# Structure and Synthesis of Goudotianine, a New 7-Methyldehydroaporphine from *Guatteria goudotiana*



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Total syntheses of 2,9-dihydroxy-1,3-dimethoxy-7-methyl-6a,7-dehydroaporphine **1a** and 3,9-dihydroxy-1,2-dimethoxy-7-methyl-6a,7-dehydroaporphine **1b** are described. Direct comparison of both with natural goudotianine isolated from *Guatteria goudotiana* R. E. Fries showed the latter to be identical with **1b**.

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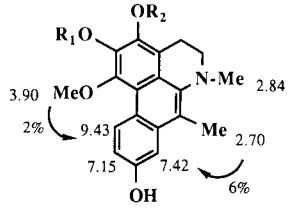
During our recent studies on the alkaloids of *Guatteria goudotiana* R. E. Fries [1] we isolated a small amount of a new alkaloid whose spectroscopical data indicated the structure of a 7-methyldehydroaporphine, **1a** or **1b**.




**1**

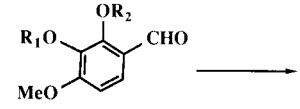
a) $R_1$=H, $R_2$=Me
b) $R_1$=Me, $R_2$=H

Figure 1

The new alkaloid, which we named goudotianine, was isolated as an amorphous, optically inactive compound. Its uv spectrum exhibited absorption bands at 220, 267, 285 (sh) and 323 nm, which upon addition of base suffered a bathochromic shift showing the phenolic nature of the compound. Its nmr showed three protons in the aromatic region at 9.43 (d, J = 9.4 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H) and 7.15 (dd, J = 9.4 and 2.5 Hz, 1H), indicating the presence of a 1,2,4-trisubstituted benzene ring, together with two methoxy groups at 4.12 (s) and 3.90 (s), two aliphatic triplets (J = 6.0 Hz, 2H each) centred at 3.30 and 3.06, corresponding to a $CH_2$-$CH_2$ system, and two 3H singlets at 2.84 and 2.70 which we attributed to N-Me and $C_7$-Me respectively. Additional data on the structure of goudotianine were obtained through nOe-difference experiments (Figure 1). In the mass spectrum of goudotianine, the molecular ion appeared at m/e (%) 339 (100), the next most significant peak being at 324 (25).

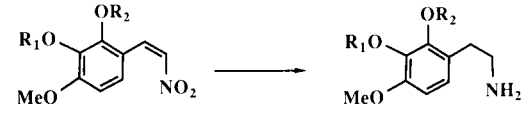
All these data were in keeping with structure **1** but we were unable to distinguish between possibilities **1a** or **1b** by means of nOe experiments. Although the location of a phenol group in structure **1** can be deduced from cmr studies [2], the lack of sufficient natural goudotianine led us to carry out the total synthesis of the new alkaloid for final identification. *A priori*, **1a** was considered the most probable structure, since its ring A substitution pattern is more usual than that of **1b** [3], whose 3,9-dihydroxyphenanthrene structure was moreover thought likely to be unstable, readily undergoing oxidation by air to the corresponding quinonoid.

Scheme 1




**2**

a) $R_1$=H, $R_2$=Me
b) $R_1$=Me, $R_2$=H
c) $R_1$=Bn, $R_2$=Me
d) $R_1$=Me, $R_2$=Bn

