51. The Total Synthesis of Ipalbidine and Ipalbine

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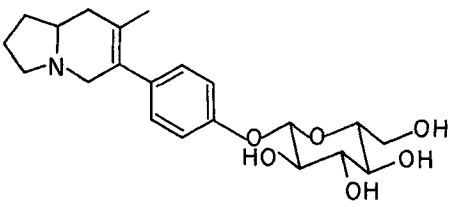
Zusammenfassung. Eine Totalsynthese des Hexahydroindolizin-Alkaloids Ipalbidin (**7**) und seines β-D-Glucosids Ipalbin (**1**) wird beschrieben. Der zentrale Syntheseschritt besteht aus einer N-Acylierung des vinylogen Amidsystems **3**, gefolgt von einer internen Kondensation zum pentasubstituierten Pyridon **4**. Die spektralen Daten von synthetischem Ipalbidin bzw. Ipalbin sind identisch mit denjenigen der entsprechenden natürlichen Verbindungen. Auf Grund des Vergleichs von optischen Drehungen wird ermittelt, dass Ipalbidin in der Natur in racemischer Form vorliegt.

In a recent communication [1], the isolation of a new hexahydroindolizine alkaloid, ipalbine (**1**), from the seeds of *Ipomoea alba L.*, was reported.



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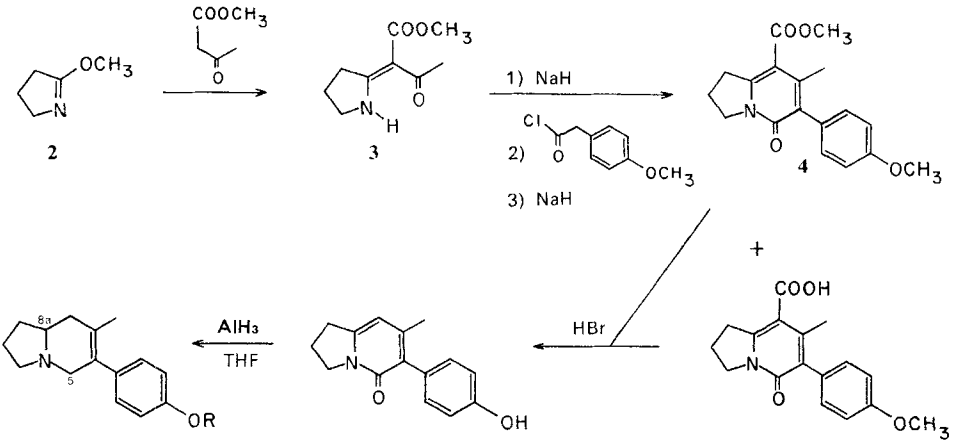
On the basis of NMR. spectroscopy, ipalbine was recognized as a β-glucopyranoside, which on mild acid hydrolysis gave D-glucose and an aglycone, ipalbidine (**7**). The structure of ipalbidine was derived from the results of its partial and total hydrogenation and its selenium dioxide oxidation.

We report here the synthesis of racemic ipalbidine (**7**)[1], and of its optically active forms **11** and **12**. Furthermore, (+)-ipalbidine (**11**) was converted to the corresponding β-D-glucoside ipalbine, whose spectral identity with the naturally occurring alkaloid corroborates structure **1**.

The starting material for our synthesis, 2-methoxy-1-pyrroline (**2**), is readily available by alkylation of 2-pyrrolidone with dimethyl sulfate [3]; an improved procedure gave **2** in 64% yield. The anticipated introduction of a three-carbon unit was accomplished by condensation of **2** with methyl acetoacetate to give the keto-ester **3**. The reaction proceeded in the absence of a solvent at 85°, which is just below the critical temperature at which rearrangement of **2** to N-methylpyrrolidone occurs [4].

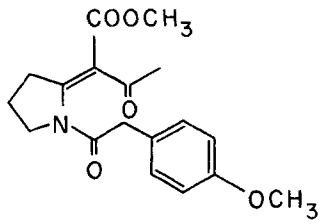
[1] Upon completion of this manuscript, a synthesis of racemic ipalbidine was reported [2].



7 (±) R = H
8 (±) R = CH_3CO
9 (+) R = CH_3CO
10 (−) R = CH_3CO
11 (+) R = H
12 (−) R = H

It may be of interest to note that the formation of **3** could not be accelerated by the addition of catalytic amounts of pyridine or triethylamine [5].

Direct acylation of **3** with *p*-methoxyphenylacetyl chloride in the presence of triethylamine failed. We ascribe this to the poor nucleophilic character of the nitrogen in such a vinylogous amide/carbamate system. The sodium salt of **3**, however, reacted smoothly with the acid chloride, yet the expected N-acylated product **13** could not be isolated from the complex reaction mixture. Instead, after the addition of a further equivalent of sodium hydride to the reaction mixture and subsequent heating at reflux temperature, the pyridone **4** was produced directly in 65% yield. In addition, nearly 10% of the corresponding acid **5** could also be isolated. The presence of the aromatic moiety in the proposed intermediate **13**, even though it bears an unfavorable *p*-methoxy group, is essential for the facile ring closure to **4**, since the reaction of **3** with caproyl chloride gave only the N-acyl derivative **14** and none of the corresponding pyridone.



