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# THE INTERMOLECULAR BENZYNE CYCLOADDITION (IBC) APPROACH TO 7-SUBSTITUTED APORPHINOIDS. MECHANISTIC CONSIDERATIONS

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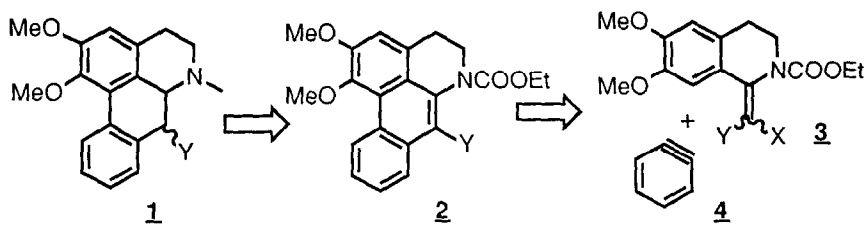
*Abstract.- 7-Alkyl-substituted aporphinoids were obtained in moderate yield through the reaction of N-protected 1-ethylidene-1,2,3,4-tetrahydroisoquinolines with benzyne. 7-Alkoxy and 7-chloro derivatives were also prepared by this route, though in lower yield. Mechanistic proposals for the aromatization step are discussed.*

Over the past few years we have developed a new strategy for the synthesis of a broad array of aporphine alkaloids. Our intermolecular benzyne cycloaddition (IBC) approach, which involves the regioselective cycloaddition of N-protected methylene isoquinolines with arynes, has allowed ready preparation dehydroaporphines[1-3], 7-oxoaporphines[4] and 4,5-dioxo-aporphines.[1] Other isoquinoline alkaloids such as berberines,[5] dibenzopyrrocolines[6] and benzophenanthridines[7], are also accessible by this route. The recent appearance in the literature of a series of 7-alkyl, 7-alkoxy and 7-hydroxy aporphinoids[10] prompted us to investigate whether these too can be synthesized by the IBC approach (Scheme1).

We describe here the reactions of the substituted methyleneisoquinolines **3a**, **3b** and **3c**, which were expected to afford series of logical precursors of the above-mentioned 7-substituted aporphine alkaloids.




Scheme 1

**Results.** The substituted isoquinolines **3a-c** (Scheme 1, Table 1) were prepared unproblematically from the corresponding functionalized phenethylamides by means of the well-

known Bischler-Napieralski cyclization reaction followed by urethane formation. The desired products were obtained as E-Z mixtures. In the case of **3a**, the major isomer (>10:1 ratio) was isolated by column chromatography and identified by $^1$H NMR (NOE dif. spectrum, fig 1) as the Z form. Pure E-**3a** was obtained by chromatographic separation of the photostationary 1:1 E-Z mixture resulting from irradiation (400 W, medium pressure Hg lamp) of a solution of Z-**3a** in EtOH; its stereochemistry was likewise confirmed by its NOE dif. spectrum (fig. 1).

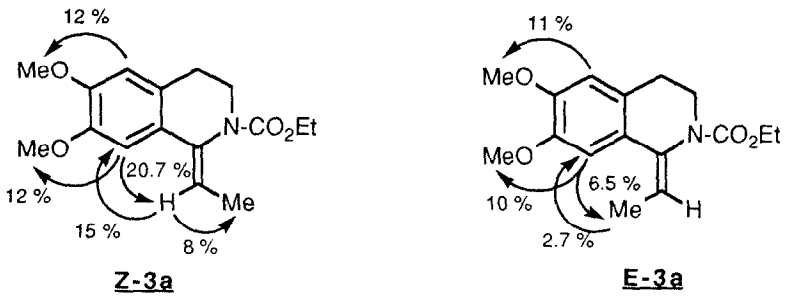



Figure 1

Reaction of the above isoquinoline derivatives **3a**, **3b** and **3c** with benzyne generated by thermal decomposition (refluxing DME) of preformed benzenediazonium-2-carboxylate[9] yielded the phenanthrene derivatives **2a**, **2b** and **2c** (identified by the presence of a multiplet at 9.60 ppm in the NMR spectra) in low to medium yields (Table 1, entries 1-5).

Table 1.

