-H), 3.76 (3H, s, OCH_3), 4.22 (2H, m, 3-H), 4.26 (2H, m, 2-H), 6.90 (1H, dd, *J* = 2.8, 8.8 Hz, 9-H), 7.02 (1H, s, 5-H), 7.08 (1H, d, *J* = 2.6 Hz, 7-H), 7.18 (1H, s, 12-H), 7.47 (1H, br d, *J* = 8.8 Hz, 10-H). ^{13}C-NMR (DMSO-d_6) δ: 12.13 (δ-C), 46.80 (γ-C), 54.42 (β-C), 55.72 (OCH_3), 64.18 (3-C), 64.22 (2-C), 112.28 (7-C), 113.18 (9-C), 115.29 (5-C), 115.81 (12-C), 123.80 (5a-C), 127.79 (10-C), 131.71 (10a-C), 132.44 (11a-C), 133.85 (6a-C), 142.01 (4a-C), 142.48 (12a-C), 157.49 (8-C), 169.34 (CO). *Anal.* Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.99. Found: C, 63.17; H, 5.95; N, 6.87.

2-Diethylamino-1-(8-methoxy-11*H*-[1,4]dioxino[2,3-b]phenothiazin-11-yl)ethan-1-one (11c)

As described above for **11a** but with 11*H*-[1,4]dioxino[2,3-*b*]phenothiazine (**4c**) (0.18 g, 0.7 mmol). After

work up, a green oil (**11c**) (0.18 g, 69 %) was obtained. ^{1}H-NMR (DMSO-d_6) δ: 0.83 (6H, t, *J* = 7.0 Hz, δ-H), 2.43 (4H, q, *J* = 7.1 Hz, γ-H), 3.38 (2H, s, β-H), 4.24 (4H, m, 2-H and 3-H), 7.01 (1H, s, 5-H), 7.16 (1H, s, 12-H), 7.28 (1H, t, *J* = 7.8 Hz, 9-H), 7.39 (1H, dt, *J* = 1.2, 7.8 Hz, 8-H), 7.53 (1H, dd, *J* = 1.0, 8.0 Hz, 7-H), 7.57 (1H, d, *J* = 8.1 Hz, 10-H). ^{13}C-NMR (DMSO-d_6) δ: 12.11 (δ-C), 46.83 (γ-C), 54.61 (β-C), 64.20 (3-C), 64.25 (2-C), 115.28 (5-C), 115.80 (12-C), 123.78 (5a-C), 126.71 (7-C), 127.39 (8-C), 127.44 (9-C), 127.70 (10-C), 132.38 (11a-C), 132.75 (6a-C), 138.95 (10a-C), 142.08 (4a-C), 142.48 (12a-C), 169.38 (CO). *Anal.* Calcd for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.99; N, 7.56. Found: C, 64.65; H, 6.30; N, 7.76.

6-Methyl-*6H*-[1,4]dioxino[2,3-*b*]acridin-11-one (12a) and 7-methyl-*7H*-[1,4]dioxino[2,3-*a*]acridin-12-one (13a)

A mixture of **4e** and **5e** (0.5 g, 1.97 mmol), potassium hydroxide (0.5 g, 8.9 mmol), water (5 mL) and acetone (40 mL) was heated at 80 °C for 15 min. A solution of dimethyl sulfate (0.2 mL, 3.2 mmol) in acetone (10 mL) was added dropwise. The reacting mixture was heated for 2 h more and concentrated to 10 mL volume. After cooling, the precipitate was recovered (0.4 g, 77 %). This crude reaction product was purified by chromatography on silica gel with ether to yield two separated fractions. Compound (**12a**) was obtained from the first fraction and compound (**13a**) from the second one.

12a was obtained as a yellow powder (0.15 g, 28 %); mp 247 °C (from ether). ^{1}H-NMR ($CDCl_3$) δ: 3.74 (3H, s, CH_3), 4.28 (2H, m, 2-H), 4.36 (2H, m, 3-H), 6.90 (1H, s, 5-H), 7.20 (1H, dt, *J* = 0.6, 7.1 Hz, 9-H), 7.40 (1H, d, *J* = 8.0 Hz, 7-H), 7.63 (1H, dt, *J* = 1.7, 6.9 Hz, 8-H), 7.97 (1H, s, 12-H), 8.48 (1H, dd, *J* =1.7, 8.0 Hz, 10-H). ^{13}C-NMR ($CDCl_3$) δ: 33.66 (CH_3), 63.99 (2-C), 65.06 (3-C), 102.00 (5-C), 114.27 (12-C), 114.33 (7-C), 117.56 (11a-C), 120.65 (9-C), 121.69 (10a-C), 127.60 (10-C), 133.13 (8-C), 138.69 (5a-C), 139.56 (12a-C), 142.38 (6a-C), 149.50 (4a-C), 176.73 (11-C). *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found C, 72.19; H, 4.67; N, 5.57.