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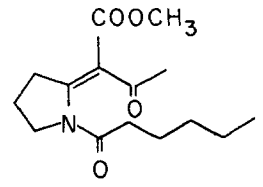
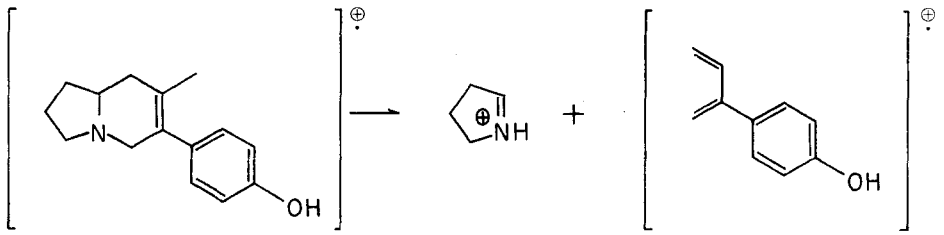


14

Compounds **4** and **5** could be demethylated and decarboxylated in hot 48% hydrobromic acid to the tetrasubstituted pyridone **6** in nearly quantitative yield. Excess aluminum chloride – lithium aluminum hydride in tetrahydrofuran (THF) [6] reduced **6** in over 80% yield to the hexahydroindolizine **7**.

Racemic ipalbidine (**7**) is a colorless crystalline compound, m.p. 149–150°, with analytical data consistent with a molecular formula $C_{15}H_{19}NO$. Its *Raman* spectrum shows the tetrasubstituted double bond at 1675 cm^{-1}; its UV.-maxima at 238 nm (ε 10600) and 277 nm (1750) are in accord with the 4-hydroxystyrene chromophore, and its NMR. spectrum exhibits, *inter alia*, a slightly broadened methyl singlet at 1.57 ppm, an *AB*-system for the protons at C5 (2.65 ppm, J = 15.5 cps; and 2.98 ppm, J = 15.5 cps), a broad triplet for the proton at C8a, and an A_2B_2 system for the aromatic protons. Especially revealing is the mass spectrum with a molecular ion at 229 *m/e* and strong signals for both partners of a retro-*Diels-Alder* cleavage.

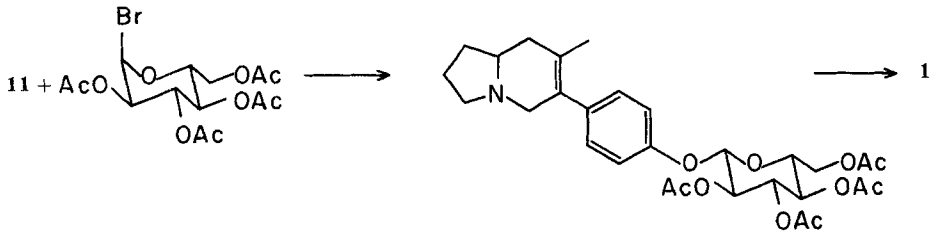


Three crystalline derivatives of **7**, namely the hydrochloride, methiodide and picrate, with compatible analytical and spectral data, were prepared (Table 1).

Difficulties were encountered in attempted resolution of the free aminophenol **7**. Its O-acetyl derivative **8**, however, readily gave crystalline salts with either (+)- or (–)-di-O-*p*-toluoyl-tartaric acid, and enantiomeric salts of **9** and **10** could be recrystallized to constant melting points and constant rotations. Removal of the resolving acids gave the enantiomeric O-acetyl derivatives **9** and **10**, which were hydrolyzed in dilute sodium hydroxide to (+)- and (–)-ipalbidine (**11** and **12**). The enantiomers could be crystallized only from a mixture of benzene and cyclohexane to give highly regular hexagonal plates which, according to NMR. and elemental analysis, contained various amounts of solvent. Pure (+)- and (–)-ipalbidine could be obtained as glassy products by Kugelrohr distillation under high vacuum. Samples of the enantiomers **11** and **12** thus obtained showed almost equal rotations, except for their sign, and gave correct analytical and spectral data.

Since the (+)-enantiomer **11** was anticipated (cf. Table 2 in the discussion section) to be an integral part of ipalbine, it was used as the starting material for the synthesis of **1**; the (–)-enantiomer **12** was converted to optically active forms of the previously described derivatives.

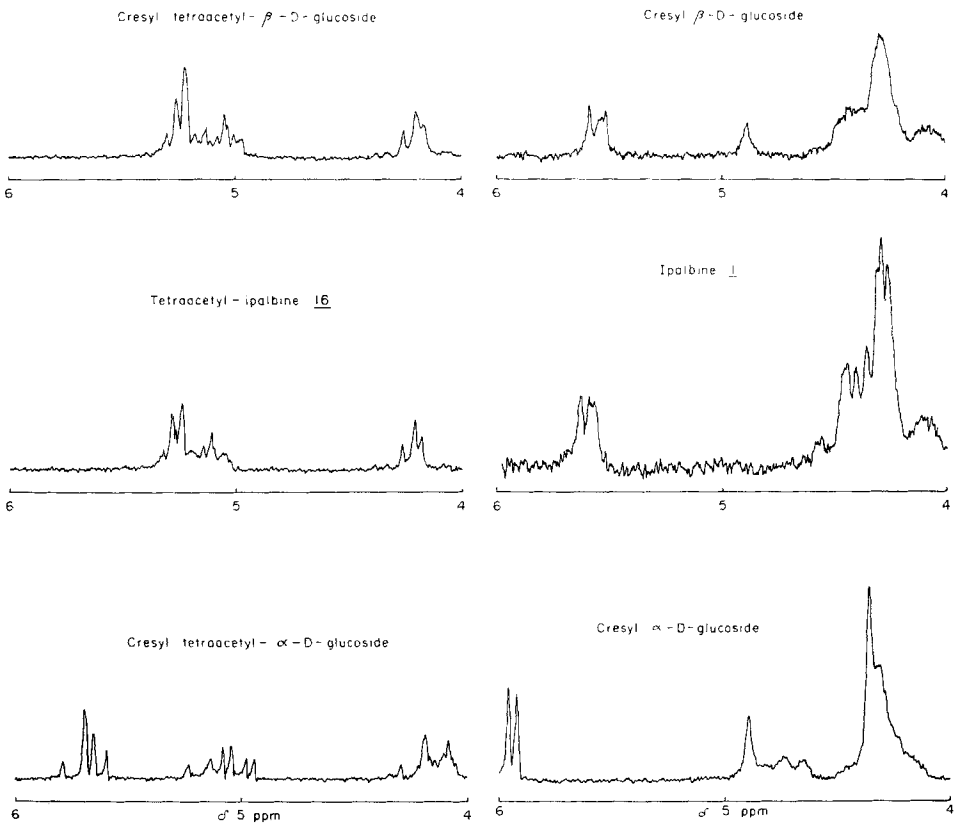
Although numerous methods for glycoside formation are available [7], few are suitable for the synthesis of phenolic glycosides; of those, only the least sophisticated method proved to be of value for the preparation of the alkaloid **1**. Thus, the reaction of (+)-ipalbidine (**11**) with tetraacetyl-α-D-bromoglucose (**15**) in acetone in the presence of dilute aqueous sodium hydroxide produced the crystalline tetra-O-acetyl-glucoside **16** in 16% yield. When subjected to a catalytic amount of sodium methoxide in dry methanol, **16** was smoothly deacetylated to give ipalbine (**1**) in high yield. The alkaloid thus obtained was invariably contaminated with small amounts of ipalbidine (**11**), which could be removed by preparative thin-layer chromatography.