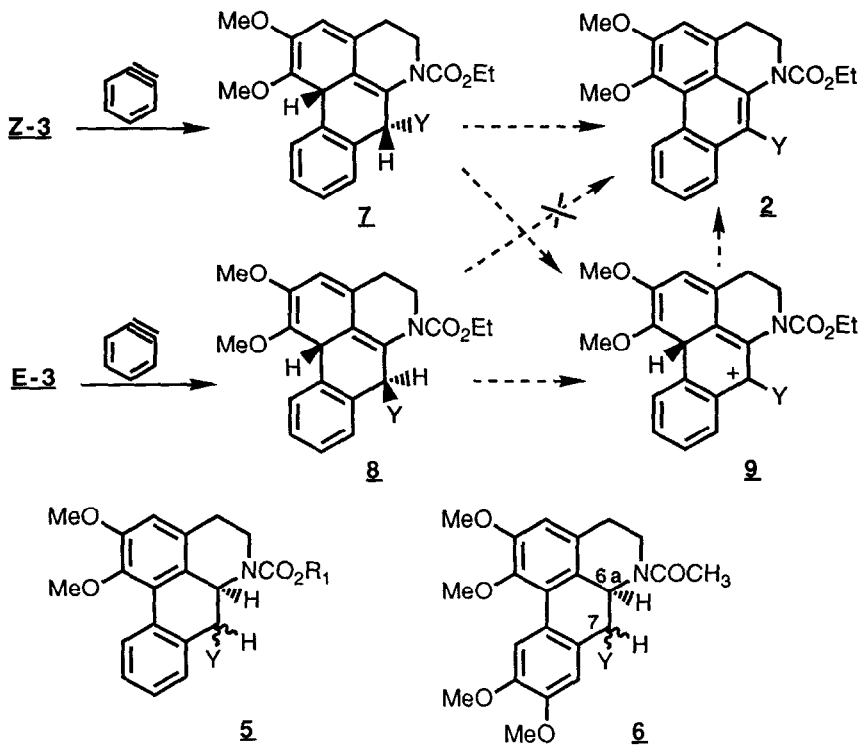
| Entry | Reagent | Product | Yield (%) |
|---|---|---|---|
| 1 | **3a** (Y=Me, X =H) E+Z | **2a** (Y=Me) | 53 |
| 2 | **3a** " " Z | " " | 52 |
| 3 | **3a** " " E | " " | 44 |
| 4 | **3b** (Y=OMe, X=H) Z | **2b** (Y=OMe) | 15 |
| 5 | **3c** (Y=H, X=Cl) Z | **2c** (Y=H) | 50 |
| 6 | **3d** (Y=X= Cl) | **2d** (Y=Cl) | <5 |

The main conclusion drawn from the data shown in Table 1 is that whereas 7-alkyl substituted derivatives are easily accessible by this route, the corresponding 7-heteroatom substituted aporphinoids cannot be satisfactorily prepared by means of the IBC approach. This difference must clearly be due to some feature of the mechanism of the reaction, which presumably involves a formal [4 + 2] cycloaddition followed by aromatization (by dehydrogenation,

dehydrohalogenation, or the like) of the resulting dihydrophenanthrene. This process, in essence the reaction between styrenes and arynes, has been studied previously, but a clear-cut mechanism for the dehydrogenation step has not been definitely established [10-14].

**Mechanism.** The fact that **Z-3a** , **E-3a** and a mixture of the two, on reaction with benzyne, all yielded phenanthrene **2a** (in 52, 53 and 44% yields; Table 1, entries 1,2,3) respectively, clearly shows that in this case there is no benzyne promoted 1,4 syn elimination of hydrogen[14] from the cycloadducts **7** and **8** (Scheme 2, Y=Me). Note that the $^1$H NMR spectra of samples taken at different times showed that no E-Z isomerization of **3a** took place during its reaction with benzyne.

The mechanism based on a 1,2-dehydrogenation involving hydrogens[12] at C-6a and C-7 of dihydrophenanthrene **5**, a hypothetical intermediate supposed to derive from cycloadducts **7** or **8** by a non concerted 1,3 hydrogen migration, can also be ruled out, since N-acetylnorglaucine (**6**)[15] (Scheme 2) did not yield the corresponding 6a,7-dehydroderivative under reaction conditions typical of the IBC approach, which in fact led to **6** being recovered unchanged in high yield.

