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A NEW AND IMPROVED SYNTHESIS OF A POTENTIAL ANTITUMOUR 7H-PYRIDO[4,3-c]CARBAZOLE ANALOG.

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Abstract. The 6-ethyl-10-methoxy-7H-pyrido[4,3-c]carbazole is synthesized via a novel and convenient method involving the condensation of the 2-lithio-5-methoxyindole with the appropriate alkyl pyridyl ketone. Quaternarization of this compound by means of a rigid bis(ethylpiperidyl) linking chain leads to a new potential antitumour dimer.

A large series of DNA intercalating 7H-pyridocarbazoles was synthesized in our laboratory [1]. Dimerization of the 7H-pyrido[4,3-c]carbazoles by means of a rigid linking chain strongly increases their DNA affinity leading to compounds endowed with interesting antitumour properties [2,3]. One of them, ditercalinium (NSC 335153) (Fig.1 ; R=H), is presently under clinical trial [4].

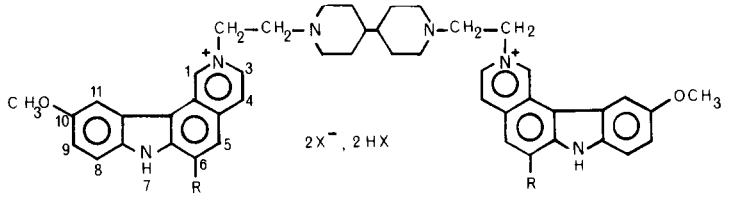
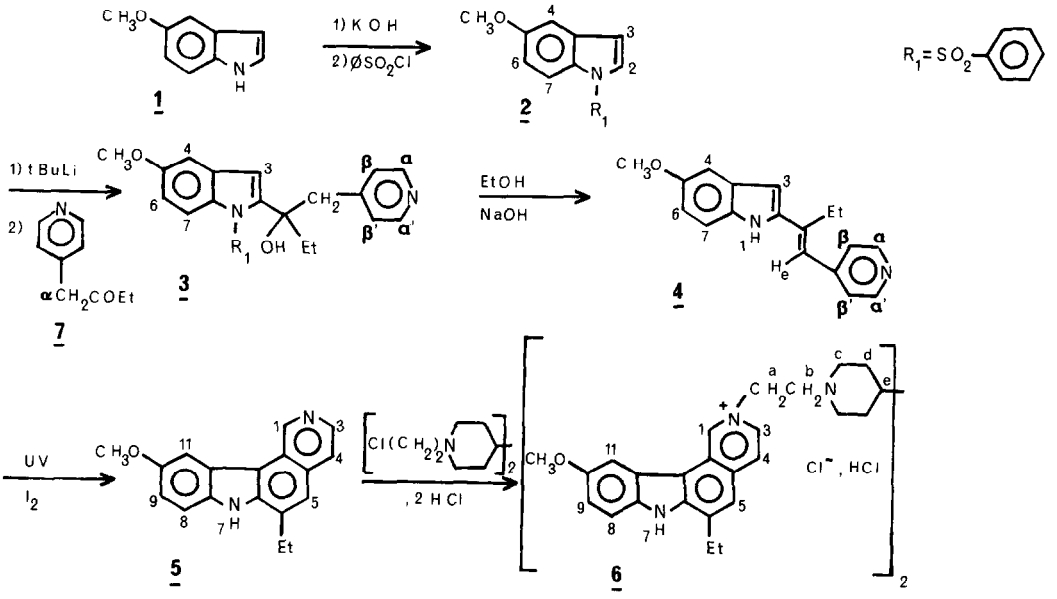


Figure 1.

This compound expresses its cytotoxicity through a new mechanism of action, completely different from that of other intercalating drugs [5,6]. Moreover pharmacological results show that substitution of ditercalinium by a methyl group in position 6 does not change the biological potency whereas a strong decrease in the antitumour activity is observed when the methyl group is introduced in other positions [7]. It was therefore of major interest to know if this activity should be retained after the replacement of the 6-methyl group by a bulky substituent. However due to its low yield, the synthetic way to the 10-methoxy-6-methyl-7H-pyrido [4,3-c]carbazole dimer (Fig. 1 ; R=CH_3) which uses a transformation of the 6-cyano derivative [8] could not be extended to the production of other 6-alkyl substituted 7H-pyridocarbazoles.