15 **16**

That the glycosides **16** and **1** indeed possess the β-configuration is clearly indicated by the chemical shift and pattern of their anomeric proton in the NMR. spectra. The relevant portions of these spectra are in good agreement with those of *p*-cresyl tetra-O-acetyl-β-D-glucoside and *p*-cresyl β-D-glucoside respectively, but are distinctly different from those of the corresponding α-anomers (Figure).

100 MHz Spectra (from 4 to 6 ppm) of model glucosides and synthetic compounds **16** *and* **1**; *spectra of acetylated compounds (left) recorded in* $CDCl_3$, *of others (right) in pyridine-*d_5 *solution*



Racemic ipalbidine (**7**), on treatment with the bromoglucose **15** and subsequent deacetylation, formed an inseparable mixture of β-D-glucosides consisting of ipalbine

(**1**) and its diastereomer. The spectral properties of this crystalline mixture are indistinguishable from those of **1**.

Discussion. The spectral data of synthetic ipalbidine and ipalbine are with one exception identical with those reported for the naturally occurring materials [1]. The only inconsistency, *i.e.* a difference in the UV. spectra of synthetic and natural ipalbidine recorded in alkaline ethanol, was eliminated by a redetermination of the UV. spectrum of naturally occurring ipalbidine: the maximum is observed at 259 nm and not, as erroneously reported, at 248 nm.

Table 1 lists the melting points of natural ipalbidine [1], of the corresponding racemic and optically active compounds **7** and **12** prepared by synthesis, and of their derivatives. It shows that the reported m.p. for the parent compound is in agreement with the one found for racemic ipalbidine (**7**), whereas the comparison of the m.p.'s of the derivatives[2]) does not reveal whether or not natural ipalbidine is racemic or optically active. However, our findings that a sample of ipalbidine hydrochloride of natural origin showed in essence no rotation[3]) establishes the racemic character of natural ipalbidine.

Table 1. *Melting points and rotations of racemic and optically active ipalbidine, and derivatives*

	7, m.p.	**12**, m.p.	$[\alpha]_D^{25}$ (CH_3OH)	reported [1], m.p.
Ipalbidine	149–150°	82– 84°	–190.5°	147–148°
hydrochloride · H_2O	107–109°	103–105°	–170.0°	104° *)
methiodide	211–213°	226–227°	–122.1°	206–207°
picrate	163–165°	184–186°	–114.4°	178°

*) A sample of ipalbidine hydrochloride · H_2O of natural origin, supplied by Dr. *McInnes*, showed m.p. 108–111° and $[\alpha]_D^{25} = +12.4°$ (CH_3OH).

The rotation measured for ipalbine (**1**) derived from (+)-ipalbidine (**11**) differs in magnitude from the one reported for natural ipalbine. Our rotation is, in contrast to the reported one, in good agreement with a value calculated from the molecular rotations of (+)-ipalbidine (**11**) and *p*-cresyl β-D-glucopyranose (Table 2). According to these calculations, natural ipalbine can be regarded as a diastereomeric mixture consisting of 85% of the β-D-glucoside derived from (+)-ipalbidine (+ ip. β) and 15% of the β-D-glucoside derived from (–)-ipalbidine (– ip. β). It is of interest to note the fact that the mixture of diastereomeric glucosides obtained from (±)-ipalbidine (± ip. β) is crystalline but inseparable, even by thin-layer chromatography; its spectral properties are identical with those of synthetic ipalbine (**1**).

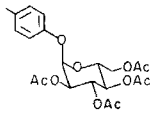
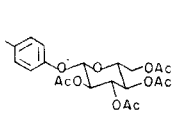
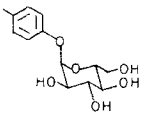
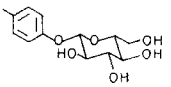
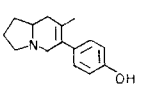
The above observations suggest that racemic ipalbidine is the biogenetic precursor of ipalbine. Partial selectivity by the plant in the formation of the β-D-glucosides from (+)- and (–)-ipalbidine, or subsequent discrimination between the two diastereomeric glucosides, would result in the formation of a mixture of diastereomers in unequal amounts. An alternative explanation for the isolation of racemic or near racemic ipalbidine is that racemization of the chiral center occurs during acid-catalysed

[2]) A 1:1 mixture of racemic and optically active ipalbidine hydrochloride failed to show a m. p. depression.

