161. A Novel Synthesis of Aporphines *via* 3-Phenylphenethylamines[1])

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Summary

rac-1,2,10-Trimethoxy-aporphine (**14**) and *rac*-2-ethoxy-10,11-dimethoxy-aporphine (**27**) have been synthesized from the 3-phenylphenethylamines **9** and **22** by a new route. The 8-phenyl-3,4-dihydroisoquinolines **11** and **24**, the oxo-aporphines **12** and **25** and the *rac*-nor-aporphines **13** and **26** were obtained as intermediates.

The synthesis of aporphines (I) has thus far been achieved by the following two major routes: a) Cyclization of appropriately substituted 1-benzyl-1,2,3,4-tetrahydroisoquinolines (II). For the coupling of rings A/D, the reactions applied are the *Pschorr* cyclization, benzyne mediated synthesis, photo-cyclizations and various oxidative processes, including enzymatic and electrochemical reactions; b) Acid-catalyzed rearrangement of different tetracyclic compounds, known or considered to be biological precursors of aporphine alkaloids, namely pro-aporphines (III), neo-proaporphines (IV) and morphinandienones (V). These synthetic approaches have been reviewed at regular intervals [1].

We now would like to report on a new scheme for the preparation of a variety of ring A/D substituted aporphines from their corresponding 3-phenylphenethylamines (VI) containing the aromatic rings A and D of the ultimate aporphines. Because of their structural relationship to the biologically active aporphines nuciferine and apomorphine, the two aporphines 1,2,10-trimethoxyaporphine (**14**) and 2-ethoxy-10,11-dimethoxyaporphine (**27**) have been chosen as target compounds. Details of this synthesis will now be discussed.

a) *Synthesis of 3-phenylphenethylamines.* In both cases, the synthesis started from a conveniently substituted benzaldehyde: 3-bromo-4,5-dimethoxybenzaldehyde (**1**), obtained in two steps from vanillin [2], was reduced to the corresponding alcohol **2** [3] with lithium borohydride. The chloride **3** and the benzyl methyl

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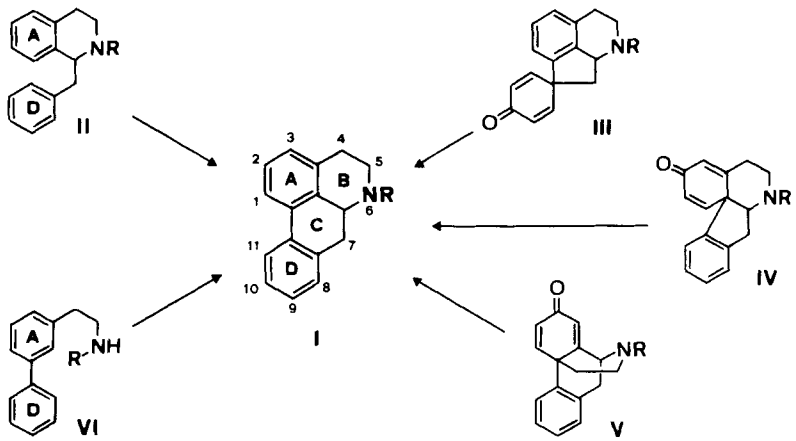
Scheme 1



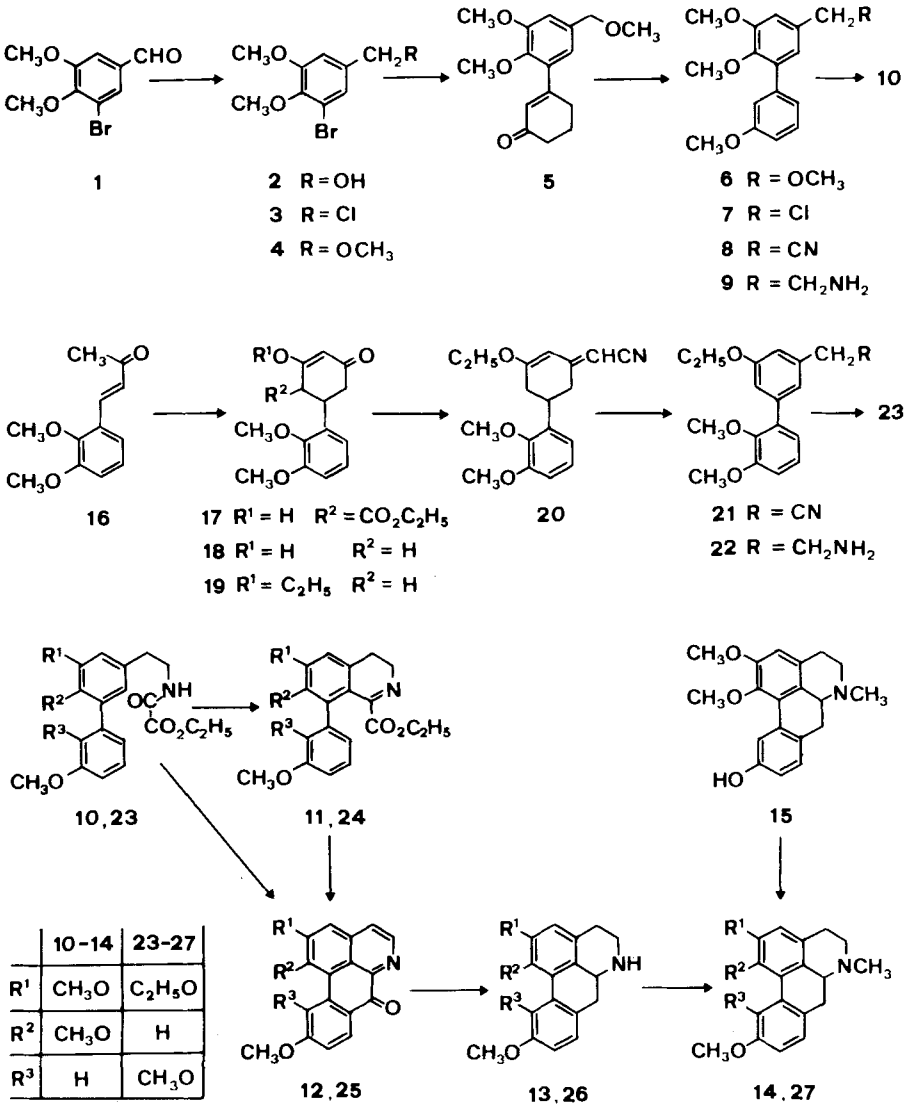
ether **4** were obtained by standard methods. The *Grignard* reagent made from **4** was reacted with 3-ethoxy-2-cyclohexen-1-one to afford the arylcyclohexenone **5**. This compound was easily dehydrogenated to the biphenyl derivative **6** by copper(II) bromide in methanol. Selective cleavage of the benzyl methyl ether group of **6** proceeded smoothly with hydrogen chloride in boiling toluene to give the chloride **7**. Conversion to the nitrile **8** and hydrogenation to the amine **9** were accomplished by standard methods.

