214. Studies on Debenzylation and Photolysis of 1-Benzyl- and 1-(β-Phenethyl)-1,2,3,4-tetrahydroisoquinolines

by **T. R. Govindachari**
8A Crescent Park Street, Madras 600 017, India
K. Nagarajan
Ciba-Geigy Research Centre, Bombay 400 063, India
S. Rajeswari, H. Suguna and **B. R. Pai**
Department of Chemistry, Presidency College, Madras 600 005, India

Dedicated to the memory of late Prof. Dr. phil. *Hans Schmid*

(2. V. 77)

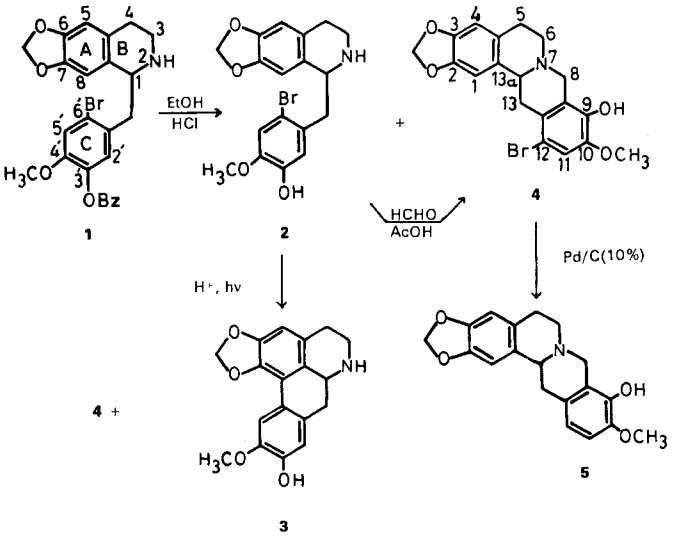
Summary

Debenzylation of 1-(3-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinolines **1**, **6**, **7** with hydrochloric acid and ethanol gave the corresponding phenolic isoquinolines **2**, **8**, **9** and tetrahydroprotoberberines **4**, **12**, **13**. Compounds **2**, **8**, **9** on photolysis also gave, besides the expected noraporphines **3**, **10**, **11**, the tetrahydroprotoberberines **4**, **12**, **13** [1–4] (*Schemes 1* and *2*). 6-Benzyloxy-1-(5-benzyloxy-2-bromobenzyl)-1,2,3,4-tetrahydroisoquinoline (**27a**) containing no methoxy or methylenedioxy groups either in ring A or C does not give protoberberine during debenzylation; but **28**, the debenzylation product of **27a**, on photolysis gives both the noraporphine **29** and the tetrahydroprotoberberine **30** (*Scheme 6*), proving that during debenzylation of 1-(3-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinolines containing additional methoxy or methylenedioxy groups, the necessary formaldehyde comes from the latter groups. During photolysis both the methoxy groups (methylenedioxy groups) and the C(3) atom of the tetrahydroisoquinoline moiety provide the formaldehyde. Veratrole under debenzylation and photolytic conditions and tetrahydroisoquinoline under the latter condition also give rise to formaldehyde (*Schemes 8* and *10*).

The novel bromohomoprotoberberine **43** along with **42** was formed during debenzylation of the 1-phenethyl-1,2,3,4-tetrahydroisoquinoline **41**. Photolysis of **42** yielded the novel nor-homoaporphine **44**, in addition to **43**; the latter was debrominated to give the homoberbine **45**.

A current synthesis of naturally occurring phenolic aporphine alkaloids consists of the preparation of phenolic 1-(2-bromobenzyl)-1,2,3,4-tetrahydroisoquinolines and subsequent photolysis. The expected products were obtained until *dl*-actinodaphnine (**3**) was synthesized by *Premila et al.* [1] (*Scheme 1*). 1-(3-Benzyloxy-6-bromo-4-methoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**1**) was debenzylated to give 1-(6-bromo-3-hydroxy-4-methoxybenzyl)-6,7-methylenedioxy-

Scheme 1



1,2,3,4-tetrahydroisoquinoline (**2**). Another compound **A** (m.p. 128–130°) was isolated (albeit in low yield) .Irradiation of **2** with UV. light in aqueous acid gave unreacted starting material, *dl*-actinodaphnine (**3**) and a small quantity of compound **B** (m.p. 128–130°, M: 405). This compound was identical with compound **A** from the debenzylation. *Suguna* [2] obtained the same results. It was further established by synthesis that **A** had structure **4**: compound **2** was allowed to react with formaldehyde and acetic under reflux to yield 12-bromonandinine (**4**), identical with compounds **A** and **B**. Reductive debromination of **4** with Pd/C (10%) gave known *dl*-nandinine (**5**), thus confirming the structure of **4** (*Scheme 1*).

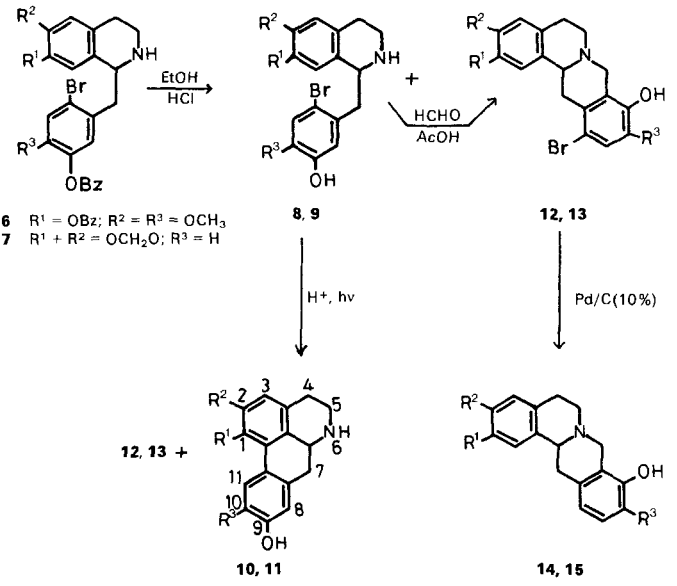
Suguna & Pai [3] [4] also synthesized the 1-benzyltetrahydroisoquinolines **6** and **7** and found berbines **12** and **13** among the products of debenzylation. These were also obtained, along with the noraporphines, *dl*-norisoboldine [3] (**10**) and *dl*-anolobine [4] (**11**) when the 6′-bromophenolic tetrahydroisoquinolines **8** and **9** were subjected to photolysis. Compounds **12** and **13** were eventually converted to the phenolic berbines scoulerine (**14**) and **15** (*Scheme 2*).