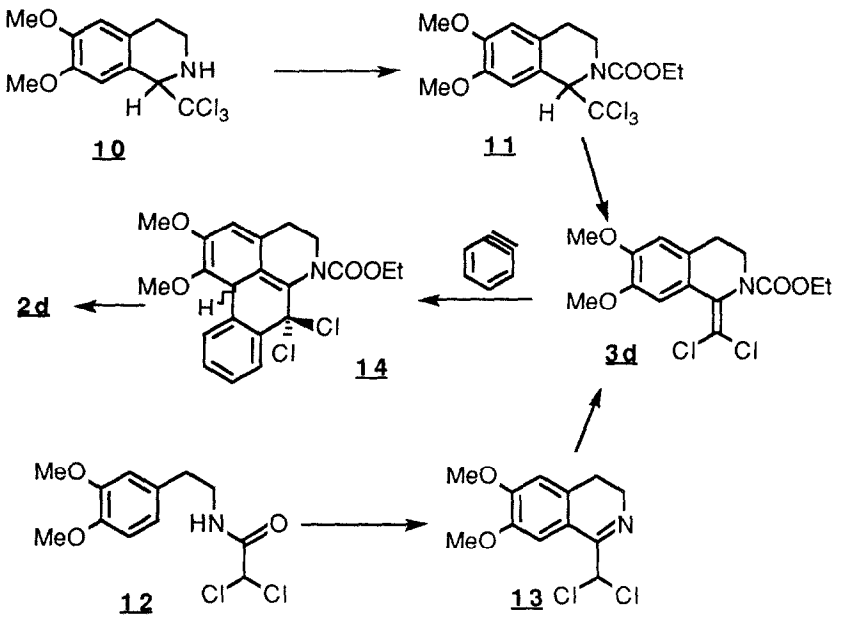



Scheme 2

Our findings suggest that the two-step mechanism proposed by Heaney[14] for the reaction of simple styrenes with tetrahalogenated arynes in basic media may also hold for IBC reactions in

which dehydrogenation competes with loss of MeOH or HCl. The aromatization of the cycloadducts formed initially may take place by benzyne-promoted loss of $Y^-$ ($H^-$, $OMe^-$, $Cl^-$) from the [4 + 2] cycloadduct **7** or **8**, followed by proton loss from the resulting carbenium ion **9** (Scheme 2).

The above results suggested a different strategy towards the desired 7-hydroxy and 7-alkoxy aporphines, namely preparation of the key 7-chloro (or 7-bromo) dehydrophenanthrene derivatives **2d,** followed by halogen-metal exchange and final oxidation. In view of the proposed mechanism, we expected the dichloromethylene-isoquinoline derivative **3d** to react with benzyne to give the cycloadduct **14** (Scheme 3), which would eventually undergo dehydrohalogenation to the desired compound **2d**.




Scheme 3

As shown in Scheme 3, compound **3d** was synthesized in two different ways: Firstly from the known trichloromethyl derivative **10**[16], by N-protection with ethyl chloroformate followed by base-promoted elimination of HCl; secondly, from **12**, by standard Bischler-Napieralski cyclization of the appropriate dichloroacetamide followed by N-protection as above. Unfortunately, when benzyne was reacted with **3d**, the desired 7-chlorophenanthrene derivative **2d** (clearly identified by the characteristic $^1H$ NMR signal at 9.60 ppm) was detected only as a very minor product (<5%), the major compound being unreacted **3d**.

The reluctance of disubstituted styrenes to react with benzyne has been loosely attributed to steric hindrance.[14] However, it is not easy to understand how two relatively small groups (Me, Cl, etc) could hinder the approach to the dienophile, taking into account that benzyne should approach in a perpendicular plane, as shown in (Figure 3). In our opinion, the reactivity of styrenes with benzyne must depend on the planarity of the styrene π system; since disubstituted styrenes such as **3d** cannot achieve planarity (because of steric repulsion between a chlorine atom and the H atom at C-8), they are unable to enter into [4+2] cycloaddition with benzyne.