[3]) No rotation for natural ipalbidine has been reported [1].

Table 2. *Upper part: measured specific and molecular rotations of model glucosides and optically pure ipalbidine* (**11** *and* **12**) *in methanol*

Lower part: calculated specific rotations of α- and β-glucosides and their tetraacetates of racemic, (+)- and (−)-ipalbidine, assuming no interaction between the sugar part and the aglycone, which could disturb either chiral property. Also tabulated are data found for synthetic compounds **1**, **16**, **17** and **18**, and data reported for natural ipalbine [1]

M.W.	438	438	270	270	229
$[\alpha]_D$	+164°	− 28°	+187°	− 65.5°	± 190.5°
$M_D \cdot 10^{-2}$	+719°	−122.5°	+505°	−177°	± 436°

compound	+ip · α	+ip · β	−ip · α	−ip · β	± ip · β	glucosides from **11**	glucosides from **7**	natural ipalbine
tetraacetyl-glucoside	+206.7°	+**57.8**°	+50.6°	−98.1°	−**20.2**°	+**54.7**°	−**19.4**°	–
glucoside	+241°	+**66.3**°	+18°	−157°	−**45.4**°	+**65.8**°	−**42.9**°	+32.5°
		calculated				found		reported

hydrolysis of ipalbine; however, this could be ruled out, because no loss of optical activity was detected when (−)-ipalbidine (**12**) was subjected to such hydrolysis conditions.

Experimental Part

Physical data were obtained as follows: M.p. (not corrected), *Reichert* hot stage; $[\alpha]_D$, *Perkin-Elmer* 141 polarimeter; IR., *Beckman* IR-9 or *Perkin-Elmer* 621; *Raman*, Spex 1401 Ramalog; UV., *Cary* 14 or 15; Mass spectra (MS.), CEC-110 or *Jeolco*-01SG at 70 eV; NMR., *Varian* A-60 or *Varian* HA-100, using tetramethylsilane as internal standard. Abbreviations: (*b*) broad, (*w*) weak, (*sh*) shoulder, (*inf*) inflection, (*ex*) exchangeable with D_2O, (*s*) singlet, (*d*) doublet, (*t*) triplet, (*q*) quartet, (*m*) multiplet.

The yields stated are those of thin-layer-chromatographically pure, crystallized, distilled or chromatographed compounds.

2-Methoxy-pyrroline (**2**). 2-Pyrrolidone (850 g, 10 moles) was added dropwise, over a period of two hours, to a stirred solution of dimethyl sulfate (1260 g, 10 moles) under a nitrogen atmosphere, causing the temperature to rise to 45°. When the addition was complete the clear mixture was stirred for 16 h at 60°. It was then poured onto ice and saturated potassium carbonate, and extracted with ether (3 × 1 l). The combined organic phase was washed with brine, dried over sodium sulfate, and the solvent removed on the rotary evaporator, keeping the heating bath at 20°. The residual liquid was distilled under vacuum into a chilled receiver to yield, after a small forerun, 635 g (64%) of 2-methoxy-1-pyrroline (**2**) as a colorless liquid, b.p. 24°/11 Torr. IR. (neat): 1660, 1350, 1010 cm^{-1}. NMR. (neat): δ 1.7–2.5 (*mb*, 4 H), 3.5 (*tb*, 2 H), 3.67 (*s*, 3 H).

Methyl α-acetyl-$\Delta^{2,\alpha}$-pyrrolidineacetate (**3**). 2-Methoxy-1-pyrroline (**2**) (450 g, 4.55 moles) and methyl acetoacetate (523 g, 4.55 moles) were stirred under nitrogen at 85°. After 65 h the UV. spectrum of the red transparent reaction mixture showed a ratio $\varepsilon_{288}:\varepsilon_{238}$ of 1.27; after 72 h this ratio had not changed, and the reaction mixture was allowed to cool to room temperature overnight, which caused 350 g of the colorless product to crystallize. The mother liquors were stirred at 80° for a further 45 h, at which time a ratio $\varepsilon_{288}:\varepsilon_{238}$ of 1.22 was measured. Upon cooling, a further 240 g of **3** crystallized; filtration of the mother liquors through a silica gel column (benzene with increasing portions of ether) and concentration under reduced pressure gave a further 51 g for a total of

641 g (77%) of slightly yellow **3**. The product can be distilled under hight vacuum without decomposition (b.p. 140°/0.65 Torr) and recrystallized from ether/petroleum ether; m.p. 74.5–75.5°. – IR. ($CHCl_3$): 3150 *b*^{w}, 1680, 1595, 1550, 1435, 1240, 1070 cm^{-1}. UV. (EtOH): 238 nm/12100, 288 nm/15200. NMR. ($CDCl_3$): δ 2.03 (*t*, J = 7, 2 H), 2.40 (*s*, 3 H), 3.17 (*t*, J = 7, 2 H), 3.65 (*t*, J = 7, 2 H), 3.74 (*s*, 3 H), 11.5 (*sb*, 1 H). MS.: 183 (44), 168 (100).

$C_9H_{13}NO_3$ (183.20) Calc. C 59.00 H 7.15 N 7.65% Found C 58.75 H 7.02 N 7.72%

Methyl 1,2,3,5-tetrahydro-6-(4-methoxyphenyl)-7-methyl-5-oxo-indolizine-8-carboxylate (**4**) *and the corresponding acid* (**5**). *p*-Methoxyphenylacetyl chloride was obtained by stirring *p*-methoxyphenylacetic acid and 1.1 eq. of thionyl chloride at room temperature for three days. Distillation gave 93.5% of slightly orange p-*methoxyphenylacetyl chloride*, b.p. 115°/1.5 Torr.

