Synthesis of 9,10,12,13,14,14a-Hexahydrodibenzo[*f,h*]pyrrolo-[2,1-*a*]isoquinoline

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The synthesis of 9,10,12,13,14,14a-hexahydrodibenzo[*f,h*]pyrrolo[2,1-*a*]isoquinoline **6** has been accomplished by a sequence involving as a key step the Friedel-Crafts intramolecular acylation of the amino acid **9** to the corresponding pentacyclic aminoketone **10**. Compounds **7**, **11** and **12** showed a significant protein synthesis inhibitory effect.

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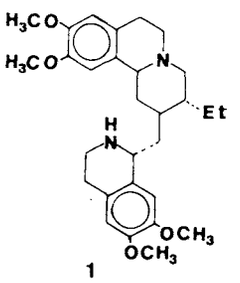
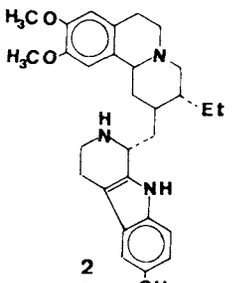
During the past few years the ipecac alkaloids emetine **1** and tubulosine **2** have been related to the phenanthrene alkaloids tylophorine **3**, tylocrebrine **4** and cryptopleurine **5**, as biosynthesis inhibitors which affect the EF-2 dependent translocation step [1-3]. The very similar mechanism of action of both groups of alkaloids led Gupta *et al.* [3] to make a first approach to the structure-activity relationship between both type of alkaloids, which further on was modified by the same authors [4].

On the other hand earlier studies realized by us [5], about which portions of the ring system of phenenthrene alkaloids are required for protein synthesis inhibitory activity showed, that ring E is not essential for protein biosynthesis inhibition.

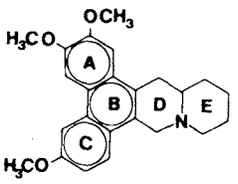
In our continuing study of phenanthrene alkaloids derivatives, we thought it would be interesting to synthesize 9,10,12,13,14,14a-hexahydrodibenzo[*f,h*]pyrrolo[2,1-*a*]isoquinoline **6**, because it encloses the essential structure of the former alkaloids showing also a higher similarity to ipecac alkaloids. The dibenzo[*f,h*]pyrrolo[2,1-*a*]isoquinoline nucleus, as well as its reduced forms, have not to our knowledge been described. We report here a convenient synthesis of **6** based on a Friedel-Crafts intramolecular acylation of 2-[2-(9-phenanthryl)pyrrolidinyl]acetic acid **9** (Scheme 1).



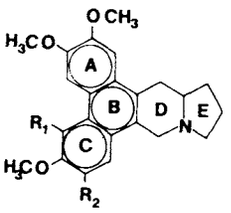
1
EMETINE



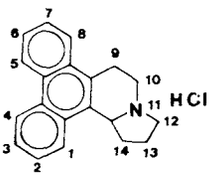
2
TUBULOSINE



5
CRYPTOPLEURINE



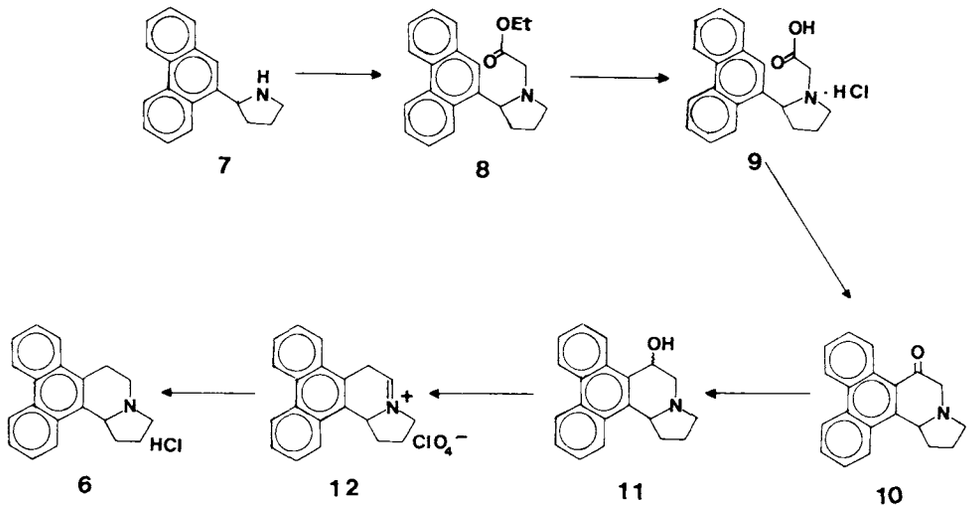
3 R_1 = H R_2 = OCH_3 TYLOPHORINE
4 R_1 = OCH_3 R_2 = H TYLOCREBRINE



