Synthesis of 4,8-Dimethoxy-3*H*-benz[*f*]indol-3-one. Anomalous Behaviour to Cyclization of 1,4,5-Trimethoxy-3-amino-γ-chloroalkylnaphthalene Intermediates

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A new linear benz[*f*]indole derivative **15** bearing two methoxyls in the fused naphthalene moiety was prepared as a potential chemotherapeutic agent. The anomalous behaviour of two trimethoxynaphthalene intermediates in parallel stages of the planned synthesis route is emphasized, and the corresponding mechanisms for these cyclizing reactions are proposed and discussed.

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Introduction.

As part of our program on the preparation, characterization and study of the properties of novel planar polycyclic compounds as possible new chemotherapeutic agents, we have been synthesizing some variously substituted benzoindoles for some time now.

We recently described the preparation and characterization of some linear benzoindole derivatives, either tetrahydrogenated or fully aromatic, and having methoxy groups in the central benzene ring of the tricyclic fused system [1-3].

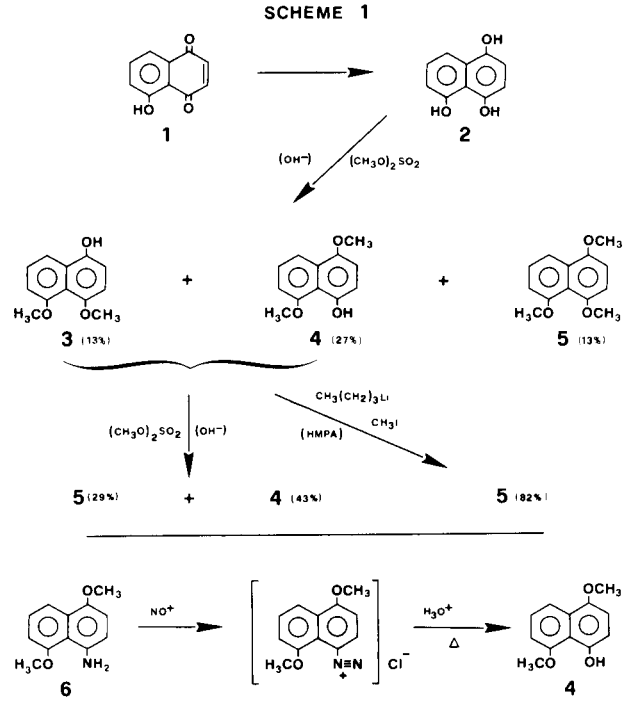
In this paper we report new synthetical studies with a view to preparing other compounds bearing more oxygenated functions in the moiety.

Chemistry.

According to a previously described synthetic route [4-6], the starting commercially available 5-hydroxynaphthalene-1,4-dione (juglone **1**) (see Scheme 1) was easily reduced to the corresponding trihydroxy derivative **2** by shaking its ethereal solution with aqueous sodium hydrosulfite at room temperature. This compound **2** was then methylated by reaction with dimethyl sulfate in alkali, yielding a mixture of three polymethylated compounds, which was partially resolved both by column silica gel chromatography and preparative high-pressure liquid chromatography. By the latter route the trimethoxy derivative **5** on one hand [7], and the mixture of two dimethoxy isomers **3** and **4** on the other were separated, although in scarce yields.

The quali-quantitative composition of the latter mixture was determined by means of a new partition chromatography employing for this purpose a more selective solvent and identifying one of two separated isomers through comparison with an authentic specimen of 1,5-dimethoxy-4-hydroxynaphthalene (**4**). This compound, already described and characterized only by its mp [8], was prepared by us through an unambiguous synthesis starting from 1,5-dimethoxy-4-aminonaphthalene (**6**) [9] *via* diazotisation and later thermal decomposition in protic medium. However, by subjecting the mixture of the two demethylated isomers **3** and **4** to further methylation by dimethyl sulfate in alkali, the new compound **5** (29%) was obtained after separation by column silica gel chromatography. On the other hand, the methylation of the same isomeric mixture achieved by methyl iodide and *n*-butyllithium in hexamethylphosphoramide [10] yielded 82% of trimethoxy derivative **5**. However, methylation of trihydroxy compound **2**, directly carried out at the above-mentioned operative conditions (methyl iodide and *n*-butyllithium in HMPA under an inert nitrogen atmosphere) did not give appreciable results, since the yield in trimethoxynaphthalene was both discontinuous and

