# Benzomorphan Related Compounds. XVII [1]. Oxidative Cyclization of *N*-Arylethyl-6,7-benzomorphans [2]



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The synthesis of two new bridged polycyclic systems (I and II), possessing a rigid *N*-arylethylbenzomorphan structure, by mercuric acetate cyclization of the corresponding seco derivatives (IV and VI, respectively) is described. The relative configuration of these compounds and the preferred indolo[2,3-*a*]- or benzo[*a*]quinolizidine conformation is assigned.

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One of the more studied aspects in the 6,7-benzomorphan series [3] has been the effect of the nitrogen substituent on the morphine-like activity of these compounds. In this sense, it has been established that *N*-phenethyl derivatives show generally enhanced activity compared to the parent *N*-methyl compounds not only in 6,7-benzomorphans but also in morphine itself and in related synthetic analgesics [4]. Nevertheless, a limited number of 6,7-benzomorphans with *N*-arylethyl substituents other than phenethyl have been prepared [5], and very little is known about the influence that the orientation of the aromatic ring of such substituents can have from a pharmacological standpoint.

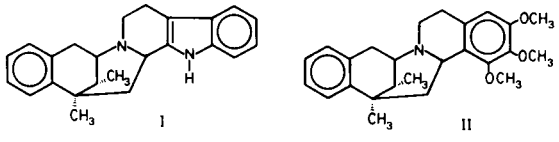


Figure 1

In connection with our studies on benzomorphan related compounds [6] we now wish to report the synthesis of two new polycyclic systems, I and II, with a rigid *N*-arylethylbenzomorphan structure that implies a conformational restriction of the piperidine nitrogen substituent by connection of the aryl and piperidine rings. Similar conformationally restrained analogues of fentanyl analgesics have been recently described [7]. On the other hand, compounds I and II can be considered respectively as bridged indolo[2,3-*a*]- and benzo[*a*]quinolizidines [8], structural moieties common to many natural products, in which the piperidine ring is part of a 6,7-benzomorphan system.

Benzomorphan IIIb, the starting material for our synthesis, was conveniently prepared in four steps following a similar procedure to that previously reported [9,10]. Thus, condensation between 1,3,4-trimethylpyridinium iodide and benzylmagnesium chloride followed by sodium borohydride reduction [11] led to a 2-benzyltetrahydropyridine, whose cyclization with 48% hydrobromic acid [12] afforded a 10:1 diastereomeric mixture from which the major $\alpha$-isomer IIIa was separated by fractional crystallization of its hydrochloride. The von Braun *N*-demethylation of IIIa furnished the desired dimethylbenzomorphan IIIb [10].

Compound IV was obtained in 75% yield by direct alkylation of the secondary amine IIIb with 2-(3-indolyl)ethyl bromide in the presence of *N,N*-dimethylformamide as a solvent [13,14]. In turn, phenethylamine VI was prepared in 68% overall yield by acylation of IIIb with 3,4,5-trimethyloxyphenylacetyl chloride followed by lithium aluminum hydride reduction of the resulting amide V [16]. The nmr spectrum of V shows, as the more noteworthy aspects, duplicate singlets due to the aromatic protons ($\delta$ 6.25, 1.2 H and $\delta$ 6.35, 0.8 H) and the methylene group of the acyl moiety ($\delta$ 3.43, 1.2 H and $\delta$ 3.51, 0.8 H), thus indicating the existence of rotamers [17].