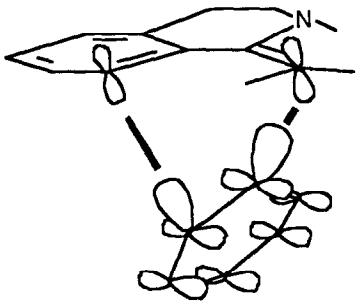



Figure 2

To sum up, the IBC approach to 7-substituted phenanthrene derivatives gives good results in the case of 7-alkyl substituted phenanthrene derivatives (aporphine numbering). 7-Heteroatom-substituted phenanthrenes are obtained in very low yield from the corresponding heteroatom-substituted methylene isoquinoline derivatives, which supports Heaney's two step mechanism for the benzyne-promoted aromatization undergone by the [4+2] cycloadducts derived from reaction between styrene derivatives and benzyne.

## EXPERIMENTAL PROCEDURE

**General Procedures.** All melting points were determined in a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker 250 MHz spectrometer with $SiMe_4$ as internal standard Infrared spectra were taken in KBr pellets with a Pye-Unicam 1100 spectrometer. Ultraviolet-visible spectra were obtained on a Pye-Unicam 1700 instrument. Low and high resolution mass spectra were recorded on Kratos MS-25 and a Kratos MS 50 instruments, both operating at 70 eV. Combustion analyses were performed by the Servei de Microanalisi (CSIC, Barcelona). Solvents were dried using standard procedures

**(Z)-N-Carbethoxy-6,7-dimethoxy-1-ethylidene-1,2,3,4-tetrahydro-isoquinoline, Z-3a.** To a stirred solution of 1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline[17] (2 g, 9.13 mmol) in

chloroform (40 mL) were added potassium carbonate (3 g, 23.4 mmol) and ethyl chloroformate (1.98 g, 18.2 mmol) in chloroform (10 mL). Stirring was continued for 2 h at room temperature, after which potassium carbonate was filtered out and the filtrate was washed with 10% HCl, dried and concentrated in vacuo to yield 2.1 g (79%) of **3a** as a mixture of E and Z isomers. The major isomer, Z, was isolated pure after chromatography on silicagel. Mp. 95-97 °C (EtOH). UV (MeOH) $\lambda_{max}$ : 220, 260, 300 nm. IR (KBr) : 1700 $cm^{-1}$. $^1H$ NMR : 1.25 (t, J=7.0 Hz, 3H), 1.71 (d, J=7.0 Hz, 3H), 2.85 (m, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 3.88-4.02 (m, 2H), 4.15 (c, J=7.0 Hz, 2H), 6.03 (c, J=7.0 Hz, 1H), 6.56 (s, 1H), 7.02 (s, 1H) ppm. MS, m/e (%) : 291 ($M^+$, 16), 262 (100), 218 (53). Anal. Calc. for $C_{16}H_{21}NO_4$. C : 65.97 , H : 7.21 , N : 4.81. Found: C : 65.68 , H : 7.08 , N : 5.12.

**(E)-N-Carbethoxy-6,7-dimethoxy-1-ethylidene-1,2,3,4-tetrahydroisoquinoline, E-3a.** A stirred solution of **Z-3a** (100 mg, 0.34 mmol) in abs. EtOH (10 mL) was irradiated with a medium pressure Hg lamp (400 w) for 4 h. The solvent was evaporated in vacuo and the residue was chromatographed on a silicagel column to afford **E-3a** (30 mg, 30%). $^1H$ NMR : 1.25 (t, J=7.0 Hz, 3H), 1.99 (d, J=7.0 Hz, 3H), 2.79 (m, 2H), 3.70 (m, 2H), 3.88 (s, 6H), 4.18 (c, J=7.0 Hz, 2H), 5.86 (c, J=7.0 Hz, 1H), 6.68 (s, 1H), 7.01 (s, 1H) ppm. MS, m/e (%) : 291 ($M^+$, 16), 262 (100), 218 (53).

