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NEW INDOLE ALDEHYDIC ALKALOIDS OF STRYCHNOS VARIABILIS

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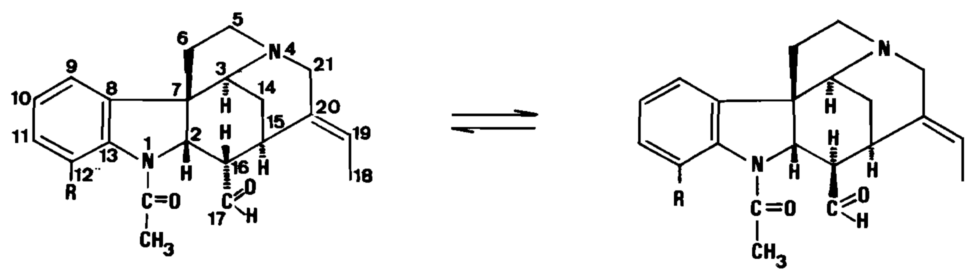
Abstract: Two isomeric pairs of novel indoline aldehydic alkaloids have been isolated from the root barks of Strychnos variabilis. The isomerism finds its origin in the facile isomerisation of C16 and is set up rapidly at room temperature. So, they could be the biogenetic starting point of two series of alkaloids which have a different stereochemistry for C16: the "retuline" series and the epimer "isoretuline" series.

We describe the isolation and structure determination of four indolinic alkaloids showing rather special properties. Their feature is the presence of the easily exchangeable proton 16. They form two pairs of diastereomeric equilibrating alkaloids:

A RETULINAL (1) $\rightleftharpoons$ ISORETULINAL (2)

B 12-HYDROXYRETULINAL (3) $\rightleftharpoons$ 12-HYDROXYISORETULINAL (4)

They are converted quickly into one another.



1 R=H

3 R=OH

RETULINE SERIES

2 R=H

4 R=OH

ISORETULINE SERIES

The dried root barks of Strychnos variabilis DE WILD - an African species - were extracted with MeOH. The extract was concentrated and the resulting solution made acetic. This solution was brought to pH_8 and was directly extracted with $CHCl_3$. This extract was subjected to column chromatography Lobar^R over silicagel with acetone (+ 0 to 10 % of MeOH). The first eluted B pair, was directly followed by the A pair.

These alkaloids were isolated in double groups because it's impossible to isolate them in various solvent systems although their Rf value is different.

A bidimensional chromatography of each pair, in the system: acetone/MeOH/petroleum spirit (1:1:0,04) shows that each spot unfolds in a second migration.

A. RETULINAL $\rightleftharpoons$ ISORETULINAL

This couple alkaloids is very important in Strychnos variabilis: it represents 15 to 20 % of the total alkaloids and 75 % of the monomers. Indeed the dimers are in majority in the root barks [1]. In the above-mentioned system, the Rf are 0,27 and 0,11. The two spots are coloured orange with $FeCl_3/HClO_4$ reagent (0,2 M $FeCl_3$ in 35 % $HClO_4$) after a five minutes heating at 90°C.

UV, MS, IR data have established the structure but they don't allow the detection of the two equilibrated diastereoisomers. The UV spectrum [λ^{MeOH}_{nm} (log ε) 212(4,4); 251(4,07); 282 (3,46)] indicates a N-acetyl indolinic chromophore. This spectrum remains unchanged in alkaline or acidic medium. In the mass spectrum 70 eV, the molecular ion peak is found at m/e 336 confirming the molecular formula $C_{21}H_{24}N_2O_2$; peaks at m/e (relative abundance in % of base peak: 336(35),335(5),334(5),322(12),321(6),318(6),308(13),307(14),295(10),294(14),293(49),291(7), 186(24),185(8),165(14),164(81),149(13),145(14),144(100%),143(28),136(19),130(23),123(12),122(15), 121(30),119(21),115(14),109(35),108(16). The 121 peak is typical of a piperidine ring with an ethylidenic chain [2]. The 130,143,144 peaks support the structure of an indole alkaloid and confirm that the aromatic ring is unsubstituted [2]. The 185(143+42) and 186(144+42) peaks show that the indole nitrogen is indeed acetylated. The 164 peak is characteristic of a "retuline" type alkaloid with an aldehydic function at C 16 [3]. The IR spectrum [$\tilde{\nu}^{KBr}_{max}$ cm^{-1} 2930,2820,2730, 1715,1625,1600,1590,1485,1460,1445,1435,1400.....778] shows bands which can be assigned to the N_a - Acetyl dihydroindole and to the aldehydic group. The ^1H NMR spectrum (360 MHz) confirms that structure and allows to establish the stereochemistry. The study was easy because of the comparison with the ^1H NMR spectrum of retuline and isoretuline [4]. The equilibrium between the two forms varies according to the solvent and the temperature. In $CDCl_3$ and at room temperature there are about 10 % of retulinal and 90 % of isoretulinal. The restricted rotation around the N_a-CO-CH_3 bond can give rise to two rotamers: rotamer a (acyl oxygen oriented towards the aromatic ring) and rotamer b.

