give unreactive iodine results in decreased yields of iodination. It is anticipated that the KIO_3/KI/HCl system will complement the already used iodination methods opening the way to the synthesis of new iodoaryls.[7]

Experimental Section

General. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. Melting points are uncorrected and taken on a Thomas-Hoover apparatus. NMR spectra (Me_2SO-d_6, D_2O, Me_4Si) were recorded on a Varian EM 360. All evaporations were accomplished on a Buchi Rotovapor-RE at ≤45 °C. Resorcinol and phloroglucinol·$2H_2O$ were obtained from Aldrich Chemical Co., Milwaukee, Wis. ICl was obtained from Matheson Coleman and Bell.

2,4-Diiodoresorcinol (1). To 11.0 g (0.10 mol) of resorcinol in 250 ml of H_2O was added 16.7 ml (0.20 mol) of concentrated HCl. To this stirred solution was added at a drop rate over a 1-h period a second solution prepared from 14.3 g (0.067 mol) of KIO_3, 22.1 g (0.13 mol) of KI, and 500 ml of H_2O. (Note that nascent iodine color formed in situ after each drop dissipates in about 1 s.) Stirring was continued an additional 1.5 h before extracting the (essentially iodine free) reaction mixture with EtOAc (4 × 100 ml). Evaporation of the EtOAc layer gave an oil which was dissolved in boiling CCl_4, filtered while hot to clarify, then cooled to obtain 20.3 g (56%) of white solid title compound, mp 87–89 °C.[3]

Anal. Calcd for $C_6H_4I_2O_2$: C, 19.91; H, 1.11; I, 69.99. Found: C, 19.63; H, 1.02; I, 70.13.

2-Iodoresorcinol (2). Using the same procedure as for **1**, 11.0 g (0.10 mol) of resorcinol and 8.3 ml (0.10 mol) of concentrated HCl in 250 ml of H_2O was combined with 7.1 g (0.033 mol) of KIO_3 and 11.1 g (0.067 mol) of KI in 250 ml of H_2O. Thus was obtained an oil which was dissolved in $CHCl_3$ adjusted to turbidity with petroleum ether and placed in the freezer for several days to obtain tan solid. Twice recrystallized from benzene this material gave 7.6 g (32%) of white, crystalline **2**, mp 105–108 °C (lit.[2,3] 100 °C).

2,4,6-Triiodophloroglucinol (3).[6] To 10.0 g of phloroglucinol·$2H_2O$ (0.062 mol) slurried in 250 ml of H_2O with 15.1 ml (0.18 mol) of concentrated HCl was added at a drop rate, in 2 h, a solution of 13.2 g (0.062 mol) of KIO_3 and 20.5 g (0.12 mol) of KI in 400 ml of H_2O. The reaction slurry was stirred overnight and then the crude product collected by filtration, washed with H_2O, and dried in vacuo to obtain a pink powder, mp 160 °C dec. Recrystallization from boiling $CHCl_3$ gave 27.8 g (89%) of white, crystalline **3**, mp 171–172 °C dec. Anal. Calcd for $C_6H_3I_3O_3$: C, 14,30; H, 0.60; I, 75.57. Found: C, 14.56; H, 0.81; I, 75.51.

2,4,6-Triiodoresorcinol (4). A. Using the same procedure as for **1**, 5.5 g (0.050 mol) of resorcinol and 12.5 ml (0.15 mol) of concentrated HCl in 100 ml of H_2O was combined with 10.7 g (0.050 mol) of KIO_3 and 16.6 g (0.10 mol) of KI in 350 ml of H_2O. After stirring for an additional 2 h, Na_2SO_3 was added to decolorize (I_2) the reaction mixture, then EtOAc (4 × 100 ml) was used to extract all products. Evaporation of the organic layer gave tan solid dried in vacuo over P_2O_5 to give 19.3 g (79% of expected weight) of tan solid. NMR showed this material to consist of a 43/57 mixture of 2,4,6-triiodo- and 2,4-diiodorescorcinol, respectively.

