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Pyrrolo- and Pyridoacridines

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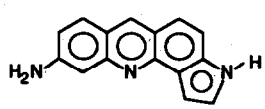
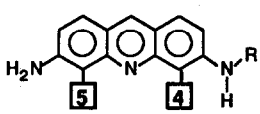
***Abstract** : The synthesis of 9-amino-(3H)-pyrrolo[2,3-c]acridine 3 and 10-amino-benzo[b]-[1,7]phenanthroline 4 starting from proflavine 1 is described. NMR was used to ascertain their "angular" structure.*

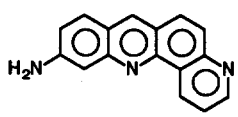
Acridines represent a class of compounds which exhibit a large variety of biological activities[1]. Anticancer drugs have been developed, among which nitracrine[2] and amsacrine[3] are representative examples. The activities are frequently associated with their binding properties to DNA. In the course of a program devoted to the study of 3,6-diaminoacridine[4] (proflavine) **1**, we noticed that hydrogens H-4 and H-5 are exchanged in fairly mild conditions. When warmed at 65°C in D_2O, pD 4.6 (deuterioacetate buffer), the H-4 and H-5 in 3-ethylamino-6-aminoacridine **2** are exchanged with half-lives being respectively 10 h and 40 h[5]. No other C-H proton is exchanged in these conditions. We took advantage of this particular reactivity of the 4 and 5 positions to build up new rings onto the acridine nucleus. We report here the preparation of 9-amino-(3H)-pyrrolo[2,3-c]acridine **3** and 10-amino-benzo[b]-[1,7]phenanthroline **4**[6].



3



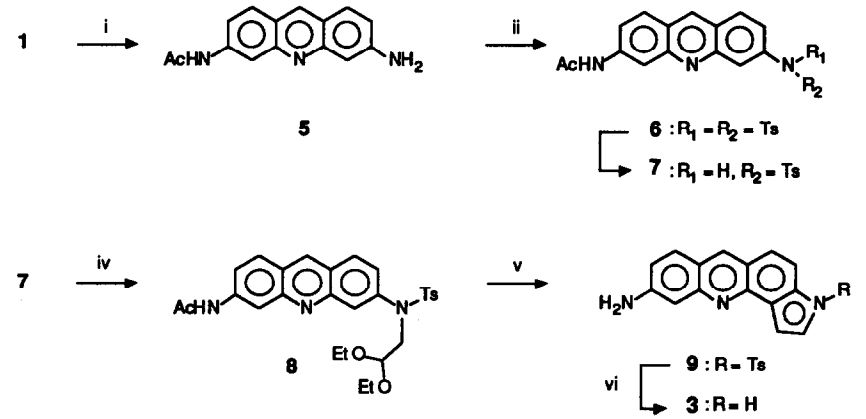
1 : R = H
2 : R = Et



4

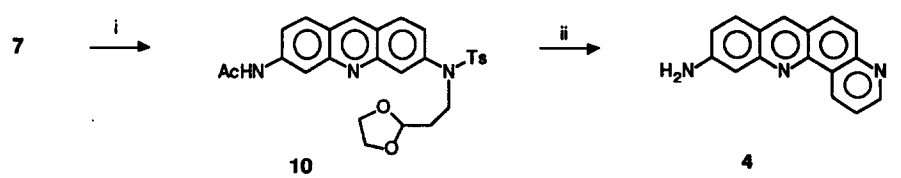
Starting from proflavine **1**, the synthesis requires protection of one of the two identical exocyclic amino functions. Selective monosulfonylation (tosylation, mesylation) could not be achieved. However monoacetylation (83 % yield) was obtained by treating proflavine **1** with acetic anhydride in propionic acid at -20°C. This protected proflavine **5** was used in all further transformations. Activation of the second amino group was

achieved by tosylation. Treatment of **5** with p-toluenesulfonyl chloride in pyridine in the presence of triethylamine afforded a mixture of the di- and monotosyl compounds **6** and **7**. Treatment of this crude mixture with CO_3K_2 in DMF-H_2O (6:1) for 14 h at 100°C selectively hydrolyzes the ditosyl **6** into the monotosyl derivative **7** so that the overall yield **5** → **7** is higher than 75 %. The pyrroloacridine **3** was obtained from **7** in three steps : alkylation with bromoacetaldehyde diethyl acetal in DMF in the presence of CO_3K_2, acidic treatment (CH_3SO_3H in CH_2Cl_2) of the resulting **8** which led to deprotection of the acetal function, ring formation[7] and acetamide cleavage, the last step being deprotection of the N-tosyl group in **9** in alkaline conditions (KOH; DMF-H_2O). The structure of **3** was confirmed by the ^1H 400 MHz NMR spectrum, which shows in particular two AB doublets at 7.44 and 7.51 (J_{AB} = 3. 1Hz) corresponding to the two pyrrole hydrogens (Figure).



i : $(CH_3CO)_2O$, $CH_3CH_2CO_2H$, -20°C, 10 h ; ii : TsCl, Py, Et_3N, 4°C, 10 h, yield **6** : 30 %, **7** : 65 % ; iii : DMF-H_2O, CO_3K_2, 100°C, 14 h, yield 76 % from **5** ; iv : DMF, CO_3K_2, $BrCH_2CH(OEt)_2$, 80°C, 4 d ; v : CH_3SO_3H/CH_2Cl_2 (1:9), reflux, 24 h, 40 % ; vi : KOH, DMF-H_2O, 70°C, 5 h, 75 %