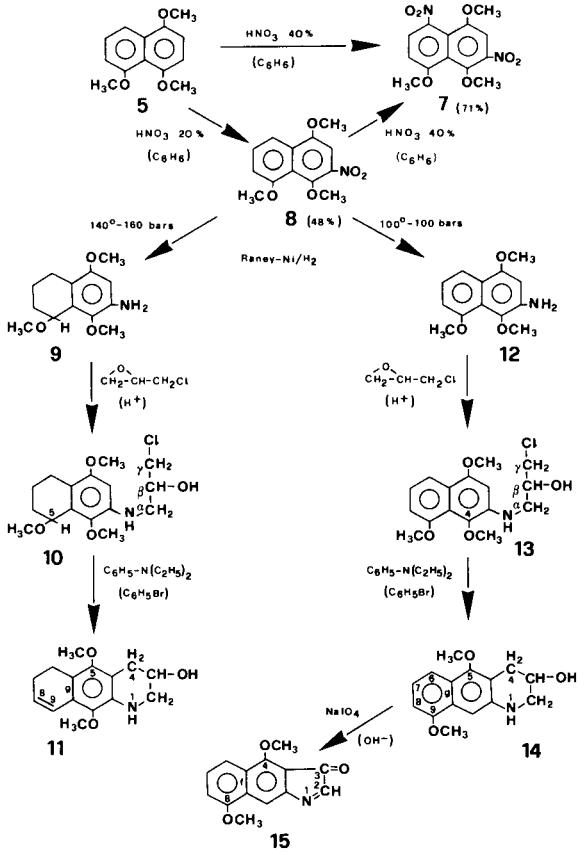
SCHEME 1



smaller than that obtained by the classical method of dimethyl sulfate in aqueous alkaline solution.

After describing satisfactory conditions to prepare 1,4,5-trimethoxynaphthalene, with the aim of nitrating it suitably, the best conditions were studied (see Scheme 2). Contrary to a reasonable expectation regarding a naphthalene compound which presents an α-position readily available for electrophilic attack, it was observed that nitration, achieved under quite mild operating conditions in benzene solution, occurred at C-3 position. Only by later working under more powerful nitrating conditions did mononitrated compound **8** undergo a second electrophilic substitution at C-8 position of the second condensed ring, to give dinitro derivative **7**. The structural assignment of compounds **8** and **7** was also supported by ^{13}C-nmr spectroscopy [11]. Then, in order to transform the nitro group into an amino group, an essential condition for continuing the planned synthesis, the 3-nitro-1,4,5-trimethoxynaphthalene (**8**) was subjected to a catalytic reduction under hydrogen pressure. In addition to the 3-amino-1,4,5-trimethoxynaphthalene (**12**), we also prepared the analogous aminic compound **9**, tetrahydrogenated in the mono-substituted benzene ring. We were also interested in the synthesis of 3-amino-1,4,5-trimethoxy-5,6,7,8-tetrahydronaphthalene (**9**), in order to study an alternative route which might operate with aminotetrahydronaphthalene compounds, close to simpler aniline derivatives which, in the preceding experiments, had proved to be more suitable in the later synthetic stages.

SCHEME 2



Both amino derivatives **9** and **12** were condensed with epichlorohydrin in methanolic protonated medium by shaking each mixture at room temperature for several days. Satisfactory yields of pure chlorinated condensation products **10** and **13**, respectively, were obtained from the crude reaction products by means of repeated chromatographies on silica gel columns.

These two *N*-(γ-chloro-β-hydroxypropyl)trimethoxyaminonaphthalenes were duly characterized before subsequent cyclization carried out by refluxing them in bromobenzene solution with excess diethylaniline for several days. In this manner the crude 1,2,3,4-tetrahydro-3-hydroxybenzoquinolines were obtained and purified to give compounds **11** and **14**, respectively, in satisfactory yields. As indicated in Scheme 2, during the above described cyclizing process, an anomalous behaviour was noted in both trimethoxy compounds: while compound **11** showed that it had retained only two methoxy groups, both in the central aromatic ring of the neo-formed fused tricyclic system, and that it had a double bond at C-8 and C-9 positions, compound **14** proved to have undergone cyclization with expulsion of the methoxyl present previously on the C-4 position of the tri-substituted benzene ring. The characterizations of the new tricyclic compounds **11** and **14** were established by ^1H-nmr spectroscopy, mass spectrometry and quantitative analysis of methoxy contents. Confirmatory evidence for this monodemethylation during the above cyclizing process, carried out either in the presence of atmospheric oxygen or in an inert nitrogen atmosphere, was obtained by checking, in the refluxed reaction mixtures, the presence either of methanol by gas-chromatographic analysis [12] (in the case of compound **10**) or of formaldehyde both by gas chromatography [12] and chemical assays [13] (in the case of compound **13**). In both cases, the loss of an oxymethyl took place by breaking of an ethereal oxygen-carbon bond (cyclic-alkyl or cyclic-aryl). This mechanistic behaviour is more easily explainable in the case of conversion from compound **10** into compound **11**, because of cleavage of an asymmetrical dialkyl ether *via* α-elimination. However, in the case of the cyclization of compound **13**, cleavage involves an oxymethyl bonded with a carbon belonging to an aryl system, *i.e.*, a very unusual event [13]. Which of the three methoxy groups had been freed in both compounds and the positions in which the cyclization took place were ascertained by comparison of ^1H-nmr chemical shifts with those of some of our similar unambiguous compounds [9].

