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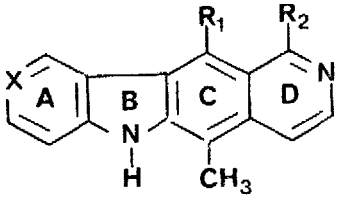
6H-INDOLO [3,2-b] NAPHTHYRIDINES.AZA-ANALOGUES OF ELLIPTICINE

F. Nivoliers, A. Decormeille, A. Godard and G. Quéguiner*

Laboratoire de Chimie Organique Hétérocyclique de l'Institut Scientifique de Haute-Normandie, de l'Institut National Supérieur de Chimie Industrielle de Rouen et Centre anticancéreux Becquerel de Rouen, I.U.T., B.P. 47, 76130 Mont Saint Aignan, France.

Abstract : The Friedlander quinoline synthesis is applied to prepare new potential DNA - intercalative compounds : The 6H-indolo [3,2-b] naphthyridines.

The olivacine type indole alkaloïds, olivacine 1, ellipticine 2, and their analogues are of interest because of their antitumor and antileukemic activity (1). The pharmacological activity of ellipticines has stimulated widespread interest in its synthesis and in that of related compounds (2).



1 : X = CH ; R_1 = H ; R_2 = CH_3

2 : X = CH ; R_1 = CH_3 ; R_2 = H

3 : X = N ; R_1 = CH_3 ; R_2 = H

4 : X = N ; R_1 = H ; R_2 = $NH(CH_2)_3 N(C_2H_5)_2$

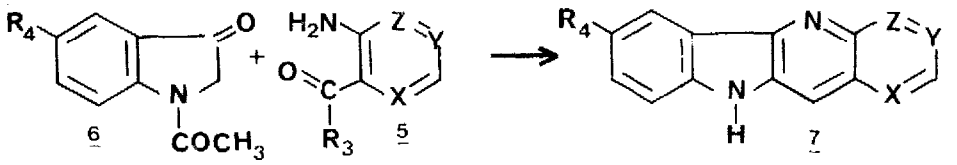
A way of increasing the strength of the intercalative binding is to prepare analogues of ellipticine containing polar groups. Bisagni and coll. (3) recently described the synthesis of dipyridoindoles 3 and 4 which have structures and biological properties closely similar to those of ellipticine (4). In these compounds ring A is replaced by a pyridine nucleus.

We report here the synthesis of the new ellipticine analogues : 6H-indolo [3,2-b] naphtyridines 7 in application of the Friedlander quinoline synthesis. This process may be of synthetic utility in providing a number of compounds which present a great variety of structural modifications compared to the pyrido-carbazole system found in ellipticine and contribute to the study of structure activity relationships.

Starting form the aminoformyl pyridines 5a, 5b, 5c prepared from the corresponding amino pyridine carboxylic acids with an original pathway (5) we have synthetized (6) successively : 6H-indolo [3,2-b] naphthyridine-1,5 7a : Solid.F > 250°C. NMR (DMSO,δppm/HMDS) : H_7, H_8, H_9 and H_2 : 7,6 (m)(3H), 7,3 (m)(1H) ; H_5 : 8,25 (s)(1H) ; H_{10} : 8,32 (m)(1H) ; H_1 : 8,53 (q)(1H) ; H_3 : 8,91 (q)(1H) ; H (NH) : 11,55 (s)(1H).

6H-indolo [3,2-b] naphthyridine-1,7 7b : Solid.F > 250°C. NMR (DMSO,δppm/HMDS) : H_7, H_8 and H_9 : 7,63 (m)(2H), 7,3 (m)(1H) ; H_4 : 7,95 (d)(1H) ; H_5 : 8,23 (s)(1H) ; H_{10} : 8,36 (m)(1H) ; H_3 : 8,41 (d)(1H) ; H_1 : 9,50 (s)(1H) ; H (NH) : 11,7 (s)(1H).

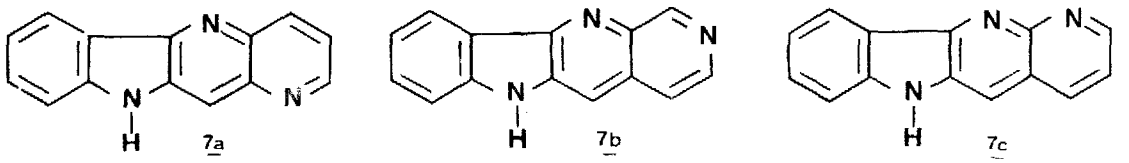
6H-indolo [3,2-b] naphthyridine-1,8 7c : Solid.F > 250°C. NMR (DMSO,δppm/HMDS) : H_7, H_8, H_9 and H_3 : 7,40 (m)(4H) ; H_5 : 8,30 (s)(1H) ; H_2 : 8,93 (q)(1H) ; H_4 and H_{10} : 8,5 (m)(2H) ; H (NH) : 11,5 (s)(1H).



6 5 7

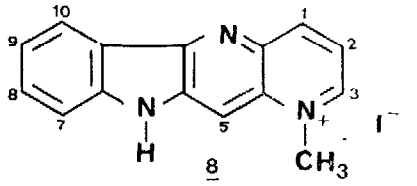
a (R_3 = H ; X = N ; Y = Z = CH)
b (R_3 = H ; Y = N ; X = Z = CH)
c (R_3 = H ; Z = N ; X = Y = CH)

a (R_3 = R_4 = H ; X = N ; Y = Z = CH)
b (R_3 = R_4 = H ; Y = N ; X = Z = CH)
c (R_3 = R_4 = H ; Z = N ; X = Y = CH)



7a 7b 7c

The increasing activity of quaternarized ellipticine through the probable interaction of the positively 2-nitrogen atom with the PO_4^{2-} anions of the phosphodiesters backbonehas been of particular interest (7). By analogy we have synthetized quarternarized 6H-indolo-naphthyridines. The structures was established by comparison of NMR spectra of quaternized and non quaternized products. For exemple :



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Methyl-5 6H-indolo [3,2-b] naphthyridinium-1,5 iodide 8. NMR (DMSO,δppm/HMDS) : H(CH_3): 4,67 (s)(3H) ; H_7, H_8 and H_9 : 7,66 (m)(2H), 7,36 (m)(1H) ; H_2 : 8,11 (q)(1H) ; H_{10} : 8,30 (m)(1H) ; H_5 : 8,53 (s)(1H) ; H_1 : 9,21 (q)(1H) ; H_3 : 9,43 (q)(1H).

The new one step synthesis described above has demonstrated that the Friedlander reaction is an efficiant route to new isosteres of ellipticine. We now intend to prepare a series of substituted derivatives of the 6H-indolo-naphthyridine system by this way in order to complete the pharmacological study referred to earlier in this paper.

References and notes

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(6) A solution of 0,005 mole of 5 and 0,005 mole of 6 in MeOH and few drops of KOH 5 % was kept at room temperature for 3 days, under nitrogen. Compounds 7 were collected by filtration.

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