The synthesis of the phenylphenethylamine **22** started from 2,3-dimethoxybenzaldehyde, which was converted to the known benzalacetone **16** [4]. *Michael* addition of malonic ester followed by cyclization afforded the enolized ethyl cyclohexanedionecarboxylate **17**, which was saponified, decarboxylated and etherified to the β-diketone enol ether **19**. A *Horner* type condensation with deprotonated diethyl cyanomethylphosphonate gave the nitrile **20**, which was dehydrogenated to the biphenyl derivative **21** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). Hydrogenation with *Raney* nickel in methanol containing ammonia afforded **22**.

b) *Cyclization to 8-phenyl-3,4-dihydroisoquinolines and oxo-aporphines.* The 3-phenylphenethylamines **9** and **22** were converted to the corresponding oxamic esters **10** and **23** by heating with diethyl oxalate. *Bischler-Napieralsky* cyclization with phosphorus oxychloride in acetonitrile or in toluene afforded only very low yields of the corresponding dihydroisoquinolines. In contrast, mild heating of **10** and **23** with polyphosphoric ester [5] proved to be an efficient method for the cyclization to **11** and **24**. Ring closure between rings B and D to afford the oxo-aporphines **12** and **25** succeeded in polyphosphoric acid with yields of 50 and 87% respectively. The oxidation of ring B occurs probably during work-up. The oxo-aporphine **25** was also obtained directly from **23** with polyphosphoric acid, although in lower yield.

c) *Aporphines* **14** *and* **27**. The oxo-aporphines **12** and **25** were reduced to the corresponding nor-aporphines **13** and **26** with zinc and acid, following known procedures. *N*-Methylation with formaldehyde and formic acid or with formaldehyde and sodium borohydride afforded the new *rac*-aporphine **27** and the known *rac*-

Scheme 2



	10-14	23-27
R^1	CH_3O	C_2H_5O
R^2	CH_3O	H
R^3	H	CH_3O

aporphine **14** [6] [7]. The spectroscopic data of **14** are in good agreement with the published data. Moreover, **14** proved to be identical with a sample obtained by *O*-methylation of *rac*-nuciferoline (**15**)[4]).

The present synthesis opens new routes to polyoxygenated oxo-aporphines, noraporphines and aporphines. For the cyclization of rings B and C, oxygen functions (or other activating groups) are necessary on carbon atoms 2 and 10 of the ultimate

[4]) *rac*-Nuciferoline was prepared by Prof. *K. Bernauer* by rearrangement of *rac*-pronuciferine [8]. We thank Prof. *Bernauer* for a sample of this compound.

aporphine. The synthesis of the 3-phenylphenethylamines necessitate a relatively high number of steps. This apparent disadvantage is counterbalanced by the good yields obtained, especially in the cyclization steps.

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Experimental Part

(with the assistance of *G. Falk* and *A. Peyrilloux*)

General remarks: Melting points (m.p.) were taken on a *Tottoli* apparatus using open capillaries and are not corrected. Column chromatography was performed on silica gel (*Merck*, 0.63–0.2 mm) or on neutral aluminum oxide, activity grade III (*Woelm*). Reactions were routinely monitored by thin layer chromatography (TLC.) on silica gel F 254 TLC. plates (*Merck*). Solvent systems used: 1) benzene alone or containing 1 to 10% of methanol; 2) Chloroform/2-propanol/acetic acid/water 20:20:6:4. UV. spectra: taken in ethanol; λ_{max} are given in nm, ($\log\varepsilon$) in parentheses. IR. spectra: recorded on *Beckmann* IR 9 spectrometer, solid substances in KBr, liquids as thin films; ν_{max} are given in cm^{-1}. ^{1}H-NMR.: 60 MHz spectra were recorded on *Varian* A 60 or on *Varian* EM-360, 80 MHz on WP 80 CW *Bruker-Spectrospin*, 100 MHz on *Varian* HA 100, 90 MHz on *Bruker* HX 90 E (FT mode) spectrometers. Chemical shifts are given in ppm (internal standard: tetramethylsilane ($\delta = 0$); *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplet, *m* = multiplet, br. = broad). Mass spectra (MS.) were recorded on *AEI* MS 902 spectrometer; mass numbers are given in *m/e*, relative intensity in % in parentheses. Abbreviations: RT. = room temperature, i.V. = in vacuum, i.HV. = in high vacuum.

3-Bromo-4,5-dimethoxybenzyl alcohol (**2**). A solution of lithium borohydride (44 g) in tetrahydrofuran (2.6 l) was cooled to 10° under argon. A solution of 3-bromo-4,5-dimethoxybenzaldehyde (**1**, 500 g) [2] was added dropwise with stirring and cooling (10°) during 45 min. After 2.5 h at 10°, 6N aqueous HCl (300 ml) was added with caution at 10 to 12°. The tetrahydrofuran was evaporated i.V. and the residue was partitioned between water and benzene. The organic layer was washed (brine), dried (Na_2SO_4) and evaporated to dryness to yield 504 g of **2** as an oil. A sample was distilled; b.p. 140°/0.1 Torr [3]. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.65 (*s*, 1H, OH); 3.80 (*s*, 6 H, 2 OCH_3); 4.57 (*s*, 2 H, CH_2OH); 6.83 and 7.07 (2*d*, $J = 2.5$, 1H each, H–C(2) and H–C(6)). – MS.: 246 (100, M^+), 231 (22, $M - CH_3$), 124 (26), 96 (58).