89.6 g (0.49 mole) of **3** in 250 ml of dry benzene were added dropwise under nitrogen to a stirred suspension of sodium hydride (11.8 g, 0.49 mole) in 300 ml of dry benzene which was kept at 0°, giving a clear, slightly orange, viscous solution. This was filtered from some suspended material through cotton into another addition funnel and added dropwise, under nitrogen and initial cooling to keep the reaction mixture at room temperature, to a stirred solution of *p*-methoxyphenylacetyl chloride (90 g, 0.49 mole) in 200 ml of dry benzene. The mixture was stirred at room temperature overnight, filtered through a Celite bed into a fresh addition funnel, added dropwise to sodium hydride (11.5 g, 0.48 mole) in 200 ml of dry benzene, and refluxed for 15 h. After cooling to room temperature, glacial acetic acid (29 g, 0.5 mole) was added, the mixture filtered through Celite and concentrated on the rotary evaporator, whereby **4** (45 g), m.p. 143–145°, crystallized. The mother liquors were made alkaline with 1N sodium hydroxide and extracted 3 times with methylene chloride. The organic phase was washed with water, dried over sodium sulfate, and the solvent removed. The residue was crystallized from carbon tetrachloride to give another 55 g of **4**, m.p. 143–145°, for a total yield of 100 g (65.5%). A sample was recrystallized from carbon tetrachloride: m.p. 144.5–145.5°. – IR. ($CHCl_3$): 1718, 1640, 1610^{sh}, 1565^w, 1545^w cm^{-1}. UV. (EtOH): 274 nm/11530, 305 nm/10400. NMR. ($CDCl_3$): δ 2.18 (*s*, 3 H), 2.29 (*quint.*, J = 7.5, 2 H), 3.41 (*t*, J = 7.5, 2 H), 3.83 (*s*, 3 H), 3.84 (*s*, 3 H), 4.20 (*t*, J = 7.5, 2 H), 6.93 (A_2B_2, J = 9, 2 H), 7.16 (A_2B_2, J = 9, 2 H). MS.: 313 (89), 312 (100).

$C_{18}H_{19}NO_4$ (313.34) Calc. C 68.99 H 6.11 N 4.47% Found C 68.79 H 6.03 N 4.37%

From the alkaline aqueous phase, upon acidification with 1N hydrochloric acid, 14 g (9.6%) of **5** crystallized; it was recrystallized from methanol/methylene chloride: m.p. 231–233°. – IR. (KBr): 2600*b*, 1700, 1605, 1545, 1530 cm^{-1}. UV. (EtOH): 262 nm/9360, 309 nm/10560. NMR. ($(CD_3)_2SO$): δ 2.20 (*m*, 2 H), 2.22 (*s*, 3 H), 3.35 (*t*, J = 9, 2 H), 3.78 (*s*, 3 H), 4.02 (*t*, J = 9, 2 H), 7.01 (A_2B_2, J = 9, 4 H), 12.68 (*sb*, 1 H). MS.: 299 (98), 298 (100).

$C_{17}H_{17}NO_4$ (299.33) Calc. C 68.22 H 5.72 N 4.68% Found C 68.05 H 5.53 N 4.94%

N-Caproyl derivative (**14**) *of* **3**. **14** was obtained under the conditions given above with caproyl chloride in place of *p*-methoxyphenylacetyl chloride; m.p. 55–56°. – IR. ($CHCl_3$): 1700, 1665b, 1120 cm^{-1}. UV. (EtOH): 232 nm/4020, 297 nm/7310. NMR. ($CDCl_3$): δ 0.9–2.2 (*mb*, 11 H), 2.25 (*s*, 2 H), 2.36 (*s*, 3 H), 3.05 (*t*, J = 7, 2 H), 3.73 (*s*, 3 H), 3.75 (*t*, J = 7, 2 H). MS.: 281 (6), 238 (64), 183 (52), 168 (100), 152 (23), 151 (51).

$C_{15}H_{23}NO_4$ (281.36) Calc. C 64.05 H 8.24 N 4.98% Found C 64.12 H 8.48 N 4.84%

2,3-Dihydro-6-(4-hydroxyphenyl)-7-methyl-indolizin-5(1H)-one (**6**). 32 g (102 mmoles) of **7** in 400 ml of 48% hydrobromic acid were heated to 135°; after 2 h the evolution of carbon dioxide subsided. After 22 h the reaction mixture was taken to dryness on the rotary evaporator to give a heavy orange oil. The oil was dissolved in 20 ml of methanol and pipetted slowly into 600 ml of water which was stirred at 50°. The off-white precipitate, which formed immediately, was collected, washed thoroughly with cold water, then ether, and dried under vacuum. 24 g (95.5%) of **6**, m.p. 230–233°, was obtained, a sample of which was recrystallized from methanol to give analytically pure **6**, m.p. 232–234°. – IR. (KBr): 3400–2400, 1645, 1560*b*, 1510^{sh} cm^{-1}. UV. (EtOH): 222 nm/10800 (*infl.*), 241 nm/7300 (*sh*), 308 nm/12250. NMR. ($(CD_3)_2SO$): δ 1.97 (*s*, 3 H), 2.08 (*quint.*, J = 7.5, 2 H), 3.03 (*t*, J = 7.5, 2 H), 3.96 (*t*, J = 7.5, 2 H), 6.10 (*s*, 1 H), 6.78 (A_2B_2, J = 9, 2 H), 6.95 (A_2B_2, J = 9, 2 H), 9.29 (*s*, *ex*, 1 H). MS.: 241 (62), 240 (100).

$C_{15}H_{15}NO_2$ (241.30) Calc. C 74.66 H 6.27 N 5.81% Found C 74.91 H 6.35 N 6.10%

Treatment of **5** (5.7 g) under the same conditions gave 4.6 g (100%) of **6**.

