Drugs of the Future

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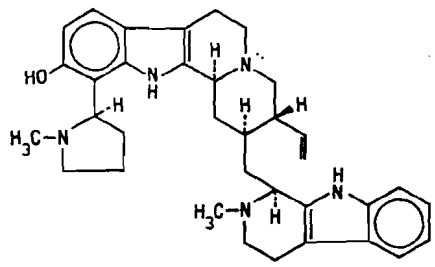
STRYCHNOPENTAMINE

18,19-Didehydro-12-(1-methyl-2-pyrrolidinyl)-16-(2,3,4,9-tetrahydro-2-methyl-1*H*-pyrido[3,4-*b*]indol-1-yl)-17-norcorynan-11-ol
[CAS-63209-34-7]
EN = 107-841
Antimitotic



$C_{35}H_{43}N_5O$; Mol wt: 549.76
C 76.47%; H 7.88%; N 12.74%; O 2.91%

Extraction and Structure

The dried leaves of *Strychnos usambarensis*, collected in Rwanda as well as in Tanzania, are extracted with MeOH; the extract is concentrated and the resulting solution brought to pH 8 is directly extracted with $CHCl_3$. This extract is subjected to preparative TLC over silica gel (1). After elution, strychnopentamine is isolated by crystallization in C_2H_5OH-H_2O (1).

X-Ray crystallography has established the relative configuration of this new compound. Crystals of $C_{35}H_{43}N_5O.3.5H_2O$ were tetragonal, space group $P_{4,2,2}$ with $a = b = 13{,}895$, $c = 36{,}105$ A. The crystal structure was solved by direct methods and refined to a final conventional R value of 8.4% (2125 reflections).

Strychnopentamine is the first alkaloid with five amines found in a *Strychnos* species; a methylpyrrolidine group is joined to the benzene ring of the corynane part of the molecule. The configuration, determined on the basis of biogenetic arguments, is 3*S*, 4*R*, 15*S*, 17*S*, 20*R*, 72*R*, C(72) being the first atom of the pyrrolidinic group. Compound and water molecules are linked together by seven non-equivalent hydrogen bonds (2).

Description

Colorless tetragonal crystals, mp. 246-8°. UV λ MeOH (log ε): 204 (4.28), 226 (4.38), 275 (3.82), 291 (3.74). ^{1}HNMR ($CDCl_3$) = δ 7.5-7.1 (m; 5H arom.); 6.6 (d, J = 8 Hz; 1H, H_{10}); 5.75 (m; 1H $CH=CH_2$); 5.2 (m; 2H, $-CH=CH_2$); 3.6 (m; 1H, H_{17}) 3.31 (t; 1H, H_{72} pyrrol.); 2.47 (s; 3 H, N-CH_3); 2.27 (s; 3H, N-CH_3). CD MeOH $[\Theta]_{276} = +8190$.

History

During the past fifteen years, African *Stychnos* species have been pharmacologically and chemically screened by some European Universities. The research program of the University of Liege on *Strychnos* alkaloids is an offshoot of an inventory of medicinal and toxic plants in Rwanda, carried out during the years 1969-70 (3).

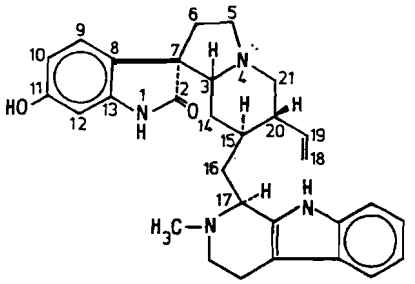
Strychnos usambarensis roots and leaves are used in Central Africa for the preparation of a curarizing arrow poison (4). Our investigations have shown that the roots contain well-known curarizing diquaternary alkaloids and many other bases devoid of activity (5). Among the toxic plants, the species which are ingredients of arrow poisons are worth studying because the research into those poisons remains closely connected with current activities in the never-ending search for new and better drugs by providing molecular structures for study by organic chemists and as models for study by pharmacologists.