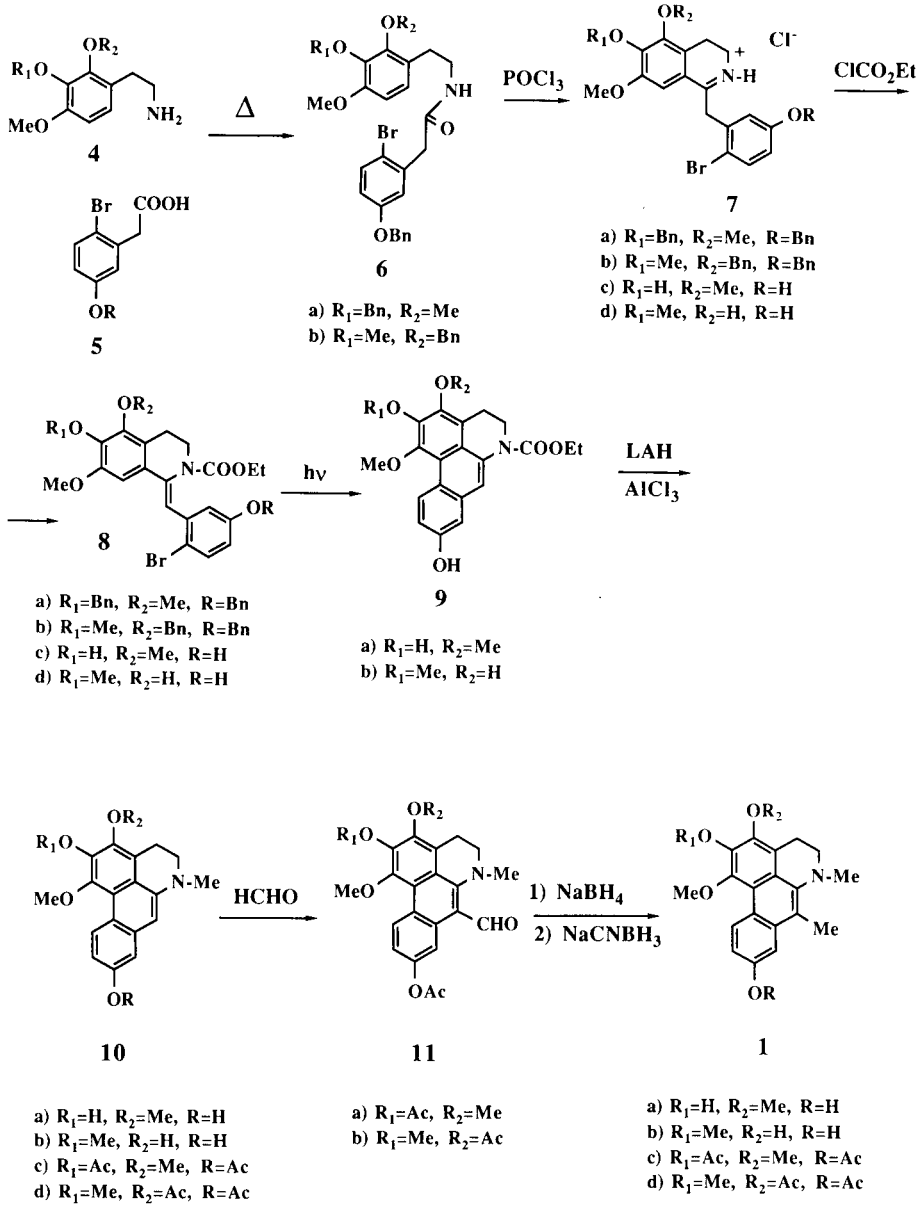



**3** **4**

a) $R_1$=Bn, $R_2$=Me
b) $R_1$=Me, $R_2$=Bn

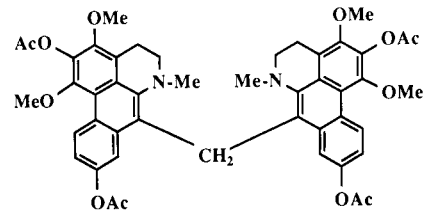
The total synthesis of compound **1a** was achieved as indicated in scheme 2. By heating a mixture of 5-benzyloxy-2-bromophenylacetic acid **5** and 2-(3-benzyloxy-2,4-dimethoxyphenyl)ethylamine **4a** (readily prepared from 3-hydroxy-2,4-dimethoxybenzaldehyde **2a** *via* the nitrostyrene **3a**), the amide **6a** was obtained. Compound **6a** was subjected to Bischler-Napieralski cyclization to give the imine **7a**, which on treatment with ethyl chloroformate under Schotten-Bauman conditions yielded stilbene **8a**. Attempts at photodehydrobromination of **8a** to obtain the corresponding phenanthrene were unsuccessful; it was necessary to remove the benzyl protecting groups in order to achieve cyclization. Acid hydrolysis of the benzyloxy groups in **7a** afforded compound **7c**, which was reacted

Scheme 2




with ethyl chloroformate in the presence of sodium bicarbonate to yield stilbene **8c** as the major compound together with a small amount of ethoxycarbonate-protected phenolic material. When subjected to photodehydrobromination both compound **8c** and the mixture of stilbenes obtained in the preceding reaction gave phenanthrene **9a** in moderate yield. Lithium aluminium hydride reduction of **9a** afforded the dehydroaporphine **10a**.

An attempt to obtain compound **1a** by direct methylation of position 7 of **10a**, by heating with formaldehyde [4] under an inert atmosphere, was unsuccessful; the mixture of products obtained suggested the need to protect the hydroxy groups. When the *O*-acyl-protected dehydroaporphine **10c** was heated with formaldehyde, compound **12** was obtained as the only product [5]. Preparation of compound **1a** from **10c** was finally accomplished by con-



12

Figure 2

secutive sodium borohydride and cyanoborohydride reductions of the 7-formyl derivative **11a**, followed by basic hydrolysis of the acetates. Compound **11a** is readily available by Vilsmeier formylation of **10c**.

Direct comparison of compound **1a** with natural goudotianine by tlc showed the spots to have slightly different Rf values and different distinctive colours on exposure to iodine vapour. The nmr spectra of the two compounds also differed slightly in the position of the methoxy groups. As a consequence natural goudotianine must have the alternative structure **1b**. This hypothesis was corroborated unequivocally by carrying out the total synthesis of compound **1b**. The same scheme as for **1a** was used, except that the starting materials were 2-(2-benzyloxy-3,4-dimethoxyphenyl)ethylamine **4b** (readily prepared from 2-hydroxy-3,4-dimethoxybenzaldehyde **2b**) and 5-benzyloxy-2-bromophenylacetic acid **5**. The synthetic compound **1b** proved to be identical in all respects (tlc, uv, ir nmr) to natural goudotianine isolated from *Guatteria goudotiana*.

## EXPERIMENTAL

Melting points were taken on a Büchi or Kofler-Thermogeräte apparatus and are uncorrected. Infrared spectra were determined in potassium bromide on a Pye Unicam SP-1100 spectrophotometer. Ultraviolet spectra were recorded in ethanol solution on a Pye Unicam SP-1700 spectrophotometer. The nuclear magnetic resonance spectra were determined on a Varian CFT-20 or a Bruker WM-250 apparatus in deuteriochloroform solution (unless otherwise specified) containing tetramethylsilane as the internal standard. Mass spectra were obtained on a Kratos MS-25 mass spectrometer. Elemental analyses were performed on a Perkin Elmer 240-B apparatus at the Inorganic Chemistry Department. Photolyses were carried out with medium-pressure mercury vapor arc lamps (Hanovia, 450 watts), using pyrex-filtered light and cooling by water. Thin layer chromatography (tlc) was performed using GF-254 type 60 silica gel and chloroform-methanol or chloroform-ethanol mixtures as eluent; the tlc spots were visualized with ultraviolet light or iodine vapour. Column chromatography was carried out using Merck type 60 silica gel. Solvents were purified as in reference [6].

3-hydroxy-2,4-dimethoxybenzaldehyde **2a** [7] was prepared from commercial isovanillin by standard methods: bromination [8,9] followed by the replacement of bromine by a methoxy group [10]; 2-hydroxy-3,4-dimethoxybenzaldehyde **2b** [11] was also prepared from 2-bromoisovanillin by *O*-methylation [9] followed by substitution of a hydroxy group for the bromine [11]; 5-benzyloxy-2-bromophenylacetic acid **5** [12] was likewise prepared from 3-hydroxybenzaldehyde using standard methods [13].

3-Benzyloxy-2,4-dimethoxybenzaldehyde (**2c**).

A mixture of 3-hydroxy-2,4-dimethoxybenzaldehyde (**2a**) [7] (24.93 g, 0.137 mole), sodium carbonate (18 g), absolute ethanol (150 ml) and benzyl chloride (30 ml) was refluxed for 24 hours. The mixture was filtered and the filtrate concentrated *in vacuo* to give compound **2c** (33 g, 88%) as a brown syrup which was used without further purification; nmr (80 MHz): δ 3.87 (s, 3H, OMe), 3.99 (s, 3H, OMe), 5.02 (s, 2H, $OCH_2Ph$), 6.72 and 7.60 (AB, J = 8.7 Hz, 2H, H-5 and H-6), 7.28-7.55 (m, 5H, Ph), 10.24 (s, 1H, CHO).

