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PHOSGENATION OF BENZYLTETRAHYDROISOQUINOLINES

A NEW METHOD OF BERBINES AND BERBIN-8-ONES SYNTHESIS[1]

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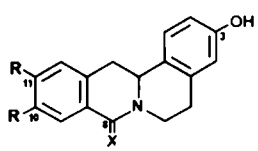
Abstract—A novel synthesis of the berbine ring skeleton by the way of the berbin-8-ones is reported. Treatment of 1-benzyl-1,2,3,4-tetrahydroisoquinolines **1a–d** with phosgene gas gave a new series of N-chloroformyl derivatives **2a–d**. Intramolecular ring closure of these compounds in presence of a Lewis acid catalyst afforded berbin-8-ones **3a–d** in good yield. The choice of the cyclization catalyst is discussed. Reduction of products **3a–d** with lithium aluminium hydride gave the berbines **4a–d**. Hydrolysis of berbines **4b,c** gave the new 3-hydroxyberbines **4e,f**. Preparation of new starting benzyltetrahydroisoquinolines **1b,c** are described.

During our synthetic works[2,3] we have investigated the preparation of berbine compounds **4a–f**. The classical methods[4] failed for the preparation of new 3-hydroxyberbine **4e** and its 10,11-dimethoxy derivative **4f**. Therefore we have developed a new synthetic procedure for their preparations. The potential of this route was established by the total syntheses of berbines **4a–d**. After hydrolysis, berbines **4b,c** gave respectively 3-hydroxyberbines **4e,f**.

This new method involves the initial reaction of 1-benzyl-1,2,3,4-tetrahydroisoquinolines **1a–d** with phosgene gas to afford N-chloroformyl derivatives **2a–d**, followed by intramolecular catalysed cyclization to obtain berbin-8-ones **3a–d** which were reduced to berbines **4a–d**.

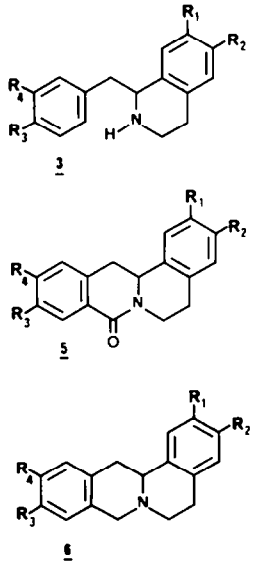
The reaction of phosgene gas with benzyltetrahydroisoquinolines **1a–d** in the presence of triethylamine, to trap the emission of hydrochloric acid in the course of the reaction, is a good way to isolate 1-benzyl-2-chloroformyl-1,2,3,4-tetrahydroisoquinolines **2a–d** in good yield. This new series of isoquinoline derivatives is essentially marked, in the NMR spectrum, by the proton signal of C-1 at about δ 5.3 as a tripled peak (^3J = 6.7 Hz) and, in the IR spectrum, by the strong absorption of the CO group in the 1720 cm^{-1} region.

The cyclization of chloroformyl products **2a–d** was carried out by intramolecular Friedel–Crafts reactions with a well chosen catalyst in refluxing benzene or at room temperature in chloroformic solution. The choice of the Lewis acid catalyst was based on the activation of the benzyl ring at the C-1 position and the stability of the substituent of the isoquinoline ring of chloroformyl compounds. When the benzyl ring is substituted by activating groups, **2c,d** ($R_2 = R_3 = OCH_3$), a weak Lewis acid, such as zinc chloride, was sufficient to realize the ring closure. In this case 10,11-dimethoxyberbin-8-ones **3c,d** were obtained. When the benzyl ring carries no activating group, **2a,b** ($R_2 = R_3 = H$), a more acid catalyst was required, like aluminium or stannic chloride. The stannic chloride gave a homogeneous chloroformic solution and allowed to carry out the cyclization at ambient temperature. When the isoquinoline ring of **2a–d** showed an unstable substituent, it was necessary to choose between a catalyst not too acid to respect it, but acid enough to realize the ring closure. For example the benzyloxy group of **2c** was debenzylated in the presence of aluminium or stannic chloride, but was respected in



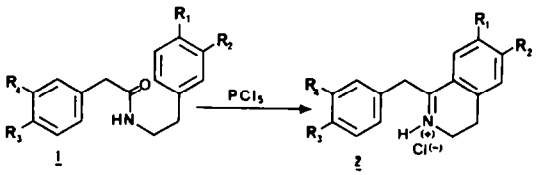
5k R = H, X = O
5l R = OCH_3, X = O
6k R = H, X = H_2
6l R = OCH_3, X = H_2

Scheme 1.



