POLYMETHOXYLATED ISOQUINOLINES AS POTENTIAL ANTIMITOTIC AGENTS

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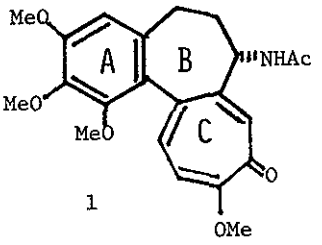
Several polymethoxylated isoquinolines related to the alkaloids sendaverine and cryptostyline III have been prepared from mescaline. Using colchicine as a standard none of these compounds did show any binding affinity to the rat brain microtubule protein.

Within the last few years it has become clear that antimitotic activity and the antigout effect of colchicine (1) are the result of an interaction with the microtubule protein tubulin[3]. Good correlation has been found between antimitotic activity and the ability to inhibit either ^{3}H-colchicine binding to rat brain microtubule protein and/or tubulin polymerisation in vitro[3,4]. It can be learned from such studies that much simpler structures than that of colchicine (1) exhibit antimitotic activity[3,4]. Allocolchicine (2) and N-acetylcolchinol (OH in 2 instead of COOMe), both having a six membered ring C, are quite active indicating that the tropolone ring in 1 can be replaced by another aromatic moiety[4]. Even compounds lacking the acetamido substituted carbon bridge in ring B, such as the tropolone 3, display excellent activity[4]. The corresponding tropolone lacking the aromatic methyl ether functions in the phenyl ring is considerably less active, suggesting that the presence of several aromatic ether functions next to each other ("crowded") might be an important requirement[4,5].



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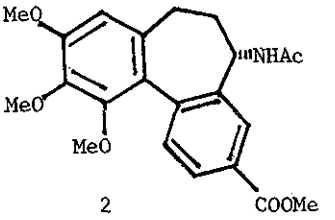

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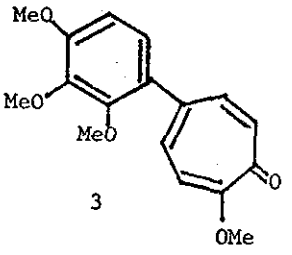

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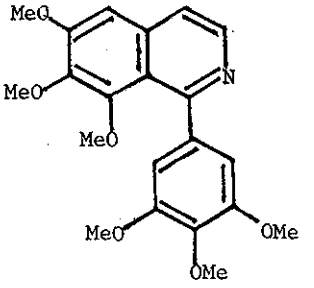

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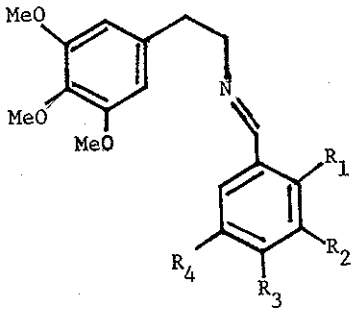
The nonspecificity of the colchicine structure with regard to its binding to tubulin is remarkable and we are therefore evaluating these findings including chemical manipulations. In this paper we report the synthesis of several polymethoxylated isoquinolines and their tubulin binding ability. Compounds 6a,b are closely related to the alkaloid sendaverine[6],

whereas compounds 10,11,12 can be considered analogs of cryptostyline III[7]. The structure of the latter shows in addition a remarkable resemblance to podophyllotoxine, another antimitotic agent which binds to tubulin[8], if one disregards the isoquinoline nitrogen function.