3-Bromo-α-chloro-4,5-dimethoxytoluene (**3**). Thionyl chloride (195 ml) was added dropwise during 1 h to a boiling solution of **2** (495 g) in benzene (1850 ml) and the mixture refluxed for 10 min. Excess thionyl chloride and solvent were evaporated i.V. and the residue taken up in benzene (2 l). This solution was filtered through a silica gel column (525 g). Elution with benzene and evaporation of the solvent afforded 448.5 g (84.3%) of **3** as an oil, which was used as such for the next step. For the analysis, a sample was crystallized from hexane; m.p. 62°. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 3.80 (*s*, 6 H, 2 OCH_3); 4.42 (*s*, 2 H, CH_2Cl); 6.82 and 7.14 (2*d*, $J = 2.5$, 1H each, H–C(2) and H–C(6)).

$C_9H_{10}BrClO_2$ (265.5) Calc. C 40.71 H 3.80% Found C 40.41 H 3.79%

3-Bromo-α,4,5-trimethoxytoluene (**4**). To a solution of sodium methoxide prepared from methanol (1.7 l) and sodium (82 g), a warm solution of **3** (577 g) in methanol (900 ml) was added during 10 min at 40 to 45°. The mixture was stirred at 50° for 12 h and then evaporated to dryness i.V. The residue was taken up in toluene (2 l) and water (0.5 l), the layers separated and the toluene solution washed to neutrality (brine), dried (Na_2SO_4) and evaporated to dryness i.V., affording 570 g of nearly pure **4**. For analysis, a sample was distilled at 80–88°/0.1 Torr. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 3.35 (*s*, 3 H, CH_2OCH_3); 3.80 and 3.84 (2*s*, 3 H each, 2 OCH_3 at the arom. ring); 4.35 (*s*, 2 H, CH_2OCH_3); 6.85 and 7.08 (2*d*, $J = 2.5$, 1H each, H–C(2) and H–C(6)). – MS.: 260 (91, M^+), 229 (100, $M - OCH_3$), 181 (31), 152 (31), 139 (31).

$C_{10}H_{13}BrO_3$ (261.1) Calc. C 46.00 H 5.02% Found C 45.89 H 4.95%

3-[2,3-Dimethoxy-5-(methoxymethyl)phenyl]-2-cyclohexen-1-one (**5**). 112 g of **4** were added dropwise, with stirring, to magnesium turnings (11.2 g) in tetrahydrofuran (260 ml) so that a gentle refluxing was maintained. Heating to reflux temperature was continued for 1 h. The solution was then cooled to 25°, and 3-ethoxy-2-cyclohexen-1-one (64 g) [9] added dropwise at 22 to 25° during 20 min. The reaction mixture was then heated to reflux during 1 h. The solvent was then removed i.V. and the residue partitioned between benzene and ammonium chloride solution. The organic layer was washed to neutrality (brine), dried (Na_2SO_4), concentrated i.V. and then chromatographed through aluminum oxide (1270 g). Elution with benzene afforded 93.1 g (78%) of **5** as an oil. For analysis, a sample was distilled at 177–180°/0.5 Torr. – IR.: 1672 (C=O conj.), 1611 (C=C), 1583, 1484 (aromatic rings), 1252, 1191, 1158, 1007 (aryl ether), 1118 (ether). – ^{1}H-NMR. (60 MHz, $CDCl_3$): 1.98 to 2.85 (*m*, 6 H, 3 CH_2); 3.41 (*s*, 3 H, CH_2OCH_3); 3.80 and 3.91 (2*s*, 3 H each, 2 OCH_3); 4.40 (*s*, 2 H, CH_2OCH_3); 6.18 (*t*, 1H, =CH–); 6.77, 6.96 (2*d*, J=2, H arom.). – MS.: 276 (100, M^+), 245 (53, $M-OCH_3$), 231 (25, $M-CH_2OCH_3$), 216 (20), 115 (20), 45 (45).

2,3,3'-Trimethoxy-5-(methoxymethyl)biphenyl (**6**). To a solution of **5** (70 g) in methanol (750 ml), copper(II) bromide (114 g) was added, and the mixture was stirred for 3 h at RT. The mixture was then cooled to –5° and the precipitated copper(I) bromide filtered off. The filtrate was evaporated to dryness i.V. and the residue was partitioned between water and benzene. The benzene solution was washed 3 times with water, twice with 2N NaOH, and then 3 times with water. The solvent was removed i.V., yielding 75 g of **6** as an oil. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 3.38 (*s*, 3 H, CH_2OCH_3); 3.55, 3.79 and 3.88 (3*s*, 3 H each, 3 OCH_3 arom.); 4.40 (*s*, 2 H, CH_2OCH_3); 6.75 to 7.42 (*m*, 6 H arom.). – MS.: 288 (100, M^+), 273 (13, $M-CH_3$), 256 (79), 241 (20), 45 (24).

5-(Chloromethyl)-2,3,3'-trimethoxybiphenyl (7). A solution of **6** (80 g) in toluene (1.3 l) was saturated with HCl at 20° during 4 h, and then left overnight at RT. Removal of volatile components i.V. and finally i.HV. left a residue of oily 7 in nearly quantitative yield. For analysis, a sample was chromatographed on silica gel and eluted with benzene. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 3.60, 3.82 and 3.91 (3*s*, 3 H each, 3 OCH_3); 4.55 (*s*, 2 H, CH_2Cl); 6.65 to 7.50 (*m*, 6 H arom.). – MS.: 292 (8, M^+), 257 (17, $M-Cl$), 186 (22), 151 (100), 107 (15).