	R_1	R_2	R_3	R_4
a	H	H	H	H
b	H	OCH_3	H	H
c	OCH_3	OCH_3	H	H
d	H	H	OCH_3	OCH_3
e	O-CH_2	-O	H	H
f	H	$OCH_2C_6H_5$	H	H
g	H	OCH_3	OCH_3	OCH_3
h	OCH_3	OCH_3	OCH_3	OCH_3
i	O-CH_2	-O	OCH_3	OCH_3
j	H	$OCH_2C_6H_5$	OCH_3	OCH_3

Scheme 2.



	R_1	R_2	R_3	R_4
b	H	OCH_3	H	H
c	OCH_3	OCH_3	H	H
e	O-CH_2-O		H	H
f	H	$OCH_2C_6H_5$	H	H
g	H	OCH_3	OCH_3	OCH_3
h	OCH_3	OCH_3	OCH_3	OCH_3
i	O-CH_2-O		OCH_3	OCH_3
j	H	$OCH_2C_6H_5$	OCH_3	OCH_3

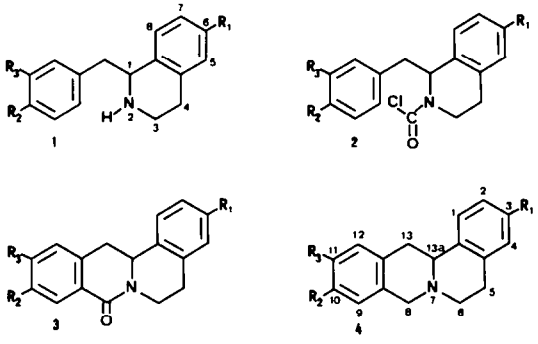
Scheme 3.

presence of zinc chloride to afford the corresponding berbine-8-one **3c**.

Table 1 shows the possible Lewis acid catalysts which have been used for the cyclization of the N-chloroformyl series of products **2a–d** and the principal physical characteristics of the resulting berbin-8-ones **3a–d**.

The reduction of berbin-8-ones **3a–d** with lithium aluminium hydride in tetrahydrofuran at ordinary temperature gave finally berbines **4a–d**. And the new desired 3-hydroxyberbines **4e,f** were prepared by hydrolysis of respectively 3-methoxyberbine **4b** with hot concentrated bromhydric acid and 3-benzyloxy-10,11-dimethoxyberbine **4c** with hot acetochlohydric acid.

The preparation of starting products **1a–d** was realized by standard procedures involving the initial fusion of β-phenethylamine and phenylacetic acid to



	R_1	R_2	R_3
a	H	H	H
b	OCH_3	H	H
c	$OCH_2C_6H_5$	OCH_3	OCH_3
d	OCH_3	OCH_3	OCH_3
e	OH	H	H
f	OH	OCH_3	OCH_3

Scheme 4.

Table 1. Berbin-8-ones **3** produced by cyclization of N-chloroformyl derivatives **2** in the presence of different Lewis acids as catalyst†

Compounds 3	R_1	R_2	R_3	Crude yield % Methods A $AlCl_3$‡	B $SnCl_4$§	C $ZnCl_2$‡	m.p.‖ °C	Spectral data¶ IR ($CHCl_3$) cm^{-1}	NMR δ ($CDCl_3$)
(a) Berbin-8-one	H	H	H	76	83	—	170–171 lit. 169–170[11]	νC=O 1638, 1605, 1580	8.20 (1H, m, 9-H), 7.33 (7H, m, other ArH), 4.93 (2H, m, 6 and 13a-H), 3.56-2.58 (3H, m).
(b) 3-Methoxy-berbin-8-one	OCH_3	H	H	70	78	—	110 lit. 111[12]	νC=O 1635, 1605, 1575	8.17 (1H, m, 9-H), 7.58–7.02 (4H, m, 1 + 10 + 11 and 12-H), 6.80 (2H, m + s, 2 and 4-H), 4.85 (2H, m, 6 and 13a-H), 3.75 (3H, s, OCH_3), 3.42–2.51 (5H, m).
(c) 3-Benzyloxy-10,11-dimethoxy berbin-8-one	$OCH_2C_6H_5$	OCH_3	OCH_3	—	—	45	144	νC=O 1635, 1600, 1580	7.68 (1H, s, 9-H), 7.56–6.80 (8H, m, other ArH), 6.70 (1H, s, 4-H), 5.04 (2H, s, CH_2 benzyloxy), 4.80 (2H, m, 6 and 13a-H), 3.89 (6H, s, 2 × OCH_3), 3.40-2.49 (5H, m).
(d) 3,10,11-Tri-methoxy-berbin-8-one	OCH_3	OCH_3	OCH_3	61	69	55	161	νC=O 1640, 1605, 1590	7.71 (1H, s, 9-H), 7.22 (1H, d, J = 8 Hz, 1-H) 6.84 (3H, m + s, 2 + 4 and 12-H), 4.89 (2H, m, 6 and 13a-H), 3.93 (6H, s, C-10 OCH_3 and C-11 OCH_3), 3.82 (3H, s, C-3 OCH_3), 3.42–2.60 (5H, m).