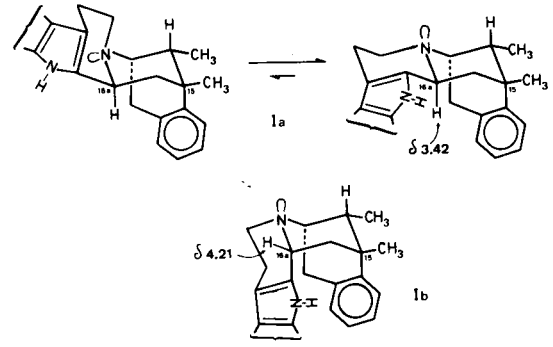
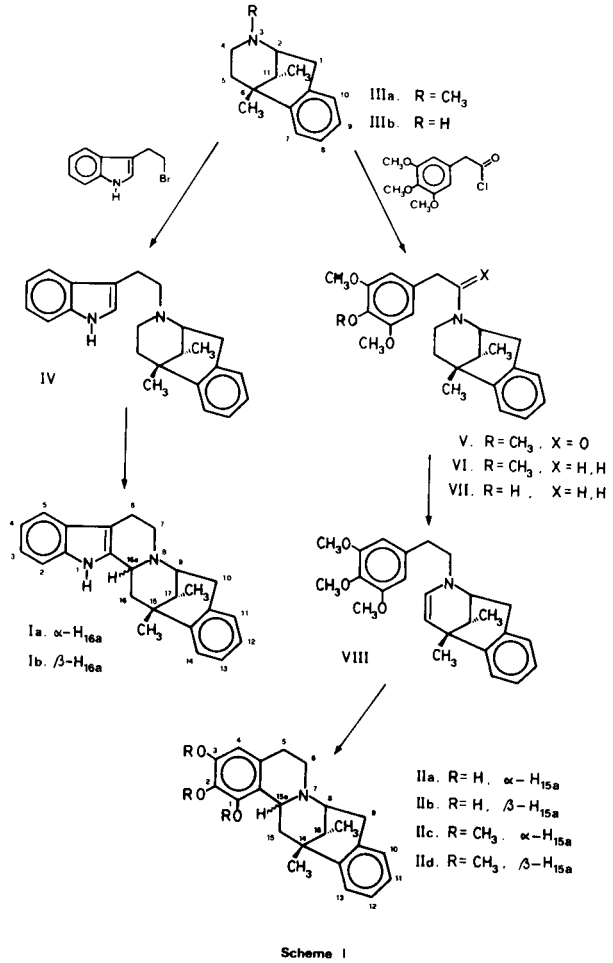


Figure 2

Oxidative cyclization of IV was initially carried out by heating in the presence of a large excess of mercuric acetate in 5% acetic acid followed by hydrogen sulfide treatment and sodium borohydride reduction of the possible over-oxidized products. Operating in this way amine IIIb, formed by hydrolysis of the exocyclic iminium salt generated by oxidation at the terminal carbon atom of the indolylethyl chain, was obtained as the major product (44% yield). The desired cyclization product Ia, formed by

electrophilic attack of the endocyclic iminium salt upon the indole 2-position, was isolated in low yield (16%). Formation of epimer Ib was not observed under these conditions. This result was somewhat surprising since formation of indolo[2,3-*a*]quinolizidines by mercuric acetate cyclization of 1-(3-indolylethyl)piperidines has been widely used in the synthesis of indole alkaloids [18]. In these cases oxidation occurs predominantly at the $\alpha$-piperidine carbon atoms to give the expected cyclization products *via* the corresponding tetrahydropyridinium salts whereas the isomeric exocyclic iminium salt is formed in very small extent [18b,c].

However, when oxidation was carried out in the presence of ethylenediaminetetraacetic acid disodium salt [18a,c,d] and then the reaction mixture was treated with sodium borohydride, a nearly equimolecular epimeric mixture of cyclization products Ia and Ib was obtained in 75% yield. Their stereochemical assignment was effected by nmr [19] from the chemical shift of the C-16a proton in both isomers ($\delta$ 3.42 and $\delta$ 4.21), taking into account that the piperidine ring of our indolo[2,3-*a*]quinolizidines can only adopt one chair conformatiod since it is included in a rigid bridged system. Accordingly, two quinolizidine conformations (*cis* and *trans*) are possible for the isomer Ia (a *trans* $C_{16a}$-H/$C_{15}$-$CH_3$ relationship) and only one (*cis* fusion) for Ib (a *cis* $C_{16a}$-H/$C_{15}$-$CH_3$ relationship). In the first case, the *trans* conformation is expected to be the preferred one because of the equatorial position of the *N*-substituent [20].




Scheme I

Therefore, the higher field isomer ($\delta$ 3.42, *trans* conformation) [19] corresponds to Ia and the lower field isomer ($\delta$ 4.21, *cis* conformation) [19] is assigned to Ib.

