Synthesis of New Tetracyclic Derivatives of 10H-Phenoxazine, 10,11-Dihydro-5H-Dibenzo[b,f]Azepine and (9)10H-Acridinone Through Isatinic Intermediates

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A síntese de sistemas tetracíclicos incorporando anéis de 5 e 7 membros aos núcleos de 10H-fenoxazina, 10,11-diidro-5H-dibenzo[b,f]azepina e (9)10H-acridinona é descrita, utilizando como intermediários chaves as isatinas correspondentes.

The synthesis of tetracyclic systems presenting five and seven-memberedrings fused to the nucleus of 10H-phenoxazine, 10,11-dihydro-5H-dibenzo[b,f]azepine and (9)10H-acridinone is described, employing the corresponding isatins as key intermediates.

Key words: *phenoxazine; dibenzozepine; acridone.*

Introduction

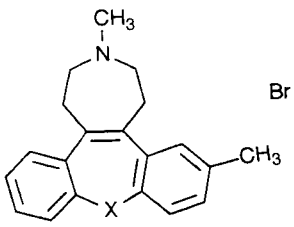
Serotonergic antagonists have been one of the most explored fields in the last years in search for more effective and therapeutically safer drugs for the management of psychotic and depressive pathologic states[1]. One of the commonest strategies in this area of drug design has been to introduce a new fused heterocyclic ring to the "usual" tricyclic frameworks, as exemplified by compounds **1**[2], **2**[2] and **3**[3], that show antipsychotic activity without liability to produce negative, extrapyramidal effects, and **4**[4], which present an effective antidepressive profile.

In connection with our previous work describing the preparation of tetracyclic derivatives of **5**[5] and exploring further our improved route to indole derivatives from isatins[6], we wish to report the synthesis in good yields of compounds presenting five and seven-membered rings, fused to 10H-phenoxazine **6**[7], 10,11-dihydro-5H-dibenzo[b,f]azepine **7**[8] and (9)10H-acridinone **8**[9]

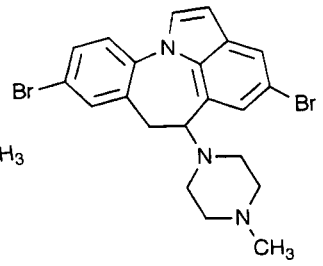
Experimental

Melting points were obtained on a Kofler apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 137-B and 283-B spectrometers. ^{1}H (100 MHz) and ^{13}C (25.2 MHz) NMR spectra were taken on a Varian XL-100 spectrometer. All chemical shifts are reported in delta downfield from tetramethylsilane as internal reference. Mass spectral data were obtained from a Varian MAT-CH5-DF spectrometer operating at 70 eV.

Preparations of isatins **15** - To a solution of 3.4 ml (5 g; 40 mmol) of oxalyl chloride in 10 ml of THF, under magnetic stirring and reflux were added dropwise (*ca.* 1h) 3.7 g (20 mmol) of 10H-phenoxazine **14b**[10] in 40 ml of THF. After 4 h, the mixture was cooled to room temperature, the excess of oxalyl chloride removed under reduced pressure and the residue dissolved in 100 ml of CS_2, under reflux and magnetic stirring. To this solution were added portionwise (*ca.* 30 min.), 5.3 g (40 mmol) of anhydrous $AlCl_3$. After 18 h, the



1 X= O
2 X = NCH_3



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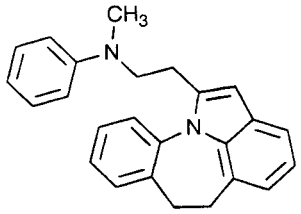

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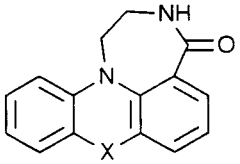
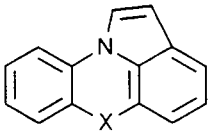


5 X = S
6 X = O
7 X = CH_2CH_2
8 X = CO
12 X = CH_2



9 X = S
10 X = O
11 X = CH_2CH_2
13 X = CH_2

solvent was removed and the residue taken in 60 ml of 0.6 N HCl at 0° C and the mixture extracted with $CHCl_3$ (3 x 50 ml). The organic phases were collected, washed with water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The isatin **15**b was obtained as a crystalline residue (4.2 g; 89%), and directly used in the next step. Isatins **15**c and **15**e were prepared in a similar way from 10,11 dihydro-5H-dibenzo[b,f]azepine **14**c[11] and 9,10-dihydroacridine **14**e, respectively.