Kametani et al. [5] studied the reaction of 1-(3-hydroxy-4-methoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**16**) with hydrochloric acid in ethanol. They isolated the two berbines **5** and **17** (*Scheme 3*).

Based on these facts, it was suggested that a berbine-bridge carbon atom would come in the debenzylation reaction from either the methoxy and/or methylenedioxy group. On the other hand, the formation of protoberberines **21** and **22** in the photolysis of **18** would implicate the C(3) atom in the isoquinoline ring system [5]. A photo-induced *retro-Diels-Alder* reaction [6] of the tetrahydroisoquinoline **18** could give the imine **19**, which provides formaldehyde (**20**), which in turn reacts with **18** to give the two isomeric protoberberines **21** and **22** (*Scheme 4*).

All the 1-benzyltetrahydroisoquinolines that gave the protoberberines had the following structural features: 1. a 3′ (or 5′) benzyloxy group in ring C of 1-benzyl-

Scheme 2

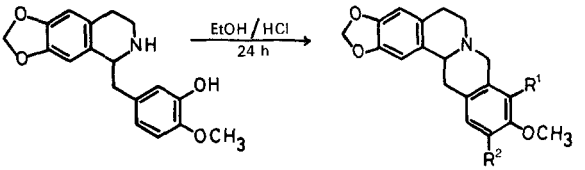


6 $R^1 = OBz$; $R^2 = R^3 = OCH_3$
7 $R^1 + R^2 = OCH_2O$; $R^3 = H$

8, 9 **12, 13** **10, 11** **14, 15**

8, 10, 12 und **14** $R^1 = OH$; $R^2 = R^3 = OCH_3$
9, 11, 13 und **15** $R^1 + R^2 = OCH_2O$; $R^3 = H$

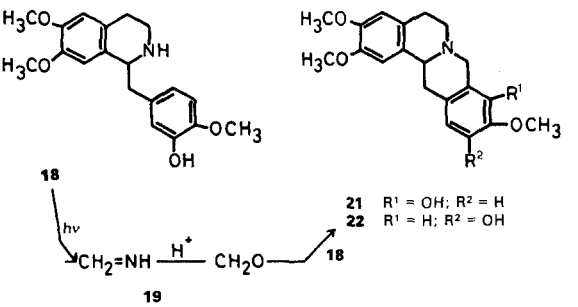
Scheme 3



16

5 $R^1 = OH$; $R^2 = H$
17 $R^1 = H$; $R^2 = OH$

Scheme 4



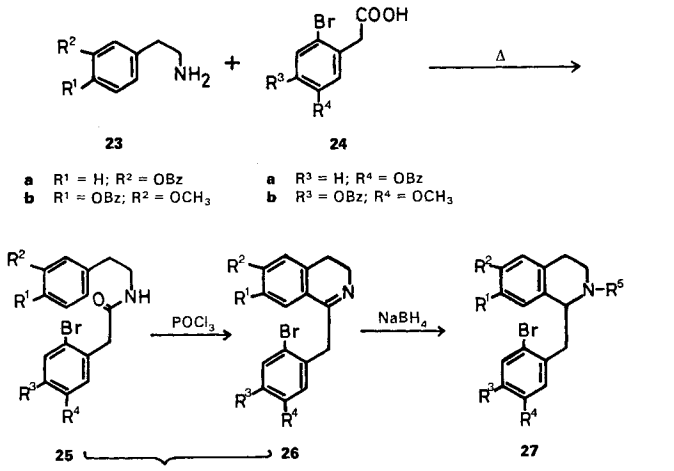
21 $R^1 = OH$; $R^2 = H$
22 $R^1 = H$; $R^2 = OH$

tetrahydroisoquinoline; 2. a free amino group, and 3. one or more methoxy and/or methylenedioxy groups in ring A and/or C.

Although yields of protoberberines in the two stages were low, their very formation was intriguing. The present work was undertaken to extend this study. Specifically, the source of formaldehyde in the acidic debenzylation and photolytic reactions was sought, and the scope was extended to 1-phenethylisoquinolines.

Initially, compounds **27** (**a–c**) were synthesized (*Scheme 5*), in order to study the debenzylation and photolysis. In the case of the **b** series, **26b** was quaternized with methyl iodide and the salt **26d** reduced by $NaBH_4$ to **27b**.

Scheme 5



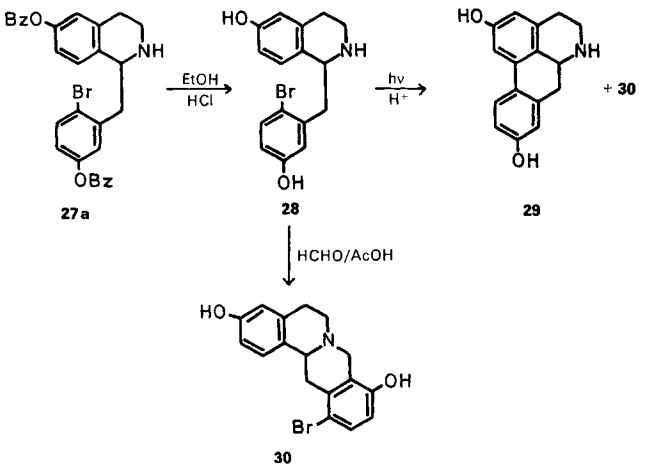
26d methiodide of **26b**

Debenzylation of **27a** yielded the diphenolic tetrahydroisoquinoline **28** as its hydrochloride in excellent yield. Careful chromatography did not reveal the presence of any other compounds in the mother-liquor.

No trace of a berbine could be detected even though the necessary precursor **28** was available, indicating that formaldehyde was not produced during the debenzylation of **27a**, and that a benzyl group cannot serve as a formaldehyde source. When the hydrochloride of **28** was irradiated for 11 h in water containing sodium hydrogensulfite, however, the product contained the noraporphine **29** and another compound. The latter was identical with **30** prepared from **28** by *Mannich* type reaction with formaldehyde and acetic acid. The structures **29** and **30** were supported by mass and UV. spectral data (*Scheme 6*).