ROTAMER a **ROTAMER b**

Retulinal shows these two rotamers in the proportion 2/3, 1/3. Richard and co-workers have isolated earlier isoretulinal from the same Strychnos [5]. They claim that this alkaloid does not isomerise in alkaline medium, a result at variance with our observations. This is probably due to the fact that retulinal is the minor component of the equilibrium and to the complexity of its NMR spectrum. But, we distinguish very well the H_2 at δ 4,83(66%) A_1 rot. b J_{2-16} = 8,3 Hz and at δ 4,29(33%) A_1 rot. a J_{2-16} = 8,4 Hz and the aldehydic protons H_{17} at δ = 9,38(66%) J_{17-16} = 1 Hz and at δ = 9,31(33%) J_{17-16} = 2 Hz. In the case of isoretulinal, they are also two rotamers but rot. b is largely predominant. However a tiny signal at δ = 8,09 can be due to aromatic proton 12 of rot. a. Chemical shifts and coupling constants in isoretulinal rot. b: at δ = 9,67 (d. H_{17} J_{17-16} = 4,8 Hz); 7,27 (t. H_{11});7,22(d.H_9);7,14(t. H_{10});7,12(d.H_{12});5,55 (d.q. H_{19} $J_{19-Me18}$ = 6,8 Hz, $J_{19-21\beta}$ uncalculated);5,04 (d.H_2 J_{2-16} = 9,6 Hz);3,60($H_{21\alpha}$ $J_{21\alpha-21\beta}$ = 14,2 Hz);3,57(H_3 J_{3-14S} = J_{3-14R} = 3,2 Hz);3,25($H_{21\beta}$$J_{21\beta-Me18}$ = 2 Hz);3,22(H_{5A} J_{5A-5B} = 12,2 Hz,J_{5A-6A} = 8 Hz,J_{5A-6B} = 9,6 Hz);3,03(H_{15} J_{15-14S} = 3,5 Hz, J_{15-14R} uncalculated);2,92 (H_{5B} J_{5B-6A} = 8 Hz, J_{5B-6B} = 3,9 Hz);2,52(H_{6A} J_{6A-6B} = 13,6 Hz);2,42(N-Acδ);2,27(d.t.H_{16});2,01 (H_{14S} $J_{14S-14R}$ = 13,6 Hz);1,93(H_{6B});1,62(H_{14R});1,54(d.d.Me_{18}).In DMSO at 100°C, the proportion vary. There are 30 % of retulinal and 70 % of isoretulinal. At this temperature, we notice the average of the two rotamers of the retulinal which allow to explain the different protons more easily. Retulinal at δ= 9,23(d.H_{17} J_{17-16} = 1,2 Hz);5,42(q.H_{19} $J_{19-Me18}$ = 7 Hz);4,48(H_2);3,80 (H_3);3,65(d.$H_{21\alpha}$ $J_{21\alpha-21\beta}$ = 14,8 Hz);2,83(d.$H_{21\beta}$);2,32(s.N-Ac.);1,60(d.Me_{18}). Isoretulinal at δ = 9,55(d.H_{17} J_{17-16} = 5 Hz);7,37(d.H_{12});7,31(d.H_9);7,24(t.H_{11});7,11(t.H_{10});5,44(d.q.H_{19} $J_{19-Me18}$= 6,8 Hz,$J_{19-21\beta}$=1,6 Hz);4,85(d.H_2 J_{2-16} = 9,4 Hz);3,50(t.H_3 J_{3-14S} = J_{3-14R} = 3 Hz); 3,37(d.$H_{21\alpha}$ $J_{21\alpha-21\beta}$= 14 Hz);3,15(d.t.$H_{21\beta}$ $J_{21\beta-Me18}$ = 2 Hz);3,08(H_{5A} J_{5A-5B} = 12 Hz,J_{5A-6A} = 6,8 Hz,J_{5A-6B} = 9,2 Hz);2,97(H_{15} J_{15-14S} = 3,5 Hz,J_{15-14R} = 2,9 Hz);2,79(H_{5B} J_{5B-6A} = 8,6 Hz, J_{5B-6B} = 4 Hz);2,44(H_{6A} J_{6A-6B} = 13,3 Hz);2,29(s.N-Ac.);2,28(H_{16} hidden by N-Ac.);1,83(H_{14S} $J_{14S-14R}$ = 13,4 Hz;1,76(H_{6B});1,51(H_{14R});1,46(d.d.Me_{18}).