6

2-(9-Phenanthryl)pyrrolidine (**6**) is reacted with ethyl bromoacetate to give the ethyl 2-[2-(9-phenanthryl)pyrrolidinyl]acetate **8** in good yields. The ^{1}H nmr enabled us to determine for the amino-ester **8** a conformational rigidy, probably caused by a resticted rotation of the acetic group due to the presence of the phenanthrene system. The exocyclic methylene protons form an AB quartet with chemical shifts of 3.14 and 3.61 ppm and coupling constant J = 16.2 Hz, which indicates a non equivalence of this protons. The amino-ester **8** is carefuly hydrolyzed with concentrated hydrochloric acid, affording the amino-acid **9** in 77% yield. Intramolecular Friedel-Crafts cyclization of **9** in polyphosphoric acid at 105° under a nitrogen atmosphere goes to the pentacyclic aminoketone **10**. As **10** is very sensitive to aerial oxidation, it is characterized only by spectroscopic means, exhibiting its ^{1}H nmr spectrum a singlet at δ 3.72 ppm, assignable to a magnetic equivalence of the C-10 protons. Compound **10** is immediately reduced by sodium borohydride to a mixture of two diastereoisomeric alcohols in a 23/77 proportion as indicate the nmr studies of proton C-9, which shows two triplets at δ 5.2 (23%) and 5.09 (77%) ppm.

The amino-alcohols **11** are dehydrated with 70% perchloric acid, to give the immonium perchlorate **12** in high yields, whose structure is confirmed by the characteristic



7 8 9 10 11 12 6

SCHEME 1

immonium derivative ir band at 1735 cm^{-1} [7]. The quaternary salt **12** is reduced easily with sodium borohydride to the hexahydrodibenzo[*f,h*]pyrrolo [2,1-*a*]isoquinoline **6** in almost quantitative yields. Mass spectroscopic examination of **6** and **11** confirms the structure of these compounds showing a tetrahydroisoquinoline system characteristic retro-Diels-Alder fragmentation.

The effects of compounds **6**, **11** and **12** on poly(U)-directed polyphenylalanine synthesis in yeast cell-free systems [8] were tested, showing a good protein synthesis inhibitory activity [9].

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer 577 spectrometer. The nmr spectra were measured using tetramethylsilane as the internal standard, with a Perkin-Elmer mod. R-24B (60 MHz) and a Varian EM 390 (90 MHz) spectrometer. Microanalyses were done with a Carlo Erba 1104 analyser. The mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M spectrometer.

Ethyl 2-[2-(9-Phenanthryl)-1-pyrrolidinyl]acetate (**8**).

A solution of 8.6 g (35 mmoles) of 2-(9-phenanthryl)pyrrolidine (**6**) in 120 ml of dry benzene and 1.95 ml (17.5 mmoles) of ethyl bromoacetate was refluxed during 7 hours. After cooling, the suspension was filtered and the solid 2-(9-phenanthryl)pyrrolidine bromhydrate washed with benzene. The combined layers were evaporated *in vacuo* and the residue extracted with petroleum ether (50-70). Evaporation of the solvent *in vacuo* gave 5.06 g (87%) of a white solid which recrystallized in ethanol/water, mp 79-80°; nmr (deuteriochloroform): (90 MHz) δ 8.77 (dd, 2H, H-4', H-5'), 8.21 (m, 1H, H-8'), 8.06 (s, 1H, H-10'), 7.88 (m, 1H, H-1'), 7.57 (m, 4H, H-Ar), 4.48 (t, 1H, J = 7.5 Hz, H-2), 4.1 (q, 2H, J = 7 Hz, $-CH_2-$), 3.61 and 3.14 (ABq, 2H, J = 16.2 Hz, $CO-NH_2-N$), 3.54 (m, 1H, H-5 eq), 2.73 (q, 1H, J = 8 Hz, H-5 ax), 2.42 (m, 1H, H-3), 1.93 (m, 3H, H-3, H-4), 1.21 (t, 3H, J = 7 Hz, $-CH_3$); ir (potassium bromide): ν 1745 cm^{-1}.

Anal. Calcd. for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.52; H, 6.86; N, 4.20.

2-[2-(9-Phenanthryl)-1-pyrrolidine]acetic Acid Hydrochloride (**9**).

A suspension of 4.9 g (14.3 mmoles) of compound **8** in 30 ml of concentrated hydrochloric acid was refluxed on a 105° bath during 2 hours. The hot solution was purified with animal charcoal and, after cooling, the resulting white precipitate was collected by filtration, yield, 3.85 g (77%), mp 190-191° dec (chloroform/ether), ir (potassium bromide): ν 1740 cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}ClNO_2$: C, 70.27; H, 5.90; N, 4.10. Found: C, 69.98; H, 6.02; N, 4.05.

9,10,12,13,14,14a-Hexahydrodibenzo[*f,h*]pyrrolo[2,1-*a*]isoquinolin-9-one **10**.