Thus photolysis of **28** did give a 12-bromoberbine **30** besides the noraporphine **29**; therefore, since the compound contains no methoxy or methylenedioxy groups, the source of formaldehyde in the photolytic formation of berbine in this case cannot be

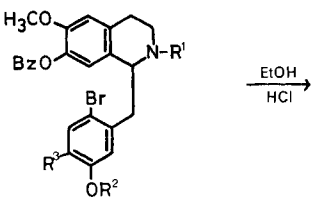
Scheme 6



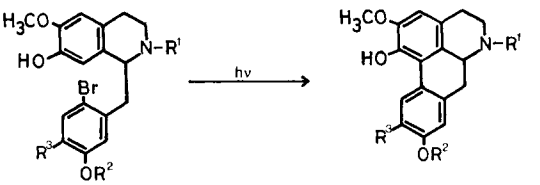
a peripheral methoxy group, but the benzyl isoquinoline nucleus, probably the C(3) atom [5].

We next examined trapping the formaldehyde product in the debenzylation and photolytic experiments, either by blocking the secondary nitrogen atom of the tetrahydroisoquinoline by a suitable group such as a methyl group, or by rendering the phenyl moiety of the 1-benzyl group less attractive for cyclization. Compounds **27b** and **27c** represent suitable substrates for these endeavours.

Scheme 7



27b $R^1 = CH_3$; R^2 = Bz; R^3 = H
c R^1 = H; $R^2 = CH_3$; R^3 = OBz



31a $R^1 = CH_3$; $R^2 = R^3$ = H
b R^1 = H; $R^2 = CH_3$; R^3 = OH

32a $R^1 = CH_3$; $R^2 = R^3$ = H
b R^1 = H; $R^2 = CH_3$; R^3 = OH
c $R^1 = R^2 = CH_3$; R^3 = OH

Debenzylation of **27b** gave, as expected, only the phenolic tetrahydroisoquinoline **31a** with no protoberberine. Photolysis of **31a** as usual, did not yield a 12-bromoberbine derivative, but as expected, only the aporphine **32a** (*Scheme 7*). Formaldehyde could, however, be detected in the photolysed solution by the chromotropic acid test [7] and also in the debenzylation of **27b**. There is no detectable *N*-demethylation under debenzylation or photolytic conditions and hence although formaldehyde may be generated in either process, ring closure to a berbine derivative does not occur for want of a free amino group (*Scheme 7*).

Debenzylation of **27c** yielded only the diphenolic tetrahydroisoquinoline **31b** as its hydrochloride, and did not afford any detectable amount of the corresponding berbine derivative. Likewise, photolysis of **31b** yielded only the noraporphine **32b**, which was converted into its triacetate (*Scheme 7*). Formaldehyde was detectable in the photolysis solution, but was not formed at all in the corresponding 'dark' reaction. This indicates that (i) formaldehyde is a true product of photolysis and (ii) even when free amino and methoxy groups are present, tetrahydroprotoberberine formation requires activation of the 2′ (6′) position by a phenolic OH at the 3′ (5′) position. A methoxy group is not sufficiently electron donating for this electrophilic cyclisation.

The reaction above is the first synthesis of norbracteoline (**32b**), which is not yet reported to occur in nature, though bracteoline **32c** (*N*-methyl derivative of **32b**) has been isolated from *Papaver bracteatum* LINDL. [8] and synthesized [9].

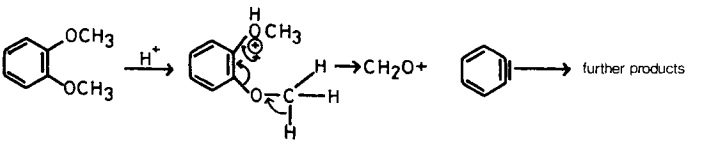
All the experiments indicate that during *debenzylation* of 1-(3 (or 5)-benzyloxybenzyl)tetrahydroisoquinolines, the methoxy (or methylenedioxy) groups serve as a source of formaldehyde and contribute to the formation of berberines. During *photolysis*, the methoxy (or methylenedioxy) group or the C(3) atom of the isoquinoline ring B may be responsible for the source of formaldehyde, which in turn forms the tetrahydroprotoberberine. But in the absence of methoxy (or methylenedioxy) groups, the source of formaldehyde could only be the C(3) atom of the tetrahydroisoquinoline and this occurs only during photolysis.

When compound **6** was heated under reflux with water instead of ethanol and concentrated hydrochloric acid, very little of the phenolic tetrahydroisoquinoline **8** could be isolated. The protoberberine **12** was formed in very small yield but its presence could be detected by TLC. comparison with an authentic sample. Thus, the unlikely possibility of solvent ethanol being responsible for the one carbon bridge was ruled out.

In order to estimate the amount of formaldehyde formed under debenzylation conditions of compounds containing methoxy groups, veratrole was heated in boiling absolute ethanol and concentrated hydrochloric acid for 20 h. Aliquots of the reaction mixture were tested at intervals for the presence of formaldehyde; the tests were positive. After 12 h, the colour developed with chromotropic acid reagent on an aliquot was compared with that from standard formaldehyde solutions (0.42 mg of HCHO/3 g of veratrole). Blank experiments carried out with ethanol and hydrochloric acid or veratrole alone showed no formation of formaldehyde. Similarly, 1,2,3,4-tetrahydroisoquinoline was heated in boiling ethanol and hydrochloric acid for 12 h and tested for the presence of formaldehyde at intervals; the tests were negative. Therefore the methoxy groups in the isoquinolines were responsible for the formation of formaldehyde under debenzylation conditions.

The formation of formaldehyde from methylenedioxy aryl compounds under acidic conditions is known and easily understood [9a]. There is no obvious explanation for its formation from veratrole which should only give methyl halide or methanol, further oxidation being necessary. The problem is further mystified by our observation that neither anisole nor 1,3-dimethoxybenzene produces detectable amounts of formaldehyde with ethanolic HCl-solution under reflux; nor is methanol alone or in presence of phenol oxidized to formaldehyde in ethanolic acid. The following, intriguing possibility would then merit attention[1]) (*Scheme 8*).