2-Benzyloxy-3,4-dimethoxybenzaldehyde (**2d**).

Starting from 2-hydroxy-3,4-dimethoxybenzaldehyde (**2b**) [11] the same procedure as above gave compound **2d** in 90% yield as a brown syrup which was used without further purification; nmr (250 MHz): δ 3.90 (s, 3H, OMe), 3.92 (s, 3H, OMe), 5.20 (s, 2H, $OCH_2Ph$), 6.76 and 7.58 (AB, J = 8.8 Hz, 2H, H-5 and H-6), 7.30-7.40 (m, 5H, Ph), 10.10 (s, 1H, CHO).

3-Benzyloxy-2,4-dimethoxy-β-nitrostyrene (**3a**).

A mixture of 3-benzyloxy-2,4-dimethoxybenzaldehyde (**2c**) (37.54 g, 0.138 mole), nitromethane (49.3 ml), methylamine hydrochloride (4.1 g) and anhydrous sodium acetate (4.1 g) was stirred at room temperature for 16 hours. The reaction mixture was diluted with water (400 ml) and extracted with methylene chloride. The organic extracts were dried with anhydrous sodium sulphate and concentrated *in vacuo*. The residue was crystallized from ethanol to give 42 g (87%) of 3-benzyloxy-2,4-dimethoxy-β-nitrostyrene (**3a**) as yellow crystals, mp 74-75°; ir (potassium bromide): 1625, 1590, 1500, 1450, 1330, 1280, 1105 $cm^{-1}$; nmr (80 MHz): δ 3.88 (s, 3H, OMe), 3.96 (s, 3H, OMe), 5.01 (s, 2H, $OCH_2Ph$), 6.70 and 7.20 (AB, J = 8.8 Hz, 2H, H-5 and H-6), 7.25-7.50 (m, 5H, Ph), 7.73 and 8.10 (AB, J = 13.5 Hz, 2H, CH=CH).

*Anal.* Calcd. for $C_{17}H_{17}NO_5$: C, 64.76; H, 5.40; N, 4.44. Found: C, 65.20; H, 5.95; N, 4.44. (A more satisfactory elemental analysis was not obtained).

2-Benzyloxy-3,4-dimethoxy-β-nitrostyrene (**3b**).

Nitrostyrene **3b** was obtained in 92% yield from 2-benzyloxy-3,4-dimethoxybenzaldehyde (**2d**) as yellow crystals, mp 100-102° (ethanol); nmr (250 MHz): δ 3.91 (s, 3H, OMe), 3.94 (s, 3H, OMe), 5.20 (s, 2H, $OCH_2Ph$), 6.74 and 7.18 (AB, J = 8.8 Hz, 2H, H-5 and H-6), 7.30-7.50 (m, 5H, Ph), 7.63 and 8.02 (AB, J = 13.6 Hz, 2H, CH=CH).

*Anal.* Calcd. for $C_{17}H_{17}NO_5$: C, 64.76; H, 5.40; N, 4.44. Found: C, 64.76; H, 5.75; N, 4.44.

2-(3-Benzyloxy-2,4-dimethoxyphenyl)ethylamine (**4a**).

A solution of 5 g (15.87 mmoles) of 3-benzyloxy-2,4-dimethoxy-β-nitrostyrene (**3a**) in dry tetrahydrofuran (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (3 g) in dry tetrahydrofuran (100 ml). The mixture was refluxed for two hours and after cooling, a saturated solution of sodium sulphate was added dropwise. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic extracts were washed with water, dried with anhydrous sodium sulphate and evaporated *in vacuo* to give 4.4 g (92%) of amine **4a** as a brown oil which was used without further purification; nmr (250 MHz): δ 1.95 (bs, 2H, $NH_2$), 2.70 (t, J = 7.0 Hz, 2H, $CH_2$), 2.89 (t, J = 7.0 Hz, 2H, $CH_2$), 3.82 (s, 3H, OMe), 3.88 (s, 3H, OMe), 5.02 (s, 2H, $OCH_2Ph$), 6.62 and 6.85 (AB, J = 8.5 Hz, 2H, H-5 and H-6), 7.30-7.60 (m, 5H, Ph).

2-(2-Benzyloxy-3,4-dimethoxyphenyl)ethylamine (**4b**).

Amine **4b** was prepared in 90% yield by the same procedure as above; nmr (250 MHz): δ 1.90 (bs, 2H, $NH_2$), 2.65 (t, J = 6.5 Hz, 2H, $CH_2$), 2.83 (t, J = 6.5 Hz, 2H, $CH_2$), 3.86 (s, 3H, OMe), 3.90 (s, 3H, OMe), 5.06 (s, 2H, $OCH_2Ph$), 6.64 and 6.84 (AB, J = 8.5 Hz, 2H, H-5 and H-6), 7.30-7.50 (m, 5H, Ph).

5-Benzyloxy-*N*-[2-(3'-benzyloxy-2',4'-dimethoxyphenyl)ethyl]-2-bromophenylacetamide (**6a**).

A mixture of 2-(3-benzyloxy-2,4-dimethoxyphenyl)ethylamine (**4a**) (1g, 3.5 mmoles) and 5-benzyloxy-2-bromophenylacetic acid (**5**) [12] (1.12 g, 3.5 mmoles) was heated at 140-150° for 0.5 hours. The mixture was dissolved in methylene chloride and this solution was washed successively with diluted hydrochloric acid, saturated sodium bicarbonate solution and water, and dried with sodium sulphate. The solvent was then distilled off to obtain the crude amide **6a**, which on crystallization from methanol afforded 1.88 g (90% yield) of white crystals, mp 109-110°; uv: 214, 233 (sh), 285 nm; ir: 3300, 1645, 1600, 1550, 1495, 1465, 1240, 1105 $cm^{-1}$; nmr (250 MHz): δ 2.70 (t, J = 6.6 Hz, 2H, $CH_2$), 3.42 (dt, J = 6.6 and 5.3 Hz, 2H, $CH_2NH$), 3.62 (s, 2H, $CH_2CO$), 3.78 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.97 (s, 2H, $OCH_2Ph$), 4.99 (s, 2H, $OCH_2Ph$), 5.79 (bt, J = 5.3 Hz, 1H, NH), 6.54 and 6.72 (AB, J = 8.5 Hz, 2H, H-5' and H-6'), 6.75 (dd, J = 8.9 and 3.0 Hz, 1H, H-4), 6.95 (d, J = 3.0 Hz, 1H, H-6), 7.30-7.50 (m, 11H, Ar-H).