The following oxidation of both compounds **11** and **14** was performed by refluxing their acetone solutions with an

aqueous mixture of sodium periodate and sodium borate in excess. In the case of compound **11**, the oxidative process was unsuccessful, and it was possible to separate uncharacterizable products only. In the case of compound **14**, either it did not take place at all or relatively small amounts of a crude gummy product were obtained by prolonging the reflux time, giving a crystalline yellow substance, separated by silica gel column chromatography.

The structure of the new compound **15** was established by ir, ^{1}H-nmr and mass spectrometries. In detail, the new compound **15** showed an intense characteristic ir absorption band in the 1695-1715 cm^{-1} range due to the presence of a carbonyl group; its ms spectrum revealed a diagnostic peak at m/z 241 corresponding to the molecular ion. In this way the new compound was identified as 4,8-dimethoxy-3*H*-benz[*f*]indol-3-one **(15)**, a novel and interesting linear benzoindole structure whose possible biological properties will be studied in the near future.

EXPERIMENTAL

Melting points were determined with a Büchi-Tottoli SMP-20 capillary melting point apparatus, and are uncorrected. The ir spectra were recorded using a Perkin-Elmer 457 spectrophotometer; values are expressed in cm^{-1}. The ^{1}H-nmr spectra were obtained using a Varian FT-80A instrument; chemical shift values are reported in parts per million on the δ scale with tetramethylsilane as internal reference; J values are given in Hertz. Splitting patterns are designed as follows: s, singlet; d, doublet; dd, doublet of doublets; m, multiplet; b, broadened. Mass spectra were run on a YG ZAB 2F instrument operating at 70 eV (200 μA); the samples were introduced in DEI conditions [14]. Column chromatography was carried out on Merck silica gel 60 (70-230 mesh ASTM) and thin layer chromatography (tlc) was performed on silica gel F_{254} plates. High-pressure liquid chromatography (hplc) was carried out on a Waters Prep. LC/System 500A apparatus using Prep. Pak 500/Silica Waters cartridges. Gas-chromatography analyses were carried out on Perkin-Elmer Sigma 1B instrument. Evaporation of solvents took place under reduced pressure using a rotary evaporator (water aspirator) at steam bath temperature. The starting 5-hydroxy-1,4-naphthoquinone (juglone **1**) was obtained from Janssen Chimica Company. Elemental analyses were performed by the Microanalytical Laboratory of the Department of Pharmaceutical Sciences of the University of Padua, using a Perkin-Elmer Elemental Analyzer Model 240B.

Preparation of 1,4,5-Trihydroxynaphthalene (**2**).

The title compound, already described by Willstätter and Wheeler [15], was prepared by shaking an ethereal solution of juglone (**1**) (40 g in 6 *l*) with a saturated aqueous solution of sodium hydrosulfite at room temperature for six hours. After anhydrification with sodium sulfate, removal of the organic solvent produced 38.4 g (96%) of a crystalline brown product, mp 165°. An analytical specimen of mp 168° (lit [15] 148°) was obtained by recrystallization from ethanol; nmr (deuteriodimethylsulfoxide): δ 6.54 (1H, d, J = 8.2 Hz, HC-3), 6.67 (1H, d, J = 8.2 Hz, HC-2), 6.71 (1H, dd, J = 7.4 and 1.3 Hz, HC-6), 7.17-7.25 (1H, 2d, J = 8.4 and 7.4 Hz, HC-7), 7.51 (1H, dd, J = 8.4 and 1.3 Hz, HC-8), 9.30 (1H, bs, OH at C-4), 10.30 (1H, bs, OH at C-1), 10.67 (1H, bs, OH at C-5).

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.02; H, 4.48.