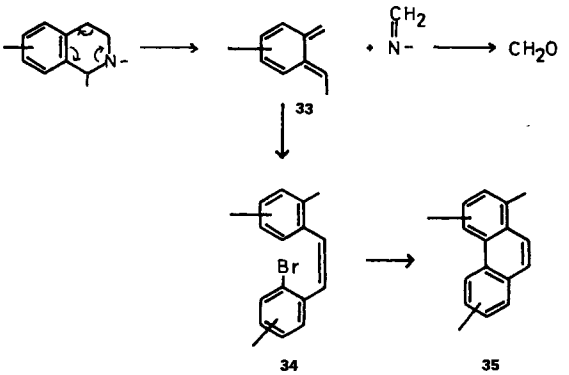
Scheme 8



The same estimation was done with veratrole under photolytic conditions, by irradiation for 10 h in aqueous acidic medium. The test for the presence of formaldehyde was positive. During photolysis, methoxy aryl compounds can generate methoxy radicals which can form formaldehyde by loss of a hydrogen radical, or be transformed into methanol, which on further photolytic oxidation would yield formaldehyde. The photochemical conversion of methanol to formaldehyde has been studied and quantified by *Havinga et al.* [10]. Photolytic oxidation of methanol to formaldehyde and ethanol to acetaldehyde has also been demonstrated by *Yang et al.* [11].

Lastly, photolysis of 1,2,3,4-tetrahydroisoquinoline and its 2-methyl derivative in aqueous acidic medium of pH about 2.5, generated formaldehyde. One explanation would be a *retro-Diels-Alder* reaction [5], releasing C(3) of the isoquinoline as formaldehydeimine (*Scheme 9*).

Scheme 9

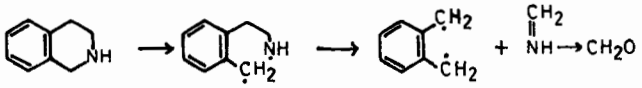


In the case of 1-benzyltetrahydroisoquinolines, the other major fragment **33** would be expected to rearrange to stilbene **34** and further undergo photolytic conversion to **35**. We are making attempts to isolate this.

[1]) We thank Dr. *K. K. Balasubramanian*, IIT, Madras, for this suggestion.

Perhaps a more acceptable mechanism of photolytic cleavage of tetrahydroisoquinoline would be *via* a diradical intermediate of type **36** (*Scheme 10*).

Scheme 10



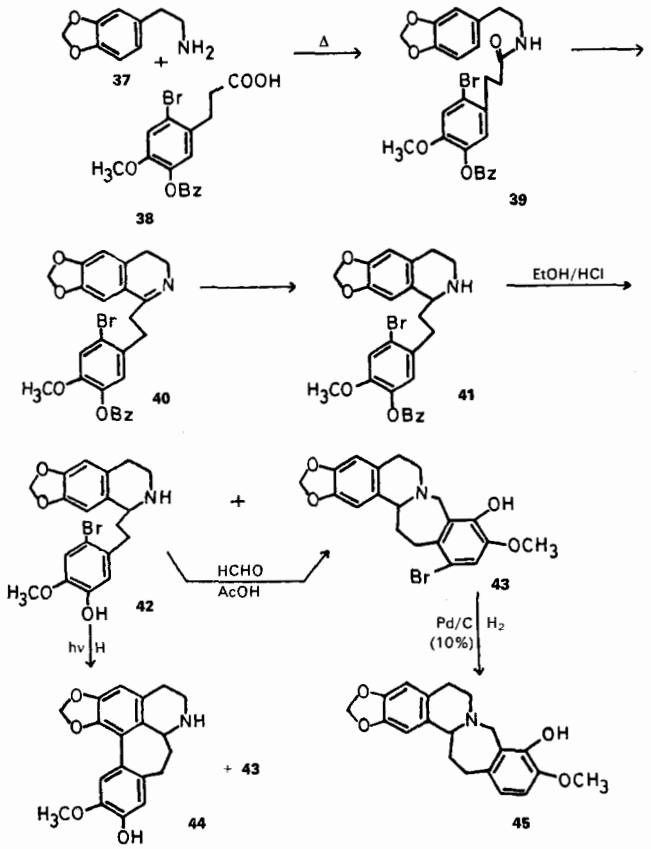
36

Definite proof for the appearance of C(3) atom as formaldehyde is now sought by substituting that position with a methyl group. Photolysis should now yield acetaldehyde.

In the photolysis of 1-benzyltetrahydroisoquinolines, it was postulated [5] that the benzyl group may appear as a benzaldehyde whose CO group may be converted to formaldehyde. This speculation is definitely ruled out by our finding that protocatechuic aldehyde (3,4-dihydroxybenzaldehyde) does not produce formaldehyde on photolysis.

We were anxious to determine the effect of debenzylation and photolysis on 1-phenethyl-1,2,3,4-tetrahydroisoquinolines having all the three structural features mentioned earlier. For this purpose, isoquinoline **41** was synthesized (*Scheme 11*).

Scheme 11



Debenzylation of **41** yielded the phenolic isoquinoline **42** and another compound identical with **43** prepared from **42** by *Mannich* type reaction. The hydrochloride of **42** was irradiated for 11 h, in water containing sodium hydrogen sulfite. The product contained N-*norhomoaporphine* **44** and the homoberbine derivative **43**, identical with that obtained during debenzylation. The *N*-norhomoaporphine **44**, had UV. spectra in ethanol and in ethanol + NaOH characteristic of 1,2,10,11-substituted homoaporphines [12].

The fragmentation observed in the mass spectrum of **43** was similar to that reported for homoprotoberberines [13]. Reductive debromination of **43** was effected with 10% Pd/C to yield **45**.

No naturally occurring homoprotoberberines (5,6,8,13,14,14a-hexahydro-isoquino[2,1,*b*]2-benzazepine) and *N*-norhomoaporphines are known. However, by analogy with the homologated alkaloids like homoaporphines [14] and homoproaporphines [15], there is a fair possibility that such species will eventually be isolated from plant sources. The synthesis of 10-hydroxy-11-methoxy-1,2-methylenedioxy-*N*-norhomoaporphine (**44**) is the first photolytic synthesis of a *N*-norhomoaporphine. Synthesis of the 'hypothetical alkaloids' homoprotoberberines has been reported [16].

Experimental part

Melting points are uncorrected. UV. spectra (nm (log ε)), were run on a *Beckman* DK 2A spectrophotometer. 95% EtOH-solutions were used unless otherwise stated. IR. spectra were run on *Perkin Elmer* Infracord and Model 421 IR. spectrophotometers. NMR. spectra refer to proton spectra from a *Varian* A60 spectrometer. Chemical shifts are quoted in ppm downfield from TMS used as internal reference. Mass spectra are from a *Varian Mat* CH7 mass spectrometer.

