Synthesis of New Cyclopenta-acridinone and -phenothiazine Derivatives

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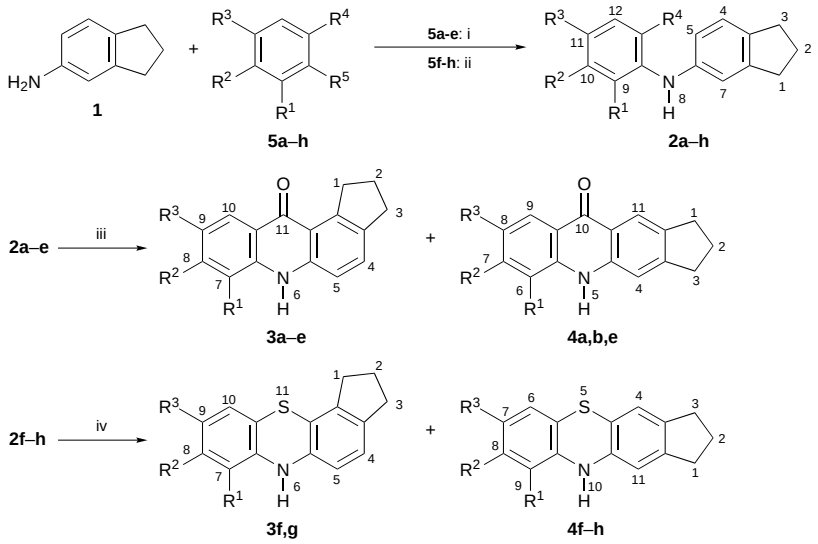
The synthesis of new cyclopenta-acridinones and -phenothiazines by cyclization of *N*-aryl indanes under acidic conditions or *via* Bernthsen thionation is reported.

Acridines and phenothiazines are well known therapeutic agents[1] and some significant derivatives have been prepared with a supplementary heterocyclic fourth ring.[3,5,6]

We are interested in the preparation of a new class of tetracycles bearing a cyclopentane ring fused to an acridine or phenothiazine moiety. The indane **1** was used as starting material and we prepared both cyclopenta-acridinones and cyclopenta-phenothiazines according to the synthetic pathway shown in Scheme 1. The substitution patterns of the derivatives are given in Tables 1–3.

The aminoindane **1** was first arylated with the benzoic acids **5a–e** in order to obtain the corresponding *N*-substituted anthranilic acids **2a–e** in 33–66% yields. The next step involved cyclization of these acids by either PPA or sulfuric acid.

Depending on the regioselectivity of the cyclization position (5 or 7, Scheme 1), either one or two isomers could be obtained: the angular [*a*]-fused tetracycle (type **3**) and/or its homologue, the linear [*b*] isomer (type **4**). In the case of **2a**, **2b** and **2e**, a mixture of both isomers was obtained, purification and separation of which led to the corresponding 1,2,3,6-tetrahydrocyclopenta[*a*]acridin-11-ones **3a**, **3b** and **3e** and to



Scheme 1 *Reagents and conditions:* i, Cu, K_2CO_3, pentan-1-ol, 110 °C, 4–12 h; ii, CH_2Cl_2, $Cu(OAc)_2$, room temp., 4 h; iii, PPA or H_2SO_4, 90 °C, 2 h; iv, S_8, I_2, *o*-$C_6H_4Cl_2$, reflux, 6 h

Table 1 Synthesis of *N*-arylamines derivatives **2a–h**

Starting material						
Compound no.	R^1	R^2	R^3	R^4	R^5	Product
5a	H	H	H	CO_2H	Cl	**2a**
5b	H	H	OMe	CO_2H	Br	**2b**
5c	H	H	NO_2	CO_2H	Cl	**2c**
5d	H	NO_2	H	CO_2H	Cl	**2d**
5e	NO^2	H	H	CO_2H	Br	**2e**
5f	H	H	H	H	$Bi(OAc)_2$	**2f**
5g	H	H	OMe	H	$Pb(OAc)_3$	**2g**
5h	H	H	Me	H	$Pb(OAc)_3$	**2h**

Table 2 Synthesis of acridinones derivatives **3a–e**, **4a**, **b** and **e**

Starting material					
Compound no.	R^1	R^2	R^3	R^4	Products
2a	H	H	H	CO_2H	**3a/4a**
2b	H	H	OMe	CO_2H	**3b/4b**
2c	H	H	NO_2	CO_2H	**3c**
2d	H	NO_2	H	CO_2H	**3d**
2e	NO_2	H	H	CO_2H	**3e/4e**

Table 3 Synthesis of phenothiazines derivatives **3f**, **g** and **4f–h**

Starting material					
Compound no.	R^1	R^2	R^3	R^4	Products
2f	H	H	H	H	**3f/4f**
2g	H	H	OMe	H	**3g/4g**
2h	H	H	Me	H	**4h**

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Table 4 ^{1}H NMR chemical shifts of *N*-aryl amines **2a–h** (δ values, [$^2H_6$]DMSO)