Compound **9** (4.2 g, 12.2 mmoles) and 20 g of polyphosphoric acid were kept under nitrogen, in a parafin bath, with stirring at 105° for 6 hours. After cooling, the dark viscous solution was poured slowly on ice water (120 ml) and basified, at 30°, with 50% potassium hydroxide to *p*H 8. The mixture was extracted several times with chloroform, dried over sodium sulfate and evaporated, *in vacuo* at 35°, to give a viscous yellow oil in a yield of 81%, which was not further purified; nmr (dueteriochloroform): δ 9.4 (m, 1H, H-8), 8.65 (m, 2H, H-4, H-5), 8.05 (m, 1H, H-1), 7.62 (m, 4H, Ar-H), 4.95 (t, 1H, J = 7 Hz, H-14a), 3.72 (s, 2H, H-10), 3.05 (m, 2H, H-12), 2.75 (m, 1H, H-14 eq), 1.88 (m, 3H, H-13, H-14 ax); ir (sodium chloride): ν 1675 cm^{-1}.

9,10,12,13,14,14a-Hexahydrodibenzo[*f,h*]pyrrolo[2,1-*a*]isoquinolin-9-ol (**11**).

To a magnetically stirred solution of 2.9 g (10 mmoles) of aminoketone **10** in 80 ml of absolute ethanol was added 1.4 g sodium borohydride in small portions. When the addition was complete, stirring was continued for 16 hours at room temperature. The solution was poured into 80 ml of water. The excess of sodium borohydride was destroyed with 15 ml 2*N* acetic acid and made basic by addition of 30% sodium hydroxide. The mixture was extracted with chloroform, the organic layers dried over sodium sulfate and evaporated to give a solid in a 2.2 g (77%) yield, mp 200-201° dec (acetone); rf (benzene/acetone/methanol = 65/25/10): isomer A = 0.26 (23%), isomer B = 0.18 (77%); nmr (deuteriochloroform): (90 MHz) δ 8.5 (m, 3H, H-1, H-4, H-5), 7.93 (m, 1H, H-8), 7.8-7 (m, 4H, Ar-H), 5.2 (t, 0.23 H, J = 2 Hz, H-9), 5.09 (t, 0.77 H, J = 2 Hz, H-9), 4.78 (m, 1H, H-14a), 3.8-3.2 (m, 2H, H-10), 3.2-2.5 (m, 3H, H-12, H-13), 2.2-1.3 (m, 3H, H-13, H-14); ir (potassium bromide): ν 3350-3150, 1070 cm^{-1}; ms: m/e 289 (M^+), 288, 272 (base peak), 270, 261, 260, 244, 189, 165.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.89; H, 6.53; N, 4.63.

12,13,14,14a-Tetrahydro-9*H*-dibenzo[*f,h*]pyrrolo[2,1-*a*]isoquinolinium Perchlorate (**12**).

A solution of 1.25 g (4.3 mmoles) of amino-alcohol **11** in 45 ml glacial acetic acid and 2.4 ml 70% perchloric acid was refluxed for 90 minutes. The hot mixture was purified with animal charcoal and filtered. After cooling to 5° the precipitated product was filtered off and recrystallized in dimethylsulfoxide, yield, 1.24 g (78%), mp 294-296° dec; ir (potassium bromide): ν 1735, 1085 cm^{-1}.

Anal. Calcd. for $C_{20}H_{18}ClNO_4$: C, 64.61; H, 4.88; N, 3.77. Found: C, 64.52; H, 4.60; N, 3.69.

9,10,12,13,14,14a-Hexahydrodibenzo[*f,h*]pyrrolo[2,1-*a*]isoquinoline Hydrochloride (**6**).

To a magnetically stirred solution of 1 g (2.7 mmoles) of compound **12** in 100 ml of absolute ethanol was added 0.4 g of sodium borohydride in small portions. When the addition was complete, stirring was continued for 30 minutes. The mixture was concentrated to a small volume, poured on 60 ml water and 15 ml of 2*N* acetic acid were added to destroy the excess of sodium borohydride. The solution was made basic with 30% sodium hydroxide and extracted with chloroform. The organic layers were dried, concentrated *in vacuo*, and the syrupy residue extracted with hot petroleum ether (50-70°). The ethereal layers were evaporated to yield 0.45 g (61%) of a solid which melted at room temperature. The hydrochloride was formed by passing dry hydrogen chloride through a benzene solution. The white precipitate obtained after addition of dry ether was recrystallized in ethanol/ether, mp, 283-285°; nmr (deuteriumchloride): (90 MHz) δ 8.67 (m, 2H, H-4, H-5), 7.96 (m, 2H, H-1, H-8), 7.56 (m, 4H, Ar-H), 4.8 (t, 1H, J = 7.5 Hz, H-14a), 3.4-2.9 (m, 6H, H-9, H-10, H-12), 2.7 (m, 1H, H-14), 2.1-1.6 (m, 3H, H-13, H-14); ir (potassium bromide): ν 3025, 2550-2350, 1605, 1495 cm^{-1}; ms: m/e 273 (M^+), 272, 245 (base peak), 231, 230, 217, 203, 202, 189, 165.

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