B. Solid resorcinol (22.0 g, 0.20 mol) was added at once to a stirred solution of 875 ml of 0.8 N ICl in 1.6 N HCl and held at 50 °C for 1 h. Next Na_2SO_3 was added to decolorize (I_2) the mixture, and product was collected by filtration and recrystallized from boiling $CHCl_3$ to obtain 49.5 g (51%) of tan, crystalline **4**, mp 154–157 °C (lit.[2] 154 °C).

4,6-Diiodoresorcinol (5). Using the exact procedure of Nicolet and Sampey,[4] 5.0 g (30%) of crude white solid **5** was obtained, mp 145–158 °C (lit. 145 °C). NMR showed this compound to be isomerically pure (Table I).

Acknowledgments. This work was supported by the National Institutes of Health Grant GM 16593. My thanks also is deserved by Dr. Milos Sovak for his continuing encouragement and Mr. Terry Williams for his devoted assistance.

Registry No.—**1**, 41046-69-9; **2**, 41046-67-7; **3**, 57730-42-4; **4**, 19403-92-0; **5**, 19514-91-1; KIO_3, 7758-05-6; KI, 7681-11-0; resorcinol, 108-46-3; phloroglucinol, 108-73-6.

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Stereochemistry and Conformation of Biogenetic Precursors of Indole Alkaloids[1]

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The biosynthetic pathway of indole alkaloids found in several plant genera, notably in the Apocynaceae family, commences with tryptophan and mevalonic acid.[3] Upon transformation of the latter into loganin (**1a**) and secologanin (**2a**) the metabolic substances meet in the form of vincoside (**3a**). It appears currently that **3a** or, in at least one instance, isovincoside (**3b**)[4] is a biogenetic precursor of many, structurally diverse indole alkaloids.[3,5] In order to facilitate investigations of the chemistry and metabolism of loganin (**1a**), secologanin (**2a**), the vincosides (**3a** and **3b**), and their lactams (**4a** and **4b**), provide NMR spectral parameters for the vincosides and the lactams, and reinforce and extend the ORD-based determination of the C(3) configuration of these substances,[6] a ^{13}C NMR analysis of **1a** and derivatives **1b**, **2b**, **3c–e**, and **4c,d** was undertaken.

The ^{13}C NMR analysis was initiated on the natural glucoside loganin (**1a**). The carbon shifts of the β-glucosyl unit were assigned on the basis of known literature values,[7] while all but the methine shifts were recognized by the characteristic field position and/or multiplicity of the signals of the unique aglycone carbon centers.[8] Carbon 19 was distinguished from the two other methines by its shift perturbation on acetylation of the neighboring 3-hydroxy group (vide infra). The differentiation of the remaining methines, C(15) and C(20), was founded on the shift difference of related carbons in dihydropyran and the expected strong deshielding of the homoallylic vs. allylic carbon by the neighboring methyl and glucosyloxy groups.

The ^{13}C NMR spectra of loganin pentaacetate (**1b**) revealed expected deshielding of C(3) and shielding of C(14) and C(19) as well as a shift pattern for the sugar moiety reminiscent of methyl tetraacetyl-β-D-glucopyranoside.[9] Rupturing the five-membered ring, i.e., loganin pentaacetate (**1b**) → secologanin tetraacetate (**2b**), caused no shift changes in the glucose unit, but induced ca. 2–5 ppm shift alterations for the characteristic dihydropyran ring carbons. The shift assignment for C(15) and C(20) of the secologanin derivative **2b** was confirmed by a correlation of the H(15) and H(20) shifts with the carbon resonances.[10,11] All δ values of compounds **1a**, **1b**, and **2b** are listed in Table I.

Table I. Carbon Shifts of Loganin and Secologanin Derivatives[a]

	1a[b]	1b[c]	2b[c]
C(3)	72.8	76.9	198.6
C(14)	40.9	38.7	43.0
C(15)	30.2	29.7	25.0
C(16)	112.0	113.3	109.2
C(17)	150.2	148.8	150.9
C(18)	11.4	12.3	120.7
C(19)	40.2	38.7	131.9
C(20)	44.6	45.3	43.5
C(21)	95.8	94.5	95.6
C=O	167.7	166.7	166.3
OMe	50.3	51.0	51.0
C(1′)	98.1	95.7	95.6
C(2′)	73.3	70.5	70.4
C(3′)	76.1	72.3[d]	72.2[d]
C(4′)	69.7	68.1	67.9
C(5′)	76.1	72.0[d]	72.0[d]
C(6′)	61.1	61.6	61.5