† The activities of Lewis acids follow the order $AlCl_3 > SnCl_4 > ZnCl_2$.[5]
‡ $AlCl_3$ and $ZnCl_2$ were used in refluxing benzene.
§ $SnCl_4$ was used in chloroformic solution at ambient temperature.
‖ All products were recrystallized in 95% EtOH.
¶ Berbin-8-ones exhibited identical spectral values as those described by other authors.[4a,6]

afford N-phenethylphenylacetamide, followed by Bischler–Napieralski cyclization to yield 1-benzyl-3,4-dihydroisoquinoline which gave after reduction 1-benzyl-1,2,3,4-tetrahydroisoquinolines **1a–d**. Compounds **1a**[7] and **1d**[8] were prepared according to the literature.

Benzyltetrahydroisoquinolines **1b,c** were unknown and their preparations are described in the experimental. For the ring closure of corresponding N-phenethylphenylacetamides we have applied a modified Bischler–Napieralski reaction using phosphorus pentachloride in chloroformic solution at room temperature. This modified method has the great advantage to isolate directly the dihydroisoquinoline as the perfectly stable hydrochloride. On the other hand the usual methods (phosphorus oxychloride or pentaoxide in refluxing toluene) failed for the preparation of **1c** or afforded, for **1b**, after extraction the dihydroisoquinoline as the base form, known to be easily oxidizable in the presence of air in alkaline or neutral conditions.[9] The reduction of these cyclization products with sodium borohydride gave the tetrahydroisoquinolines **1b,c**.

In conclusion the method using phosgene as reagent of cyclization of benzyltetrahydroisoquinolines is a new efficient route to berbine ring system synthesis. By this way we have prepared berbines **4a–d** and 3-hydroxy derivatives **4e,f**. Compared to the usual methods this one presents the advantage to give berbines in high yield especially when the benzyl ring of isoquinolines is not activated for the ring closure. A second advantage is the easy chemical access to the class of berbine-8-one compounds.

EXPERIMENTAL

Standard experimental procedures

Microanalyses were performed by Microlab. Chem. Inst. Strasbourg. All compounds have C, H, N analyses within the usual limits. M.ps were observed on a Kofler hot-stage apparatus. The NMR spectra were recorded on a Perkin–Elmer R-12A 60 MHz spectrometer using TMS as internal standard. The IR spectra were obtained on a Beckman IR 4230 spectrophotometer. All TLC were performed on Merck Silica Gel F-254 plates (chloroform–ethyl acetate–triethylamine, 25:25:1).

1-*Benzyl*-1,2,3,4-*tetrahydroisoquinolines* **1b,c**

N-*Phenethylphenylacetamides*. A mixture of an equimolar quantity of **1b** or **1c**, **1b** or the 3,4-dimethoxy derivative **1c** was heated in a metal bath at 180–200° until the effervescence ceased (2–3 hr), poured in a mortar and left to cool. The crude amide crystallized, was pulverized and washed with diisopropyl ether to give **1b** (93%); m.p. 54° (EtOH); IR ($CHCl_3$): νNH 3430, νC=O 1655, 1600, 1585 cm^{-1}; NMR ($CDCl_3$): δ 7.20 (7H, m), 6.50 (2H, m, ArH α OCH_3), 5.85 (1H, m, NH), 3.70 (3H, s, OCH_3), 3.45 (4H, s + m, $CH_2CO + CH_2N$), 2.64 (2H, t, J = 6.7 Hz, $\underline{CH_2}CH_2N$); or **1c** (96%); m.p. 98° (EtOH); IR ($CHCl_3$): νNH 3420, νC=O 1655, 1605, 1580 cm^{-1}; NMR ($CDCl_3$): δ 7.62–6.55 (12H, m, ArH), 5.67 (1H, m, NH), 5.04 (2H, s, CH_2 benzyloxy), 3.80–3.84 (6H, 2s, 2 × OCH_3), 3.47 (4H, s + m, $CH_2CO + CH_2N$), 2.71 (2H, t, J = 6.7 Hz, $\underline{CH_2}CH_2N$).