*Anal.* Calcd. for $C_{32}H_{32}BrNO_5$: C, 65.08; H, 5.42; N, 2.37. Found: C, 64.94; H, 5.31; N, 2.48.

5-Benzyloxy-*N*-[2-(2'-benzyloxy-3',4'-dimethoxyphenyl)ethyl]-2-bromophenylacetamide (**6b**).

Amide **6b** was obtained in 90% yield as white crystals, mp 116-118° (methanol); uv: 215, 230 (sh), 280 nm; ir: 3290, 1635, 1600, 1545, 1495, 1465, 1280, 1240, 1160, 1100 $cm^{-1}$; nmr (250 MHz): δ 2.62 (t, J = 6.6 Hz, 2H, $CH_2$), 3.34 (dt, J = 6.6 and 5.3 Hz, 2H, $CH_2NH$), 3.54 (s, 2H, $CH_2CO$), 3.83 (s, 3H, OMe), 3.86 (s, 3H, OMe), 5.00 (s, 2H, $OCH_2Ph$), 5.02 (s, 2H, $OCH_2Ph$), 5.65 (bt, J = 5.3 Hz, 1H, NH), 6.56 and 6.72 (AB, J = 8.5 Hz, 2H, H-5' and H-6'), 6.78 (dd, J = 8.8 and 3.0 Hz, 1H, H-4), 6.91 (d, J = 3.0 Hz, 1H, H-6), 7.30-7.50 (m, 11H, Ar-H).

*Anal.* Calcd. for $C_{32}H_{32}BrNO_5$: C, 65.08; H, 5.42; N, 2.37. Found: C, 64.98; H, 5.37; N, 2.43.

6-Benzyloxy-1-(5'-benzyloxy-2'-bromobenzyl)-5,7-dimethoxy-3,4-dihydroisoquinoline Hydrochloride (**7a**).

A solution of amide **6a** (0.6 g, 1.0 mmoles) and phosphorus oxychloride (0.25 ml) in dry chloroform (7 ml) was stirred at room temperature for 1 hour and then refluxed for 2.5 hours. The mixture was evaporated to dryness to afford, in quantitative yield, the crude hydrochloride **7a**, which was used without further purification; nmr (250 MHz): δ 2.97 (t, J = 7.6 Hz, 2H, H-4), 3.78 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.86 (m, 2H, H-3), 4.60 (s, 2H, $CH_2C{=}N$), 5.05 (s, 2H, $OCH_2Ph$), 5.17 (s, 2H, $OCH_2Ph$), 6.22 (bs, 1H, NH), 6.81 (dd, J = 8.9 and 2.7 Hz, 1H, H-4'), 6.94 (d, J = 2.7 Hz, 1H, H-6'), 7.06 (s, 1H, H-8), 7.20-7.50 (m, 10H, Ar-H), 7.46 (d, J = 8.9 Hz, 1H, H-3').

5-Benzyloxy-1-(5'-benzyloxy-2'-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Hydrochloride (**7b**).

Obtained as above, in quantitative yield, from 1.05 mmoles of amide **6b**; nmr (250 MHz): δ 2.62 (t, J = 7.6 Hz, 2H, H-4), 3.66 (bt, J = 7.6 Hz, 2H, H-3), 3.81 (s, 3H, OMe), 4.02 (s, 3H, OMe), 4.61 (s, 2H, $CH_2C{=}N$), 5.03 (s, 2H, $OCH_2Ph$), 5.06 (s, 2H, $OCH_2Ph$), 6.82 (dd, J = 8.5 and 2.6 Hz, 1H, H-4'), 6.84 (bs, 1H, H-6'), 7.03 (s, 1H, H-8), 7.25-7.40 (m, 10H, Ar-H), 7.48 (d, J = 8.5 Hz, 1H, H-3').

1-(5'-Benzyloxy-2'-bromobenzylidene)-6-benzyloxy-2-carbethoxy-5,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8a**).

A solution of ethyl chloroformate (0.31 ml) in chloroform (2 ml) was added dropwise to a cooled, stirred mixture of hydrochloride **7a** (0.48 g), chloroform (7 ml) and 10% aqueous sodium carbonate (7 ml). After a further 10 hours stirring at room temperature, the organic layer was separated, washed with water and 5% hydrochloric acid, dried with sodium sulphate and evaporated *in vacuo* to give 0.41 g (80%) of compound **8a**; uv: 220, 245 (sh), 305 nm; nmr (250 MHz): δ 1.33 (t, J = 6.5 Hz, 3H, $CH_2$-$CH_3$), 2.85 (t, J = 6.0 Hz, 2H, $CH_2$), 3.80 (m, 2H, $CH_2$), 3.84 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.29 (q, J = 6.5 Hz, 2H, $CH_2$-$CH_3$), 5.01 (s, 2H, $OCH_2Ph$), 5.03 (s, 2H, $OCH_2Ph$), 6.70 (dd, J = 8.7 and 2.8 Hz, 1H, H-4'), 7.00 (s, 1H, Ar-H), 7.11 (s, 1H, Ar-H), 7.30-7.60 (m, 12H, Ar-H).

Irradiation of Urethane **8a**.

A stirred mixture of bromourethane **8a** (348 mg, 0.54 mmole), potassium *t*-butoxide (0.6 g), *t*-butyl alcohol (60 ml) and benzene (140 ml) was irradiated under argon at room temperature for 10 hours (Hanovia 450 W lamp, Pyrex filter). The solvent was then evaporated, the residue treated with 5% hydrochloric acid and the resulting solution extracted with chloroform. The extract was dried (sodium sulphate), and the chloroform was evaporated off to leave a residue which showed by tlc a complex mixture of products.

1-(2'-bromo-5'-hydroxybenzyl)-5,7-dimethoxy-6-hydroxy-3,4-dihydroisoquinoline hydrochloride (**7c**).