N-*β*-(*3-Benzyloxyphenethyl*)-*5-benzyloxy-2-bromophenylacetamide* (**25a**). A mixture of 3 g *β*-(3-benzyloxyphenyl)ethyl amine [17] (**23a**) and 3.5 g (2-bromo-5-benzyloxyphenyl)acetic acid [4] (**24a**) was heated on an oil bath at 180–185° for 2 h, then cooled to RT. and extracted with $CHCl_3$. The extract was washed with dil. HCl-, saturated $NaHCO_3$-solution and water, then dried (Na_2SO_4); the solvent was distilled, and the residual crude amide **25a** crystallized from benzene; 3.5 g, m.p. 138–140°. – IR. (CH_2Cl_2): 3440 (NH), 1670 (C=O). – NMR. ($CDCl_3$): 5.05 (*s*, 4H, 2 × OCH_2Ph); 5.58 (br.*s*, 1H, NH, exchangeable with D_2O); 6.66–7.08 (*m*, 6H, arom.H); 7.33–7.51 (*m*, 11H, arom.H).

$C_{30}H_{28}BrNO_3$ (530.4) Calc. C 67.93 H 5.32 N 2.64% Found C 68.20 H 5.64 N 2.50%

1-(5-Benzyloxy-2-bromobenzyl)-6-benzyloxy-1,2,3,4-tetrahydroisoquinoline (**27a**). The solution of 2 g of amide **25a** in 5 ml freshly distilled phosphorus oxychloride and 20 ml dry benzene was heated under reflux for 2 h. Hexane was added, and the mixture was kept overnight. The insoluble was repeatedly washed with hexane and the gum was dissolved in 50 ml methanol. To the solution 1 g $NaBH_4$ was added in portions. After 15 min at RT., the reaction mixture was heated under reflux for 30 min and the solvent was removed *in vacuo*. The residue was treated with water and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and distilled to leave the tetrahydroisoquinoline **27a**, which was crystallized from benzene/petroleum ether (b.p. 40–60°); 1.4 g, m.p. 88–89°. – UV.: 283 (3.61). – NMR. ($CDCl_3$): 1.90 (br.*s*, 1H, NH, exchangeable with D_2O); 4.41 (*q*, 1H, H–C(1)); 5.10 (*s*, 4H, 2 × OCH_2Ph); 6.70–7.00 (*m*, 4H, arom.H); 7.17–7.51 (*m*, 12H, atom.H). – MS.: 515 (M^+, Br^{81}), 513 (M^+, Br^{79}).

$C_{30}H_{28}BrNO_2$ (514.4) Calc. C 70.04 H 5.49% Found C 70.13 H 5.72%

1-(2-Bromo-5-hydroxybenzyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (**28**). The solution of 2 g of the benzyl ether **27a** in 150 ml abs. ethanol and 150 ml conc. HCl-solution was heated for 12 h under reflux, then evaporated to dryness; crystallization of the residue from methanol/ether yielded **28** as its hydrochloride; 1.05 g, m.p. 300° (dec.).

$C_{16}H_{16}BrNO_2 \cdot HCl$ (370.7) Calc. C 51.86 H 4.60 N 3.78%
Found C 52.38 H 4.90 N 3.47%

The liberated base **28** was crystallized from chloroform/methanol, m.p. 174–175°. – UV.: 225 (4.24), 283 (3.51). – UV. (EtOH + NaOH): 247 (3.83), 301 (4.44). – NMR. ($CDCl_3$ + DMSO-d_6): 4.14 (*q*, 1H, H–C(1)); 5.36 (br.*s*, 3H, NH and 2 × OH, exchangeable with D_2O); 6.56–7.43 (*m*, 6H, arom. H). – MS.: 334 [$(M-1)^+$, Br^{81}], 332 [$(M-1)^+$, Br^{79}], 252, 187, 185, 148, 146.

$C_{16}H_{16}BrNO_2$ (334.2) Calc. C 57.48 H 4.83 N 4.17% Found C 57.34 H 5.07 N 4.05%

Photolysis of **28** HCl: *formation of berbine* **30** *and noraporphine* **29**. The solution of 1 g of **28** ·HCl in 1000 ml distilled water containing 0.3 g $NaHSO_3$ was irradiated for 10 h using an immersion type *Hanovia* mercury lamp with a *Pyrex* filter, then concentrated *in vacuo* to about 150 ml, cooled, basified with ammonia and repeatedly extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to leave 0.45 g of a brown solid. This was chromatographed over 20 g silica gel in $CHCl_3$. Elution with $CHCl_3$/methanol (97:3, *v/v*; fractions 7–12) gave berbine **30**, crystallized from chloroform/methanol; 15 mg, m.p 268–269°, identical (m.p., IR., MS.) with **30** synthesized from **28** (spectral data *vide infra*).

Elution with $CHCl_3$/methanol (95:5, *v/v*; fractions 15–30) gave 0.2 g of the starting phenolic isoquinoline **28** (IR.).

Elution with $CHCl_3$/methanol (90:10, *v/v*; fractions 36–42) gave the noraporphine **29**, which was crystallized from $CHCl_3$/methanol, 45 mg, m.p. 220–222°. – UV.: 220 (3.73), 235 (3.62), 276 (3.60), 315 (3.32). – UV. (EtOH + NaOH): 225 (3.84), 254 (3.72), 300 (3.66), 325–330 (3.50). – MS.: 253 (M^+), 252 $(M-1)^+$.

*12-Bromo-3,9-dihydroxy-5,6,13,14-tetrahydro-8*H*-dibenzo*[a,g]*quinolizine* (*12-bromo-3,9-dihydroxyberbine*) (**30**). A mixture of 0.5 g **28**, 5 ml 37% formalin and 5 ml glacial acetic acid was heated for 30 min under reflux and the volatiles were removed *in vacuo*. The residue was basified with ammonia and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated to leave a gum which was crystallized from $CHCl_3$/methanol: 0.3 g, m.p. 268–269°. – UV.: 282 (3.67). – UV. (EtOH + NaOH): 298 (3.96). – IR. (KBr): 2840–2720 (*Bohlmann* bands). – NMR. (DMSO-d_6): 4.09 (*d*, 1H, J = 16 Hz, H–C(8)); 6.60, 6.76 (2*s*, 2H, arom. H); 7.11–7.35 (*m*, 3H, arom. H). – MS.: 347 (M^+, Br^{81}), 345 (M^+, Br^{79}), 200, 198, 148, 146.