1-*Benzyl*-3,4-*dihydroisoquinolines*. The previous amide (30 g) was dissolved in $CHCl_3$ (150 ml) and PCl_5 (36 g) was cautiously added. After stirring for 6 hr at room temp, light petroleum (150 ml) was slowly added. The ppt or the oil was separated dissolved in EtOH (50 ml). An excess of ether (200 ml) was added to precipitate the crude hydrochloride which was removed and dried to give **1b** (80%); m.p. 159–161°; IR ($CHCl_3$): $\nu\hat{N}H$ 2780–2240, $\nu C{=}\hat{N}$ 1650, 1610, 1560 cm^{-1}; NMR (DMSO-d_6): δ 8.20 (1H, d, J = 9.3 Hz, 8-H), 7.69–7.24 (5H, m, ArH benzyl), 7.04 (2H, m + s and 5-H), 4.71 (2H, s, CH_2 benzyl), 3.91 (5H, m + s, 3-H and OCH_3), 3.09 (2H, t, J = 8 Hz, 4-H); or **1c** (70%); m.p. 125–130°; IR ($CHCl_3$): $\nu\hat{N}H$ 2780–2240, $\nu C{=}\hat{N}$ 1650, 1615, 1600 cm^{-1}; NMR (DMSO-d_6): δ 8.16 (1H, d, J = 9.3 Hz, 8-H), 7.41 (5H, m, ArH benzyloxy), 7.21–6.82 (5H, m, other ArH), 5.24 (2H, s, CH_2 benzyloxy), 4.44 (2H, s, CH_2 benzyl at C-1), 3.98–3.60 (8H, m + 2s, 3-H and 2 × OCH_3), 3.00 (2H, t, J = 8 Hz, 4-H).

Reduction of 1-*benzyl*-3,4-*dihydroisoquinolines*. Dihydroisoquinoline hydrochloride (20 g) was dissolved in MeOH (180 ml) and $NaBH_4$ (2 g) was added in several portions. After addition the soln was stirred for 30 min at room temp. Water (100 ml) was added and the mixture was first made acidic with AcOH then basic with 10% Na_2CO_3 aq. The mixture was extracted with $CHCl_3$. The organic phases were washed, dried ($MgSO_4$) and the solvent removed. The residual syrup was triturated in diisopropyl ether to crystallize **1b** (76%); m.p. 42°; IR ($CHCl_3$): νNH 3320, 2980–2810, 1605, 1575 cm^{-1}; NMR ($CDCl_3$): δ 7.29 (5H, m, C_6H_5), 7.13 (1H, d, J = 9.3 Hz, 8-H), 6.73 (2H, m + s, 5 and 7-H), 4.22 (1H, dd, J_1 = 9 Hz, J_2 = 4 Hz, 1-H), 3.76 (3H, s, OCH_3), 3.51–2.62 (m), 2.49 (1H, m, NH); or **1c** (88%); m.p. 98–102°; IR ($CHCl_3$): νNH 3320, 2975–2780, 1600, 1585 cm^{-1}; NMR ($CDCl_3$): δ 7.58–6.53 (11H, m, ArH), 5.04 (2H, s, CH_2 benzyloxy), 4.14 (1H, dd, J_1 = 9 Hz, J_2 = 4 Hz, 1-H), 3.80–3.83 (6H, 2s, 2 × OCH_3), 3.40–2.49 (6H, m), 2.10 (1H, s, NH).