We report here the synthesis of the 6-ethyl-10-methoxy-7H-pyrido[4,3-c]carbazole dimer using a novel and convenient method for the construction of the 7H-pyridocarbazole skeleton (Scheme A).



Scheme A.

1-benzenesulfonyl-5-methoxyindole (2) is obtained with a 80% yield by reaction of potassium hydroxide on 5-methoxyindole in dimethoxyethane (0°C, 10 min), followed by addition of benzenesulfonyl chloride (20°C, 40 min), extraction with benzene and cristallization in ether/n-hexane, according to Kikugawa et al.[9]. (2) : mp = 99°C ; MS : m/e 287. 2-Butanone 1-(4-pyridyl) (7) is obtained with a 43% yield according to Raynolds et al. [10]. (7) : bp = 89°C/1mm Hg (lit. 86-88.5°C/1mm Hg). The structure of compounds (2) and (7) is confirmed by ^{1}H NMR.

The synthesis of the alcohol (3) is performed in two steps : i) regioselective 2-lithiation of (2) is achieved by tert-butyllithium (anhydrous THF, 5°C, 20 min) [11] to afford the 1-benzenesulfonyl-2-lithio-5-methoxyindole ; ii) the red solution of 2-lithio-5-methoxy-N-protected indole (anhydrous THF, 0°C) is then rapidly treated with the 2-butanone 1-(4-pyridyl) and hydrolyzed (aqueous HCl). Extraction with CH_2Cl_2 and evaporation of the solvent in vacuo give a viscous red oil which affords the alcohol (3) with a 14% yield when triturated with hot ether. (3) :mp = 184°C ; MS : m/e 436. ^{1}H NMR ($(C^2H_3)_2SO$) : δ (ppm) 8.28 (d, 2H, Hα,α') ; 7.86 (d, 1H, H_7) ; 7.63 (d, 2H, Ha,a') ; 7.57 (m, 1H, H_c) ; 7.46 (t, 2H, $H_{b,b'}$) ; 7.07 (d, 2H, Hβ,β') ; 6.97 (d, 1H, H_4) ; 6.82 (q, 1H, H_6) ; 6.67 (s, 1H, H_3) ; 5.25 (s, 1H, OH) ;

3.68 (s, 3H, $O\underline{CH_3}$) ; 3.45 (d, 1H, $-\underline{CH_A}$-pyr) ; 3.33 (d, 1H, $-\underline{CH_B}$-pyr) ; 2.08 (m, 1H, $-\underline{CH_A}-CH_3$) ; 1.80 (m, 1H, $-\underline{CH_\beta}-CH_3$) ; 0.64 (t, 3H, $\underline{CH_3}-CH_2-$). The unreacted indole (**2**) cristallizes from the oily residue by addition of n-hexane. The aqueous layer is alcalinized to pH 12 and extracted with ether. The reagent (**7**) is thus easily recovered by distillation of the ethereal layer.

The second step is the limiting one (yield : 14%). Considering the studies of Saulnier et al. [12] on 2-lithio-N-protected indoles, several attempts to optimize the experimental conditions (temperature and reaction time) were performed but failed. This was explained by a fast and important (80%) exchange of the two hydrogens of the $\alpha-CH_2$ group of the reagent (**7**), in accordance with a mobility related to their position between a pyridine ring and a carbonyl group. The exchange process was monitored in ^1H NMR by following the decrease of the $\alpha-CH_2$ signal, concomittently with the reappearance of the indolic H_2 signal when aliquots of the reaction mixture were hydrolyzed with D_2O and analysed. This rapid hydrogen-metal exchange dramatically reduces the amount of reactive 2-lithioindole, thus explaining the low yield of this second step. Nevertheless, one can note that the reagents (**2**) and (**7**) are easily recovered as pure materials for further use.