$C_{17}H_{16}BrNO_2$ (382.7) Calc. C 53.35 H 4.48% Found C 53.45 H 4.83%

30 HCl, m.p. 300° (dec.).

N-*β*-(*4-Benzyloxy-3-methoxyphenethyl*)-(*5-benzyloxy-2-bromophenyl*)*acetamide* (**25b**). This was prepared from *β*-(4-benzyloxy-3-methoxyphenyl)ethyl amine and (5-benzyloxy-2-bromophenyl)-acetic acid, in the same manner as **25a**, and crystallized from benzene; m.p. 117–118°. – IR. (CH_2Cl_2): 3440 (NH), 1680 (C=O). – NMR. ($CDCl_3$): 3.80 (*s*, 3H, OCH_3); 5.50 (br.*s*, 1H, NH, exchangeable with D_2O); 4.98, 5.06 (2*s*, 4H, 2 × OCH_2Ph); 6.50–7.00 (*m*, 6H, arom. H); 7.23–7.50 (10H, arom. H). – MS.: 561 (M^+, Br^{81}), 559 (M^+, Br^{79}), 480 $(M-Br)^+$.

$C_{31}H_{30}BrNO_4$ (560.4) Calc. C 66.40 H 5.40 N 2.50% Found C 66.69 H 5.70 N 2.41%

1-(5-Benzyloxy-2-bromobenzyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline (**26b**). The solution of 2 g amide **25b** in 5 ml freshly distilled phosphorus oxychloride and 20 ml dry benzene was heated 1 h under reflux. After the addition of 150 ml hexane, the reaction mixture was allowed to stand at RT. overnight and the supernatant liquid was removed by decantation. The syrupy residue was washed several times with hexane and dried *in vacuo*. On adding KI-solution and heating on a waterbath for 10 min and cooling, yellow crystals of **26b**. HI separated, which were filtered off, dried and recrystallized from methanol; 1.9 g, m.p. 204–205°. – UV. (EtOH): 252 (4.22), 310 (4.10), 367 (4.10). – UV. (EtOH + NaOH): 260 (4.18), 292 (4.01). – NMR. ($CDCl_3$ + DMSO-d_6): 4.00 (*s*, 3H, OCH_3); 5.00, 5.05 (2*s*, 4H, 2 × OCH_2Ph); 6.70–7.30 (*m*, 15H, arom. H).

$C_{31}H_{28}BrNO_3 \cdot HI$ (670.5) Calc. C 55.56 H 4.40 N 2.10%
Found C 56.32 H 4.35 N 2.48%

1-(5-Benzyloxy-2-bromobenzyl)-7-benzyloxy-6-methoxy-2-methyl-3,4-dihydroisoquinolinium iodide (**26d**). The mixture of 1.9 g of dihydroisoquinoline **26b**, 5 ml $CHCl_3$ and 2 ml CH_3I was heated in a sealed tube on a water-bath for 40 min when a yellow solid separated. The solvent was removed *in vacuo*, the solid was filtered off, washed, dried and recrystallized from methanol; 1.9 g, m.p. 217–218°. – UV.: 305 (3.96), 360 (3.96). – UV. (EtOH + NaOH): 256 (4.17), 295 (3.91).

$C_{32}H_{31}BrINO_3$ (684.4) Calc. C 56.13 H 4.57 N 2.06% Found C 56.27 H 4.74 N 2.18%

7-Benzyloxy-1-(5-benzyloxy-2-bromobenzyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**27b**). To 1.5 g **26d** in 100 ml methanol, 1 g of $NaBH_4$ was added in portions. After 15 min at RT., the mixture was heated for 30 min under reflux and the solvent was removed *in vacuo*. The residue was treated with water and extracted with $CHCl_3$. The extract was washed with water, dried ($NaSO_4$) and the solvent distilled to yield the tetrahydroisoquinoline **27b**, which was crystallized from benzene/petroleum ether (b.p. 40–60°); 1 g, m.p. 57–58°. – UV.: 235 (sh. 4.37), 284 (3.71). – NMR. ($CDCl_3$): 2.48 (*s*, 3H, N–CH_3); 3.86 (*s*, 3H, OCH_3); 4.86, 4.95 (2*s*, 4H, 2 × OCH_2Ph); 6.23 (*s*, 1H, H–C(8)); 6.62–6.80 (*m*, 3H, arom. H); 7.23–7.48 (*m*, 11H, arom. H).

$C_{32}H_{32}BrNO_3$ (558.5) Calc. C 68.80 H 5.78% Found C 69.40 H 6.13%

1-(2-Bromo-5-hydroxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**31a**). A mixture of 2 g **27b**, 100 ml abs. ethanol and 100 ml conc. HCl-solution was heated on a water-bath for 12 h. The solvent and reagent were removed *in vacuo*. The residue was flushed with 50 ml benzene/ethanol 1:1, basified with ammonia and extracted with $CHCl_3$. The extract was washed, dried (Na_2SO_4) and evaporated to leave a gum which was crystallized from benzene/petroleum ether (b.p. 40–60°) to give **31a**; 1.0 g, m.p. 120°. – UV.: 285 (3.91). – UV. (EtOH + NaOH): 300 (3.91). – NMR. ($CDCl_3$): 2.40 (*s*, 3H, N–CH_3); 3.83 (*s*, 3H, OCH_3); 4.00 (*m*, 1H, H–C(1)); 6.20 (*s*, 3H, arom. H and 2 × OH, 2H exchangeable with D_2O); 6.33–6.66 (*m*, 3H, arom. H); 7.18 (*s*, 1H, arom. H).