1-*Benzyl*-2-*chloroformyl*-1,2,3,4-*tetrahydroisoquinolines* **2a–d**

A 3-necked flask was equipped with a reflux condenser, a dropping funnel, a magnetic stirrer and an inlet of phosgene gas. A satisfactory gas absorption trap[10] was fitted at the top of the condenser and connected to the water pump. The phosgene gas was evolved (60–80 ml/mn) in a soln of $CHCl_3$ (100 ml) and Et_3N (15 ml) in the flask, during 5 min before adding dropwise (15 min) the soln of **1a–d** (15 g) and Et_3N (15 ml) in $CHCl_3$ (100 ml). After addition the apparatus was purged with the water pump. The soln was evaporated *in vacuo* and the residue was triturated with anhyd acetone to separate the great majority of the insoluble $Et_3N \cdot HCl$ by filtration. The filtrate was evaporated and the residue dissolved in dry benzene. After standing 1 hr the soln was filtered to remove the remaining $Et_3N \cdot HCl$. The benzene soln was evaporated under reduced pressure to give a residual syrup which was dissolved in EtOH. On standing the chloroformyl product precipitated; **2a** (76%) m.p. 60–61°, IR νC=O 1720, 1600 cm^{-1}; NMR ($CDCl_3$): δ 7.30–6.62 (9H, m, ArH), 5.40 (1H, t, J = 6.7 Hz, 1-H), 4.44–3.22 (2H, m, 3-H), 3.08 (2H, d, J = 6.7 Hz, CH_2 benzyl), 2.76 (2H, m, 4-H); or the derivatives **2b** (79%); m.p. 118°; IR ($CHCl_3$): νC=O 1720, 1610, 1580 cm^{-1}; NMR ($CDCl_3$): δ 7.91–6.53 (8H, m, ArH), 5.41 (1H, t, J = 6.7 Hz, 1-H), 4.41–3.28 (5H, m + s, 3-H and OCH_3), 3.11 (2H, d, J = 6.7 Hz, CH_2 benzyl), 2.79 (2H, m, 4-H); **2c** (76%); m.p. 108°; IR ($CHCl_3$): νC=O 1720, 1600, 1590 cm^{-1}; NMR ($CDCl_3$): δ 7.33 (5H, m, ArH benzyloxy), 6.86–6.35 (6H, m, other ArH), 5.34 (1H, t, J = 6.7 Hz, 1-H), 5.00 (2H, s, CH_2 benzyloxy), 4.32–3.21 (8H, m + 2s, 3-H and 2 × OCH_3), 3.06 (2H, d, J = 6.7 Hz, CH_2 benzyl at C-1), 2.69 (2H, m, 4-H); **2d** (71%); m.p. 80–81°; IR ($CHCl_3$): νC=O 1720, 1610, 1590 cm^{-1}; NMR ($CDCl_3$): δ 6.83–6.35 (6H, m, ArH), 5.33 (1H, t, J = 6.7 Hz, 1-H), 4.33–3.20 (11H, m + 2s, 3-H and 3 × OCH_3), 3.03 (2H, d, J = 6.7 Hz, CH_2 benzyl at C-1), 2.71 (2H, m, 4-H).

Berbin-8-*ones or* 5,6,13,13a-*tetrahydro*-8H-*dibenzo* [*a,g*] *quinolizin*-8-*ones* **3a–d**

Method A: *cyclization with* $AlCl_3$. To a stirred soln of **2a,b,d** (10 g) in dry benzene (110 ml) was added an equimolar quantity + 5% excess of anhyd $AlCl_3$. The mixture was heated under reflux for 3 hr, cooled and the solvent evaporated *in vacuo*. The residue was treated with cracked ice and water, then extracted with $CHCl_3$. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to dryness. The solid residue

was collected, washed with ether, recrystallized to give **3a**, the derivatives **3b** or **3d**.

Method B: *cyclization with* $SnCl_4$. Diluted fuming $SnCl_4$ (4 ml) in $CHCl_3$ (10 ml) was added dropwise (15 min) into a stirred chloroformic soln (100 ml) of pure **2a,b,d** (10 g). After stirring at ambient temp for 30 min, water (50 ml) and conc HCl (10 ml) were added. The mixture was heated under reflux until the two phases were clear. The organic phase was decanted, washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residual solid was collected, washed with ether and dried to give **3a,b,d**.

Method C: *cyclization with* $ZnCl_2$. The same procedure as with $AlCl_3$ was used but 10% excess anhyd $ZnCl_2$ was required to afford **3c** or **3d** derivatives.