The different stereochemical result in the oxidative cyclization of IV in the absence or in the presence of EDTA can be interpreted by considering that in the first case the indole nucleus is metallated [21] by mercuric acetate and that cyclization occurs, after destruction of the mercury complexes, during the hydrogen sulfide treatment. Attack of the indole ring upon the less hindered face of the iminium salt would lead stereoselectively to the isomer Ia. On the contrary, in the presence of EDTA, metallation of indole would be partially inhibited and the cyclized product, formed during the oxidation step, could be over-oxidized in part to a hexacyclic iminium salt. The stereoselective attack of hydride ion upon the less hindered face of this iminium salt during the final sodium borohydride treatment would justify the formation of isomer Ib under these conditions.

The oxidative cyclization of phenethylamine VI in the absence of EDTA under the same conditions initially used for indolylethylamine IV was unsuccessful. Oxidation to the iminium salt take actually place, as demonstrated by isolation of enamine VIII in 80% yield when the final reducing sodium borohydride treatment was omitted [22]. However, the cyclization step could not be achieved under these conditions and the starting amine VI was recovered in almost quantitative yield after reduction with sodium borohydride. In fact, cyclizations of iminium salts upon benzene rings are known to require more vigorous conditions than upon indole ones [23].

The enamine VIII shows a characteristic absorption at 1630 $cm^{-1}$ (C=C) in the ir spectrum, shifted toward 1688 $cm^{-1}$ (C=N<) in the perchlorate salt [24,25]. On the other hand, in the nmr spectrum of VIII the vinylic protons of the enamine system appear as two doublets at $\delta$ 4.02 and $\delta$ 5.61. Their coupling constant (J = 7.5 Hz) reveals a *cis* configuration and, therefore, an endocyclic position of the double bond [26]. In the nmr spectrum of the perchlorate salt a broadened singlet at $\delta$ 8.57 was observed for the proton attached to the carbon of the iminium grouping [25].

The cyclization of enamine VIII offered some difficulties. Thus, phenethylamine VI was obtained when VIII was refluxed in 50% acetic acid for 4 hours or in 15% hydrochloric acid for 3 hours, and then treated with sodium borohydride. Upon heating in 50% hydrochloric acid at 100° for 6 or 24 hours and subsequent sodium

borohydride reduction VIII was converted into phenol VII, which was transformed into VI by treatment with excess ethereal diazomethane solution. Finally, cyclization was achieved after prolonged heating (18 hours at 100°) of VIII in concentrated hydrochloric acid, the product being an epimeric mixture of the hydrochlorides of triphenols IIa and IIb. Since attempts to separate and purify this material by fractional crystallization resulted in darkening and the corresponding bases were air sensitive, the mixture was allowed to react without further purification with excess diazomethane. The resulting trimethoxy compounds IIc and IId were separated by column chromatography and assigned as *trans* and *cis*, respectively, (relative orientation of the hydrogen atom at C-15a and the methyl group at C-14) by nmr as above in the indole series.

## EXPERIMENTAL

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous magnesium sulfate powder. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer model R-24 B Spectrometer (60 MHz, tetramethylsilane at $\delta$ 0.0 ppm as internal standard) and chemical shifts are reported as $\delta$ values in parts per million (ppm). Infrared spectra were determined on a Perkin-Elmer model 577 Spectrophotometer. Column chromatography were carried out on silica gel (silica gel 60, Merck, 63-200 $\mu$m), and the spots were located with uv light or iodoplatinate reagent. Elmental analyses were performed by Instituto de Química Bio-Orgánica, Barcelona.

*rel*-(2*R*,6*R*,11*S*)-6,11-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (IIIb).