$C_{18}H_{20}BrNO_3$ (387.3) Calc. C 55.80 H 5.33% Found C 55.54 H 5.79%

dl-*1,9-Dihydroxy-2-methoxyaporphine* (**32a**). The solution of 0.5 g of **31a** · HCl in 500 ml water containing 0.15 g $NaHSO_3$ was irradiated for 11 h, then concentrated *in vacuo* to about 150 ml, cooled, basified with ammonia and repeatedly extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated *in vacuo* to leave 0.26 g of a brown gum. This was chromatographed over 15 g silica gel. Elution with $CHCl_3$/methanol (97:3, *v/v*: fractions 18–25) gave the aporphine **32a** as white needles; 50 mg, m.p. 218–220°. – UV.: 222 (4.25), 278 (4.22), 302 (3.97), 314 (3.77). – UV. (EtOH + NaOH): 224 (4.33), 254 (4.16), 296 (4.12), 328 (4.12). – NMR. (DMSO-d_6): 2.47 (*s*, 3H, N–CH_3); 3.87 (*s*, 3H, OCH_3); 6.50–6.93 (*m*, 3H, arom. H); 8.22 (1H, H–C(11). – MS.: 297 (M^+), 296 ($M-1$)$^+$, 282, 280, 266, 254, 239, 236, 222.

$C_{18}H_{19}NO_3$ (297.3) Calc. C 72.70 H 6.44 N 4.71% Found C 72.97 H 6.60 N 4.24%

1-(2-Bromo-4-hydroxy-5-methoxybenzyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**31b**). The solution of 2 g 1-(4-benzyloxy-2-bromo-5-methoxybenzyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline [18] (**27c**) in 100 ml abs. ethanol and 100 ml conc. HCl-solution was heated for 12 h under reflux, then evaporated to dryness by distillation *in vacuo*. Crystallization of the residue from methanol yielded **31b** · HCl; 1.2 g, m.p. 192–193° (base, m.p. 210–211°). – UV.: 235 (sh. 4.08), 285 (3.96). – UV. (EtOH + NaOH): 300 (4.03). – NMR. (CF_3CO_2H): 4.00 (*s*, 6H, 2 × OCH_3); 5.10 (*q*, 1H, H–C(1)); 6.86 (*s*, 3H, arom. H); 7.30 (*s*, 1H, arom. H). – MS.: 395 (M^+, Br^{81}), 393 (M^+, Br^{79}), 313, 312, 178, 176.

$C_{18}H_{20}BrNO_4$ (394.3) Calc. C 54.83 H 5.11 N 3.55% Found C 54.87 H 5.39 N 3.51%

1,10-Dihydroxy-2,9-dimethoxynoraporphine (**32b**). The solution of 0.5 g **31b** · HCl in 500 ml distilled water containing 0.15 g $NaHSO_3$ was irradiated for 10 h, then concentrated *in vacuo* to about 150 ml, cooled, basified with ammonia and repeatedly extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated *in vacuo* to leave 0.3 g of a brown solid. This was chromatographed over 10 g silica gel. Elution with $CHCl_3$/methanol (97:3, *v/v*; fractions 17–26) gave recovered **31b**; 0.23 g (m.p., IR. identical with those of an authentic sample).

Elution with $CHCl_3$/methanol (96:4, *v/v*; fraction 36–40) gave **32b** as a gum; 50 mg. – UV.: 230 (4.10), 277 (4.00), 305 (3.82). – UV. (EtOH + NaOH): 254 (4.17), 282 (3.75), 336 (3.64). The gum was acetylated by keeping with acetic anhydride and pyridine overnight. Excess reagents were removed *in vacuo*; the residue was treated with water and extracted with ether. The extract was washed with water, dried (Na_2SO_4) and evaporated to leave a solid, which was crystallized from benzene/ether: triacetate of **32b**, 25 mg, m.p. 224–225°. – MS.: 439 (M^+) ($C_{24}H_{25}NO_7$ = 439.4).

N-*β-(3,4-Methylenedioxyphenethyl)-3-(5-benzyloxy-2-bromo-4-methoxyphenyl)propionamide* (**39**). A mixture of 3 g homopiperonyl amine (**37**) and 6 g 3-(5-benzyloxy-2-bromo-4-methoxyphenyl)propionic acid [19] (**38**, m.p. 104–105°; methyl ester, m.p. 64°) was heated on an oil bath at 180–185° for 2 h. The product was cooled to RT. and extracted with $CHCl_3$. The extract was washed with dil. HCl-

solution, water, saturated $NaHCO_3$-solution and water, then dried (Na_2SO_4); the solvent was distilled to leave **39**, which was crystallized from benzene; 6.2 g, m.p. 140–142°. – IR. (CH_2Cl_2): 3450 (NH), 1670 (C=O). – NMR. ($CDCl_3$): 3.85 (*s*, 3H, OCH_3); 5.11 (*s*, 2H, OCH_2Ph); 5.53 (br.*s*, 1H, NH, exchangeable with D_2O); 5.95 (*s*, 2H, OCH_2O); 6.63–7.08 (*m*, 5H, arom.H); 7.30–7.55 (*m*, 5H, arom.H). – MS.: 513 (M^+, Br^{81}), 511 (M^+, Br^{79}); 432 $(M-Br)^+$.

$C_{26}H_{26}BrNO_5$ (512.4) Calc. C 60.95 H 5.12 N 2.73% Found C 61.33 H 5.68 N 2.63%

1-(5-Benzyloxy-2-bromo-4-methoxyphenethyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (**40**). The solution of 4 g of **39** in 10 ml freshly distilled phosphorus oxychloride and 40 ml dry benzene was heated for 2 h on a water-bath. Hexane was added and the mixture left overnight. The supernatants were poured off; the residue was repeatedly washed with hexane and crystallized from methanol/ether. The separated crystals of **40** · HCl were collected, washed, dried and recrystallized from methanol/ether; 3.6 g, m.p. 214°. – UV.: 233 (4.34), 283 (3.90), 315 (3.87).

$C_{26}H_{24}BrNO_4 \cdot HCl \cdot {}^1/_2H_2O$ (539.8) Calc. C 57.86 H 4.85 N 2.60% Found C 57.55 H 5.20 N 2.74%

1-(5-Benzyloxy-2-bromo-4-methoxyphenethyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**41**). 3.6 g of **40** · HCl was dissolved in 100 ml methanol and reduced with 1.8 g $NaBH_4$ as before. Work-up gave a gum which was crystallized from benzene/petroleum ether (b.p. 40–60°) to yield **41**; 2.7 g, m.p. 134–136°. – UV.: 288 (3.89). – NMR. ($CDCl_3$): 1.63 (*s*, 1H, NH, exchangeable with D_2O); 3.86 (*s*, 3H, OCH_3); 5.15 (*s*, 2H, OCH_2Ph); 5.90 (*s*, 2H, OCH_2O); 6.58 (*s*, 2H, arom.H); 6.86 (*s*, 1H, arom.H); 7.10 (*s*, 1H, arom.H); 7.30–7.58 (*m*, 5H, arom.H). – MS.: 496 $[(M-1)^+, Br^{81}]$, 494 $[(M-1)^+, Br^{79}]$, 416 $(M-Br)^+$.