Berbines or 5,6,13,13a - *tetrahydro* - 8H - *dibenzo* [*a,g*]*quinolizines* **4a–f**

Reduction with $LiAlH_4$: **4a–d**. To a stirred suspension of $LiAlH_4$ (1 g) in dry ether (50 ml) was added dropwise (15 min) a soln of **3a–d** (5 g) in dry THF (100 ml). After addition the mixture was stirred for 30 min at room temp, then water (1 ml), 15% NaOH aq (1 ml) and water (3 ml) were added respectively. The resulting hydroxides were separated by filtration and washed thoroughly with THF. The combined filtrates were evaporated to dryness and the residual solid was recrystallized to afford **4a** (93%); m.p. 85° (light petroleum), lit.[7] 83–85°, hydrochloride m.p. 237°, lit.[7] 237–238°; IR ($CHCl_3$): 2805–2720 (Bohlmann bands), 1600, 1585 cm^{-1}; NMR ($CDCl_3$): δ 7.33–6.89 (8H, m, ArH), 3.97 (1H, d, J = 15 Hz, 8-H), 3.80–2.26 (8H, m); or the derivatives **4b** (95%); m.p. 88° (diisopropyl oxide), lit.[12], hydrochloride decp > 200°; IR ($CHCl_3$): 2840–2720 (Bohlmann bands), 1605, 1580 cm^{-1}; NMR ($CDCl_3$): δ 7.15 (5H, m, ArH), 6.89–6.71 (2H, m + s, 2 and 4-H), 4.03 (1H, d, J = 15 Hz, 8-H), 3.76 (3H, s, OCH_3), 3.69–2.35 (8H, m); **4c** (96%); m.p. 155° (CH_3OH), hydrochloride decp 202–208°; IR ($CHCl_3$): 2830–2740 (Bohlmann bands), 1600, 1580 cm^{-1}; NMR ($CDCl_3$): δ 7.40 (5H, m, C_6H_5), 7.22 (1H, d, J = 8 Hz, 1-H), 6.98–6.51 (4H, m, other ArH), 5.07 (2H, s, CH_2O) 3.84 (6H, s, 2 × OCH_3), 3.71–2.38 (8H, m); **4d** (94%); m.p. 143° (MeOH), lit.[8] 128–131°, hydrochloride decp > 200°; IR ($CHCl_3$) 2830–2720 (Bohlmann bands), 1605, 1575 cm^{-1}; NMR ($CDCl_3$): δ 7.20 (1H, d, J = 8.6 Hz, 1-H), 6.93–6.50 (4H, m, other ArH), 3.86 (6H, s, C-10 OCH_3 and C-11 OCH_3), 3.77 (3H, s, C-3 OCH_3), 3.70–2.37 (8H, m).

3 - *Hydroxy* - 5,6,13,13a - *tetrahydro* - 8H - *dibenzo*[*a,g*] *quinolizine* **4e**. Compound **4b** (5 g) and conc HBr (45 ml) were stirred under reflux for 2 hr. After cooling the mixture was poured in water (125 ml) and the solid was collected, dissolved in 5% NaOH aq. After filtration the filtrate was acidified to pH 7.5–8 with HCl to precipitate **4e** as the base. The solid was collected, dried and recrystallized in EtOH–water (80–20) to give **4e** (90%); m.p. 120–122°, hydrochloride decp > 180°; IR ($CHCl_3$): νOH 3580, 2810–2750 (Bohlmann bands), 1605, 1585 cm^{-1}; NMR (DMSO-d_6): δ 7.06 (5H, m), 6.63 (2H, m, 2 and 4-H), 4.01 (1H, d, J = 9.7 Hz, 8-H), 3.78–2.32 (8H, m).

10,11 - *Dimethoxy* - 3 - *hydroxy* - 5,6,13,13a - *tetrahydro* - 8H - *dibenzo*[*a,g*]*quinolizine* **4f**. A mixture of **4c** (5 g) AcOH (50 ml), conc HCl (25 ml) and water (40 ml) was refluxed for 3 hr. The soln was evaporated to dryness and the residue dissolved in 5% NaOH aq. After filtration the filtrate was acidified to pH 7.5–8 with HCl to precipitate **4f** as the base. The solid was collected, washed with water, dried to give after recrystallization **4f** (94%); m.p. 220–222° (EtOH), hydrochloride decp > 220°; IR ($CHCl_3$): νOH 3580, 2830–2740 (Bohlmann bands), 1605, 1585 cm^{-1}; NMR (DMSO-d_6): δ 7.13 (1H, d, J = 8.7 Hz, 1-H), 6.64 (4H, m, other ArH), 3.80 (7H, m + s, 8-H + 2 and 2 × OCH_3), 3.70–2.40 (8H, m).

Acknowledgement—This work was supported by URPHA industry (Union pour la Recherche Pharmaceutique Paris).

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