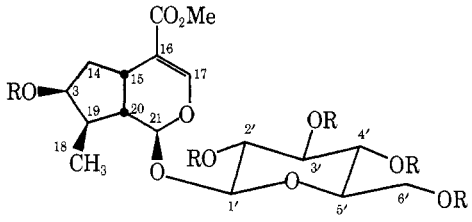
[a] δ values in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Enough methanol added to effect solution. [c] The acetyl groups show δ(Me) and δ(C=O) values of 20.4 ± 0.5 and 169.4 ± 0.9 ppm, respectively. [d] Signals may be reversed in any vertical column.

Table II. Carbon Shifts of Vincoside Derivatives[a]

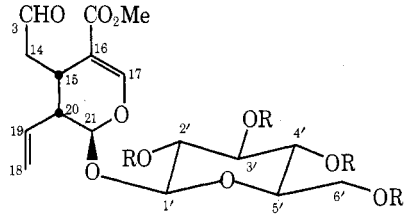
	3c[b]	3d[c]	3e[c]	4c	4d
C(2)	134.9	134.6	134.9	133.9	133.9
C(3)	51.1	45.9	47.7	53.3	53.6
C(5)	44.1	40.4	40.9	39.5	43.4
C(6)	16.9	21.5	21.5	21.1	19.0
C(7)	106.7	107.0	106.8	108.2	109.6
C(8)	127.2	126.6	126.4	126.9	127.7
C(9)	117.8	117.7	117.6	117.9	117.7
C(10)	118.9	119.1	119.0	119.0	119.0
C(11)	121.1	121.4	121.3	121.4	121.3
C(12)	110.6	110.9	111.0	111.2	111.4
C(13)	135.5	135.8	136.1	136.8	136.6
C(14)	33.7	33.1	33.4	31.5	26.3
C(15)	26.3	27.1	28.0	26.6	24.3
C(16)	111.7	110.9	110.3	109.1	109.6
C(17)	150.4	151.2	150.5	146.2	145.8
C(18)	119.4	120.1	120.9	119.8	119.9
C(19)	133.7	133.3	132.2	132.5	132.9
C(20)	42.1	42.8	43.4	42.7	42.9
C(21)	96.2	95.3	95.3	96.3	95.1
C=O	167.2	167.4	167.0	162.4	163.9
OMe	51.1	51.3	51.1		

[a] δ values in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. The tetraacetyl-β-D-glucopyranosyl carbon shifts are the same as those denoted in Table I. [b] The shifts for the benzyl group are δ(CH_2) 56.9, δ(ipso-C) 139.6, δ(o-C) 128.2, δ(m-C) 129.4, and δ(p-C) 126.7 ppm. [c] The carbonyl shift of the N-acetyl group is within the range of the δ values of the O-acetyl functions described in Table I, while the N-acetyl δ(Me) is 21.9 ppm.

The ^{13}C NMR data of secologanin tetraacetate (**2b**) (vide supra) and of tryptamine and carboline derivatives[12] permitted a first-order shift analysis of the tetraacetyl derivatives of N_b-benzylvincoside (**3c**), N_b-acetylvincoside (**3d**) and N_b-acetylisovincoside (**3e**). Inspection of the ^{13}C NMR spectra of vincoside lactam tetraacetate (**4c**) and the corresponding isovincoside derivative (**4d**) showed the ring closure of the vincosides to yield no ambiguous shift perturbations. All chemical shifts of compounds **3c–e** and **4c,d** are listed in Table II.