A mixture of hydrochloride **7a** (1 g, 1.65 mmoles), concentrated hydrochloric acid (5 ml) and ethanol (5 ml) was refluxed under argon for 1.5 hours. On cooling, hydrochloride **7c** precipitated out in quantitative yield and was filtered off and washed with ether. Crystallization from ethanol afforded white crystals, mp 276-278°; nmr (deuteriochloroform + methanol-$d_4$, 250 MHz): δ 3.09 (t, J = 8.0 Hz, 2H, H-4), 3.86 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.91 (t, J = 8.0 Hz, 2H, H-3), 4.56 (s, 2H, $CH_2C{=}N$), 6.69 (dd, J = 8.8 and 2.9 Hz, 1H, H-4'), 6.98 (d, J = 2.9 Hz, 1H, H-6'), 7.15 (s, 1H, H-8), 7.40 (d, J = 8.8 Hz, 1H, H-3').

*Anal.* Calcd. for $C_{18}H_{19}BrClNO_4$: C, 50.41; H, 4.43; N, 3.27. Found: C, 50.10; H, 4.15; N, 3.30.

1-(2'-Bromo-5'-hydroxybenzyl)-6,7-dimethoxy-5-hydroxy-3,4-dihydroisoquinoline Hydrochloride (**7d**).

Obtained by debenzylation of **7b** as above, in almost quantitative yield, as white crystals, mp 210-212° (ethanol); nmr (deuteriochloroform + methanol-$d_4$, 250 MHz): δ 3.00 (t, J = 7.9 Hz, 2H, H-4), 3.77 (s, 3H, OMe), 3.86 (m, 2H, H-3), 3.91 (s, 3H, OMe), 4.50 (s, 2H, $CH_2C{=}N$), 6.63 (dd, J = 8.7 and 2.6 Hz, 1H, H-4'), 6.84 (d, J = 2.6 Hz, 1H, H-6'), 6.89 (s, 1H, H-8), 7.34 (d, J = 8.7 Hz, 1H, H-3').

*Anal.* Calcd. for $C_{18}H_{19}BrClNO_4$: C, 50.41; H, 4.43; N, 3.27. Found: C, 50.12; H, 4.53; N, 3.18.

1-(2'-Bromo-5'-hydroxybenzylidene)-2-carbethoxy-5,7-dimethoxy-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (**8c**).

A solution of ethyl chloroformate (0.31 ml) in chloroform (2 ml) was added dropwise to a cooled, stirred mixture of hydrochloride **7c** (0.34 g, 0.79 mmole), chloroform (7 ml) and 10% aqueous sodium carbonate (7 ml). After stirring for a further 10 hours at room temperature, the organic layer was separated, washed with water and 5% hydrochloric acid, dried with sodium sulphate and evaporated to dryness. The residue (0.35 g) was mainly phenolic urethane **8c** together with a small amount of a mixture of urethanes whose hydroxy groups were totally or partially protected as carbonates. The mixture was easily separated by chromatography or used without purification in the next step. Urethane **8c** crystallizes from methylene chloride-hexane, affording white crystals, mp 150-152°; uv: 218, 250 (sh), 325 nm; ir: 3400, 2920, 2840, 1760, 1690, 1600, 1500, 1465, 1235 $cm^{-1}$; nmr (250 MHz): δ 1.38 (t, J = 7.1 Hz, 3H, $CH_2$-$CH_3$), 2.88 (t, J = 6.0 Hz, 2H, H-4), 3.80 (m, 2H, H-3), 3.85 (s, 3H, OMe), 3.96 (s, 3H, OMe), 4.31 (q, J = 7.1 Hz, 2H, $CH_2$-$CH_3$), 6.90 (s, 1H, Ar-H), 6.94 (dd, J = 8.7 and 2.8 Hz, 1H, H-4'), 7.09 (s, 1H, Ar-H), 7.28 (d, J = 2.8 Hz, 1H, H-6'), 7.58 (d, J = 8.7 Hz, 1H, H-3'); ms: 465, 463 ($M^+$, 50), 436, 434 (35), 392, 390 (12), 384 (M-Br, 12), 312 (40), 311 (100), 310 (22), 296 (18).

*Anal.* Calcd. for $C_{21}H_{22}BrNO_6$: C, 54.31; H, 4.74; N, 3.02. Found: C, 53.97; H, 5.00; N, 3.21.

1-(2'-Bromo-5'-hydroxybenzylidene)-2-carbethoxy-6,7-dimethoxy-5-hydroxy-1,2,3,4-tetrahydroisoquinoline (**8d**).

Prepared from hydrochloride **7d** in 80% yield by a procedure analogous to that used for **8c**, mp 148-150° (methylene chloride-hexane); uv: 220, 246 (sh), 320 nm; ir: 3400, 2920, 2840, 1760, 1690, 1600, 1500, 1465, 1235 $cm^{-1}$; nmr (250 MHz): δ 1.37 (t, J = 7.1 Hz, 3H, $CH_2$-$CH_3$), 2.84 (t, J = 6.0 Hz, 2H, H-4), 3.80 (m, 2H, H-3), 3.92 (s, 3H, OMe), 3.94 (s, 3H, OMe), 4.32 (q, J = 7.1 Hz, 2H, $CH_2CH_3$), 6.91 (s, 1H, H-8), 6.95 (dd, J = 8.8 and 2.6 Hz, 1H, H-4'), 6.96 (s, 1H, CH=C), 7.28 (d, J = 2.6 Hz, 1H, H-6'), 7.58 (d, J = 8.8 Hz, 1H, H-3'); ms: 465, 463 ($M^+$, 50), 436, 434 (43), 419, 417 (23), 392, 390 (22), 384 (M-Br, 30), 353 (22), 312 (50), 311 (90), 310 (78), 297 (30), 296 (100).

*Anal.* Calcd. for $C_{21}H_{22}BrNO_6$: C, 54.31; H, 4.74; N, 3.02. Found: C, 53.90; H, 5.00; N, 3.12.

6-Carbethoxy-2,9-dihydroxy-1,3-dimethoxy-6a,7-dehydronoraporphine (**9a**).