Methylation of 1,4,5-Trihydroxynaphthalene.

To a mixture of **2** (34.9 g, 0.198 moles) and dimethyl sulfate (112.6 ml, 1.188 moles) in an inert nitrogen atmosphere, a solution of potassium hydroxide (67.32 g, 1.2 moles) in 200 ml of water was added dropwise under magnetic stirring at 60° for forty-five minutes. After the mixture had then been stirred at room temperature for twelve hours, it was poured into cold water (600 ml). The separated product was then collected by suction, washed with water until neutralization, and dried under vacuum at 60° to yield 36.66 g of a crude mixture, which was partially resolved by hplc [16]; 20.48 g of this mixture was dissolved in 440 ml of benzene and chromatographed, using the same organic solvent as eluent (6.6 *l*). The tlc pure fractions produced 5.62 g (13%) of pure 1,4,5-trimethoxynaphthalene (**5**), mp 119° (lit [7] 116-118°); nmr (deuterioacetone): δ 3.81 (3H, s, OCH_3 at C-4), 3.88 (3H, s, OCH_3 at C-1), 3.91 (3H, s, OCH_3 at C-5), 6.79 (2H, s, HC-2 and HC-3), 6.94 (1H, dd, J = 7.8 and 1.2 Hz, HC-6), 7.32-7.40 (1H, 2d, J = 7.8 and 8.4 Hz, HC-7), 7.80 (1H, dd, J = 8.4 and 1.3 Hz, HC-8).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; OCH_3, 42.66. Found: C, 71.32; H, 6.45; OCH_3, 42.35.

By the same hplc of the crude methylation reaction product a mixture (16.2 g, 40%) of two dimethoxyhydroxynaphthalenes was also collected. Part of this mixture (2.2 g) was resolved by column silica gel chromatography, by elution with carbon tetrachloride to give 1-hydroxy-4,5-dimethoxynaphthalene (**3**) and 4-hydroxy-1,5-dimethoxynaphthalene (**4**) in 13% and 27% yields, respectively.

1-Hydroxy-4,5-dimethoxynapthalene (**3**).

This compound was obtained as colorless needles, mp 109°; nmr (deuterioacetone): δ 3.93 (3H, s, OCH_3 at C-4), 4.06 (3H, s, OCH_3 at C-5), 6.78 (1H, d, J = 8.9 Hz, HC-2), 6.84 (1H, d, J = 8.9 Hz, HC-3), 6.82 (1H, dd, J = 7.5 and 1.3 Hz, HC-6), 7.29-7.38 (1H, 2d, J = 8.3 and 7.5 Hz, HC-7), 7.65 (1H, dd, J = 8.3 and 1.3 Hz, HC-8), 9.45 (1H, bs, OH).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.36; H, 5.99.

1,5-Dimethoxy-4-hydroxynaphthalene (**4**).

This compound was obtained as colorless crystals, mp 160° (lit [8] 155-156°); nmr (deuterioacetone): δ 3.92 (3H, s, OCH_3 at C-1), 4.12 (3H, s, OCH_3 at C-5), 6.67 (1H, d, J = 8.4 Hz, HC-3), 6.85 (1H, d, J = 8.4 Hz, HC-2), 7.01 (1H, dd, J = 7.7 and 1.2 Hz, HC-6), 7.32-7.40 (1H, 2d, J = 8.4 and 7.7 Hz, HC-7), 7.79 (1H, dd, J = 8.4 and 1.2 Hz, HC-8), 8.89 (1H, s, OH).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92; OCH_3, 30.39. Found: C, 70.26; H, 5.94; OCH_3, 30.11.

Remethylation of Mixture of Compounds **3** and **4**.

a) With Dimethyl Sulfate in Alkali.

Aqueous potassium hydroxide (45 g in 105 ml) was added dropwise at 60° with stirring and under a nitrogen stream to a suspension containing 7.9 g (38.7 mmoles) of the above-mentioned mixture obtained by hplc and 45 ml of dimethyl sulfate. Following this addition, the reaction mixture was stirred at room temperature for fifteen hours, then diluted with 200 ml of cold water. The solid product which separated was filtered and washed repeatedly with water. After drying, the crude reaction product (7.38 g) was divided by silica gel column chromatography using benzene:dichloromethane (1:6 v/v) as eluent to give 2.45 g (29%) of compound **5** and 3.40 g (43%) of pure compound **4**.

b) With Methyl Iodide and *n*-Butyllithium in HMPA.