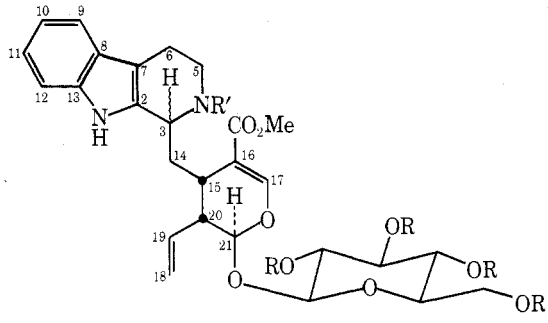


1

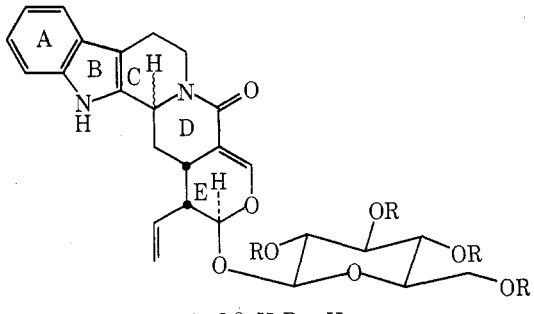


2

a, R = H
b, R = Ac



3a, 3β-H, R = R′ = H
b, 3α-H, R = R′ = H
c, 3β-H, R = Ac; R′ = $CH_2C_6H_5$
d, 3β-H, R = R′ = Ac
e, 3α-H, R = R′ = Ac

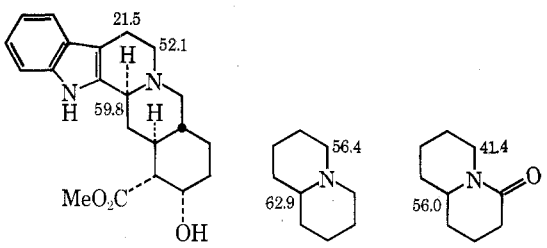


4a, 3β-H, R = H
b, 3α-H, R = H
c, 3β-H, R = Ac
d, 3α-H, R = Ac

Comparison of the ^{13}C NMR data on the N_b-acetylvincosides **3d** and **3e** shows C(3) epimerization to have little shift effect. The difference of the δ(C-3) values can be attributed to a difference of rotamer populations of the side chain whose exact nature is difficult to assess.[13] However, the shift difference of several carbon sites of tetraacetylvincoside lactam (**4c**) and tetraacetylisovincoside lactam (**4d**) reveals both the C(3) stereochemistry and the conformation of the fused pentacyclic nucleus of the two lactams.

The chemical shifts of C(3) and C(6) of yohimboid and ajmalicinoid alkaloids, pentacyclic substances (cf. **5**) structurally related to **4c** and **4d**, have been shown to be diagnostic parameters for the conformational analysis of these compounds.[14] Conversion of the quinolizidine unit,

i.e., rings C and D, into a quinolizidone system is expected to change the C(3) shift. Furthermore, the presence of a β-oxy-α,β-unsaturated carbonyl moiety flattens rings D and E to such an extent as to preclude nonbonded interactions between H(3) and ring E hydrogens or substituents, i.e., γ and δ effects. As a consequence the δ (C-3) value contains little stereochemical information, a prediction in accord with the identity of the C(3) shift of **4c** and **4d.** The Δδ value for the methine of quinolizidine (**6**)[12] and quinolizidone (**7**) can be used in conjunction with the C(3) shift of

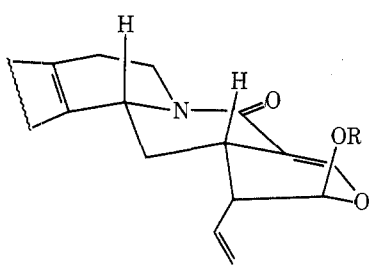


5 **6** **7**

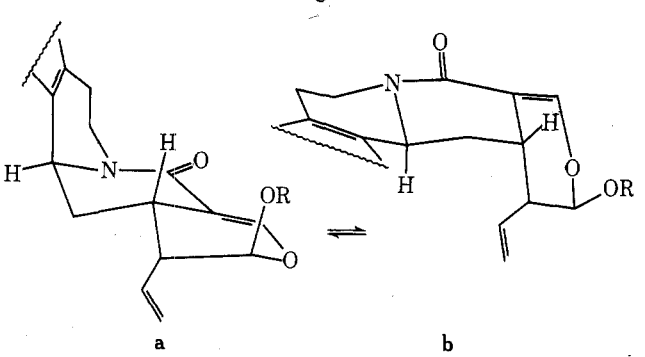
yohimbine (**5**)[14] for the evaluation of δ (C-3) of **4c** and **4d.** The calculated value 52.9 ppm fits well the observed resonances of 53.3 and 53.6 ppm, respectively.