Reaction [9] between 1,3,4-trimethylpyridinium iodide (74.7 g, 0.30 mole) and benzylmagnesium chloride (from 14 g of magnesium and 73 g of benzyl chloride in 350 ml of ether) followed by sodium borohydride (11 g, 0.30 mole) reduction in a methanol-water solution of sodium hydroxide afforded 49.7 g of 2-benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine. This compound was refluxed in 550 ml of 48% hydrobromic acid to give, after distillation (108-110°/1 mm Hg), 36.7 g of a 10:1 epimeric mixture from which the major isomer was separated by fractional crystallization of its hydrochloride. After basification, 24.7 g (38% overall yield) of pure IIIa was obtained. This base (20 g, 93 mmoles) was allowed to react with cyanogen bromide (12 g, 113 mmoles) in accordance with a previously described procedure [10] to give 9.7 g (52% yield) of IIIb; picrate, mp 228-229° (ethanol) (lit [10] 232-233°).

*rel*-(2*R*,6*R*,11*S*)-3-[2-(3-Indolyl)ethyl]-6,11-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (IV).

A stirred mixture of IIIb (0.73 g, 3.62 mmoles), 2-(3-indolyl)ethyl bromide [27] (0.81 g, 3.62 mmoles), anhydrous potassium carbonate (dried at 190° for 30 minutes) (1.05 g, 7.59 mmoles) and 25 ml of anhydrous *N,N*-dimethylformamide was heated at 75-80° for 24 hours. After cooling, the mixture was poured into 100 ml of water and extracted with ether. The organic extract was dried, the solvent was removed, and the residue was purified by column chromatography. Elution with chloroform-methanol (99:1) gave 0.94 g (75% yield) of IV, mp 54-56° (acetone-ether); ir (chloroform): 3480 $cm^{-1}$ (N-H); nmr (carbon tetrachloride): $\delta$ 0.80 (d, CH-C*H*$_3$, 3H, J = 7 Hz), 1.29 (s, C-CH$_3$, 3H), 1.2-3.4 (complex signal, CH$_2$ and CH, 12H), 6.77 (s, indole C-2H, 1H), 6.8-7.2 (m, benzene and indole protons, 7H), 7.41 (m, indole C-7H, 1H), 8.60 (s, N-H, 1H); hydrochloride, mp 235-237° (acetone-ethanol).

*Anal.* Calcd. for $C_{24}H_{29}ClN_2$: C, 75.66; H, 7.67; N, 7.35; Cl, 9.30. Found: C, 75.45; H, 7.80; N, 7.26; Cl, 9.49.

*rel*-(9*R*,15*R*,16a*S*,17*S*)- and *rel*-(9*R*,15*R*,16a*R*,17*S*)-15,17-Dimethyl-1,6,7,9,10,15,16,16a-octahydro-9,15-methanobenzo[*e*]azocino[1′,2′-1,2]-pyrido[3,4-*b*]indole (Ia and Ib).

Method A.

A solution of IV (0.51 g, 1.47 mmoles) and mercuric acetate (4.70 g, 14.77 mmoles) in 30 ml of 5% aqueous acetic acid was refluxed for 3 hours under nitrogen atmosphere, and then hydrogen sulfide was bubbled through the solution for 45 minutes at the same temperature. After filtration, the mixture was concentrated to one half of its volume, basified with solid sodium carbonate, diluted with methanol (30 ml) and cooled to 0°. To the resulting solution was added portionwise 0.28 g (7.35 mmoles) of sodium borohydride. After this mixture was stirred at room temperature for one hour, the solution was concentrated to a small volume, diluted with water (40 ml) and extracted with ether. The ethereal extacts were dried, filtered, and evaporated to dryness to give an oil (0.26 g) which was chromatographed over silica gel. Elution with benzene-chloroform (1:4) gave 0.08 g (16% yield) of Ia; nmr (deuteriochloroform): $\delta$ 0.85 (d, CH-C*H*$_3$, 3H, J = 7 Hz), 1.37 (s, C-CH$_3$, 3H), 1.2-2.2 (complex signal, CH$_2$ and C*H*-CH$_3$, 3H), 2.5-3.2 (complex signal, Ar-CH$_2$, N-CH$_2$ and N-CH, 7H), 3.42 (dd, $C_{16a}$-H, 1H, $J_{aa}$ = 10 Hz, $J_{ae}$ = 6 Hz), 6.9-7.4 (m, benzene and indole protons, 8H); hydrochloride, mp 302-304° (acetone); picrate, mp 218-219° dec (ethanol). Elution with benzene-chloroform-diethylamine (29:70:1) gave 0.12 g (44% yield) of amine IIIb.