Three g of the mixture of compounds **3** and **4** (14.7 mmoles) arising from hplc was dissolved in 30 ml of HMPA (hexamethylphosphoramide) and, after dropwise addition of 15 ml of *n*-butyllithium in hexane (1.6 M) 24 mmoles) with magnetical stirring (a green to red color developed after this addition), 12 ml (37 mmoles) of methyl iodide were introduced. Methylation occurred rapidly under these conditions and workup could follow within fifteen minutes of adding the halide. The mixture was then poured into water and the separated product was collected by suction and washed repeatedly with water. Drying in vacuum at 60° produced 2.76 g (86%) of pure (tlc) compound **5**. By repeating this procedure several times, the general yield was 82%.

1,4,5-Trimethoxy-3,8-dinitronaphthalene (**7**).

Aqueous 40% nitric acid (50 ml) was added to a solution of **5** (3 g, 13.7

mmoles) in benzene (30 ml). The resulting two-phase mixture was stirred for two hours at room temperature. The aqueous solution was extracted with benzene (3 x 200 ml) and the combined extracts were washed with water, dried over sodium sulfate and evaporated to give 3.87 g of crude residue, which was crystallized from absolute ethanol, yielding 3.01 g (71%) of yellow compound **7**, mp 174°; nmr (deuterioacetone): δ 3.95 (3H, s, OCH_3 at C-1), 3.98 (3H, s, OCH_3 at C-5), 4.16 (3H, s, OCH_3 at C-4), 7.25 (1H, d, J = 8.5 Hz, HC-6), 7.48 (1H, s, HC-2), 7.87 (1H, d, J = 8.5 Hz, HC-7).

Anal. Calcd. for $C_{13}H_{12}N_2O_7$: C, 50.65; H, 3.92; N, 9.09. Found: C, 50.93; H, 3.91; N, 9.03.

1,4,5-Trimethoxy-3-nitronaphthalene (**8**).

To a solution of **5** (6 g, 27.5 mmoles) in benzene (60 ml) aqueous 20% nitric acid (60 ml) was added and the resulting mixture was stirred at room temperature for two hours. The reaction mixture was extracted with benzene (3 x 300 ml). The combined extracts were washed with water, dried over sodium sulfate, and evaporated to dryness to yield 6.9 g of a crude sticky red product, which was purified by silica gel column chromatography. Elution with *n*-hexane:ethyl acetate 7:3 furnished in the following order 3.47 g (48%), of tlc pure red compound **8**, 0.085 g (1%) of pure compound **7**, and 0.042 g (0.8%) of compound which was identified as 5-methoxynaphthalene-1,4-dione, mp 88° [17].

Compound **8** had mp 127-128°; nmr (deuterioacetone): δ 3.92 (3H, s, OCH_3 at C-5), 4.04 (3H, s, OCH_3 at C-1), 4.07 (3H, s, OCH_3 at C-4), 7.19 (1H, dd, J = 7.7 and 1.2 Hz, HC-6), 7.20 (1H, s, HC-2), 7.55-7.65 (1H, 2d, J = 8.4 and 7.7 Hz, HC-7), 7.87 (1H, dd, J = 8.4 and 1.4 Hz, HC-8).

Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.55; H, 4.77; N, 5.09.

Subjecting compound **8** to the same procedure described above, but varying only the concentration of aqueous nitric acid (40%), dinitro compound **7** in 62% yield was obtained. In this way it was unequivocally demonstrated that the first nitration took place at C-3 position and that only later did the second nitration at C-8 occur.

1,4,5-Trimethoxy-3-aminonaphthalene (**12**).

To a solution of 2.61 g of compound **8** (9.9 mmoles) in 160 ml of absolute ethanol, activated Raney-Nickel catalyst was added and the mixture was placed under a hydrogen atmosphere (100 bars) in a Prolabo autoclave, and heated at 100° with stirring for a total of twelve hours. The catalyst was then filtered off and the filtrate evaporated to dryness to afford 1.95 g (84%) of a crystalline white-violet nearly pure product, mp 121-122°. An analytical sample was obtained by recrystallization from toluene, mp 125°; nmr (deuterioacetone): δ 3.70 (3H, s, OCH_3 at C-4), 3.88 (3H, s, OCH_3 at C-1), 3.90 (3H, s, OCH_3 at C-5), 4.64 (2H, bs, NH_2), 6.60 (1H, s, HC-2), 6.84 (1H, dd, J = 7.6 and 1.5 Hz, HC-6), 6.99-7.07 (1H, 2d, J = 8.0 and 7.6 Hz, HC-7), 7.63 (1H, dd, J = 8.0 and 1.5 Hz, HC-8).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.61; H, 6.57; N, 5.95.