15b. mp (210-2) °C; IR (KBr): 1720, 1650, 1590, 1480, 1360,860 cm^{-1}; ^1H NMR δ ($CDCl_3$): 6.85-7.30 (6H, m), 8.16 (1H, dd, J = 8 and 2 Hz); MS m/z (%): 237 (12), 209 (75), 181 (100) and 153 (22).

15c. mp (179-181) °C; IR (KBr): 1740, 1610, 1490, 1350, 1160, 930, 780, 760, 730 cm^{-1}; ^1H NMR δ ($CDCl_3$): 3.10 (4H, s), 6.95-7.83 (7H, m); MS m/z (%): 249 (25), 221 (100), 182 (47) and 96 (22).

15e. mp (218-20) °C; IR (KBr): 1720, 1640, 1600, 1450, 1360, 900, 770, 750 cm^{-1}; ^1H NMR δ ($CDCl_3$): 4.18 (2H, s), 7.05-7.55 (6H, m), 8.61 (1H, dd, J = 8 and 2 Hz); MS m/z (%): 235 (17), 207 (100), 178 (45), 89 (30) and 76 (26).

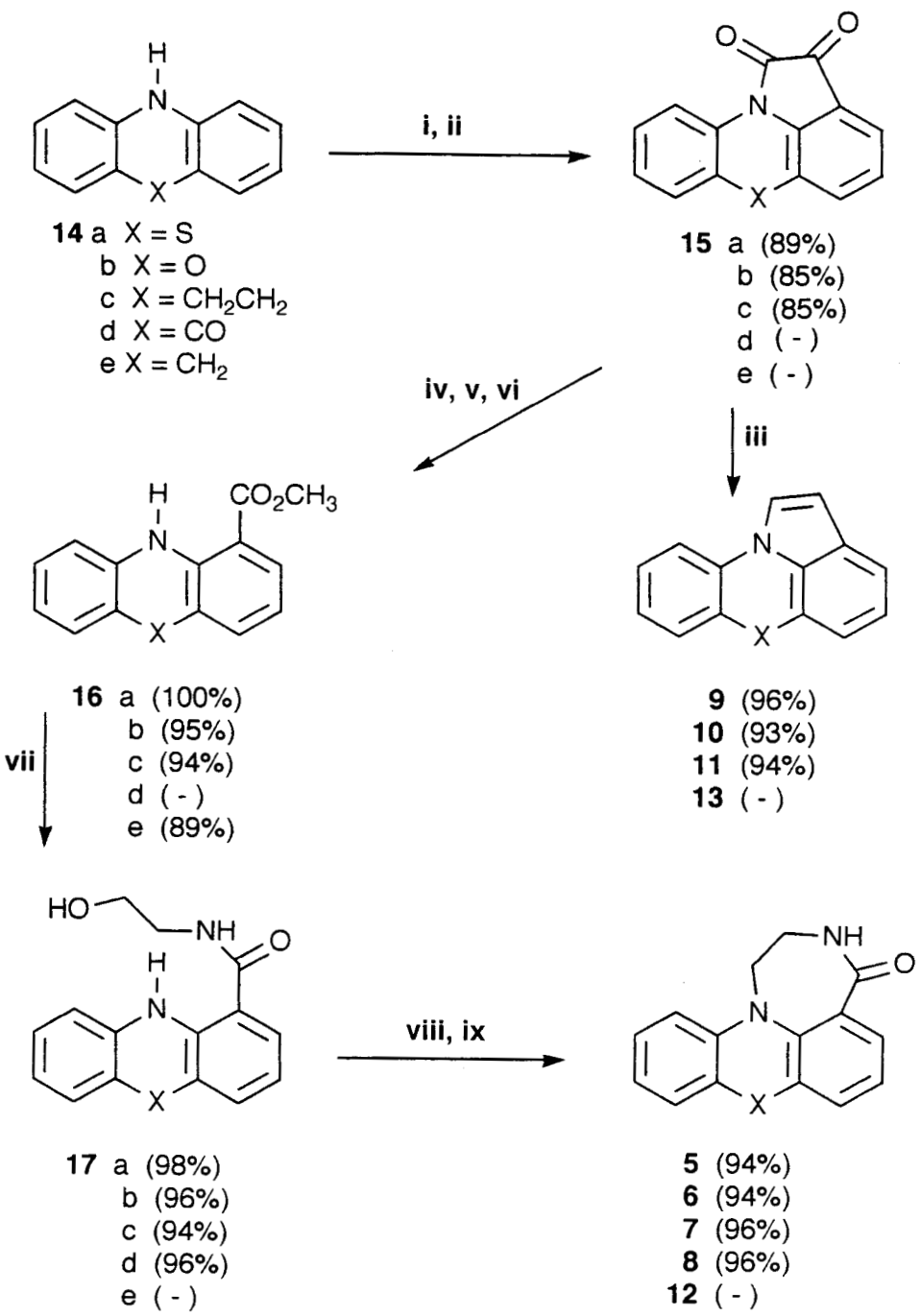
Preparation of esters **16**b, **16**c *and* **16**e - *Isatin* **15**b (1.9 g, 8 mmol) was suspended in aqueous 25 N NaOH (3 ml). After stirring for one hour at room temperature, 75 ml of water were added and the mixture left for a further one hour period. To this suspension were added dropwise (*ca.