Method B.

Mercuric acetate (4.64 g, 14.56 mmoles) and ethylenediaminetetraacetic acid disodium salt dihydrate (6.50 g, 17.46 mmoles) were added to a solution of IV (0.50 g, 1.45 mmoles) in 50 ml of 5% aqueous acetic acid. Dry nitrogen was bubbled for 10 minutes through the solution, and then this was refluxed for one hour. After cooling, the solution was made alkaline with solid sodium carbonate, and a freshly prepared solution of sodium borohydride (1 g, 26.43 mmoles) in methanol (15 ml) was added portionwise at 0° with stirring. The precipitate was removed by filtration *in vacuo*, and the clear solution was evaporated to dryness. The residue was distributed between water and ether, the organic layer was decanted, and the aqueous one was extracted several times with ether. The whole ethereal extracts were dried and evaporated to give 0.37 g (75% yield) of an epimeric Ia and Ib mixture, which was separated by column chromatography. On elution with benzene-chloroform (2:3), 0.19 g (38% yield) of Ia were obtained whereas elution with chloroform gave 0.17 g (34% yield) of Ib; nmr (deuteriochloroform): $\delta$ 0.87 (d, CH-C*H*$_3$, 3H, J = 7 hz), 1.38 (s, C-CH$_3$, 3H), 1.3-2.3 (complex signal, CH$_2$ and C*H*-CH$_3$, 3H), 2.5-3.5 (complex signal, Ar-CH$_2$, N-CH$_2$ and N-CH, 7H), 4.21 (t, $C_{16a}$-H, 1H, J = 6 hz), 6.8-7.3 (m, benzene and indole protons, 8H); hydrochloride, mp 308-'309° (acetone); picrate, mp 177-179° dec (ethanol).

*Anal.* Calcd. for $C_{30}H_{29}N_5O_7$ (mixture of epimers): C, 63.04; H, 5.11; N, 12.25. Found: C, 63.03; H, 5.11; N, 12.21.

*rel*-(2*R*,6*R*,11*S*)-6,11-Dimethyl-3-(3,4,5-trimethoxyphenylacetyl)-1,2,3,-4,5,6-hexahydro-2,6-methano-3-benzazocine (V).

A solution of 3,4,5-trimethoxyphenylacetyl chloride (28) (10.2 g, 41.7 mmoles) in chloroform (100 ml) was added dropwise over one hour period to a stirred mixture of IIIb (8.4 g, 41.7 mmoles), sodium carbonate decahydrate (8.2 g, 28.6 mmoles), chloroform (100 ml) and water (100 ml). After stirring at room temperature for two hours, the organic layer was decanted and evaporated. The residue was dissolved in ether, and the resulting solution was successively washed with 10% hydrochloric acid and saturated sodium bicarbonate solution. The ethereal layer was dried and evaporated *in vacuo* to give an oil which was filtered through a silica gel column. Elution with chloroform gave 13.5 g (79% yield) of amide V as a syrup oil; ir (chloroform): 1618 $cm^{-1}$ (C=O); nmr (carbon tetrachloride): $\delta$ 0.87 (d, CH-C*H*$_3$, 3H, J = 7 Hz), 1.31 (s, C-CH$_3$, 3H), 1.3-2.0 (complex signal, C-CH$_2$ and C*H*-CH$_3$, 3H), 2.1-3.3 (complex signal, Ar-CH$_2$ and CON-C$_4$-H axial, 3H), 3.43 and 3.51 (2 singlets, Ar-CH$_2$CO, 2H), 3.64 and 3.67 (2 singlets, *para*-OCH$_3$, 3H), 3.70 and 3.73 (2 singlets, *meta*-OCH$_3$,

6H), 3.8-4.2 (2 partially masked signals, CON-$C_4$-H equatorial, 1H), 4.40 and 4.78 (2 broad signals, CON-$C_2$-H, 1H), 6.25 and 6.35 (2 singlets, aromatic, 2H), 6.97 (m, aromatic, 4H). An analytical sample was obtained by distillation on a Büchi GKR-50 Kugelrohr apparatus, bp 230-240°, 0.01 mm Hg (oven temperature).