$C_{16}H_{17}ClO_3$ (292.8) Calc. C 65.64 H 5.85 Cl 12.11% Found C 65.51 H 5.87 Cl 12.03%

3',5,6-Trimethoxy-3-biphenylacetonitrile (**8**). A solution of 7 in DMSO (110 ml) was dropped during 30 min, at 10°, to a solution of NaCN (29.2 g) in water (33 ml) and DMSO (350 ml). The reaction mixture was then stirred overnight at RT. After addition of water, the solution was extracted with benzene. The benzene extract was washed (water), dried (Na_2SO_4), and the solvent removed i.V., affording 113 g of **8** (84%) as an oil. – IR.: 2836 (CH_3O), 2250 (CN), 1596, 1579, 1515, 1491, 1477 (aromatic rings), 1285, 1264, 1233, 1184, 1157, 1043, 1006 (aryl ether), 840, 789, 702 (*m*-disubstituted benzene). – ^{1}H-NMR. (60 MHz, $CDCl_3$): 3.57, 3.80 and 3.89 (3*s*, 3 H each, 3 OCH_3); 3.72 (*s*, 2 H, CH_2OCH_3); 6.8 to 7.5 (*m*, 6 H arom.).

$C_{17}H_{17}NO_3$ (283.3) Calc. C 72.07 H 6.05 N 4.94% Found C 71.54 H 6.05 N 4.89%

*3,4-Dimethoxy-5-(*m*-methoxyphenyl)phenethylamine* (**9**). A solution of **8** (100 g) and ammonia (60 g) in methanol (1850 ml) was hydrogenated for 20 h at 100° at 40 atm in the presence of *Raney* nickel (55 g). The catalyst was filtered off and the filtrate was evaporated to dryness i.V., affording 95 g (94%) of **9** as an oil. An analytical sample of the hydrochloride was prepared with ethanolic HCl-solution and recrystallized from ethanol/ether.

9 · HCl, m.p. 142°. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.9 to 3.4 (*m*, 4 H, CH_2CH_2); 3.53, 3.77 and 3.87 (3*s*, 3 H each, 3 OCH_3); 6.7 to 7.4 (*m*, 6 H arom.); 8.35 (br., 3 H, NH_3^+). – MS.: 287 (17, M^+), 258 (100, $M-CH_2NH$), 243 (27), 227 (9), 30 (41, $CH_2NH_2^+$).

$C_{17}H_{21}NO_3 \cdot HCl$ (323.8) Calc. C 63.06 H 6.85 N 4.33% Found C 62.77 H 6.76 N 4.27%

Ethyl N-*[3,4-dimethoxy-5-(*m*-methoxyphenyl)phenethyl]oxamate* (**10**). A solution of **9** (94 g) in diethyl oxalate (380 ml) was dropped during 1 h to diethyl oxalate (380 ml) stirred at 100°. After an additional hour at 100°, the mixture was cooled, diluted with hexane and chromatographed through silica gel (1500 g). Excess diethyl oxalate and some impurities were eluted with hexane and benzene. Elution with benzene and benzene/methanol 19:1 afforded 105 g (82.8%) of **10** as an oil. For analysis, a sample was chromatographed again through silica gel and eluted with benzene. – ^{1}H-NMR. (60 MHz,

$CDCl_3$): 1.37 (*t*, $J=7$, 3 H, CH_2CH_3); 2.7 to 3.05 and 3.45 to 3.75 (2*m*, 2 H each, CH_2CH_2N); 3.60, 3.83 and 3.90 (3*s*, 3 H each, 3 OCH_3); 6.7 to 7.5 (*m*, 6 H arom. and NH). – MS.: 387 (17), 314 (4), 270 (100), 257 (42).

$C_{21}H_{25}NO_6$ (387.4) Calc. C 65.10 H 6.50 N 3.62% Found C 65.31 H 6.48 N 3.42%

*Ethyl 6,7-dimethoxy-8-(*m*-methoxyphenyl)-3,4-dihydro-1-isoquinolinecarboxylate* (**11**). A mixture of **10** (32 g) and polyphosphoric ester (200 g; prepared according to [5]) was heated under argon to 80° during 7.5 h. The reaction mixture was quenched with ice and extracted 4 times with ether. The aqueous phase was adjusted to pH 7 with 25% aqueous ammonia and then extracted 4 times with chloroform. Removal of the solvent i.V. afforded 22 g (72%) of **11** as an oil. For analysis, a sample was chromatographed through silica gel and eluted with benzene. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 1.09 (*t*, $J=7$, 3 H, CH_2CH_3); 2.45 to 2.95 and 3.4 to 3.9 (2*m*, 2 H and 4 H, 3 CH_2); 3.50, 3.80 and 3.93 (3*s*, 3 H each, 3 OCH_3); 6.75 to 7.47 (*m*, 5 H arom.). – MS.: 369 (100, M^+), 340 (28), 325 (37), 310 (28), 296 (46), 266 (18).

$C_{21}H_{23}NO_5$ (369.4) Calc. C 68.28 H 6.28 N 3.79% Found C 68.18 H 6.19 N 3.64%

*1,2,10-Trimethoxy-7*H*-dibenzo[*de,g*]quinolin-7-one* (**12**). A mixture of **11** (10 g) and polyphosphoric acid (250 g) was heated, under argon, 2.5 h to 60° and 16 h to 45°. The mixture was quenched with ice, adjusted to pH 7 with 25% aqueous ammonia and extracted 5 times with chloroform. The solvent was removed i.V., the residue (7.8 g) was dissolved in hot ethanol (200 ml) and then concentrated to a small volume. After cooling in an ice bath, the yellow crystals were filtered off to afford 4.4 g (50.5%) of **12**, m.p. 200°[5]). – UV.: 240 (4.49), 268 (4.47), 282*s* (4.20), 302*s* (3.86), 309 (3.87), 348 (4.09), 385 (4.02). – IR.: 1655 (C=O), 1608, 1594, 1496, 1486 (aromatic rings), 1256, 1236, 1169, 1134, 1054, 1014 (aryl ether), 810 (vicinal arom. H). – ^{1}H-NMR. (90 MHz, DMSO-d): 3.99, 4.01 (2*s*, 9 H, 3 OCH_3); 7.05 (*d*×*d*, $J=9$ and $J=2.5$, 1H, H–C(9)); 7.05 (*s*, 1H, H–C(3)); 7.59 (*d*, $J=5.5$, 1H, H–C(4)); 8.49 (*d*, $J=9$, 1H, H–C(8)); 8.60 (*d*, $J=2.5$, 1H, H–C(11)); 8.78 (*d*, $J=5.5$, 1H, H–C(5)). – MS.: 321 (100), 307 (16), 306 (10), 278 (63), 263 (8), 235 (8), 163 (11), 139 (12).