A stirred mixture of bromourethane **8c** [14] (250 mg, 0.54 mmoles), potassium *t*-butoxide (0.6 g), *t*-butyl alcohol (60 ml) and benzene (140 ml) was irradiated under argon at room temperature for 10 hours. The solvent was evaporated off and the residue treated with 5% hydrochloric acid and extracted with chloroform. The extracts were dried (sodium sulphate) and the chloroform evaporated off to leave a residue which was chromatographed on silica gel. Elution with 5% methanol in methylene

chloride afforded 170 mg (41%) of dehydroaporphine **9a**, which crystallized from methylene chloride-hexane as white crystals, mp 187-189°; uv: 210, 252 (sh), 268, 324 nm; ir: 3350, 2930, 1680, 1615, 1460, 1230 $cm^{-1}$; nmr (250 MHz): δ 1.34 (t, J = 7.1 Hz, 3H, $CH_2$-$CH_3$), 3.18 (t, J = 5.6 Hz, 2H, H-4), 3.80 (s, 3H, OMe), 3.94 (s, 3H, OMe), 4.04 (t, J = 5.6 Hz, 2H, H-5), 4.31 (q, J = 7.1 Hz, 2H, $CH_2$-$CH_3$), 7.11 (dd, J = 9.2 and 2.7 Hz, 1H, H-10), 7.18 (d, J = 2.7 Hz, 1H, H-8), 7.70 (s, 1H, H-7), 9.15 (d, J = 9.2 Hz, 1H, H-11); ms: 383 ($M^+$, 100), 294 (40), 280 (28).

*Anal.* Calcd. for $C_{21}H_{21}NO_6$: C, 65.80; H, 5.48; N, 3.66. Found: C, 66.00; H, 5.53; N, 3.60.

6-Carbethoxy-3,9-dihydroxy-1,2-dimethoxy-6a,7-dehydronoraporphine (**9b**).

Obtained in 40% yield by irradiation of bromourethane **8d** under the same conditions as above, mp 183-185° (methylene chloride-hexane); uv: 210, 250 (sh), 268, 322 nm; ir: 3350, 2920, 1650, 1600, 1430, 1395, 1225, 1190 $cm^{-1}$; nmr (250 MHz): δ 1.34 (t, J = 7.1 Hz, 3H, $CH_2$-$CH_3$), 3.12 (t, J = 5.8 Hz, 2H, H-4), 3.90 (s, 3H, OMe), 4.04 (t, J = 5.8 Hz, 2H, H-5), 4.10 (s, 3H, OMe), 4.30 (q, J = 7.1 Hz, 2H, $CH_2$-$CH_3$), 7.08 (dd, J = 9.2 and 2.8 Hz, 1H, H-10), 7.18 (d, J = 2.8 Hz, 1H, H-8), 7.78 (s, 1H, H-7), 9.29 (d, J = 9.2 Hz, 1H, H-11); ms: 383 ($M^+$, 100), 294 (12), 280 (12).

*Anal.* Calcd. for $C_{21}H_{21}NO_6$: C, 65.80; H, 5.48; N, 3.66. Found: C, 65.50; H, 5.51; N, 3.57.

2,9-Dihydroxy-1,3-dimethoxy-6a,7-dehydroaporphine (**10a**).

Aluminium chloride (56 mg) and lithium aluminium hydride (38 mg) were added to a cooled solution of *N*-carbethoxynoraporphine **9a** (100 mg, 0.26 mmole) in dry ether (35 ml). After stirring for 20 hours at room temperature, water was added cautiously, the ether phase was separated and the aqueous phase was extracted with chloroform. The combined organic extracts were dried (sodium sulphate) and evaporated to leave a residue which was chromatographed on silica gel. Elution with methylene chloride and crystallization from methylene chloride gave white crystals of aporphine **10a** (59.33 mg, 70%), mp 155-157°; uv: 216, 245 (sh), 265, 330 nm; uv (basic media): 210, 282, 340 nm; ir: 3330, 2895, 2790, 1585, 1435, 1300 $cm^{-1}$; nmr (250 MHz): δ 3.06 (s, 3H, NMe), 3.24 (t, J = 5.2 Hz, 2H, $CH_2$), 3.30 (t, J = 5.2 Hz, 2H, $CH_2$), 3.83 (s, 3H, OMe), 3.94 (s, 3H, OMe), 6.49 (s, 1H, H-7), 6.90 (dd, J = 9.1 and 2.7 Hz, 1H, H-10), 7.01 (d, J = 2.7 Hz, 1H, H-8), 9.09 (d, J = 9.1 Hz, 1H, H-11); ms: 325 ($M^+$, 100), 310 (95), 264 (29), 210 (26).

*Anal.* Calcd. for $C_{19}H_{19}NO_4$: C, 70.15; H, 5.85; N, 4.31. Found: C, 70.10; H, 6.00; N, 4.35.

3,9-Dihydroxy-1,2-dimethoxy-6a,7-dehydroaporphine (**10b**).

Was obtained from **9b**, by the above procedure, in 73% yield, as white crystals, mp 140-142° (methylene chloride); uv: 210, 240 (sh), 262, 332 nm; uv (basic media): 210, 283 nm; ir: 3200, 2880, 2800, 1590, 1435, 1300, 1270, 1160 $cm^{-1}$; nmr (250 MHz): δ 3.06 (s, 3H, NMe), 3.18 (t, J = 6.0 Hz, 2H, $CH_2$), 3.31 (t, J = 6.0 Hz, 2H, $CH_2$), 3.91 (s, 3H, OMe), 4.07 (s, 3H, OMe), 6.63 (s, 1H, H-7), 6.92 (dd, J = 9.2 and 2.8 Hz, 1H, H-10), 7.04 (d, J = 2.8 Hz, 1H, H-8), 9.18 (d, J = 9.2 Hz, 1H, H-11); ms: 325 ($M^+$, 100), 310 (28), 296 (12), 295 (14), 293 (14), 292 (12), 278 (10), 267 (10).

*Anal.* Calcd. for $C_{19}H_{19}NO_4$: C, 70.15; H, 5.85; N, 4.31. Found: C, 70.00; H, 6.00; N, 4.30.

Reaction of Dehydroaporphine **10a** with Formaldehyde.

A mixture of dehydroaporphine **10a** (80 mg) and 37% formaldehyde (5 ml) was heated at 100° for 8 hours under argon. The mixture was then treated with aqueous ammonia and extracted with chloroform to give, after concentration, a complex mixture of products (as shown by tlc).

2,9-Diacetoxy-1,3-dimethoxy-6a,7-dehydroaporphine (**10c**).