1,4,5-Trimethoxy-5,6,7,8-tetrahydro-3-aminonaphthalene (**9**).

The hydrogenation reaction of **8** was carried out in essentially the same manner as indicated in the last paragraph of this section, although reaction times and some operative parameters underwent slight variations.

To a solution of **8** (3.43 g, 13 mmoles) in 150 ml of absolute ethanol Raney-Nickel was added and the mixture was hydrogenated for twenty-four hours at 140° under a hydrogen pressure (160 bars). After filtration the solution was evaporated to give a crude oil residue (3.23 g) which was chromatographed on a silica gel column, eluting with *n*-hexane-ethyl acetate (7:3) to provide 1.05 g (34%) of **9** as a colourless solid, mp 85°; nmr (deuteriochloroform): δ 1.62 (2H, m, H_2C-6), 2.20 (2H, m, H_2C-7), 2.56 (2H, m, H_2C-8), 3.45 (3H, s, OCH_3 at C-5), 3.72 (3H, s, OCH_3 at C-4), 3.73 (2H, m, NH_2), 3.80 (3H, s, OCH_3 at C-1), 4.51 (1H, m, HC-5), 6.27 (1H, s, HC-2).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.91; H, 8.27; N, 5.74.

N-(γ-Chloro-β-hydroxypropyl)-1,4,5-trimethoxy-5,6,7,8-tetrahydro-3-aminonaphthalene (**10**).

1,4,5-Trimethoxy-3-amino-5,6,7,8-tetrahydronaphthalene (**9**) (1.74 g, 7.33 mmoles) was dissolved in 7.5 ml of methanol (1*M*) and epichlorohydrin (0.49 ml, 7.6 mmoles) in 7.6 ml of methanol was added slowly under magnetic stirring. To the mixture 0.2 ml of concentrated hydrochloric acid was then added and stirring was continued for eight days at room temperature. The reaction mixture was then poured into water, the acid neutralized with sodium hydrogen carbonate and the product extracted exhaustively with benzene (4 x 100 ml). After drying over anhydrous sodium sulfate, the benzene was removed yielding a crude gummy residue (1.99 g) which was chromatographed on a silica gel column, eluting with ethyl acetate. The desired pure (tlc) title compound (1.45 g, 60%) appeared as a viscous oil which, on standing overnight at room temperature, solidified into a dense violet mass; nmr (hexadeuterioacetone): δ 1.71 (4H, m, H_2C-6 and H_2C-7), 2.28 (2H, m, H_2C-8), 3.36 (3H, s, OCH_3 at C-5), 3.42 (1H, m, HC-β), 3.64 (1H, m, NH), 3.72 (3H, s, OCH_3 at C-4), 3.75 (3H, s, OCH_3 at C-1), 3.78 (2H, m, H_2C-γ), 4.04 (1H, m, HC-5), 4.52 (2H, m, H_2C-α), 6.38 (1H, s, HC-2).

Anal. Calcd. for $C_{16}H_{24}ClNO_4$: C, 58.27; H, 7.33; N, 4.25; Cl, 10.75. Found: C, 58.25; H, 7.42; N, 4.21; Cl, 10.99.

1,2,3,4,6,7-Hexahydro-3-hydroxy-5,10-dimethoxybenz[*g*]quinoline (**11**).

To a solution of *N*-(γ-chloro-β-hydroxypropyl)-1,4,5-trimethoxy-5,6,7,8-tetrahydro-3-aminonaphthalene (**10**) (1.2 g, 3.64 mmoles) in 180 ml of bromobenzene, 3.5 ml (21.9 mmoles) of diethylaniline was added and the mixture was heated at reflux for five days, during which tlc analysis showed that the starting amino derivative had been satisfactorily condensed. The reaction mixture was then extracted with 5% hydrochloric acid (4 x 60 ml) and the aqueous phase was washed accurately with benzene (3 x 50 ml). The acid solution was then neutralized with saturated sodium bicarbonate solution and extracted with benzene (4 x 100 ml). The combined organic layers were washed with water, dried over sodium sulfate, and evaporated to leave a remarkably pure oil (0.78 g, 82%), which was later purified by distillation at 135° and 10^{-2} torr. The crystalline white sublimate had mp 100°; nmr (deuterioacetone): δ 2.25 (2H, m, H_2C-7), 2.60 (2H, m, H_2C-6), 2.82 (2H, m, H_2C-4), 3.13 (2H, m, H_2C-2), 3.39 (1H, m, NH), 3.61 (6H, s, 2 x OCH_3), 3.90 (1H, m, HC-3), 4.71 (1H, bs, OH, deuterium oxide exchangeable), 5.99 (1H, d, J = 9.8 Hz, HC-8), 6.66 (1H, d, J = 9.8 Hz, HC-9); ms: 261 (M^+, 72.7), 246 (M −15, 100).