**N-Carbethoxy-1-chloromethylene-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline 3c**. Under an argon atmosphere, a cooled (-20°C), stirred solution of 1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride[18] (550 mg, 1.99 mmol) and dry pyridine (2.50 g, 25.95 mmol) in dry chloroform (35 mL) was treated dropwise with ethyl chloroformate (4.77 ml, 38.76 mmol). The solution was stirred for 4 h at room temperature.The reaction mixture was then diluted with chloroform (final volume 100 mL) and the resulting solution washed with dil. HCl (2 x 50 mL), 3% $Na_2CO_3$ solution (2 x 50 mL) and water (2 x 50 mL). The organic phase was dried over anh. $Na_2SO_4$ and concentrated in vacuo. The residue was purified by column chromatography to afford 400 mg (64% yield) of N - carbethoxy -1- choromethylene -6 ,7- dimethoxy -1, 2, 3, 4 - tetrahydroisoquinoline, **3c.** Mp. 139-141°C (petrol ether). UV (EtOH) $\lambda_{max}$ : 228, 278 307 nm. IR (KBr): 1680 $cm^{-1}$. $^1H$ NMR : 1.28 (m, 3H), 2.84 (broad s, 2H), 3.87 (s, 3H), 3.87-3.91 (m, 2H), 3.89 (s, 3H), 4.21 (m, 2H), 6.53 (s, 1H), 6.59 (s, 1H), 6.91 (s, 1H) ppm. MS, m/e (%) : 311 (5), 276 (100), Anal. Calc. for $C_{15}H_{18}NO_4Cl$ : C : 57.79 , H : 5.82 , N : 4.40. Found : C : 57.59 , H : 5.73 , N : 4.38.

**N-(3,4-Dimethoxyphenethyl)methoxyacetamide**. A mixture of 3,4-dimethoxy-phenylethylamine (10 g, 55.2 mmol) and methoxyacetic acid (5.05 g, 55.5 mmol) was heated at 180-200°C for 1 h. The mixture, which solidified after cooling at room temperature, was dissolved in dichloromethane (50 mL), washed with 10% NaOH (2 x 25 mL), 10%HCl (2 x 25 mL) and water (2 x 25 mL), dried over anh. $Na_2SO_4$ and concentrated in vacuo. This yielded 11.45 g (84%) of the desired compound as an oil which crystallized from AcOEt/petrol ether. Mp. 49-50 °C. UV (EtOH) $\lambda_{max}$ : 229, 278 nm. IR (film) : 1660 $cm^{-1}$. $^1H$ NMR : 2.79 (t, J=7.0 Hz, 2H), 3.36 (s, 3H), 3.54 (m,

2H), 3.87 (s, 3H), 3.88 (s, 8H), 6.59 (broad s, 1H), 6.73-6.76 (m, 2H), 6.81 (d, J=8.0 Hz, 1H) ppm. MS, m/e (%) : 253 (4), 164 (100), 151 (37), 149 (10). Anal. Calc. for $C_{13}H_{19}NO_4$ : C : 61.64, H : 7.56, N : 5.53. Found: C : 61.42, H : 7.20, N : 5.49

**6,7-Dimethoxy-1-methoxymethyl-3,4-dihydroisoquinoline.** $POCl_3$ (4.2 mL, 45.8 mmol) was added dropwise to a refluxing solution of N-(3,4-dimethoxyphenethyl)-methoxyacetamide (5 g, 19.8 mmol) in toluene (50 mL) and the mixture was refluxed for 1 h. The solution was then decanted, at room temperature, the oily residue was diluted with water, and the resulting solution was washed with ether. The aqueous phase was made alkaline with $NH_4OH$ and extracted with dichloromethane. The organic phase was dried over anh. $Na_2SO_4$ and the solvent evaporated in vacuo to yield 4.20 g (90%) of 6,7-dimethoxy-1-methoxy-methyl-3,4-dihydroisoquinoline as an oil. UV (EtOH) $\lambda_{max}$ : 233, 283, 312, 408 nm. IR (film) : 1620 $cm^{-1}$ . $^1H$ NMR : 2.66 (m, 2H), 3.43 (s, 3H), 3.72 (m, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 4.45 (s, 2H), 6.70 (s, 1H), 7.15 (s, 1H) ppm. MS, m/e (%) : 235 ($M^+$, 3), 204 (100), 203 (34). Anal. Calc. for $C_{13}H_{17}NO_3$ .HCl. $H_2O$ : C : 53.89 , H : 6.96 , N : 4.83. Found: C : 53.93 , H : 6.79 , N : 4.60