	Amine							
Proton	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**
1-H	2.83	2.79	2.84	2.85	2.76	2.80	2.84	2.77
2-H	2.00	1.99	2.02	2.07	1.97	1.99	2.06	1.97
3-H	2.83	2.79	2.84	2.85	2.76	2.77	2.84	2.75
4-H	7.17	7.15	7.26	7.26	7.06	7.08	7.08	7.04
5-H	6.95	6.91	7.04	7.06	6.66	6.88	6.73	6.91
7-H	7.08	7.04	7.14	7.14	6.78	7.00	6.84	7.81
8-H	9.59	9.11	10.29	9.80	9.90	7.97	5.40	6.93
9-H	7.10	7.16	6.99	7.70	—	7.04	7.03	7.00
10-H	7.32	7.06	8.09	—	8.17	7.19	6.85	—
11-H	6.69	—	—	7.43	7.02	6.76	—	—
12-H	7.87	7.37	8.66	8.07	8.03	—	—	—
OCH_3	—	3.70	—	—	—	—	3.79	2.20
CH_3	—	—	—	—	—	—	—	

Table 5 ^{1}H NMR chemical shifts of acridinones **3a–e**, **4a**,**b** and **e** (δ values, [$^2H_6$]DMSO)

	Acridinone							
Proton	**3a**	**4a**	**3b**	**4b**	**3c**	**3d**	**3e**[a]	**4e**[a]
1-H	3.53	2.95	3.55	2.96	3.48	3.50	3.62	2.99
2-H	2.07	2.05	2.07	2.05	2.08	2.08	2.18	2.12
3-H	2.87	2.95	2.86	2.96	2.88	2.86	2.96	2.99
4-H	7.55	7.46	7.52	7.33	7.60	7.61	7.56	7.30
5-H	7.31	12.13	7.29	11.56	7.32	7.31	7.21	11.20
6-H	11.51	7.58	11.50	7.48	12.09	11.95	11.16	—
7-H	7.45	7.66	7.45	7.34	7.54	8.29	—	8.68
8-H	7.65	7.18	7.34	—	8.35	—	8.65	7.29
9-H	7.17	8.18	—	7.60	—	7.85	7.25	8.86
10-H	8.14	—	7.58	—	8.85	8.32	8.77	—
11-H	—	8.02	—	8.03	—	—	—	8.24
OCH_3	—	—	3.83	3.83	—	—	—	—

[a] $CDCl_3$ as solvent.

Table 6 ^{1}H NMR chemical shifts of phenothiazines **3f**, **g** and **4f–h** (δ values, [$^2H_6$]DMSO)

	Phenothiazine				
Proton	**3f**	**4f**	**3g**	**4g**	**4h**
1-H	2.62	2.70	2.63	2.70	2.70
2-H	1.96	1.93	1.97	1.93	1.93
3-H	2.69	2.68	2.72	2.68	2.70
4-H	6.79	6.74	6.79	6.77	6.75
5-H	6.45	—	6.42	—	—
6-H	8.37	6.89	8.14	6.56	6.72
7-H	6.63	6.72	6.63	—	—
8-H	6.96	6.94	6.59	6.58	6.76
9-H	6.68	6.69	—	6.58	6.57
10-H	6.87	8.42	6.56	8.19	8.30
11-H	—	6.59	—	6.58	6.56
OCH_3	—	–	3.64	3.65	—
CH_3	—	—	—	—	2.12

the linear 1,2,3,5-tetrahydrocyclopenta[*b*]acridin-10-ones **4a**, **4b** and **4e**. In other cases only the angular acridinones were recovered.

Cyclopenta-phenothiazines were also prepared from commercial **1** but using a copper-catalysed arylation with organometallic reagents such as **5f–h**. Under mild conditions, the diarylamines **2f–h** were synthesized in good yields (64–85%) and subsequently cyclized by Bernthsen thionation in *o*-dichlorobenzene. Work-up of mixtures gave also the corresponding angular or linear cyclopenta[*b*] or -[*c*]-phenothiazines **3f**,**g** and **4f–h**. Moreover, difficulties associated with the method of purification and rapid oxidation of the final products could explain the absence of [*c*]-fused **3h**.

All the compounds prepared were characterized unambiguously by ^{1}H and ^{13}C NMR spectroscopy. In particular, the multiplet pattern of the C-ring protons of the final products was especially checked: 4-H and 5-H would resonate as two doublets in the case of [*a*] or [*c*] fusion, but as two singlets in the case of [*b*] fusion (4-H and 11-H). We found, for example, two doublets at δ 7.55 and 7.31 which correspond to 'bent' 1,2,3,6-tetrahydrocyclopenta[*a*]acridin-11-one **3a** and two singlets at 7.46 and 8.02 ppm respectively for linear 1,2,3,5-tetrahydrocyclopenta[*b*]acridin-1-one **4a** (4-H and 11-H).

All the ^{13}C NMR chemical shifts are given in the Experimental section of the full paper.

Techniques used: ^{1}H and ^{13}C NMR

Referneces: 13

Scheme:1

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