Moreover, one recent study has described an attempt to correlate results obtained from the NCI plant antitumor screening program with selected types of folkloric uses (6). From these data it would appear that one would increase by a factor of about five the number of plant species that could show experimental *in vitro* or *in vivo* cytotoxicity or antitumor activity if the plants were selected on the basis of alleged use as arrow poisons. Indeed, it was found that a $CHCl_3$ extract of *S. usambarensis* leaves exhibited activity against lymphatic leukemia P388 *in vivo* in mice.

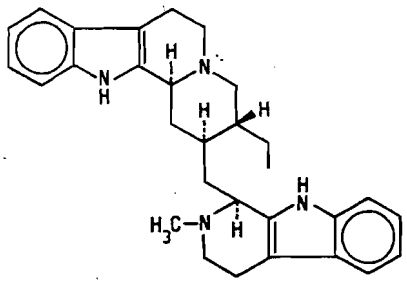
Thus, we have carried out experiments on the cytotoxic and antitumor properties of pure alkaloids isolated from *S. usambarensis*.

Pharmacological Activity

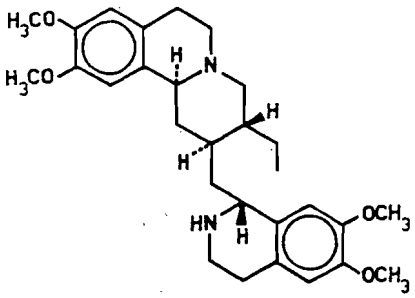
Antimitotic activity tests were carried out as previously described (7) on a) cultured hepatoma cells derived from HW165 hepatoma of Wistar rats, b) cultured B16 melanoma cells derived from C57BL mouse melanoma, and c) cultured Ehrlich ascites cells (line ELT) derived from a mouse mammary gland carcinoma and transplanted into C57BL mouse peritoneal cavity. Three alkaloids of the leaves (strychnofoline [I], dihydrousambarine [II] and



[I]



[II]



[III]

strychnopentamine) possessing the usambarane skeleton, were first tested. They are structurally similar to emetine [III] and may be regarded as indole analogs of this last compound. Emetine acts by means of protein synthesis inhibition and has been evaluated clinically as an antimitotic drug. The structural similarities prompted us to evaluate the cytotoxic properties of these alkaloids. Strychnofoline and dihydrousambarine showed a certain degree of antimitotic activity at relatively high doses (10 μg/ml and mainly 50 μg/ml) (7). Strychnopentamine was about 10 times more potent than strychnofoline and 18,19-dihydrousambarine as an antimitotic agent in animal tumor cell cultures, since it inhibited 50% of the cells in mitosis at a concentration of 1 μg/ml (1.8 μm) (8). The comparison of their molecular structures induced us to hypothesize that the presence of an *N*-methylpyrrolidine group increases the antimitotic activity of these alkaloids. Strychnopentamine was also more potent than some planar β-carboline alkaloids such as sempervirine, whose patent as an antitumor drug is pending (9, 10), and many other indole alkaloids (11).

Considering this *in vitro* antimitotic activity (similar to that of ellipticine, another indole alkaloid) we have undertaken preliminary experiments to search for a possible antitumor activity of this molecule in animals. Our experiments have been carried out on Ehrlich ascites tumor cells in male mice (10). When mice received strychnopentamine in a single injection of 1 mg, there was a medium decrease of cell number (about 50%). At a single dose of 2 mg, a very marked decrease of tumor cell number was observed (>80%). Very quick regression was obvious, but mice rapidly showed signs of intoxication, since 40% died soon after the injection. Similar tests are now being carried out with strychnopentamine and other derived alkaloids at various dosages and in repeated injections, in order to establish a more exact structure-activity relationship and to discover less toxic derivatives.

Acknowledgements

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Source

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