**Z-N-Carbethoxy-6,7-dimethoxy-1-methoxymethylene-1,2,3,4-tetrahydro-isoquinoline, 3b.** Ethylchloroformate (4 mL, 42 mmol) was added to a stirred solution of 6,7-dimethoxy-1-methoxymethyl-3,4-dihydroisoquinoline (520 mg, 2.21 mmol) in chloroform (50 mL) containing $K_2CO_3$ (0.8 g, 6.24 mmol) and the stirring maintained for 3 h. The solution was washed with water, dried over anh. $Na_2SO_4$ and evaporated in vacuo. The residue was purified by chromatography ($Al_2O_3$, 1:1 ether-petrol ether ), to afford 239 mg (35%) of **Z 3b** and 152 mg (22%) of **E 3b**. The Z isomer was crystallized from petrol ether . Mp. 118-119°C. UV (EtOH) $\lambda_{max}$ : 218, 271, 310 nm. IR (KBr) 1675 $cm^{-1}$. $^1H$ NMR : 1.26 (t, J=7.1 Hz, 3H), 2.81 ( broad s, 2H), 3.5-3.9 (m, 2H), 3.80 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.18 (c, J=7.1 Hz, 2H), 6.53 (s, 1H), 6.56 (s, 1H), 6.82 (s, 1H) ppm. MS, m/e (%) : 307 (52), 292 (15), 235 (16), 234 (100), 220 (85). The E isomer had the following spectroscopic characteristics : UV (EtOH) $\lambda_{max}$ : 216, 272, 300 nm. IR (KBr) 1680 $cm^{-1}$. $^1H$ NMR : 1.26 (t, J=7.1 Hz, 2H), 2.82 (m, 2H0, 3.77 (m , 2H), 3.82 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.15 (c, J=7.0 Hz, 2H), 6.42 (s, 1H), 6.59 (s, 1H), 7.74 (s, 1H). Anal. Calc. for $C_{16}H_{21}NO_5$: C : 62.53 , H : 6.89 , N : 4.56. Found: C : 62.54 , H : 6.75 , N : 4.54

**N-(3,4-Dimethoxyphenethyl)dichloroacetamide, 12.** To a cooled (-20°C), stirred solution of 3,4-dimethoxyphenethylamine (5.73 g, 31.6 mmol) and pyridine (2.7 mL, 34.8 mmol) in chloroform (12 mL) was added dropwise a solution of dichloroacetyl chloride (5.13 g, 34,8 mmol) in chloroform (14 mL), and the mixture was stirred overnight. The chloroform solution was washed with 10% NaOH (50 mL), 10% HCl (50 mL) and water (50 mL), dried over anhydrous sodium sulphate and evaporated in vacuo. The solid residue was crystallized from AcOEt-petrol ether to yield 7.67 g (83%) of **12** as crystals. Mp. 121-3 °C. UV (EtOH) $\lambda_{max}$ : 227, 279 nm. IR (KBr) 1665 $cm^{-1}$. $^1H$ NMR : 2.82 (t, J=6.80 Hz, 2H), 3.57 (m, 2H), 3.88 (s, 6H), 5.91 (s, 1H), 6.55 (broad s, 1H), 6.72-6.77 (m, 2H), 6.84 (d, J=8.0 Hz, 3H) ppm. MS, m/e (%) : 291 ($M^+$, 6), 208 (4), 164 (100), 151

(90). Anal. Calc. for $C_{12}H_{15}NO_3Cl_2$: C : 49.33 , H : 5.17, N : 4.79 . Found: C : 49.21 , H : 5.19 , N : 4.75

**1-Dichloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline, 13.** A solution of N-(3,4-dimethoxyphenethyl)dichloroacetamide (860 mg, 2.93 mmol), acetonitrile (50 mL) and $POCl_3$ (2 mL, 22 mmol) was refluxed overnight and then concentrated in vacuo. The residue was dissolved in water and the solution washed with ether. The aqueous phase was made alkaline with 10% NaOH and extracted with dichloromethane. The organic extracts were dried and concentrated, and the resulting residue crystallized from MeOH-$H_2O$, to furnish 720 mg (89%) of **13**. Mp. 89-90°C. UV (EtOH) $\lambda_{max}$ : 233, 283, 316 nm. IR (KBr) :1513 $cm^{-1}$. $^1H$ NMR : 2.70 (m, 2H), 3.80 (m, 2H), 3.94 (s, 6H), 6.54 (s, 1H), 6.73 (s, 1H), 7.60 (s, 1H) ppm. Anal. Calc. for $C_{12}H_{13}NO_2Cl_2$ : C : 52.57 , H : 4.78 , N : 5.11. Found: C : 52.54 , H : 4.73 , N : 5.13