The diastereomeric relation of the two alkaloids was independently proved by the following reduction reaction: a MeOH solution of the alkaloid pair (20 mg in 10 ml) is submitted to $NaBH_4$, at room temperature for two hours. We have added 5 ml of water and distilled MeOH under reduced pressure. The aqueous alkaline solution is extracted by 3 x 10 ml of $CHCl_3$. The $CHCl_3$ solution is evapored and submitted to silicagel chromatography and eluted with: ethylacetate/ isopropanol/NH_3 dil. (60:25:15) to give two spots having the same Rf as authentic retuline and isoretuline.

B. 12-HYDROXYRETULINAL $\rightleftharpoons$ 12-HYDROXYISORETULINAL

Their hydroxylated derivatives are six to seven times less abundant in the plant than(1) and(2). In the acetone/MeOH/petroleum spirit(1:1:0,04) system,the Rf are 0,3 and 0,13. The two spots are coloured violet with $FeCl_3/HClO_4$ after heating. They also turn to violet with Blue Solid B. As above, the structure has been established from spectral data. UV [λ_{nm}^{MeOH} (log ε) 216,5(4,05);252(3,45);288(3,08)]. In alkali, we notice a bathochrome shift due to the phenolic group[$\lambda_{nm}^{MeOH(+OH^-)}$(log ε):221(3,96);306(3,24)].MS 70eV peaks at m/e (relative abundance in % of base peak):353(9),352(33)[$C_{21}H_{24}N_2O_3$],351(4),350(4),334(13),324(11),323(11),319(7),310(11), 309(37),295(15),293(11),281(9),221(20),207(11),202(9),186(11),165(18),164(100 %),163(11),160 (55),159(18),149(22),147(15),146(24),144(26),143(15),136(22),133(18),130(15),124(20),122(24), 121(33),119(22),111(18),109(52),108(22). We notice the existence of an extra oxygen in the molecular formula compared with the preceding pair (many peaks are increased with 16 m/e. The base peak at m/e 164 overwhelmingly demonstrates the aldehydic function in C_{16} [3].

The 146,159,160 peaks (130,143,144 + 16) are typical of indole substitued by an hydroxyl on the benzene ring. The IR spectrum shows bands $\left[\tilde{\nu}^{KBr}_{max}\,cm^{-1}\ 3420,2925,2850,1720,(-C{\lesssim}^{O}_{H}),1630(N\text{-}Ac.),1600,1475,785,732\right]$. Finally, as in the other case, the ^1H NMR spectrum in $CDCl_3$ confirms the presence of the two diastereoisomers. We notice 40 to 45 % of 12-hydroxyretulinal and 55 to 60 % of 12-hydroxyisoretulinal. So the proportions are different from those established for the non-phenolic alkaloids. In 12-hydroxyretulinal the rotamer a is preponderant due to a stabilization by a cryptophenolic function. This phenomenon gives an overall stabilization of the"retuline" (16βH) form over the 16α form in the hydroxylated derivative. So this rotamer a engaged in a cryptophenolic function would change the balance. The most important parts of this spectrum are for 12-hydroxyretulinal rot. a at δ = 10,26(OH in 12);9,27(H_{17} J_{17-16} = 1,5 Hz);7,17(H_{10});6,93(H_{11});6,78(H_9);5,68(q.H_{19});4,37(d.H_2 J_{2-16} = 8,4 Hz);2,33(s.N-Ac.);1,72(d.Me_{18}).and for 12-hydroxyisoretulinal (as in isoretulinal the rotamer b is largely dominant) at δ = 9,90(OH in 12);9,67 (d.H_{17} J_{17-16} = 1,5 Hz);7,17(H_{10});6,93(H_{11});6,78(H_9);5,58(q.H_{19} $J_{19-Me18}$ = 6,8 Hz);4,72(d.H_2 J_{2-16} = 9,6 Hz);2,49(s.N-Ac.);1,56(d.d.Me_{18} $J_{Me18-21}$ = 2 Hz).

The discovery of these diastereoisomers in Strychnos variabilis seems particularly interesting because it explains the simultaneous presence of retuline(16βH) and isoretuline (16αH) which, easily isolated, could come from the reduction of retulinal and isoretulinal, as well as their simultaneous occurence in the quantitatively important dimeric alkaloids (strychnobiline [1,6] . Moreover, Strychnos henningsii contains retuline but also derivatives of isoretuline [7].

The aldehydic diastereomeric alkaloids are possibly an intermediate stadium in the biogenesis of these Strychnos alkaloids.

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