Dehydroaporphine **10a** (500 mg, 1.5 mmoles) was dissolved in dry pyridine (3 ml) and treated with acetic anhydride (1.5 ml). The mixture was kept at room temperature for 24 hours. The solvent was evaporated off under reduced pressure and the residue was taken into methylene chloride and washed with dilute aqueous ammonia, dried (sodium sulphate) and concentrated to give, quantitatively, diacetoxy aporphine **10c** as white crystals, mp 159-161° (methylene chloride); uv: 215, 259, 320 nm; ir: 1740, 1585, 1170 $cm^{-1}$; nmr (250 MHz): δ 2.36 (s, 3H, $CH_3CO$), 2.48 (s, 3H, $CH_3CO$), 3.08 (s, 3H, NMe), 3.28 (t, J = 5.5 Hz, 2H, $CH_2$), 3.33 (t, J = 5.5 Hz, 2H, $CH_2$), 3.84 (s, 3H, OMe), 3.86 (s, 3H, OMe), 6.69 (s, 1H, H-7), 7.07 (dd, J = 9.3 and 2.5 Hz, 1H, H-10), 7.38 (d, J = 2.5 Hz, 1H, H-8), 9.29 (d, J = 9.3 Hz, 1H, H-11); ms: 409 ($M^+$, 100), 379 (9), 367 (68), 352 (16), 325 (20), 310 (40).

*Anal.* Calcd. for $C_{23}H_{23}NO_6$: C, 67.48; H, 5.62; N, 3.42. Found: C, 67.28; H, 5.60; N, 3.55.

3,9-Diacetoxy-1,2-dimethoxy-6a,7-dehydroaporphine (**10d**).

Obtained as above, in quantitative yield, by acetylation of **10b**, mp 152-154° (methylene chloride); uv: 214, 258, 332 nm; ir: 1730, 1575, 1165 $cm^{-1}$; nmr (250 MHz): δ 2.37 (s, 3H, $CH_3CO$), 2.43 (s, 3H, $CH_3CO$), 3.07 (s, 3H, NMe), 3.08 (t, J = 6.1 Hz, 2H, $CH_2$), 3.35 (t, J = 6.1 Hz, 2H, $CH_2$), 3.93 (s, 3H, OMe), 4.03 (s, 3H, OMe), 6.72 (s, 1H, H-7), 7.09 (dd, J = 9.3 and 2.6 Hz, 1H, H-10), 7.40 (d, J = 2.6 Hz, 1H, H-8), 9.43 (d, J = 9.3 Hz, 1H, H-11); ms: 409 ($M^+$, 100), 367 (40), 325 (28), 310 (20).

*Anal.* Calcd. for $C_{23}H_{23}NO_6$: C, 67.48; H, 5.62; N, 3.42. Found: C, 67.30; H, 5.65; N, 3.30.

Reaction of Dehydroaporphine **10c** with Formaldehyde.

A mixture of dehydroaporphine **10c** (100 mg) and 37% formaldehyde (5 ml) was heated under argon at 100° for 8 hours. The mixture was treated with aqueous ammonia and extracted with chloroform to give, after evaporation, 65 mg (65%) of the dimer **12** as white crystals, mp 238-240° dec; uv: 220, 260, 320 nm; nmr (250 MHz): δ 2.24 (s, 6H, 2 x $CH_3CO$), 2.47 (s, 6H, 2 x $CH_3CO$), 3.02 (s, 6H, 2 x NMe), 3.28 (bt, 4H, 2 x $CH_2$), 3.65 (bt, 4H, 2 x $CH_2$), 3.72 (s, 6H, 2 x OMe), 3.92 (s, 6H, 2 x OMe), 5.20 (s, 2H, $CH_2$), 7.09 (dd, J = 9.3 and 2.5 Hz, 2H, Ar-H), 8.34 (d, J = 2.5 Hz, 2H, Ar-H), 9.33 (d, J = 9.3 Hz, 2H, Ar-H); ms: 423 (10), 422 (9), 421 (30), 410 (21), 409 (86), 381 (10), 379 (25), 368 (25), 367 (100), 352 (18), 325 (26), 310 (44).

*Anal.* Calcd. for $C_{47}H_{46}N_2O_{12}$: C, 67.95; H, 5.54; N, 3.37. Found: C, 67.73; H, 5.34; N, 3.33.

2,9-Diacetoxy-1,3-dimethoxy-7-formyl-6a,7-dehydroaporphine (**11a**).

Phosphorus oxychloride (1 ml) was added dropwise to 5 ml of anhydrous *N,N*-dimethylformamide. The mixture was stirred for a few minutes and was then cooled in an ice bath. On addition of 600 mg (1.47 mmoles) of dehydroaporphine **10c** in one portion, the solution became deep red; stirring was continued until it reached room temperature. After monitoring by tlc, the reaction was worked up by slow addition of ice-water (*ca.* 600 ml), and after basification with a saturated sodium bicarbonate solution the mixture was extracted with cold [15] methylene chloride and treated with a small amount (*ca.* 1 ml) of 5% aqueous sodium hydroxide (the solution turned yellow at this point) before separation of the organic layer. The extracts were washed with water, dried (sodium sulphate) and concentrated to give a residue which was crystallized from ethanol, affording 604 mg (94%) of 7-formyldehydroaporphine **11a** as yellow crystals, mp 131-132°; uv: 212, 265, 282 (sh), 324, 426 nm; ir: 1750, 1730, 1615, 1350, 1170 $cm^{-1}$; nmr (250 MHz): δ 2.37 (s, 3H, $CH_3CO$), 2.48 (s, 3H, $CH_3CO$), 3.20 (t, J = 6.7 Hz, 2H, $CH_2$), 3.40 (s, 3H, NMe), 3.62 (t, J = 6.7 Hz, 2H, $CH_2$), 3.74 (s, 3H, OMe), 3.86 (s, 3H, OMe), 7.09 (dd, J = 9.1 and 2.5 Hz, 1H, H-10), 8.47 (d, J = 2.5 Hz, 1H, H-8), 9.10 (d, J = 9.1 Hz, 1H, H-11), 10.09 (s, 1H, CHO); ms: 437 ($M^+$, 100), 409 (82), 395 (45), 378 (63), 367 (71), 352 (34), 336 (38), 325 (32), 310 (45).