The δ (C-6) values of 21.5 ± 0.5 and 16.5 ± 0.5 ppm of yohimboid substances containing *trans*- and *cis*-quinolizidine units, respectively,[14] indicate **4c** to adopt the *trans*-quinolizidone conformation and **4d** to tend toward a *cis*-quinolizidone structure. While C(6) of **4d** is less shielded than expected, the limiting δ (C-6) value cannot be assessed. The lactam carbonyl group imposes trigonality on N_b thereby reducing nonbonded interactions on H(6) within a C/D cis conformation.[15] Finally, since **4c** and **4d** differ stereochemically only at C(3), the difference of their quinolizidone conformation limits them to H(3)–H(15) cis and trans stereochemistry, respectively.

Besides the C(6) shift three other resonances are in agreement with conformation **8** for lactam **4c** and **9a** for lactam **4d.** Comparison of the aminomethylene shift of quinolizidine (**6**) with the amidomethylene resonance of quinolizidone (**7**) yields a Δδ value of 15.0 ppm, while Δδ (C-5) between yohimbine (**5**) and tetraacetylvincoside lactam



8



a **b**

9

(**4c**) as well as its 3 epimer **4d** is 12.6 and 8.7 ppm, respectively.[16] Since the shielding of C(5) on introduction of the nuclear carbonyl group is largely due to an added γ effect[17] and since the nonbonded interaction of the carbonyl oxygen with the C(5) hydrogens is nearly identical in the *trans*-quinolizidone conformations **8** and **9b** but different in the *cis*-quinolizidone form **9a,** the Δδ (C-5) values agree with the above conformational assignment. The γ effect of the carbonyl oxygen, which induces shielding of C(5) of **4c** relative to **4d,** is reflected also, albeit in reduced form, by the carbonyl carbon being more shielded in **4c** vs. **4d.** Carbon 19 experiences a 1,3-diaxial nonbonded interaction with H(14α) in conformations **8** and **9a,** but not in **9b.** Since the C(19) shift is nearly the same in **4c** and **4d,** it also confirms the above stereochemical argument.

Experimental Section

All carbon shifts were recorded on Brucker HFX-90E and Varian XL-100-15 NMR spectrometers operating in the Fourier transform mode at 22.6 and 25.2 MHz, respectively. The shifts on formulas **5, 6,** and **7** refer to deuteriochloroform solutions; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm.

Acknowledgment. A gift of lactams **4a** and **4b** by Dr. G. J. O'Loughlin, ^{13}C NMR determinations by J. Blackburn, and financial support by the Public Health Service for the work at the University of Wisconsin (CA 17127 by NCI) and at Rice University are acknowledged gratefully.

Registry No.—**1a,** 18524-94-2; **1b,** 20586-11-2; **2b,** 21237-36-5; **3c,** 55855-71-5; **3d,** 22621-93-8; **3e,** 20824-30-0; **4c,** 52484-98-7; **4d,** 23141-26-6.

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(15) The shielding of C(6) in C/D cis yohimboid alkaloids relative to C/D trans compounds is due to the nonbonded interaction between axial H(6) and the axial hydrogen on the nonvicinal aminomethylene group.[8] The change of the C(6) shift of **4b** reflects a change in the spatial disposition of the interacting centers toward each other rather than the effect on the γ shift by the replacement of the aminomethylene hydrogens by a doubly bonded oxygen, since γ effects are common to both hydrogen–hydrogen and hydrogen-π bond interactions.[14]
(16) If **4b** is compared with pseudoyohimbine,[14] a C/D cis structure, Δδ becomes 7.3 ppm.
(17) For sake of comparison the Δδ(Me) values of the methylcyclohexane/2-methylcyclohexanone and *N*-methylpiperidine/*N*-methyl-α-piperidone pairs are 9.5 and 12.1 ppm, respectively.