*Anal.* Calcd. for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.44; H, 7.56; N, 3.24.

*rel*-(2*R*,6*R*,11*S*)-6,11-Dimethyl-3-(3,4,5-trimethoxyphenethyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (VI).

A solution of V (13.5 g, 33 mmoles) in 80 ml of anhydrous ether was added dropwise to a stirred suspension of lithium aluminum hydride (3.75 g, 99 mmoles) in anhydrous ether (170 ml). The resulting mixture was refluxed for 16 hours. After the solution was cooled to 0°, 20 ml of 0.5 *N* sodium hydroxide solution were added. The precipitate was removed by filtration, and the filtrate was evaporated to dryness. The resulting residue was dissolved in 20% hydrochloric acid and washed twice with ether. The aqueous solution was basified with concentrated ammonium hydroxide and extracted with ether. The evaporation of the dried ethereal extracts gave an oil (11.5 g) which was filtered through a silica gel column. On elution with chloroform-methanol (95:5), 11.2 g (85% yield) of VI were obtained; nmr (carbon tetrachloride): δ 0.87 (d, CH-C*H*$_3$, 3H), 1.39 (s, C-CH$_3$, 3H), 1.1-2.2 (complex signal, C-CH$_2$ and C*H*-CH$_3$, 3H), 2.3-3.2 (complex signal, Ar-CH$_2$, N-CH$_2$ and N-CH, 9H), 3.67 (s, *para*-OCH$_3$, 3H), 3.76 (s, *meta*-OCH$_3$, 6H), 6.28 (s, aromatic, 2H), 6.95 (m, aromatic, 4H); hydrochloride, mp 238.5-240° dec (acetone-ethanol).

*Anal.* Calcd. for $C_{25}H_{34}ClNO_3$: C, 69.50; H, 7.81; N, 3.24; Cl, 8.20. Found: C, 69.44; H, 7.96; N, 3.22; Cl, 8.34.

*rel*-(2*R*,6*S*,11*S*)-6,11-Dimethyl-3-(3,4,5-trimethoxyphenethyl)-1,2,3,6-tetrahydro-2,6-methano-3-benzazocine (VIII).

A solution of VI (1 g, 2.52 mmoles) and mercuric acetate (4 g, 12.6 mmoles) in 10% aqueous acetic acid (60 ml) was refluxed for 7 hours under nitrogen atmosphere, after which a precipitate of mercurous acetate was observed. Hydrogen sulfide was bubbled through the refluxing mixture for 45 minutes. The precipitate was filtered off and washed with 60 ml of 10% aqueous acetic acid. The combined filtrates were concentrated to one half of its volume, basified with solid sodium carbonate, and extracted with ether. The whole ethereal extracts were dried and evaporated to give 0.80 g (80% yield) of enamine VIII; ir (chloroform): 1630 cm$^{-1}$ (C=C); nmr (carbon tetrachloride): δ 0.88 (d, CH-C*H*$_3$, 3H, J = 7 Hz), 1.36 (s, C-CH$_3$, 3H), 1.85 (m, C*H*-CH$_3$, 1H), 2.4-3.3 (complex signal, Ar-CH$_2$ and N-CH, 7H), 3.64 (s, *para*-OCH$_3$, 3H), 3.68 (s, *meta*-OCH$_3$, 6H), 4.02 (d, C-C= 1H, J = 7.5 Hz), 5.61 (d, N-C= 1H, J = 7.5 Hz), 6.22 (s, aromtic, 2H), 6.96 (m, aromatic, 4H); perchlorate, mp 177.5-179 (ethanol); ir (potassium bromide): 1688 cm$^{-1}$ (C=N); nmr (hexadeuteriodimethylsulfoxide): δ 0.96 (d, CH-C*H*$_3$, 3H, J = 7 Hz), 1.46 (s, C-CH$_3$, 3H), 2.12 (m, C*H*-CH$_3$, 1H), 2.5-3.4 (complex signal, N=C-CH$_2$ and Ar-CH$_2$, 6H), 3.66 (s, *para*-OCH$_3$, 3H), 3.74 (s, *meta*-OCH$_3$, 6H), 3.9-4.5 (m, =N-CH$_2$ and =N-CH, 3H), 6.58 (s, aromatic, 2H), 7.18 (m, aromatic, 4H), 8.57 (s, N=CH, 1H).