**N-Carbethoxy-1-dichloromethylene-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline, 3d, from 1-dichloromethyl-6,7-dimethoxy-3,4-dihydro-isoquinoline (13).** A solution of **13** (453 mg, 1.65 mmol) in toluene (50 mL) was refluxed for 30 min under argon in a Dean-Stark trap[19]. Diethyl carbonate (0.32 mL, 1.87 mmol) was added to the cooled (50 °C) solution, and the mixture was stirred for 20 min. The solvent was evaporated in vacuo and the residue crystallized from petrol ether to give the desired carbamate **2d** (404 mg,70%). Mp 132-3°C. UV (EtOH) $\lambda_{max}$ : 221, 271, 300 nm. IR (KBr) 1690 $cm^{-1}$. $^1H$ NMR : 1.27 (t, J=7.1 Hz, 3H), 3.88 (s, 6H), 6.65 (s, 1H), 7.48 (s, 1H) ppm. MS m/e : 345 ($M^+$, 2), 310 (75), 282 (100). Anal. Calc. for $C_{15}H_{17}NO_4Cl_2$: C : 52.33 , H : 4.95 , N : 4.0. Found: C : 52.22 , H : 4.98 , N : 4.05

**N-Carbethoxy-6,7-dimethoxy-1-trichoromethyl-1,2,3,4-tetrahydro-isoquinoline, 11.** A mixture of 6,7-dimethoxy-1-trichloromethyl-1,2,3,4-tetrahydroisoquinoline **10**[16] (270 mg, 0.7 mmol) in dichloromethane (40 mL), potassium carbonate (500 mg, 3.9 mmol) and ethyl chloroformate (1 mL, 1.046 mmol) was stirred for 90 min. The mixture was filtered and the filtrate evaporated in vacuo. Crystallization (petrol ether) of the resulting residue afforded **11** (301 mg,80%) as a mixture of rotamers. UV (EtOH) $\lambda_{max}$ : 218, 285 nm. IR (KBr) 1602 $cm^{-1}$. $^1H$ NMR : 1.31 (m, 3H),3.88 (m, 6H), [5.92 (s) + 6.08 (s)] (1H), [6.65 (s) + 6.67 (s)] (1H), 7.22 (s, 1H) and [2.80-3.10 (m)+ 3.60-3.85 (m) + 4.10-4.50 (m)] (6H) ppm. MS, m/e (%) : 264 (100), 236 (26), 190 (26). Anal. Calc. for $C_{15}H_{18}NO_4Cl_3$ : C : 47.07 , H : 4.74 , N :3.69. Found: C : 47.01 , H : 4.69 , N : 3.61.

**N-Carbethoxy-1-dichloromethylene-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline, 3d, from N-carbethoxy-6,7-dimethoxy-1-trichoromethyl-1,2,3,4-tetra-hydroisoquinoline (11).** N-Carbethoxy-6,7-dimethoxy-1-trichloromethyl-1,2,3,4-tetrahydro-isoquinoline, **11**, was added to a freshly prepared solution of sodium ethoxide (from sodium , 1.5 g, 65.2 mmol) in dry EtOH (50 mL), and stirring was maintained for 2 h. The reaction mixture was concentrated to 10 mL, diluted with water (75 mL) and washed with dichloromethane (3 x 50 mL).

The organic phase was dried and evaporated in vacuo, and the residue crystallized from petrol ether to yield **3d** (261 mg, 95%).

**Benzyne reactions with the alkylidene isoquinolines 3. General procedure.** Isoamyl nitrite (1.6 eq) was added dropwise (1-2 min) to a stirred, cooled (0°C) solution of anthranillic acid in dimethoxyethane (DME) containing a catalytic amount of trichloroacetic acid. The reaction mixture was stirred for 15 min at 0°C and then for 60-90 min at room temperature. The supernatant of the solution containing benzenediazonium-2-carboxylate was carefully removed using a plastic syringe and a Teflon tubing (metal needles should not be employed!). The remaining brown precipitate was washed several times with DME until neutral (**Caution** : *benzenediazonium-2-carboxylate, when dry, detonates violently on being scraped or heated).* More DME was added, and the resulting suspension of diazonium-2-carboxylate was added dropwise to a refluxing solution of diene **3** in DME usinga plastic syringe with Teflon tubing. After 1-2 hours refluxing, the solvent was evaporated in vacuo and the residue chromatographed.