(±)-*Ipalbidine* (**7**). Aluminium trichloride (32.1 g, 0.24 mole) was added slowly, by means of an addition funnel, to 200 ml of freshly distilled ($LiAlH_4$) tetrahydrofuran, which was stirred at 0°. The mixture was then allowed to warm to room temperature and the resulting slightly turbid solution was added dropwise to an ice-cold stirred mixture of $LiAlH_4$ (12.2 g, 0.32 mole) and 300 ml dry tetrahydrofuran. To this mixture 24.3 g (0.1 mole) of **6** were added portionwise at room temperature causing immediate evolution of hydrogen. After the addition had been completed the mixture was kept at reflux for 7 h; during the first two hours a gradual color change from grey to green was observed. After standing at room temperature overnight ethanol was added slowly until no more hydrogen was evolved, the mixture was thrown onto ice and its pH adjusted to 8 by 1N sodium hydroxide. This caused a reversal of the color to grey, accompanied by a change in consistency of the mixture. It was extracted with chloroform (6 × 300 ml), washed with water and dried. Upon removal of the solvent 21.4 g of a green oil were obtained. Filtration in methylene chloride/methanol 19:1 through 220 g of neutral alumina, grade I, yielded **7** (19.4 g, 84.7%) as a slightly greenish viscous oil, which solidified on standing, m.p. 146–148°. Charcoal treatment in hot ethanol, filtration through Celite and crystallization from ethanol chilled to −70° gave, after drying at 80° under vacuum, analytically pure *rac*-ipalbidine (**7**), m.p. 149–150°. – IR. ($CHCl_3$): 3650^w, 1610^m, 1590^w, 1518^m cm^{-1}; *Raman*: 1675, 1618 cm^{-1}. UV. (EtOH): 238 nm/10600, 277 nm/1750; (+OH^-): 259 nm/15000, 295 nm/5750 (*sh*). NMR. ($CDCl_3$): 1.57 (*s*, 3 H), 1.5–2.6 (*mb*, 8 H), 2.98 (*AB*, *J* = 15.5, 1 H), 3.24 (*tb*, *J* = 8, 1 H), 2.67 (*AB*, *J* = 15.5, 1 H), 6.76 (A_2B_2, *J* = 9, 2 H), 6.97 (A_2B_2, *J* = 9, 2 H). MS.: 229 (51), 228 (17), 214 (28), 160 (21), 159 (21), 145 (77), 131 (21), 107 (17), 103 (21), 70 (100).

$C_{15}H_{19}NO$ (229.31) Calc. C 78.56 H 8.35 N 6.11% Found C 78.59 H 8.49 N 6.24%

Hydrochloride monohydrate of **7** (CH_3CN): m.p. 107–109°.

$C_{15}H_{20}ClNO \cdot H_2O$ (283.8) Calc. C 63.48 H 7.81 Cl 12.49 N 4.94%
Found ,, 63.41 ,, 8.02 ,, 12.73 ,, 4.91%

Methiodide of **7** (CH_3OH/Et_2O): m.p. 211–213°. NMR. ($(CD_3)_2SO$): δ 1.69 (*s*, 3 H), 1.7–2.5 (*mb*, 5 H), 2.92 (*s*, 3 H), 3.0–4.1 (*mb*, 4 H), 4.22 (*sb*, 2 H), 6.81 (A_2B_2, *J* = 9, 2 H), 7.06 (A_2B_2, *J* = 9, 2 H), 9.7 (*s*, 1 H).

Picrate of **7** (CH_3OH): m.p. 163–165°.

$C_{21}H_{22}N_4O_8$ (458.46) Calc. C 55.00 H 4.84 N 12.22% Found C 55.19 H 4.57 N 12.16%

(±)-*O-Acetyl-ipalbidine* (**8**). (±)-Ipalbidine (**7**) (10 g, 43.6 mmoles) in 10 ml of methylene chloride was added to 20 ml of acetyl chloride and stirred at room temperature. Thin-layer-chromatographic examination of the reaction mixture showed that after one hour all starting material had been consumed. The clear solution was taken to dryness, ice-cold 2N sodium hydroxide was added, and the mixture extracted 3 times with methylene chloride. The organic phases were washed with ice-cold water, combined, dried over sodium sulfate, and the solvent removed to give **8** (10.3 g, 87%) as a slightly brownish oil. Analytically pure O-acetyl-ipalbidine was obtained by Kugelrohr distillation at 170°/0.5 Torr as a colorless oil, which crystallized on standing, m.p. 67–69°. – IR. ($CHCl_3$): 1760, 1235, 1205 cm^{-1}. UV. (EtOH): 234 nm/9290. NMR. ($CDCl_3$): δ 1.58 (*sb*, 3 H), 1.72–2.4 (*mb*, 11 H), 2.26 (*s*, 3 H), 2.9 (*db*, *J* = 15, 1 H), 3.2 (*tb*, *J* = 7, 1 H), 3.6 (*db*, *J* = 15, 1 H), 7.08 (A_2B_2, *J* = 9, 4 H). MS.: 271 (100), 160 (93).

$C_{17}H_{21}NO_2$ (271.3) Calc. C 75.24 H 7.80 N 5.16% Found C 75.33 H 7.93 N 5.11%

The pH of the aqueous phase was adjusted to 8 by the addition of 1N hydrochloric acid then sodium hydrogencarbonate. Three extractions with methylene chloride gave a recovery of 1.3 g (13%) of starting material **7**.