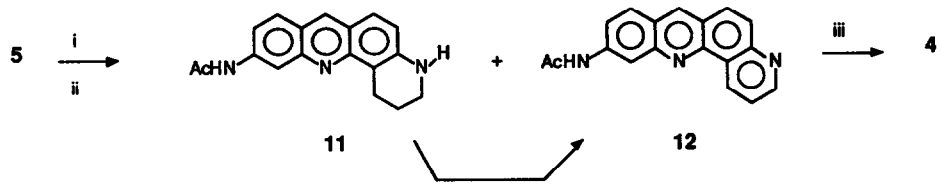
An analogous sequence was used to synthetize the benzo[b]-[1,7]phenanthroline skeleton **4** (Scheme 2). Alkylation of monoacetyl monotosyl proflavine **7** with bromopropionaldehyde ethylene acetal in DMF in the presence of CO_3K_2 gave the intermediate **10** (75 % yield). Acidic treatment (H_2SO_4, 75°C, 1.5 h) resulted in cyclisation, detosylation and deacetylation to afford **4** (40 %). The overall yield starting from proflavine is 18 %.



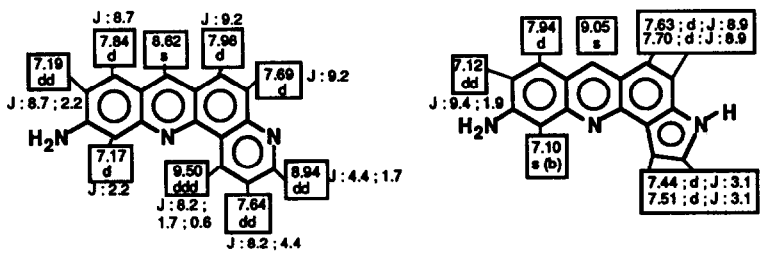
i : DMF, CO_3K_2, $BrCH_2CH_2CH(OCH_2)_2$, 80°C, 3 h, 72 % ; ii : H_2SO_4, 75°C, 1 h, 40 %

A shorter reaction scheme, derived from the classical Skraup cyclization was devised, which does not require activation of the amino function by a sulfonyl group. Reaction of protected proflavine **5** with acrolein

diethyl acetal in refluxing acetic acid (in the presence or absence of oxidizing agents) gave a mixture of the two cyclized products **11** and **12** corresponding to disproportionation of the primary reaction product, the dihydro derivative[9]. Treatment of the crude mixture with DDQ in refluxing acetic acid for 15 min gives the tetracyclic compound **12** which was deprotected to product **4** in 4M hydrochloric acid. All analytical and spectral data are in accordance with the indicated structure. All ^{1}H and ^{13}C signals were attributed. The "angular" nature of the system is indicated by the H-1, H-2 and H-3 signals[10]. The H-2 doublet of doublets centered at 7.64 ppm results from coupling with H-1 (8.2 Hz) and H-3 (4.4 Hz). The presence of only one singlet corresponding to H-7 excludes a "linear" structure (Figure).[11]



i : CH_2=CHCH(OEt)$_2$, CH_3CO_2H, reflux, 3 h ; ii :DDQ, CH_3CO_2H, 100°C, 15 min ; iii : HCl 4M, 80°C, 1 h (yield 40 % from **5**)



Figure

These synthetic results confirm the enhanced reactivity of the 4 (and 5) position in proflavine derivatives as in no case was any product observed resulting from cyclisation onto the C-2 carbon center. The tetracyclic compounds are now under study for their DNA-binding properties and cytotoxic activity[12].

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7. Using the mesyl derivative instead of the tosyl, and operating according to Sundberg R.J. to cyclize substituted anilines ($TiCl_4$, toluene, reflux[8]) or in a number of acidic conditions, leads to poor yields of cyclized compound.
8. Sundberg, R.J. ; Laurino, J.P. *J. Org. Chem.*, **1984**, *49*, 249-254.
9. The tetrahydro cyclized derivative **11** has been isolated and characterized by mass spectrometry and ^1H NMR spectrometry. **11** is quantitatively transformed to **12** by treatment with DDQ in refluxing CH_3CO_2H.
10. Spectra in DMSO-d_6 at 300 MHz.
11. All new isolated products gave correct elemental analysis and spectral data. Typical values for **3** are : mp = 200°C (dec.) ; UV (ethanol) : 450 (1010), 403 (11500) , 234 (32100) ; IR (KBr) : 3400, 3240, 1650, 1610, 1370, 1170, 1040, 1010, 900, 740 cm^{-1} ; MS : M^+ : 233, m/z : 206, 205.
    Typical data for **4** : mp = 287°C (dec.) ; UV (ethanol) : 424 (7050) , 363 (8000), 318 (27200), 310 (24900), 271 (48300), 242 (25700) ; IR (KBr) 3440, 3320, 3180, 1640, 1600, 1500, 1450, 1420, 1370, 1300, 1250, 1160, 1010, 940, 880, 810, 740 cm^{-1} ; MS : M^+ : 245, m/z : 218, 191, 164.
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