$C_{19}H_{15}NO_4$ (321.3) Calc. C 71.02 H 4.71 N 4.36% Found C 70.89 H 4.85 N 4.25%

rac-*1,2,10-Trimethoxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinoline* (**13**). To a solution of **12** (3.21 g) in a mixture of acetic acid (300 ml) and 7N HCl (350 ml), zinc powder (100 g) was added. This mixture was heated to reflux during 7 h; a second portion of zinc powder (100 g) was added after 2 h. After cooling to RT. and addition of water (1000 ml), the excess zinc was filtered off and washed with water and chloroform. The filtrate was neutralized with Na_2CO_3 and transferred to an extraction funnel. The chloroform was separated, washed (brine), dried (Na_2SO_4), filtered and evaporated to dryness i.V. The residue was dissolved in alcoholic HCl-solution. Addition of ether induced crystallization of 2.2 g (63%) of **13** · HCl, m.p. 235–237°. For analysis, a sample was recrystallized 3 times from ethanol/ether; m.p. 235–237°. – UV.: 22 (4.55), 266 (4.12), 274 (4.13), 301 (3.83). – ^{1}H-NMR. (100 MHz, DMSO-d): 2.75 to 3.65 (*m*, 3 CH_2); 3.64, 3.78 and 3.86 (3*s*, 3 H each, 3 OCH_3); 4.18 (*qa*, $J=13$, $J=5$, 1H, H–C(6a)); 6.88 (*d*×*d*, $J=8$, $J=2.5$, 1H, H–C(9)); 6.93 (*s*, 1H, H–C(4)); 7.27 (*d*, $J=8$, 1H, H–C(8)); 7.87 (*d*, $J=2.5$, 1H, H–C(11)). – MS.: 311 (59, M^+), 310 (100), 296 (24, $M-CH_3$), 280 (21), 251 (12), 36 (9).

$C_{19}H_{21}NO_3 \cdot HCl$ (347.8) Calc. C 65.61 H 6.38 N 4.03% Found C 65.56 H 6.40 N 3.87%

rac-*1,2,10-Trimethoxyaporphine* (**14**). a) *From* **13**. The base (0.26 g) isolated from **13** · HCl (0.29 g) was mixed with formic acid (0.22 g) and formaldehyde (0.1 ml of 37% aqueous solution) and heated to 100° during 15 h. The mixture was evaporated to dryness i.V. The residue was dissolved in water, alcalized with ammonia and extracted 4 times with chloroform. The solvent was evaporated, the residue dissolved in benzene and chromatographed through aluminum oxide (20 g). Elution with benzene afforded **14**, which was converted to the hydrochloride with alcoholic HCl-solution. This product was

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[5]) *S.M. Kupchan et al.* [10] have isolated, from the reaction mixture obtained from sodium/liquid ammonia cleavage of dehydrothalicarpine (0.96 g), 5 mg of a red compound, m.p. 256–258°, to which they attributed the structure of 1,2,10-trimethoxy-7*H*-dibenzo[*de,g*]quinolin-7-one. Obviously, this compound is not identical with our synthetic compound **12** (*Added in proof:* see also [11]).

recrystallized twice from ethanol, yielding 0.13 g (43%) of **14** · HCl, m.p. 250°. – UV.: 221 (4.58), 266 (4.15), 274 (4.16), 301 (3.87). – ^{1}H-NMR. (90 MHz, DMSO-d): 2.98 (*s*, N–CH_3); 3.63, 3.78 and 3.85 (3*s*, 3 H each, 3 OCH_3); 4.05 to 4.3 (*m*, 1H, H–C(6a)); 6.91 (*d*×*d*, *J*=8.5, *J*=2.5, H–C(9)); 6.95 (*s*, 1H, H–C(4)); 7.32 (*d*, *J*=8.5, 1H, H–C(8)); 7.86 (*d*, *J*=2.5, 1H, H–C(11)); 11.65 (br., 1H, HCl). – MS.: 325 (79, M^+), 324 (100), 310 (62, $M-CH_3$), 294 (39), 282 (30), 267 (25), 251 (26).

$C_{20}H_{23}NO_3 \cdot HCl \cdot 0.3\,C_2H_5OH$	Calc.	C 65.86	H 6.92 N 3.73%
("375.2")	Found	„ 66.11	„ 6.87 „ 3.50%

The base was prepared from **14** · HCl by partition between ammonium hydroxide solution and chloroform. The chloroform solution was evaporated to dryness i.V. and the residue was crystallized from diisopropyl ether/hexane.

14: m.p. 136–137°. – ^{1}H-NMR. (80 MHz, $CDCl_3$): 2.55 (*s*, 3 H, NCH_3); 2.3 to 3.25 (*m*, 7 H, 3 CH_2 and H–C(6a)); 3.76, 3.84 and 3.90 (3*s*, 3 H each, 3 OCH_3); 6.66 (*s*, 1H, H–C(3)); 6.82 (*d*×*d*, *J*=8.5, *J*=3, 1H, H–C(9)); 7.20 (*d*, *J*=8.5, 1H, H–C(8)); 8.09 (*d*, *J*=3, 1H, H–C(11)). – MS.: 325 (78, M^+), 324 (100), 310 (52, $M-CH_3$).

b) *From* rac-*nuciferoline* (**15**). *rac*-Nuciferoline hydrochloride (**15** · HCl) was dissolved in a small volume of methanol and treated with an excess of diazomethane in ether. After standing at RT. overnight, the solvents were removed i.V., the residue was dissolved in benzene and chromatographed through aluminum oxide. **14** was eluted with benzene and crystallized from diisopropyl ether/hexane, m.p. 137.5–138.5°. It was identical with **14** obtained from **13** (identical Rf values in 2 TLC. systems and superimposable IR., NMR. and mass spectra).