Anal. Calcd. for $C_{15}H_{19}NO_3$ (MW 261.31): C, 68.94; H, 7.33; N, 5.36; OCH_3, 23.75. Found: C, 69.01; H, 7.39; N, 5.34; OCH_3, 24.09.

N-(γ-Chloro-β-hydroxypropyl)-1,4,5-trimethoxy-3-aminonaphthalene (**13**).

A solution of 1,4,5-trimethoxy-3-aminonaphthalene (**12**) (2.97 g, 12.7 mmoles) in methanol (13 ml) was added dropwise to a stirred solution of epichlorohydrin (1.2 g, 14 mmoles) in methanol (14 ml). The reaction mixture was added to 0.3 ml of concentrated hydrochloric acid; stirring was continued at room temperature for fourteen days, during which tlc analysis indicated that the starting compound **12** had been strongly condensed. The violet reaction mixture was then poured into water and, after neutralization with sodium bicarbonate, exhaustively extracted with benzene (4 x 300 ml). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, and evaporated. The crude residue (3.32 g) was chromatographed on silica gel column, using ethyl acetate as the eluting solvent, and then rechromatographed on a silica gel column using a mixture of ethyl acetate-chloroform (1:4) as eluent. On evaporation, the pure tlc fractions afforded the title compound **13** (1.62 g, 39%) as a viscous violet oil; nmr (hexadeuterioacetone): δ 2.05 (1H, s, OH, deuterium oxide exchangeable), 3.45 (2H, m, H_2C-γ), 3.70 (3H, s, OCH_3 at C-4), 3.71 (2H, m, H_2C-α), 3.87 (3H, s, OCH_3 at C-1), 3.93 (3H, s, OCH_3 at C-5), 4.13 (1H, m, HC-β), 4.66 (1H, bs, NH), 6.69 (1H, s, HC-2), 6.80 (1H, dd, J = 7.6 and 1.4 Hz, HC-6), 6.98-7.06 (1H, 2d, J = 8.2 and 7.6 Hz, HC-7), 7.67 (1H, dd, J = 8.2 and 1.4 Hz, HC-8).

Anal. Calcd. for $C_{16}H_{20}ClNO_4$: C, 58.99; H, 6.19; N, 4.30; Cl, 10.88. Found: C, 59.35; H, 6.29; N, 4.30; Cl, 10.57.

1,2,3,4-Tetrahydro-3-hydroxy-5,9-dimethoxy-1*H*-benz[*g*]quinoline (**14**).

To a solution of *N*-(γ-chloro-β-hydroxypropyl)-1,4,5-trimethoxy-3-aminonaphthalene (**13**) (2.2 g, 6.75 mmoles) in 320 ml of bromobenzene (0.021 *M*), 6.47 ml of diethylaniline was added, the molar ratio of this aniline to **13** thus being 6:1. The mixture was refluxed for six days. The cyclized compound was extracted with 5% hydrochloric acid (4 x 100 ml) and the aqueous extract washed repeatedly with benzene (4 x 50 ml). The acid layer was neutralized with sodium hydroxide solution, and exhaustively extracted with benzene (4 x 300 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuum yielding 1.38 g (78%) of a nearly pure semisolid product, which was distilled at 180° and 0.2 x 10^{-1} torr to give a colorless crystalline product, mp 158°; nmr (deuterioacetone): δ 2.97 (2H, m, H_2C-4), 3.23 (2H, m, H_2C-2), 3.83 (3H, s, OCH_3 at C-5), 3.85 (3H, s, OCH_3 at C-9), 3.95 (1H, m, HC-3), 4.01 (1H, bs, OH), 4.10 (1H, m, NH), 6.32 (1H, s, HC-10), 6.79 (1H, dd, J = 7.7 and 1.7 Hz, HC-8), 6.96-7.04 (1H, 2d, J = 7.9 and 7.7 Hz, HC-7), 7.64 (1H, dd, J = 7.9 and 1.7 Hz, HC-6); ms: 259 (M^+, 90), 244 (M −15, 100).