*Anal.* Calcd. for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.26; N, 3.20. Found: C, 66.01; H, 5.09; N, 3.15.

3,9-Diacetoxy-1,2-dimethoxy-7-formyl-6a,7-dehydroaporphine (**11b**).

Obtained from **10d** in almost quantitative yield as above, as yellow crystals, mp 135-137° (ethanol); uv: 210, 265, 283 (sh), 320, 425 nm; ir: 1765, 1640, 1605, 1390, 1200 $cm^{-1}$; nmr (250 MHz): δ 2.36 (s, 3H, $CH_3CO$), 2.41 (s, 3H, $CH_3CO$), 2.98 (t, J = 6.4 Hz, 2H, $CH_2$), 3.37 (s, 3H, NMe), 3.55 (t, J = 6.4 Hz, 2H, $CH_2$), 3.81 (s, 3H, OMe), 4.04 (s, 3H, OMe), 7.11 (dd, J = 9.2 and 2.4 Hz, 1H, H-10), 8.54 (d, J = 2.4 Hz, 1H, H-8),

9.21 (d, J = 9.2 Hz, 1H, H-11), 10.10 (s, 1H, CHO); ms: 437 ($M^+$, 100), 420 (30), 409 (65), 395 (33), 378 (33), 367 (52), 352 (22), 336 (24), 325 (33), 310 (26).

*Anal.* Calcd. for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.26; N, 3.20. Found: C, 66.02; H, 5.34; N, 3.35.

2,9-Diacetoxy-1,3-dimethoxy-7-methyl-6a,7-dehydroaporphine (**1c**).

A stirred solution of 577 mg (1.32 mmoles) of 7-formyldehydroaporphine **11a** in ethanol (250 ml) was treated with an excess of sodium borohydride at room temperature until total decoloration of the solution was observed. The ethanolic solution containing the corresponding 7-hydroxymethyl derivative was acidified with concentrated hydrochloric acid to a *p*H between 3 and 7. Then sodium cyanoborohydride was added in small portions and the reaction was monitored by tlc. The solvent was evaporated, water added, and the mixture extracted with methylene chloride. The extracts were washed with water, dried and evaporated, affording 509 mg (90%) of 7-methyldehydroaporphine **1c**; nmr (250 MHz): δ 2.38 (s, 3H, $CH_3CO$), 2.48 (s, 3H, $CH_3CO$), 2.68 (s, 3H, $C_7$-$CH_3$), 2.79 (s, 3H, NMe), 3.15 (t, J = 5.7 Hz, 2H, $CH_2$), 3.34 (t, J = 5.7 Hz, 2H, $CH_2$), 3.82 (s, 3H, OMe), 3.89 (s, 3H, OMe), 7.26 (dd, J = 8.7 and 2.6 Hz, 1H, H-10), 7.70 (d, J = 2.6 Hz, 1H, H-8), 9.51 (d, J = 8.7 Hz, 1H, H-11).

3,9-Diacetoxy-1,2-dimethoxy-7-methyl-6a,7-dehydroaporphine (**1d**).

Obtained as above in almost quantitative yield from **11b**; used without further characterization in the next step.

2,9-Dihydroxy-1,3-dimethoxy-7-methyl-6a,7-dehydroaporphine (**1a**).

To a stirred solution of dehydroaporphine **1c** (50 mg) in methanol (20 ml), at room temperature, an excess of sodium bicarbonate was added and stirring was continued under argon for 4 days. After evaporation of the solvent, the residue was treated with water and extracted with chloroform, and the chloroform extracts were dried with sodium sulphate and concentrated to afford 30 mg (70%) of dehydroaporphine **1a**, which was crystallized from chloroform as white crystals, mp 157-158°; uv: 215, 232 (sh), 268, 287 (sh), 327 nm; uv (basic media): 214, 278 (sh), 290, 312 (sh), 347 nm; ir: 1590, 1435, 1410, 1380, 1370, 1270, 1160 $cm^{-1}$; nmr (250 MHz): δ 2.59 (s, 3H, $C_7$-$CH_3$), 2.78 (s, 3H, NMe), 3.13 (t, J = 5.7 Hz, 2H, $CH_2$), 3.33 (t, J = 5.7 Hz, 2H, $CH_2$), 3.83 (s, 3H, OMe), 3.97 (s, 3H, OMe), 7.08 (dd, J = 9.2 and 2.1 Hz, 1H, H-10), 7.36 (d, J = 2.1 Hz, 1H, H-8), 9.30 (d, J = 9.2 Hz, 1H, H-11); ms: 339 ($M^+$, 100), 324 (M-15, 47).

*Anal.* Calcd. for $C_{20}H_{21}NO_4$: C, 70.80; H, 6.19; N, 4.13. Found: C, 70.65; H, 6.13; N, 4.00.

3,9-Dihydroxy-1,2-dimethoxy-7-methyl-6a,7-dehydroaporphine (**1b**).

Obtained in 73% yield after hydrolysis of the corresponding diacetyl derivative **1d**, as above. Crystallized from chloroform as white crystals, mp 186-188°; uv: 210, 232 (sh), 267, 288 (sh), 326 nm; uv (basic media): 214, 282, 320 (sh), 332 (sh); ir: 3480, 2940, 1605, 1490, 1420, 1400, 1220, 1200 $cm^{-1}$; nmr (250 MHz): δ 2.63 (s, 3H, $C_7$-$CH_3$), 2.76 (s, 3H, NMe), 3.07 (t, J = 5.8 Hz, 2H, $CH_2$), 3.33 (t, J = 5.8 Hz, 2H, $CH_2$), 3.90 (s, 3H, OMe), 4.12 (s, 3H, OMe), 7.07 (dd, J = 9.3 and 2.8 Hz, 1H, H-10), 7.37 (d, J = 2.8 Hz, 1H, H-8), 9.43 (d, J = 9.3 Hz, 1H, H-11); ms: 339 ($M^+$, 100), 324 (M-15, 25).

*Anal.* Calcd. for $C_{20}H_{21}NO_4$: C, 70.80; H, 6.19; N, 4.13. Found: C, 70.69; H, 6.25; N, 3.97.

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[14] A similar result was obtained when the mixture of urethanes produced in the previous reaction was used.

[15] It is very important to keep all the solvents and solutions close to 0°.