* 30 min.) 3 ml of 30% H_2O_2 in 30 ml of water. After 2h the resulting solution was acidified with conc. HCl ensuing the precipitation of a yellow solid, which was filtered by suction and dried under vacuum. To a suspension of the dry solid in ether (30 ml) was added an ethereal solution of diazomethane at 0 °C. After 30 min, a few drops (5-6 drops) of acetic acid were added and the solution washed with aqueous 5% $NaHCO_3$. The organic phase was dried over Na_2SO_4 and the solvent removed under vacuum. The residue was chromatographed in a SiO_2 column with hexane-ethyl acetate (0-5%) leading to esther **16**b as yellow crystals (1.8g, 95%). Esthers **16**c and **16**e were prepared in an analogous fashion from the corresponding isatins.

16b. mp (126-8) °C; IR (KBr) 3330, 1680, 1580, 1500, 1460, 1270, 1230, 1200, 1150, 750 and 740 cm^{-1}; ^1H NMR δ ($CDCl_3$): 3.88 (3H, s), 6.35-6.75 (6H, m), 7.30 (1H, dd, J = 8 and 2 Hz), 8.72 (1H, broad, s); MS m/z (%): 241 (49), 209 (51) and 181 (100).

16c. mp (62-64) °C; IR (KBr): 3280, 1700, 1630, 1530, 1500, 1460, 1430, 1330, 1270, 1260, 1140, 930, 770 and 750 cm^{-1}; ^1H NMR δ ($CDCl_3$): 3.10 (4H, s), 3.92 (3H, s), 6.67-7.25 (6H, m), 7.85 (1H, dd, J = 8 and 2 Hz), 10,73 (1H, broad, s); MS m/z (%): 253 (66), 201 (90), 192 (38) and 36 (100).