Ethyl 2-(2,3-dimethoxyphenyl)-4,6-dioxocyclohexanecarboxylate (**17**). To a warm solution of sodium ethoxide prepared from sodium (18.6 g) and abs. ethanol (460 ml), diethyl malonate (131 g) was slowly added. This solution was heated to reflux for 15 min 4-(2,3-dimethoxyphenyl)-3-buten-2-one (**16**, 180.5 g of 88.5% purity) [4] was added during 40 min, and reflux maintained for 4 h more. After cooling, the reaction mixture was diluted with ether and the precipitated sodium salt of **17** was filtered off, washed with ether, and then dissolved in water. This solution was acidified with 10% hydrochloric acid. The precipitate was filtered off, washed with water and dried, yielding 213.3 g (86%) of **17**, m.p. 140–141°. From the filtrate of the sodium salt, a second crop of 14.1 g (5.6%) of **17** was obtained by evaporation to dryness, partition of the residue between benzene and Na_2CO_3-solution, and acidification of the aqueous phase. For analysis, a sample was recrystallized from ethanol, m.p. 140–141°. – IR.: 2600–2700 (OH), 1740 (C=O ester), 1610, 1588, 1485 (conj. C=O, C=C, aromatic rings), 1240 (ester), 1154, 1090 (aryl ether), 790 (1,2,3 trisubst. benzene).

$C_{17}H_{20}O_6$ (320.3) Calc. C 63.74 H 6.29% Found C 63.50 H 6.29%

5-(2,3-Dimethoxyphenyl)-1,3-cyclohexanedione (**18**). **17** (213.3 g) was dissolved in 2N aqueous NaOH and kept at RT. overnight. A slight turbidity was extracted with ether; the aqueous solution was acidified to pH 1 with 6N HCl and heated to 80° for 8 h. After cooling, the precipitate was filtered off, washed with water and dried to afford 164 g (99%) of **18**, m.p. 140–142°. For analysis, a sample was recrystallized from ethanol/ether, m.p. 142–144°. – IR.: 2542 (OH), 1603 (C=O), 1536 (C=C), 1588, 1482 (aromatic rings), 1284, 1221, 1149, 1078 (aryl ether and enol), 791 (1,2,3-trisubstituted benzene).

$C_{14}H_{16}O_4$ (248.3) Calc. C 67.73 H 6.50% Found C 67.80 H 6.51%

5-(2,3-Dimethoxyphenyl)-3-ethoxy-2-cyclohexen-1-one (**19**). A solution of **18** (164 g) and *p*-toluenesulfonic acid (3.1 g) in benzene (1300 ml) and abs. ethanol (370 ml) was refluxed with a *Dean-Stark* trap for 24 h. After cooling, the solution was extracted with a Na_2CO_3-solution and then washed with water. The organic layer was dried (Na_2SO_4) and the solvent evaporated i.V. The residue was triturated with ether, the crystals filtered off and washed with ether to afford 169 g (92%) of **19**, m.p. 100–101°. For analysis, a sample was recrystallized from ether, m.p. 101–103°. – UV.: 251 (4.23). – IR.: 1658 (C=O conj.), 1606 (C=C), 1606, 1586, 1484 (aromatic ring), 1280, 1221, 1213, 1111, 1033, 1004 (aryl and enol ether), 794 (1,2,3-trisubstituted benzene).

$C_{16}H_{20}O_4$ (276.3) Calc. C 69.55 H 7.30% Found C 69.22 H 7.31%

[5-(2,3-Dimethoxyphenyl)-3-ethoxy-2-cyclohexen-1-ylidene]-acetonitrile (**20**). NaH (from 45.6 g of a 55 to 60% dispersion in mineral oil washed several times with hexane) was suspended under argon in tetrahydrofuran (430 ml). Diethyl cyanomethylphosphonate (214.2 g) was added during 50 min at 30

to 35° with stirring. After 2 h, a dark solution was obtained, which was added dropwise during 3 h to a boiling solution of **19** (169 g) in tetrahydrofuran (300 ml). The reaction mixture was refluxed for 19 h and then evaporated to dryness i.V. The residue was partitioned between benzene and water; some insoluble tarry material was removed by decantation. The benzene solution was washed with water to neutrality, dried (Na_2SO_4) and evaporated to dryness. The residue was triturated with ether, affording crystalline **20** which was filtered off (139 g). The filtrate was evaporated to dryness and the residue chromatographed on silica gel. Some impurities were eluted with benzene, and compound **20** with benzene/ethanol 99:1. From the residue of these eluates, 24 g of **20** could be crystallized from ether, to afford a total of 163 g (89%) of **20**. For analysis, a sample was recrystallized from ether; m.p. 128–130°. – IR.: 2208 (CN conj.), 1622 (C=C), 1587, 1480 (aromatic rings), 1223 (enol ether), 794 (1,2,3-trisubstituted benzene).

$C_{18}H_{21}NO_3$ (299.4) Calc. C 72.22 H 7.07 N 4.68% Found C 71.89 H 7.22 N 4.49%

5-Ethoxy-2',3'-dimethoxy-3-biphenylylacetonitrile (**21**). To a solution of **20** (175 g) in benzene (1450 ml) 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 132.2 g) was added in small portions. The resulting suspension was stirred at reflux temperature during 8 h. The precipitated 2,3-dichloro-5,6-dicyanohydroquinone was filtered off and the filtrate chromatographed through aluminum oxide (700 g). The product **21** was eluted with benzene and benzene/ethanol 99:1 to afford 174.4 g of an oil which was directly used for the next step. For analysis, a sample was distilled at 195°/0.05 Torr. – IR.: 2258 (CN); 1598, 1580, 1480 (aromatic rings); 1266, 1230, 1125, 1050 (aryl ether); 792 (1,2,3-trisubstituted benzene). – ^{1}H-NMR. (90 MHz, $CDCl_3$): 1.43 (*t*, $J=7$, 3 H, CH_2CH_3); 3.61 (*s*, 3 H, OCH_3); 3.75 (*s*, 2 H, CH_2CN); 3.91 (*s*, 3 H, OCH_3); 4.09 (*qa*, $J=7$, 2 H, CH_2CH_3); 6.8 to 7.21 (*m*, 6 H arom.).