13a was obtained as a yellow powder (0.23 g, 43 %); mp 175 °C (from ether). ^{1}H-NMR ($CDCl_3$) δ: 3.60 (3H, s, CH_3), 4.32 (2H, m, 2-H), 4.48 (2H, m, 3-H), 6.96 (1H, d, *J* = 9.4 Hz, 6-H), 7.22 (1H, dt, *J* = 1.6, 7.1 Hz, 10-H), 7.25 (1H, d, *J* = 9.3 Hz, 5-H), 7.40 (1H, d, *J* = 8.6 Hz, 8-H), 7.64 (1H, dt, *J* = 1.7, 6.9 Hz, 9-H), 8.48 (1H, dd, *J* = 1.5, 8.5 Hz, 11-H). ^{13}C-NMR ($CDCl_3$) δ: 33.44 (CH_3), 63.69 (3-C), 64.95 (2-C), 106.72 (6-C), 113.88 (12a-C), 114.07 (8-C), 120.85 (10-C), 123.30 (5-C), 123.64 (11a-C), 127.79 (11-C), 133.12 (9-C), 137.05 (4a-C), 139.40 (6a-C), 141.82 (7a-C), 144.06 (12b-C), 177.81 (12-C). *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found C, 71.80; H, 5.26; N, 5.61.

6-[2-(Dimethylamino)ethyl]-*6H*-[1,4]dioxino[2,3-*b*]acridin-11-one (14a) and 7-[2-(dimethyl-amino)ethyl]-*7H*-[1,4]dioxino[2,3-*a*]acridin-12-one (15a).

A mixture of **4e** and **5e** (0.3 g, 1.18 mmol) and 50 % sodium hydroxide (9 mL, 0.11 mol) was warmed

until dissolution. Next triethylbenzylammonium chloride (0.14 g, 1 mmol), 2-(dimethylamino)ethyl chloride hydrochloride (0.4 g, 2.8 mmol) and toluene (20 mL) were added. The resulting mixture was heated under stirring at 100°C for 4 days. After cooling the organic phase was recovered, washed with water, dried over anhydrous magnesium sulphate, and evaporated to yield a brown oil (0.077 g, 20 %). This crude reaction product was purified by chromatography on silica gel, with ether/ethanol (1/1) to yield two separated fractions. Compound (**14a**) was obtained from the first fraction and **15a** from the second fraction.

14a was obtained as a yellow powder (0.031 g, 8 %); mp 130 °C (from ether). ^{1}H-NMR (DMSO-d_6) δ: 2.27 (6H, s, γ-H), 2.61 (2H, t, *J* = 6.9 Hz, β-H), 4.35 (4H, m, 2-H and 3-H), 4.45 (2H, m, α-H), 7.16 (1H, s, 5-H), 7.26 (1H, t, *J* = 6.9 Hz, 9-H), 7.66 (1H, d, *J* = 8.0 Hz, 7-H), 7.69 (1H, s, 12-H), 7.76 (1H, t, *J* = 6.7 Hz, 8-H), 8.27 (1H, d, *J* = 7.9 Hz, 10-H). ^{13}C-NMR (DMSO-d_6) δ: 44.31 (β-C), 45.70 (γ-C), 55.65 (α-C), 63.86 (2-C), 64.90 (3-C), 102.59 (5-C), 112.55 (12-C), 115.43 (7-C), 116.53 (11a-C), 120.76 (9-C), 120.76 (10a-C), 126.55 (10-C), 133.64 (8-C), 137.54 (5a-C), 139.60 (12a-C), 141.47 (6a-C), 149.65 (4a-C), 175.01 (11-C). *Anal.* Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.58; H, 6.48; N, 8.29.

15a was obtained as a yellow powder (0.030 g, 8 %); mp 202 °C (from ether). ^{1}H-NMR (DMSO-d_6) δ: 2.29 (6H, s, γ-H), 2.65 (2H, t, *J* = 6.9 Hz, β-H), 4.31 (4H, m, 2-H and 3-H), 4.44 (2H, m, α-H), 7.17 (1H, d, *J* = 9.2 Hz, 6-H), 7.23 (1H, t, *J* = 7.3 Hz, 10-H), 7.34 (1H, d, *J* = 9.4 Hz, 5-H), 7.66 (1H, d, *J* = 7.2 Hz, 8-H), 7.75 (1H, t, *J* = 7.5 Hz, 9-H), 8.19 (1H, d, *J* = 8.0 Hz, 11-H). ^{13}C-NMR (DMSO-d_6) δ: 44.75 (β-C), 45.58 (γ-C), 55.69 (α-C), 63.37 (2-C), 64.35 (3-C), 107.26 (6-C), 113.08 (12a-C), 115.17 (8-C), 120.81 (10-C), 122.68 (11a-C), 123.64 (5-C), 126.65 (11-C), 133.57 (9-C), 136.71 (4a-C), 138.01 (6a-C), 140.82 (7a-C), 143.57 (12b-C), 175.83 (12-C). *Anal.* Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.02; H, 6.43; N, 8.95.

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