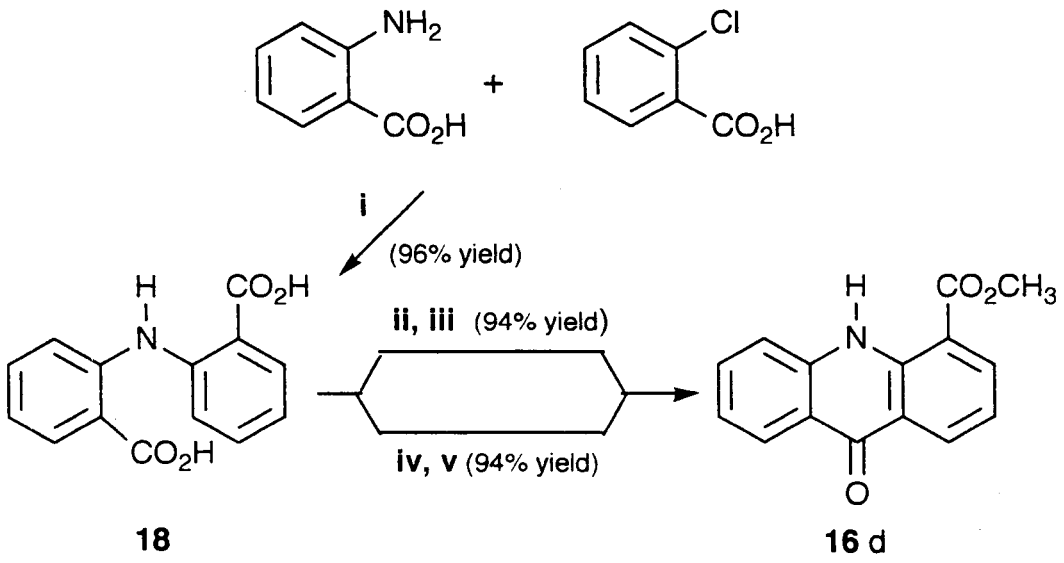
16e. mp (130-1) °C; IR (KBr): 3340, 1680, 1590, 1490, 1440, 1300, 1250, 1190, 1150, 760 and 750 cm ; H NMR δ ($CDCl_3$): 3.95 (3H, s), 4.10 (2H, s), 6.55-7.28 (6H, m), 7.75 (1H, dd, J = 8 and 1,5 Hz), 9.75 (1H, broad, s); MS m/z (%): 239 (64), 206 (100) and 178 (42).

Preparation of esther **16**d - A mixture of 7 g (51 mmol) of anthranilic acid, 8 g (51 mmoles) of o-chlorobenzoic acid, 16 g of anhydrous K_2CO_3, 0.2 g of CuO and 20 ml of DMF was heated under reflux and stirring for 4 h. The solvent was then evaporated under reduced pressure and the residue suspended in 50 ml of water, into which 2 g of activated charcoal were added under heating. After filtration the solution was dropped into 200 ml of 0.6 N HCl, leading to the precipitation of a solid, which was filtered by suction, washed with water and dried under vacuum, affording acid **18**, [12.6g; 96%; mp (292-5) °C (lit[12]. 295 °C, dec.)], which was used in the next step without further purification. Acid **18** (5.15 g; 20 mmol) was refluxed with 12.2 ml (21.5 g, 220 mmoles) of conc. H_2SO_4 (d = 1.84) for 4h. After this period, the mixture was slowly dropped into 100 ml of water under reflux. The resulting suspension was filtered and the solid taken in 50 ml of aqueous 10% Na_2CO_3. After treatment with 1 g of activated charcoal under heating and filtration, the solution was acidified with 40 ml of 0.3 N HCl. The solid thus obtained was collected by suction and washed with water. Drying at 100 °C and recrystallization in ethanol in a Sohxlet apparatus afforded 4.5 g of 9-carboxy-(9)10H-acridinone,which was esterified with diazomethane in ether in the usual way, leading to ester **16**d in 94% yield. This compound was purified by column chromatography in SiO_2 using hexane-ethylacetate (0-5%). Ester **16**d could also be obtained from acid **18** through reaction with POCl 3/MeOH. Thus, 2.6g (10 mmol) of **18** were heated for 15 min. at 80-85 °C with 9.2 ml



i) $(COCl)_2$/ THF; **ii)** $AlCl_3$/ CS_2; **iii)** BH_3/THF, 0°C/24 h; **iv)** NaOH/H_2O; **v)** H_2O_2; **vi)** CH_2N_2/Et_2O; **vii)** $HOCH_2CH_2NH_2$, C_2H_5OH; **viii)** PBr_3/THF; **ix)** K_2CO_3/ CuO/DMF