$C_{18}H_{19}NO_3$ (297.4) Calc. C 72.71 H 6.44 N 4.71% Found C 72.53 H 6.61 N 4.49%

3-(2,3-Dimethoxyphenyl)-5-ethoxyphenethylamine (**22**). A solution of **21** (209 g) in methanol (4.4 l) and ammonia (120 g) was hydrogenated during 20 h at 100° under 40 atm in the presence of *Raney* nickel (60 g). After elimination of the catalyst by filtration, the solution was evaporated to dryness i.V. The residue was dissolved in benzene and diluted aqueous ammonia. A voluminous precipitate was filtered off. The benzene layer was separated, washed with water to neutrality, dried (Na_2SO_4) and evaporated to dryness i.V. The residue (184.4 g) was distilled in 25–30 g portions at 195°/0.05 Torr, yielding 159.6 g (75.3%) of **22** as an oil.

$C_{18}H_{23}NO_3$ (301.4) Calc. C 71.74 H 7.69 N 4.65% Found C 71.58 H 7.90 N 4.37%

A 1:1 maleate was prepared by addition of an equivalent of maleic acid in acetone and was recrystallized from 2-propanol/ether. **22** · maleate 1:1, m.p. 102–103°. – ^{1}H-NMR. (60 MHz, DMSO-d): 1.40 (*t*, $J=7$, 3 H, CH_2CH_3); 2.8 to 3.3 (*m*, 4 H, CH_2CH_2); 3.63 and 3.88 (2*s*, 3 H each, 2 OCH_3); 4.11 (*qa*, $J=7$, 2 H, CH_2CH_3); 6.10 (*s*, 2 H, CH=CH); 6.8 to 7.25 (*m*, 6 H arom.); 7.7 to 8.1 (br., 3 H, H_3N^+).

$C_{18}H_{23}NO_3 \cdot C_4H_4O_4$ (417.5) Calc. C 63.30 H 6.52 N 3.35% Found C 63.12 H 6.69 N 3.21%

Ethyl N-*[3-(2,3-dimethoxyphenyl)-5-ethoxyphenethyl]oxamate* (**23**). A solution of **22** (24.8 g) in diethyl oxalate (100 ml) was dropped during 2 h to diethyl oxalate (100 ml) heated to 100°. After further 0.5 h at 100°, the reaction mixture was cooled, mixed with 1 l of hexane and chromatographed through silica gel (300 g). Unreacted diethyl oxalate was eluted with hexane and benzene and the product **23** with 3% methanol in benzene. 32 g (97%) of **23** were obtained as an oil. – IR.: 3350 (NH), 1738 (C=O ester), 1705 (C=O amide), 1595, 1580, 1480 (aromatic rings), 1531 (amide II), 1227 (ester), 1050 (aryl ether), 795 (1,2,3-trisubstituted benzene). – MS.: 401 (20, M^+), 428 (9, $M-COOC_2H_5$), 284 (100, $M-H_2NCOCOOC_2H_5$), 255 (8).

Ethyl 8-(2,3-dimethoxyphenyl)-6-ethoxy-3,4-dihydro-1-isoquinolinecarboxylate (**24**). A solution of **23** (30 g) in polyphosphoric ester (200 g; prepared according to [5]) was heated under argon to 80° for 12 h. After cooling to 0°, the mixture was quenched with ice and then extracted 5 times with ether. The aqueous layer was alkalized to pH 7.5 with aqueous ammonia and then extracted 5 times with chloroform. The residue from the chloroform extracts (30 g) was dissolved in benzene and chromatographed through silica gel (900 g). Elution with benzene containing increasing amounts of methanol (0.5 to 3%) afforded a total of 24 g (83%) of oily **24**, pure on TLC., which crystallized from isopropyl ether/hexane;

m.p. 120°. – UV.: 254*s* (4.01), 290 (4.01). – IR.: 1731 (C=O ester), 1600, 1580, 1564, 1479 (C=N and aromatic rings), 1208 (ester), 1265, 1138, 1039 (ether), 797 (1,2,3-trisubstituted benzene). – ^{1}H-NMR. (60 MHz, $CDCl_3$): 1.09 and 1.39 (2*t*, J=7, 3 H each, 2 CH_2CH_3); 2.52 to 2.88 (*m*, 2 H, 2 H–C(4)); 3.45 to 4.25 (*m*, 6 H, 2 OCH_2 and 1 NCH_2); 3.64 and 3.87 (2*s*, 2 OCH_3); 6.6 to 7.1 (*m*, 5 H arom.). – MS.: 383 (35, M^+), 354 (8), 339 (15), 324 (21), 310 (48, $M-COOC_2H_5$), 308 (100), 296 (15), 280 (16), 266 (9).