Anal. Calcd. for $C_{15}H_{17}NO_3$ (MW 259.29): C, 69.49; H, 6.61; N, 5.40; OCH_3, 23.94. Found: C, 69.21; H, 6.80; N, 5.27; OCH_3, 23.92.

Recrystallization from absolute ethanol produced a pure crystalline product, mp 303°.

Anal. Calcd. for $C_{15}H_{17}NO_3 \cdot ½\ C_2H_5OH$: C, 68.06; H, 7.14; N, 4.96. Found: C, 68.31; H, 7.25; N, 5.02.

4,8-Dimethoxy-3*H*-benz[*f*]indol-3-one (**15**).

A solution of 5,9-dimethoxy-1,2,3,4-tetrahydro-3-hydroxy-1*H*-benz[*g*]-quinoline (**14**) (0.65 g, 2.51 mmoles) in acetone (25 ml) was added to a solution of sodium periodate (3.21 g, 15 mmoles) and sodium tetraborate decahydrate (2.87 g, 7.53 mmoles) in water (100 ml). The mixture was refluxed for forty-eight hours. Upon cooling, the oxidizing agent excess was destroyed with a saturated sodium hydrosulfite solution and then extracted with ether (3 x 300 ml). The combined organic layers were washed with water, dried over sodium sulfate, and evaporated to leave a yellow residue (0.41 g), which was chromatographed on silica gel. Elution with ethyl acetate furnished a crude mixture which was rechromatographed on silica gel eluting with chloroform. Evaporation of solvent yielded a pure crystalline product (0.022 g, 3.7%), mp 177-178° dec; nmr (deuteriochloroform): δ 3.96 (3H, s, OCH_3 at C-4), 4.21 (3H, s, OCH_3 at C-8), 6.37 (1H, m, HC-7), 7.18 (1H, s, HC-2), 7.21 (1H, s, HC-9), 7.32 (1H, m, HC-6), 7.66 (1H, m, HC-5); ir (potassium bromide disc): 1695-1715 cm^{-1} (C=O); ms: 241 (M^+, 97), 199 (M −42, 100), 184 (M −57, 98).

Anal. Calcd. for $C_{14}H_{11}NO_3$ (MW 241.24): C, 69.70: H, 4.59; N, 5.80. Found: C, 70.00; H, 4.77; N, 5.93.

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[12] Chromosorb 102 column; carrier gas, nitrogen, 5.5 ml min^{-1}; column temperature, 110°; injection, 170°; FID detector 170°; retention time, 2.82 min.

[13] On the basis of various trials, it is reasonable to believe that the basic medium obviously produces carbocation on the side chain which attaches the naphthalene system at C-2 position. The loss of an enolate ion, which rapidly oxidizes oneself to produce formaldehyde, occurs contemporaneously in the newly formed tetrahydroquinoline nucleus. The formaldehyde is easily characterized in the refluxed reaction solvents by gas chromatography and chemical assays (resorcine in sulfuric acid and dimedone in acetic acid). Rearrangement of central benzene in the fused tricyclic system consequently takes place by engagement of a hydride ion from C-10. In order to gain insight into the mechanism of this cyclization, we refluxed for a long time compound **12** with bromobenzene and diethylaniline and found that this compound was recovered unchanged. This is a confirmatory evidence that only in cyclizing phase, *i.e.*, in presence of the γ-halogenated chain did the loss of an oxymethyl occur. The attack of the starting carbocation on C-2, instead of occurring at C-4 if the proposed mechanism of enolate ion formation had preceded this event, is motivated both by a greater electron-donating effect of the methoxyl at C-1 *ortho* position and by an almost negligible electron-withdrawing effect of the second fused aryl in the naphthalene system. It may be hypothesized that this behaviour (consisting in the loss of one methoxy group during the cyclizing process) is a prerogative of a naphthalene derivative bearing an alkyl substituent of this type on the amino group which presents at least two oxymethyls in the *peri* position near the amino function.

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[16] Prep. Pack 500 Silica Waters column; radial pressure (chamber pressure) 30 Atm; flow, 0.1 ℓ min^{-1}; solvent pressure, 5 Atm; chart speed, 1 cm/min.

[17] 5-Methoxynaphthalene-1,4-dione, mp 88°; nmr (deuterioacetone): δ 3.97 (3H, s, OCH_3), 6.89 (2H, s, HC-2 and HC-3), 7.53 (1H, dd, J = 7.7 and 2.0 Hz, HC-6), 7.72 (1H, 2d, J = 8.6 and 7.8 Hz, HC-7), 7.80 (1H, dd, J = 8.6 and 1.9 Hz, HC-8).