Scheme 1



i) K_2CO_3/CuO/DMF; **ii)** H_2SO_4; **iii)** CH_2N_2/Et_2O; **iv)** $POCl_3$; **v)** CH_3OH/Py

Scheme 2

(15.3 g; 100 mmol) of $POCl_3$ and then under reflux for further 2h. The excess of $POCl_3$ was removed under reduced pressure and the residue dissolved, at 0-10 °C, in 2 mL of pyridine and 10 ml of methanol. After 30 min at room temperature, the mixture was concentrated and partitioned between water (50 ml) and CHCl (3 x 50 ml). The organic extracts were collected, washed with water (3 x 50 ml), dried over Na_2SO_4 and evaporated under educed pressure. The residue was chromatographed as described above, leading to ester **16**d (2.3g, 91%)

16d. m.p. (169-70) °C; IR (KBr): 3240, 1700, 1630, 1610, 1530, 1450,1280, 1200, 1140, 800, 760, 690 cm^{-1}; ^1H NMR δ ($CDCl_3$): d 4.05 (3H, s), 7.10-7.40 (3H, m), 7.65 (1H, dd, J = 8.6 and 1.5 Hz), 8.30-8.48 (2H, m), 8.66 (1H, dd, J = 8.30 and 2 Hz), 11.65 (1H, broad, s); MS m/z (%): 253 (56), 221 (100), 193 (40), 165 (20).

Preparation of carboxamides **17**b-d - A mixture of 0.5 g (2.0 mmol) of esther **16**b, 3.0 ml (3 g; 50 mmol) of ethanolamine and 10 ml of absolute EtOH was heated under stirring and reflux for 12 h. Concentration under vacuum and partition of the residue between water (20 ml) and CH_2Cl_2 (3 x 20 ml) were of then undertaken. The organic phases were collected, washed with brine (3 x 20 ml) and water (3 x 20 ml), and dried over Na_2SO_4. Solvent removal led to **17**b (0.52 g; 96%), which was used directly in the next step. Carboxamides **17**c and **17**d were prepared in a similar way from the corresponding esters, by varying the reflux period, i.e., 12 h and 6 h, respectively.

17b. mp (179-80) °C, IR (KBr): 3350, 1620, 1500, 1460, 1280, 1070, 750 and 740 cm^{-1}; ^1H NMR δ ($CDCl_3/CD_3$ OD): 3.50 (2H, t, J = 6Hz) 3.74 (2H, t, J = 6 Hz), 7.35-7.80 (6H, m), 8.00 (1H, dd, J = 8 and 2 Hz); MS m/z (%): 270 (45), 252 (29), 209 (80) and 181 (100).

17c. mp (165-6) °C, IR (KBr): 3340, 3320, 1640, 1590, 1490, 1460, 1430, 1320, 1280, 1060, 780 and 750 cm^{-1}; ^1H NMR δ ($CDCl_3/CD_3$ OD): 3.03 (4H, s), 3.52 (2H, t, J = 6 Hz), 3.75 (2H, t, J = 6 Hz), 7.55-8.15 (6H, m), 8.40 (1H, dd, J = 8 and 1,5 Hz); MS m/z (%): 282 (46), 264 (65), 221 (100), 219 (26) and 192 (36).

17d. mp (237-8) °C, IR (KBr): 3300, 1640, 1560, 1530, 1520, 1510, 1300, 1060 and 750 cm^{-1}; ^1H NMR δ ($CDCl_3$ /$(CD_3)_2$ SO): 3.55-3.90 (4H, m), 7.12-7.76 (4H, m), 8.16-8.58 (3H, m), 12.53 (1H, broad, s); MS m/z (%): 282 (19), 264 (100), 220 (95), 193 (20) and 165 (18).