$C_{22}H_{25}NO_5$ (383.4) Calc. C 68.91 H 6.57 N 3.65% Found C 68.80 H 6.25 N 3.47%

*2-Ethoxy-10,11-dimethoxy-7*H*-dibenzo[*de,g*]quinolin-7-one* (**25**). a) *From* **24**. A mixture of **24** (24 g) and polyphosphoric acid (240 g) was heated under argon to 65° for 1.5 h. The mixture was cooled, quenched with ice, alcalized to pH 7.5 with aqueous ammonia and extracted 4 times with chloroform. The solvent was removed i.V. and the residue was suspended in hot ethanol (200 ml) to afford, after cooling, 10.9 g of **25**, m.p. 209°. The filtrate was evaporated to dryness, the residue dissolved in benzene and chromatographed through silica gel (260 g). Elution with benzene gave 3.1 g of starting material, m.p. 120°; with benzene/methanol 19:1, further 4.2 g of **25**, m.p. 206–210°, could be obtained, giving a total yield of 87% (calculated on converted **24**). For analysis, a sample was crystallized from ethanol, m.p. 210°, yellow. – UV.: 269 (4.50), 284*s* (4.28), 317 (3.80), 334*s* (3.90), 347 (4.03), 396 (3.97). – IR.: 1662 (C=O), 1616, 1584, 1495, 1484 (aromatic rings), 1284, 1246, 1190, 1081, 1080 (aryl ether), 814, 805 (vicinal arom. H). – ^{1}H-NMR. (90 MHz, $CDCl_3$): 1.53 (*t*, J=7, 3 H, CH_2CH_3); 3.96 and 4.04 (2*s*, 3 H each, 2 OCH_3); 4.35 (*qa*, J=7, 2 H, CH_2CH_3); 7.10 (*d*, J=2.5, 1H, H–C(3)); 7.14 (*d*, J=8.5, 1H, H–C(9)); 7.76 (*d*, J=5.5, 1H, H–C(4)); 8.42 (*d*, J=8.5, 1H, H–C(8)); 8.86 (*d*, J=5.5, 1H, H–C(5)); 9.08 (*d*, J=2.5, 1H, H–C(1)). – MS.: 335 (100, M^+), 321 (15), 320 (26), 292 (30), 264 (8), 193 (9), 164 (7), 144 (9).

$C_{20}H_{17}NO_4$ (335.4) Calc. C 71.63 H 5.11 N 4.18% Found C 71.68 H 5.28 N 3.95%

b) *From* **23**. A solution of **23** (9 g) in polyphosphoric acid (45 g) was heated 1 h to 80° under nitrogen. After cooling, the mixture was quenched with ice and alkalized to pH 8 with Na_2CO_3-solution and then extracted 5 times with chloroform. The chloroform solution was evaporated to dryness i.V. The residue (8.2 g) was dissolved in hot ethanol (500 ml) and treated with decolorizing charcoal. The charcoal was filtered off and the filtrate concentrated to about 50 ml. The yellow crystals were filtered off to afford 2.5 g (33%) of **25**, m.p. 205–208°. TLC. analysis of the residue from the mother liquor (3.3 g) showed it to contain mainly unreacted **23**.

rac-*2-Ethoxy-10,11-dimethoxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinoline* (**26**). A solution of **25** (4.2 g) in a mixture of acetic acid (350 ml) and 8N aqueous HCl (525 ml) was treated with zinc powder (100 g). The mixture was heated to reflux; after 1 h, zinc powder (50 g) was again added, and the mixture was refluxed 3 h more. After cooling, the solution was decanted from zinc, neutralized with aqueous ammonia (to pH 7) and extracted with chloroform. The solvent was removed i.V., the residue was dissolved in ethanol and treated with alcoholic HCl-solution. Addition of ether gave crystalline **26** · HCl (3.6 g, m.p. 255–258°; 79%), pure on TLC. For analysis, a sample was recrystallized from ethanol/ether, m.p. (dec) 270°. – UV.: 219 (4.60), 230*s* (4.50), 268 (4.20), 275 (4.19), 299 (3.80). – ^{1}H-NMR. (60 MHz, DMSO-d): 1.38 (*t*, J=7, 3 H, CH_2CH_3); 3.67 and 3.85 (2*s*, 3 H each, 2 OCH_3); 4.07 (*qa*, J=7, 2 H, CH_2CH_3); 6.82 (*d*, J=2.5, 1H, H–C(3)); 7.08 (*AB*-system, 2 H, H–C(8) and H–C(9)); 7.80 (*d*, J=2.5, 1H, H–C(1)). – MS.: 325 (55, M^+), 324 (100, $M-CH_3$), 310 (10), 296 (10), 280 (14).

$C_{20}H_{23}NO_3 \cdot HCl$	Calc.	C 66.38	H 6.69	N 3.87 Cl 9.79%
(361.9)	Found	„ 66.47	„ 6.66	„ 3.77 „ 9.89%

rac-*2-Ethoxy-10,11-dimethoxyaporphine* (**27**). The base (0.75 g) extracted from 0.83 g of **26** · HCl was dissolved in methanol (10 ml) and 1.15 ml of 37% aqueous formaldehyde was added. After 30 min at RT., $NaBH_4$ (0.4 g) was added in portions. After 1 h at RT., the methanol was removed i.V., the residue diluted with water and extracted 4 times with chloroform. The solvent was evaporated, the residue dissolved in ethanol, treated with charcoal, the charcoal filtered off and the filtrate evaporated to dryness. The residue (0.6 g) was chromatographed through silica gel. **27** was eluted with benzene/methanol 99:1, and transformed into the hydrochloride with alcoholic HCl-solution. After recrystalliza-

tion from ethanol/ether, **27** · HCl melted at 195°. – UV.: 219 (4.59), 230*s* (4.50), 268 (4.19), 275 (4.18), 298 (3.80). – ^{1}H-NMR. (90 MHz, DMSO-d): 1.34 (*t*, $J=7$, 3 H, CH_2CH_3); 2.98 (*s*, N–CH_3); 3.63 and 3.82 (2*s*, 3 H each, 2 OCH_3); 4.05 (*qa*, $J=7$, 2 H, CH_2CH_3); 6.79 (*d*, $J=2.5$, 1H, H–C(3)); 7.01 and 7.12 (*d*×*d*, $J=8.5$, 2 H, H–C(8) and H–C(9)); 7.76 (*s*, $J=2.5$, 1H, H–C(1)); 11.9 (br., 1H, HCl). – MS.: 339 (62, M^+), 338 (100), 324 (30, $M-CH_3$), 296 (19), 252 (9), 36 (8).

$C_{21}H_{25}NO_3 \cdot HCl$ (375.9) Calc. C 67.10 H 6.97 N 3.73% Found C 67.23 H 7.04 N 3.66%

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