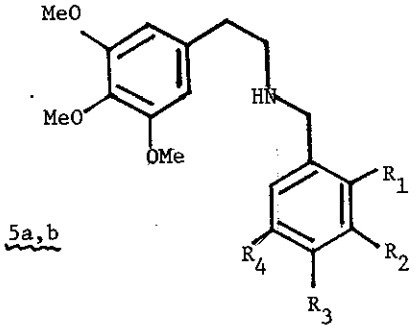
The chemical synthesis of these compounds was accomplished by standard procedures.[9] For the sendaverine analogs 6a,b mescaline was reacted with 2,4,5- and 3,4,5-trimethoxybenzaldehyde (Dean Stark trap, in benzene) to afford the Schiff's bases 4a,b, isolated as imminium salts (4a·HCl, 78%, mp 98°, ir $\nu(\overset{+}{N}H{=}CH)$ in $CHCl_3$ 1660 cm^{-1}; 4b·HCl, 98%, mp 116°, $\nu(\overset{+}{N}H{=}CH)$ in $CHCl_3$ 1675 cm^{-1}). The Schiff's bases 4a,b are not stable in the presence of acid and decompose on tlc (silica gel, AcOH-nBuOH-H_2O). Reduction with sodium borohydride in methanol gave the substituted phenethylamines 5a,b in quantitative yields (5a. HCl, mp 183-184°, MeOH; 5b.HCl, mp 204°, MeOH). Cyclization was accomplished by heating 5a,b.HCl with 1.1 equiv. of a 0.1 molar solution of CH_2O (40°, 5a.HCl 96 hr.; 5b.HCl, 38 hr., tlc monitoring). Concentration and crystallization from MeOH gave 6a.HCl (73%, mp 152-153°) and 6b.HCl[10] (97%, mp 165-166°). Under reflux temperature a mixture of compounds was obtained. For the preparation of the analogs of cyptostyline III



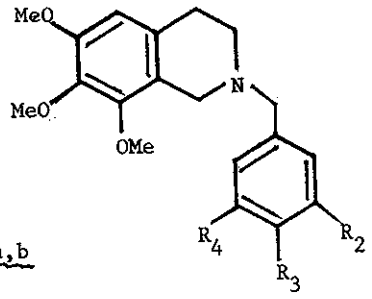
4 a,b

a, $R_1 = R_3 = R_4 = OMe$, $R_2 = H$

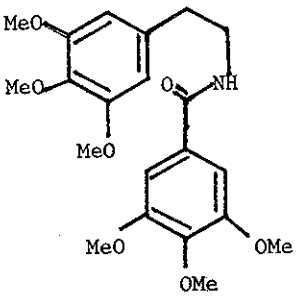
b, $R_2 = R_3 = R_4 = OMe$, $R_1 = H$



5a,b



6a,b



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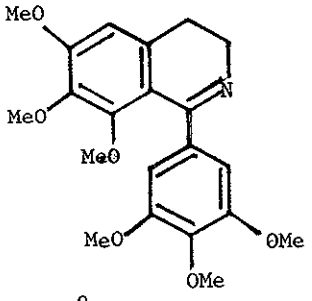

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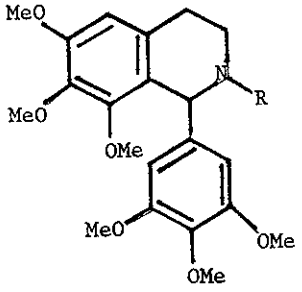
9 = Methiodide



10 R = H, 11 R = Me

the original synthesis was copied[7]: Amide 7 (mp 179°, $CHCl_3$-MeOH) was cyclized with phosphorous oxychloride to the 3,4-dihydroisoquinoline 8 (86%, HCl mp 185°, MeOH-Et_2; methiodide 9 mp 189-190°), Borohydride reduction of 8.HCl afforded the 1,2,3,4-tetrahydroisoquinoline 10 (84%, mp 109°, MeOH-Et_2O) which could easily be N-methylated with CH_2O and HCOOH to 11 (90%, oxalate mp 186-187°, MeOH-Et_2O) or dehydrogenated to 12 with Pd black in refluxing tetralin under nitrogen atmosphere (56%, 12.HCl mp 185°, MeOH-AcOEt, uv λ_{max} (MeOH): 243, 303 and 328 nm, log ε = 4.51, 4.78 and 3.73).

Results of the biological screening: The various isoquinolines and phenethylamines were tested in form of their water-soluble hydrochloride salts. The per cent of inhibition of ^{3}H-colchicine binding was measured with the method used by Zweig and Chignell[3]. The final concentrations used were 2.5×10^{-6} M for ^{3}H-colchicine whereas all model compounds were applied at a 10-fold higher concentration. None of the phenethylamines (5a,b) or isoquinolines (6a,b and 8,10,11,12) inhibits ^{3}H-colchicine binding to the rat brain microtubule protein. These negative results suggest that crowded methyl ether arrangements in a phenethylamine or isoquinoline moiety do not suffice for an interaction with tubulin.

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Literature:

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2) Present address: Laboratory of Environmental Biophysics, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA.

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