(+)- *and* (−)-*Ipalbidine* (**11** *and* **12**). (±)-O-Acetyl-ipalbidine (**8**) (10.28 g, 37.9 mmoles) in 30 ml of acetone was added to (−)-di-O-*p*-toluoyl-tartaric acid (14.7 g, 37.9 mmoles) in 30 ml of acetone; the resulting yellowish solution was warmed in the presence of charcoal and filtered through Celite. On cooling, 5.2 g of colorless material, m.p. 148–151°, $[\alpha]_D^{25} = -131.9°$ (*c* = 1, CH_3OH) crystallized; concentration of the mother liquor gave another 6.0 g, m.p. 144–146°, $[\alpha]_D^{25} = -139.8°$ (*c* = 1, CH_3OH). Both fractions were combined and recrystallized from methanol/ethanol, 1:3, to give 8.3 g (66.4%) of (−)-*O-acetyl-ipalbidine* (−)-*di-O*-p-*toluoyl-tartaric acid salt*, m.p. 148.5–149.5°, $[\alpha]_D^{25} = -144.8°$ (*C* = 1, CH_3OH). All mother liquors from above were combined,

taken to dryness, redissolved in methylene chloride, and washed with 1N ice-cold sodium hydroxide, then water, to give 6.46 g (23.85 mmoles) of oily O-acetyl-ipalbidine, strongly enriched in the (+)-enantiomer. This material, in 20 ml of methanol, was combined with 9.24 g (23.85 mmoles) of (+)-di-O-*p*-toluoyl-tartaric acid in 30 ml of ethanol, warmed and filtered through Celite. On concentration and gradual cooling, 7.6 g of (+)-*O-acetyl-ipalbidinium* (+)-*di-O*-p-*toluoyl-tartrate* crystallized, m.p. 149–150°, $[\alpha]_D^{25} = +145.9°$. Recrystallization from hot ethanol gave 6.5 g (52%) with unchanged m.p. and a rotation of +146.9° ($c = 1$, CH_3OH). To this material ice-cold 1N sodium hydroxide was added and the solution extracted three times with methylene chloride; the extracts were washed again with cold sodium hydroxide and then water, dried over sodium sulfate, and the solvent removed. The resulting (+)-*O-acetyl-ipalbidine* **9** (2.67 g, 99%) had rotation $[\alpha]_D^{25} = +149.6°$ ($c = 1$, CH_3OH).

The acetyl derivative was dissolved in 15 ml of methanol and 10 ml of 1N sodium hydroxide and stirred at room temperature for 20 min. The pH was then brought to 8 by the addition of saturated sodium hydrogencarbonate solution and the mixture extracted three times with methylene chloride; the organic phase was washed with water, dried over sodium sulfate, and the solvent removed to give 2.225 g (98.5%, 50.7% from **8**) of (+)-*ipalbidine* **11** as a colorless oil. Hexagonal crystals were obtained from benzene/cyclohexane which, after drying at room temperature under high vacuum, had m.p. 72–82°, $[\alpha]_D^{25} = +166°$ ($c = 1$, $CHCl_3$), and contained benzene and cyclohexane. Upon washing the crystals with petroleum ether and drying at 50° under vacuum, the m.p. remained unchanged; $[\alpha]_D^{25} = +233.5°$ ($c = 1$, $CHCl_3$), still contaminated with some benzene and cyclohexane according to NMR. and microanalysis. – *Picrate* (CH_3OH): m.p. 183–185°, $[\alpha]_D^{25} = +112.6°$.

From the above (–)-O-acetyl-ipalbidinium (–)-di-O-*p*-toluoyl-tartrate, (–)-ipalbidine (**12**) was obtained by the procedure described above; it was crystallized from benzene/cyclohexane to give hexagons, m.p. 77–87°, $[\alpha]_D^{25} = -168.5°$ ($c = 1$, $CHCl_3$), containing the two solvents. Bulb tube distillation at 150°/0.1 Torr gave analytically pure (–)-*ipalbidine* (**12**) as a colorless glass, m.p. 82–84°; $[\alpha]_D^{25} = -237°$ ($c = 1$, $CHCl_3$), –190.5° ($c = 1$, CH_3OH). The spectral data are identical with those of **7**.

$C_{15}H_{19}NO$ (229.31) Calc. C 78.56 H 8.35 N 6.11% Found C 78.65 H 8.33 N 5.95%

Hydrochloride monohydrate of **12** (CH_3CN): m.p. 103.5–105°, $[\alpha]_D^{25} = -170°$ ($C = 0.1$, CH_3OH).

$C_{15}H_{20}ClNO \cdot H_2O$	Calc.	C 63.48	H 7.81	Cl 12.49	N 4.94%
(283.8)	Found	,, 63.60	,, 7.80	,, 12.39	,, 4.77%

Methiodide of **12** (CH_3CN/CH_3OH/ether): m.p. 226–227°, $[\alpha]_D^{25} = -122.1°$ ($c = 1$, CH_3OH).

$C_{16}H_{22}INO$	Calc.	C 51.76	H 5.97	I 34.18	N 3.77%
(371.27)	Found	,, 51.99	,, 6.23	,, 34.37	,, 3.84%

Picrate of **12** (CH_3OH): m.p. 184–186°, $[\alpha]_D^{25} = -114.4°$ ($c = 1$, CH_3OH).