**Reaction of N-carbethoxy-6,7-dimethoxy-1-ethylidene-1,2,3,4-tetrahydro isoquinoline, Z-3a, with benzyne.** To a refluxing solution of compound Z-**3a** (100 mg, 0.34 mmol) in DME (30 ml) was added benzenediazonium-2-carboxylate prepared as above from anthranillic acid (0.270 g, 1.97 mmol) and isoamyl nitrite (0.379 g, 3.23 mmol). After workup, the residue was purified by chromatography (silica, dichloromethane) to furnish N-carbethoxy-7-methyl-6a,7-dehydronornuciferine, **2a** (64 mg, 52%). Mp 172-4 °C (MeOH), IR (KBr) : 1700 $cm^{-1}$ UV (EtOH) $\lambda_{max}$ : 258, 308, 352, 370 nm. $^1H$ NMR : 1.19 (t, J=6.8 Hz, 3H), 2.50 (s, 3H), 3.88 (s, 3H), 3.98 (s, 3H), 2.97-4.25 (m, 6H), 7.08 (s, 1H), 7.53-7.65 (m, 2H), 7.98-8.02 (m, 1H), 9.62 (m, 1H) ppm. EM m/e (%) : 365 ($M^+$, 100), 298 (28). Anal. Calc. for $C_{16}H_{21}NO_4$: C : 72.32 , H : 6.30 , N : 3.83. Found : C : 71.91 , H : 5.98 , N : 4.01

**Reaction of N-carbethoxy-1-chloromethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 3c, with benzyne.** Reaction of compound **3c** (110 mg,0.35 mmol) with benzyne as above yielded 67 mg (54%) of N-carbethoxy-6a,7-dehydronornuciferine, **2d**. Mp. 123-5°C (MeOH),(Lit.[20] 128-130 °C). IR (KBr) : 1700 $cm^{-1}$. UV (EtOH) $\lambda_{max}$ : 256, 310, 320 (sh), 354, 373 nm. $^1H$ NMR : 1.34 (t, J=7.1 Hz, 3H), 3.22 (t, J=5.7 Hz, 2H), 3.91 (s, 3H) 4.02 (s, 3H), 4.09 (t, J=5.7 Hz, 2H), 4.30 (c, J=7.1 Hz, 2H), 6.97-7.11 (m, 3H), 7.53-7.59 (m, 1H), 9.56-9.60 (m, 1H) ppm. MS , m/e (%) : 351 ($M^+$, 100), 261 (54) , 164 (86).

**Reaction of Z-N-carbethoxy-6,7-dimethoxy-1-methoxymethylene-1,2,3,4-tetrahydroisoquinoline, 3b, with benzyne.** Reaction of **3b** (87 mg, 0.28 mmol) with benzyne as in the general procedure furnished N-carbethoxy-7-methoxy-6a,7-dehydro-nornuciferine, **2b** (16 mg, 15%), and N-carbethoxydehydronornuciferine **2c** (20 mg , 18%). N-Carbethoxy-7-methoxy-6a,7-dehydronornuciferine, **2b**. Mp. 141-3°C (hexane-ether).UV (EtOH) $\lambda_{max}$ : 256, 322, 356, 374 nm. IR (KBr) : 1690 $cm^{-1}$. $^1H$ NMR : 1.23 (t, J-7.0 Hz, 3H), 3.21(broad s, 4H), 3.82 (s, 3H), 3.92 (s, 3H), 4.01 (s, 3H), 4.20 (m, 2H), 7.11 (s, 1H), 7.62 (m, 2H), 8.28 (m, 1H), 9.62 (m, 1H) ppm.

MS, m/e (%) : 381 (52), 365 (31), 322 (22), 294 (100), 279 (30), 278 (24). HRMS calc. for $C_{22}H_{23}NO_5$: 381.1576. Found 381.1578.

**Reaction of N-carbethoxy-1-dichloromethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ,3d, with benzyne.** Compound **3d** (140 mg, 0.404 mmol) in DME (50 mL) was reacted with benzyne as above. Chromatographic separation of the crude mixture thus obtained yielded unreacted starting material (129 mg, 92%) and a very minor fraction (c.a.,5 mg) containing impure N-carbethoxy-7-chloro-6a,7-dehydronornuciferine, **2d**, as shown by the $^1H$ NMR signal at 9.60 ppm.

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