$C_{26}H_{26}BrNO_4$ (496.4) Calc. C 62.91 H 5.28 N 2.82% Found C 63.25 H 5.51 N 2.62%

Debenzylation of **41**: *formation of isoquinoline* **42** *and homoberbine* **43**. The solution of 3 g of **41** in 150 ml abs. ethanol and 150 ml conc. HCl-solution was heated for 12 h under reflux, then evaporated to dryness by distillation *in vacuo*. The residue was flushed with benzene/ethanol (1:1, 50 ml) and crystallized from methanol to yield **42**, HCl; 2.1 g, m.p. 269–270° (dec.).

$C_{19}H_{20}BrNO_4 \cdot HCl$ (442.7) Calc. C 51.54 H 4.78 N 3.16% Found C 51.85 H 4.99 N 2.92%

The mother-liquor was concentrated, basified with ammonia and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated to yield 0.35 g of a solid which was crystallized from methanol, filtered off, washed with methanol and dried to yield the isoquinoline base **42**; 0.26 g, m.p. 168–169°. – UV.: 290 (3.90). – UV. (EtOH + NaOH): 296 (4.90). – NMR. ($CDCl_3$): 3.80 (*s*, 3H, OCH_3); 4.50 (br.*s*, 2H, NH, OH, exchangeable with D_2O); 5.95 (*s*, 2H, OCH_2O); 6.61 (*s*, 1H, H–C(5)); 6.70 (*s*, 1H, H–C(8)); 6.86 (*s*, 1H, H–C(6′)); 7.10 (*s*, 1H, H–C(3′). – MS.: 407 (M^+, Br^{81}), 405 (M^+, Br^{79}), 326 $(M-Br)^+$, 217, 215, 176, 174.

$C_{19}H_{20}BrNO_4$ (406.3) Calc. C 56.16 H 4.96% Found C 56.65 H 4.62%

The mother-liquor was concentrated and chromatographed over silica gel (5 g), with $CHCl_3$. Fractions 6–8 were combined and crystallized from methanol to yield the homoberbine **43**; 20 mg, m.p. 225–226°. – UV.: 292 (3.92). – UV. (EtOH + NaOH): 298 (4.03). – NMR. (DMSO-d_6): 3.85 (*s*, 3H, OCH_3); 4.64 (*d*, 1H, $J = 15$ Hz, H–C(8)); 5.93 (*s*, 2H, OCH_2O); 6.56, 6.66, 7.00 (3*s*, 3H, arom. H.) – MS.: 419 (M^+, Br^{81}), 417 (M^+, Br^{79}), 418, 416, 244, 242, 176, 174.

Photolysis of 1-(2-bromo-5-hydroxy-4-methoxyphenethyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline **42**. *Formation of homoberbine* **43** *and norhomoaporphine* **44**. The solution of 2 g of **42** · HCl in 1200 ml water containing 0.6 g $NaHSO_3$ was irradiated for 11 h, then concentrated *in vacuo* to about 150 ml and cooled. The crystals that separated were filtered off, washed with water and dried; 0.2 g of **42** · HCl (m.p., mixed m.p. and TLC.).

The mother-liquor was basified with ammonia and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated *in vacuo* to leave 1.53 g of brown gum. This was chromatographed over 30 g silica gel. Elution with $CHCl_3$ (fractions 5–6) gave 25 mg homoberbine **43**, identical with the previous sample (m.p., MS.).

$C_{20}H_{20}BrNO_4$ (418.3) Calc. C 57.42 H 4.82% Found C 57.36 H 5.10%

Elution with $CHCl_3$/methanol (99:1, *v/v*; fractions 16–22) gave 0.23 g of the isoquinoline **42**, crystallized from methanol (m.p., mixed m.p., TLC. and IR. identical with those of an authentic sample). Elution with $CHCl_3$/methanol (98:2, *v/v*; fractions 25–32) gave the *N*-norhomoaporphine **44**, which was crystallized from $CHCl_3$/methanol; 0.195 g, m.p. 184–185°. – UV.: 223 (4.44), 268 (4.10), 293 (4.06). – UV. (EtOH + NaOH): 250 (4.26), 299 (4.33), 313 (4.31). – MS.: 325 (M^+), 324, 296, 295, 294, 282, 252, 238.

12-Bromo-9-hydroxy-10-methoxy-2,3-methylenedioxy-5,6,8,13,14,14a-hexahydroisoquino[2,1-b]-2-benzazepine (**43**). A mixture of 1 g **42**, 5 ml 37% formalin and 5 ml glacial acetic acid was refluxed 30 min and the reagents were removed *in vacuo*. The residue was basified with ammonia and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated to afford a gum, which was crystallized from $CHCl_3$/methanol to give 1 g of **43**, identical with the previous samples (m.p., UV., NMR., MS.).

9-Hydroxy-10-methoxy-2,3-methylenedioxy-5,6,8,13,14,14a-hexahydroisoquino[2,1-b]-2-benzazepine (**45**). The solution of 0.5 g of 12-bromohomoberbine **43** in 150 ml ethanol was shaken with 0.2 g Pd/C (10%) in an H_2-atmosphere at 45–50 psi in a *Paar* apparatus for 5 h. The catalyst was filtered off; the solvent was removed from the filtrate *in vacuo*; the residue was basified with ammonia and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4). The solvent was evaporated to yield **45**, which was crystallized from $CHCl_3$/methanol; 0.33 g, m.p. 169–170°. – UV.: 231 (3.95), 288 (3.88). – UV. (EtOH + NaOH): 295 (4.05). – IR. (KBr): 3520 (OH). – NMR. ($CDCl_3$): 3.86 (*s*, 3H, OCH_3); 4.75 (*d*, J=15 Hz, 1H, H–C(8)); 5.90 (*s*, 2H, OCH_2O); 6.50–6.70 (*m*, 4H, arom. H). – MS.: 339 (M^+), 338, 176, 174, 164, 149.

$C_{20}H_{21}NO_4$ (339.4) Calc. C 70.78 H 6.24 N 4.13% Found C 71.02 H 6.56 N 4.25%

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