Preparation of azepinic systems **6-8** - To a solution of carboxamide **17**b (0.27 g; 1 mmol) in 20 ml of THF was added dropwise (*ca.* 30 min.), 1 ml (0.27 g; 10 mmoles) of PBr in 10 ml of THF. After 1h under reflux, the solvent was removed under reduced pressure and the residue taken in 10 ml of water at 0 °C. The mixture was then extracted with CH_2Cl_2 (3 x 20 ml). The organic phases were separated and washed with brine (2 x 20 ml) and water (2 x 20 ml) and dried over Na_2SO_4. The solvent was evaporated and the resulting yellow oil submitted to the cyclization step without further purification. The bromide was heated for 1 h with 20 ml of DMF, 0.28 g (2.0 mmol) of anhydrous K_2CO_3 and 0.02 g of CuO. After cooling to room temperature, the mixture was filtered and the solution concentrated under vacuum. Partitioning between water (20 ml) and CH_2Cl_2 (3 x 20 ml) was then undertaken and the organic extracts washed with brine (2 x 20 ml) and water (2 x 20 ml), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue chromatographed through a column of neutral Al_2O_3, using hexane-ethylacetate 1% as eluent. In this way, azepine **6** was obtained as yellow crystals (0.23 g; 91%). Similar procedures were used for compounds **7** and **8** from the corresponding carboxamides.

6. mp (107-8) °C; IR (KBr): 1640, 1610, 1490, 1450, 1290, 1270, 1250, 1140, 1000, 760 and 730 cm^{-1}; ^1H NMR δ ($CDCl_3$): 3.95-445 (4H, m), 6.35-6.80 (6H, m), 7.25 (1H,

dd, J = 8 and 2 Hz), 9.65 (1H, broad, s); ^{13}C NMR δ ($CDCl_3$): 54.6 (t), 65.8 (t), 108.6 (s), 113.8 (d) 115.1 (d), 116.8 (d), 118.5(d), 121.3 (d), 123.1 (d),123.5 (d), 130.7 (s), 134.2 (s), 143.2 (s), 143..9 (s), 163.9 (s); MS m/z (%): 252 (100), 208 (80), 181 (30) and 149 (23).

7. mp (109-11)°C; IR (KBr): 1640 1490, 1440, 1330, 1300, 1270, 1110, 1000, 960 and 750 cm^{-1}; ^{1}H NMR δ ($CDCl_3$): 3.17 (4H, s), 3.95-4.45 (4H,m), 6.55-7.15 (6H, m), 7.68 (1H, dd, J = 8 and 2 Hz), 11.60 (1H, broad, s); ^{13}C NMR d ($CDCl_3$): 35.2 (t), 35.9 (t), 54.8 (t), 65.6 (t) 111.1 (s), 116.7 (d), 117.7(s), 119.2 (d), 119.4 (d), 126.5 (d), 128.0 (d), 130.0 (d), 130.4 (s), 133.2 (d), 141.9 (s), 144.1 (s), 165.1 (s); MS m/z (%): 264 (100), 219 (39), and 193 (20).

8. mp (230-2)° C; IR (KBr): 3150, 3060, 1640, 1620, 1600, 1580, 1520, 1430, 1330, 1320, 1120,, 1110, 760 and 740 cm^{-1}; ^{1}H NMR δ ($CDCl_3$): 4.00-4.55 (4H, m), 7.00-7.70 (4H,m), 8.20 (1H, dd, J = 8 and 1 Hz), 8.52 (1H, dd, J = 8 and 1 Hz), 12.80 (1H, broad, s); ^{13}C NMR d($CDCl_3$ /(CD) SO): 54.7 (t), 66.5 (t), 112.3 (d), 117.8 (d) 119.9 (d), 121.0 (s), 121.3(s), 122.1 (d), 126.5 (d), 130.7 (d), 133.8 (d), 134.4 (d), 139.7 (s), 140.1 (s), 163.8 (s), 178.5 (s); MS m/z (%): 264 (100), 221 (26), 220 (80), 193 (7) and 165 (10).