$C_{21}H_{22}N_4O_8$ (458.46) Calc. C 55.00 H 4.84 N 12.22% Found C 54.98 H 4.81 N 12.21%

Glucoside **16**. (+)-Ipalbidine (**11**) (1.296 g, 5.66 mmoles) was dissolved in 8.5 ml of 1N aqueous sodium hydroxide and added dropwise to acetobromoglucose (1.635 g, 3.98 mmoles) in 13 ml of acetone with stirring. The initially formed precipitate dissolved again when about one-fourth of the aglycone solution had been added. After stirring the clear solution for 6 h at room temperature, no enhancement of the product spot (Rf 0.5) on thin-layer chromatography (toluene/2-propanol/triethylamine 90:5:5) in comparison to the one of **11** (Rf 0.3) could be detected. The mixture was concentrated on the rotary evaporator, dissolved in methylene chloride, and brought to pH 12 by the addition of cold 1N sodium hydroxide. It was extracted three times with methylene chloride, which was then washed with water and dried over sodium sulfate. Evaporation of the solvent gave 1.19 g of a colorless oil, which was applied to five 20 × 20 cm silica gel thick-layer plates, (1.5 to 2 mm thickness) and developed in benzene/ethyl acetate/methanol 9:9:2. The top UV. absorbing band of the plates was collected and extracted with ethyl acetate to give a total of 365 mg (16.4%) of **16** as a colorless oil, which crystallized on standing. Trituration with ether/petroleum ether 1:4 gave needles, m.p. 95–98°, $[\alpha]_D^{25} = +54.7°$ ($c = 1$, CH_3OH). A total of 620 mg (48%) of **11** was recovered from the reaction. – IR. (CH_2Cl_2): 1750, 1220 cm^{-1}. NMR. ($CDCl_3$): δ 1.57 (*s*, 3 H), 1.6–2.4 (*mb*, 8 H), 1.99 (*s*, 3 H), 2.00 (*s*, 3 H), 2.02 (*s*, 6 H), 2.88 (*A Bb*, $J = 15$, 1 H), 3.19 (*tb*, $J = 8$,

1 H), 3.54 (*ABb*, J = 15, 1 H), 3.85 (*mb*, 1 H), 4.11 (*m*, 2 H), 4.93–5.10 (*m*, 4 H), 6.95 (A_2B_2, J = 9, 2 H), 7.11 (A_2B_2, J = 9, 2 H). MS.: 559 (29), 331 (100), 169 (98).

$C_{29}H_{37}NO_4$ (559.61) Calc. C 62.24 H 6.66 N 2.50% Found C 62.22 H 6.73 N 2.22%

Ipalbine (**1**). To (+)-tetra-O-acetyl-ipalbine (**16**) (215 mg, 0.38 mmole) in 5 ml of dry methanol was added 0.5 ml of 0.2 N methanolic sodium methoxide and the mixture stirred at room temperature for 15 min. It was taken to dryness at room temperature, the resulting solid (155 mg) redissolved in a small amount of methanol/tetrahydrofuran 4:1 and applied to a 20 × 20 cm/1.5 mm silica gel thick-layer plate. The plate was developed in benzene/ethyl acetate/methanol 9:9:2 and the UV.-fluorescent band at the origin was collected. Extraction with tetrahydrofuran/methanol 1:1 gave, after removal of the solvents, 129 mg (85.5%) of **1** as a colorless solid. Crystallization was achieved from a methanol/acetonitrile (1:4) solution upon concentration under reduced pressure at room temperature; m.p. 115–118°, $[\alpha]_D^{25} = +65.8°$ (c = 0.7 EtOH). – IR. (KBr): 3400*b*^{m}, 1620^w, 1515^m, 1240^m, 1080*b* cm^{-1}. UV. (EtOH): 234 nm/10975, 275 nm/1100 *sh*. NMR. ($(CD_3)_2SO$): δ 1.57 (*s*, 3 H), 4.84 (*db*, J = 5, 1 H), 7.02 (A_2B_2, J = 9, 4 H) and unresolved multiplets; (pyridine-d_5): δ 1.60 (*s*, 3 H), 1.6–2.3 (*mb*, 8 H), 2.87 (*ABb*, J = 15, 1 H), 3.13 (*tb*, J = 6, 1 H), 3.64 (*AB*, J = 15, 1 H), 3.95–4.6 (*mb*, 6 H), 5.60 (*d*, J = 5, 1 H), 7.16 (A_2B_2, J = 16, 2 H), 7.32 (A_2B_2, J = 16, 2 H). MS.: 391 (12), 229 (10), 228 (7), 214 (7), 160 (100), 145 (31), 70 (27).

$C_{21}H_{29}NO_6$ (391.47) Calc. C 64.43 H 7.47 N 3.58% Found C 64.20 H 7.30 N 3.41%

Tetra-O-acetylglucoside **17**. The reaction, analogous to the preparation of **16**, using (±)-ipalbidine (**7**) (2.5 g, 10.9 mmoles) in 15 ml of 1N sodium hydroxide and acetobromoglucose (3.15 g, 7.66 mmoles) in 22 ml of acetone, gave 780 mg (18.2%) of the diastereomeric mixture **17**. Crystalline **17**, m.p. 127–137°, $[\alpha]_D^{25} = -19.4°$ (c = 1, CH_3OH), gave correct analysis for $C_{29}H_{37}NO_{10}$ and had spectra identical to those of **16**.

Glucoside **18**. Using the procedure described for the preparation of ipalbine (**1**), 200 mg of **17** gave 140 mg of **18**, m.p. 114–119°, $[\alpha]_D^{25} = -42.9°$ (c = 1, CH_3OH), having the correct micro-analysis and spectra identical with those of **1**.

Model glucosides [8]. – *p*-Cresyl tetra-O-acetyl-α-D-glucopyranoside: m.p. 64–66°, $[\alpha]_D^{25} = +158.8°$ (c = 1, $CHCl_3$) and +164° (c = 1, CH_3OH). –*p*-Cresyl tetra-O-acetyl-β-D-glucopyranoside: m.p. 119.5–120.5°, $[\alpha]_D^{25} = -17.4°$ (c = 1, $CHCl_3$) and −28.0° (c = 1, CH_3OH). – *p*-Cresyl α-D-glucopyranoside: m.p. 195–197°, $[\alpha]_D^{25} = +187.1°$ (c = 1, CH_3OH). – *p*-Cresyl β-D-glucopyranoside: m.p. 177–179°, $[\alpha]_D^{25} = -65.5°$ (c = 1, CH_3OH).

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