The treatment of the alcohol (**3**) (EtOH-NaOH 3M, reflux, 30 min) [13] affords the N-deprotected alkene (**4**) which cristallizes in acetone (40% yield). ^1H NMR homodecoupling and NOE' experiments establish the (E) configuration of the alkene (**4**). mp = 220°C ; MS : m/e 278 ; ^1H NMR ($(C^2H_3)_2SO$) δ (ppm) : 11.51 (s, 1H, NH) ; 8.73 (d, 2H, Hα,α') ; 7.82 (d, 2H, Hβ,β') ; 7.24 (d, 1H, H_7) ; 7.18 (s, 1H, H_e) ; 6.98 (d, 1H, H_4) ; 6.82 (s, 1H, H_3) ; 6.78 (d, 1H, H_6) ; 3.69 (s, 3H, $O\underline{CH_3}$) ; 2.80 (q, 2H, $-\underline{CH_2}-CH_3$) ; 1.24 (t, 3H, $\underline{CH_3}-CH_2$).

Oxydative photocyclization of the alkene (**4**) (UV 254 nm, I_2, 35h) [14] gives the desired product (**5**) as a yellow solid with a 71% yield. (**5**) : mp = 228°C ; MS : m/e 276 ; ^1H NMR ($(C^2H_3)_2SO$) δ (ppm) : 11.78 (s, 1H, H_7) ; 10.02 (s, 1H, H_1) ; 8.42 (s, 1H, H_3) ; 7.98 (d, 1H, H_{11}) ; 7.83 (d, 1H, H_4) ; 7.66 (s, 1H, H_5) ; 7.55 (d, 1H, H_8) ; 7.07 (d, 1H, H_9) ; 3.83 (s, 3H, $O\underline{CH_3}$) ; 3.06 (q, 2H, $-\underline{CH_2}-CH_3$) ; 1.38 (t, 3H, $\underline{CH_3}-CH_2-$).

The overall yield of 6-ethyl10-methoxy-7H-pyrido[4,3-c]carbazole (3.2%) synthesis is significantly improved as regard to that of 10-methoxy-6-methyl7H-pyrido[4,3-c]carbazole which requires a large number of steps[8].

Dimerization of (**5**) (two equivalents) with 1,1'-bis(2-chloroethyl)-4,4'-bipiperidine dihydrochloride (one equivalent) is achieved in DMF (85°C, 15h). The resulting precipitate gives (**6**) with a 40% yield. (**6**) : mp = 190°C ; MS:m/e 774. ^1H NMR ($(C^2H_3)_2SO$) : δ ppm : 12.54 (s, 1H, H_7) ; 11.60 (s, 1H, $N\underline{H}$) ; 10.40 (s, 1H, H_1) ; 8.79 (d, 1H, H_3) ; 8.60 (d, 1H, H_4) ; 8.33 (s,

1H, H_{11}) ; 8.07 (s, 1H, H_5) ; 7.71 (d, 1H, H_8) ; 7.24 (d, 1H, H_9) ; 5.43 (m, 2H, $\underline{CH_2}$a) ; 3.98 (s, 3H, OCH_3) ; 3.87 (m, 2H, $\underline{CH_2}$b) ; 3.64 (m, 2H, $\underline{CH_2}$c(eq)) ; 3.24 (q, 2H, $\underline{CH_2}$-CH_3) ; 3.00 (m, 2H, $\underline{CH_2}$c(ax)) ; 1.89 (m, 2H, $\underline{CH_2}$d(eq)) ; 1.58 (m, 2H, $\underline{CH_2}$d(ax)) ; 1.44 (t, 3H, $\underline{CH_3}$-CH_2-) ; 1.22 (m, 1H, $\underline{CH_e}$).

Preliminary pharmacological studies show that this new dimer elicits cytotoxic properties similar to those of ditercalinium [6].

The interest of this new route to 7H-pyrido[4,3-c]carbazoles lies in its possible extension to the synthesis of 6-alkyl 7H-pyrido [x,y-c]carbazoles, by condensing conveniently substituted pyridines on 2-lithio-N-protected indoles.

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