*Anal.* Calcd. for $C_{25}H_{32}ClNO_7$: C, 60.80; H, 6.52; N, 2.83; Cl, 7.17. Found: C, 61.14; H, 6.63; N, 2.79; Cl, 7.45.

*rel*-(8*R*,14*R*,15a*S*,16*S*)- and *rel*-(8*R*,14*R*,15a*R*,16*S*)-14,16-Dimethyl-1,2,3-trimethoxy-5,6,8,9,15,15a-hexahydro-14*H*-8,14-methanobenzo[*e*]azocino-[2,1-*a*]isoquinoline (IIc and IId).

A solution of the enamine VIII (0.87 g, 2.21 mmoles) in concentrated hydrochloric acid (30 ml) was heated at 95-100° for 18 hours. After cooling, the solution was washed with ether and evaporated to dryness to give 0.78 g of a IIa and IIb hydrochloride mixture as an amorphous solid (instantaneous and intense reddish purple coloration with methanolic ferric chloride); ir (potassium bromide): 3550-3100 cm$^{-1}$ (O-H); nmr (deuteriochloroform): an 1:4 integration ratio for the two aromatic signals, and no OCH$_3$ absorptions were observed.

This solid was dissolved in absolute methanol (10 ml) and treated with 40 ml of a 0.32 *M* freshly prepared ethereal solution of diazomethane (vigorous gas evolution was observed). After the solution was stirred for two hours at room temperature, additional diazomethane (40 ml) was added, and stirring was maintained for 24 hours. Excess of diazomethane was destroyed by the addition of few drops of acetic acid after which the solution was evaporated to dryness. The residue was redissolved in ether, washed with a sodium bicarbonate solution and dried. Evaporation of the solvent led to 0.60 g of a residue which was chromatographed. On elution with benzene-chloroform (1:1) and with chloroform, 0.24 g (27% yield) of IIc and 0.19 g (21% yield) of IId, respectively, were obtained; IIc, nmr (deuteriochloroform): δ 0.82 (d, CH-C*H*$_3$, 3H, J = 7 Hz), 1.24 (s, C-CH$_3$, 3H), 1.2-2.1 (complex signal, C-CH$_2$ and C*H*-CH$_3$, 3H), 2.2-3.2 (complex signal, Ar-CH$_2$, N-CH$_2$ and N-CH, 7H), 3.65, 3.69 and 3.72 (3 singlets, OCH$_3$, 9H), 3.4-3.7 (masked signal, $C_{15a}$-H, 1H), 6.27 (s, aromatic, 1H), 6.97 (m, aromatic, 4H); picrate, mp 193-195° dec (ethanol); IId, nmr (deuteriochloroform): δ 0.83 (d, CH-C*H*$_3$, 3H, J = 7 Hz), 1.25 (s, C-CH$_3$, 3H), 1.2-2.2 (complex signal, C-CH$_2$ and C*H*CH$_3$, 3H), 2.3-3.2 (complex signal, Ar-CH$_2$, N-CH$_2$ and N-CH, 7H), 3.65, 3.69 and 3.70 (3 singlets, OCH$_3$, 9H), 4.26 (broad signal, $C_{15a}$-H, 1H), 6.28 (s, aromatic, 1H), 6.08 (m, aromatic, 4H); picrate, mp 186-188° dec (ethanol).

*Anal.* Calcd. for $C_{31}H_{34}N_4O_{10}$ (mixture of epimers): C, 59.80; H, 5.50; N, 8.99. Found: C, 59.65; H, 5.52; N, 8.70.

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3.52 (t, $OCH_2$, 2H, J = 7 Hz), 6.60 (s, indole C-2 H, 1H), 6.94 (m, indole C-4, C-5 and C-6 protons, 3H), 7.37 (m, indole C-7 H, 1H), 8.02 (broad signal, N-H, 1H).

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