Preparation of indoles **10** *and* **11** - To a solution of 1 mmol of isatins **15**b and **15**c in 5 ml of anhydrous THF at 0° C was added, dropwise, 2 ml of 1 M BH_3/THF. After 2 h, at 0° C, 10 ml of cold water were added and the mixture extracted with ether (3 x 20 ml). The ethereal phase was collected, washed with water (3 x 20 ml) and dried over Na_2SO_4. The residue obtained after evaporation was filtered through a neutral Al_2O_3 column. The solvent was removed under reduced pressure, leading to indoles **10** and **11**, in 93 and 94% yields respectively.

10. mp (87-8) °C; IR (film): 1490, 1450, 1310, 1290, 1240, 1180, 830, 780 and 740 cm ; H NMR δ ($CDCl_3$): δ 6.44 (1H, d, J = 3Hz), 6.35-7.22 (7H, m), 7.26 (1H, d, J = 3 Hz); MS m/z (%): 207 (100), 178 (10) 103 (15).

11. mp (96-8) °C; IR (film): 1560, 1480, 1410, 1330, 1290, 1200, 1050, 790, 760 and 710 cm^{-1}; ^{1}H NMR δ {$CDCl_3$}: δ 3.22 (4H,s), 6.68 (1H, d, J = 4 Hz), 6.95-7.48 (7H, m), 7.53 (1H, d, J = 4 Hz); MS (%): 219 (100), 204 (15), 108 (23), 95 (12).

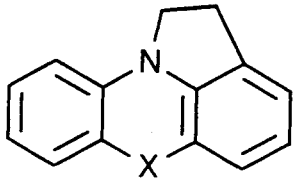
Results and Discussion

The general route to **5-8**, **12** and **9-11**, **13** is outlined on Scheme I. The preparation of isatins **15** from the corresponding tricyclic precursors **14** was straightforward via Stollé's methodology[7], except for **15**d, whose "central" carbonyl group is most certainly deactivating the aromatic rings towards the electrophilic attack of the acylium-aluminum chloride complex. To circumvent this problem, the required ester **16**d was obtained from acid **18** through two alternative, albeit very efficient routes (Scheme II).

Towards the synthesis of seven-membered ring compounds, the previously described[5] sequence was employed. This methodology compares very favourably in terms of yields and simplicity with the classical routes involving N-alkylation or N-acylation reactions, followed by ring closure through an intramolecular electrophilic substitution reaction[13]

The hydrolytic cleavage of isatins **15**, followed by oxidative decarboxylation with hydrogen peroxide and diazomethane esterification, afforded esters **16** in excellent yields[14]. From these compounds, carboxamides **17** were generated in almost quantitative yields, except for **17**e. Ester **16**e, when treated with ethanolamine, led to the acridine amide corresponding to **17**e, via oxidation: reactions of **17** under Schirch's methodology[5] afforded the azepine amides in more than 90% yields.

Exploring the several methodologies of reduction of isatins to indoles[15], the procedures of Kano[16], using TiCl /$NaBH_4$ or[17] BH_3 /THF , were investigated. Careful experimental conditions are required as both methods may generate, after longer reaction times (24 hours) and/or higher temperatures, the corresponding dihydroindole derivatives[10]. This problem was particularly troublesome in the case of **15**e, that even under the optimized reaction conditions, afforded a mixture of **13** and **19**e, which was very prone to darkening and could not be separated by usual chromatographic procedures.



19 a-c

The borane reduction procedure was shown to be simpler and to lead to better product yields than Kano's methodology. Further modifications of this indole synthesis, as well as the introduction of substituents on the nitrogen of the prepared seven-membered ring systems after reduction, are currently being explored in our laboratories.

Acknowledgements

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