Synthesis and Analysis of Compounds Having the Skeleton of Ergot Alkaloids with the Nitrogen Atom in the D-Ring Transposed

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Alkylation-amination of the enamine 2 in the presence of ethyl α,α-bis(dibromomethyl)acetate, triethyl-amine, and methylamine lead to the construction of the aza-transposed ergoline 3. Sequential reduction, hydrolysis, reesterification, and indolization of 3, produced three diastereomers of 6. The structure of these three diastereomers was assigned on the basis of nmr and ir spectral analysis to be (α-cis) syn, (β-cis) anti, and (α-trans) syn. The isomer (β-cis) anti was reduced with lithium aluminum hydride to the corresponding alcohol.

Synthetic and semisynthetic ergot alkaloids have become of great clinical interest because of their ability to exhibit a wide variety of pharmacological properties of which those upon the central nervous and endocrine systems have been the most extensively studied [2]. In all these normal ergolines the nitrogen atom of the D-ring is separated by two carbon atoms from the benzene nucleus (A), or the pyrrole nucleus (B), a relationship which occurs also in dopamine and serotomine. On the other hand, compounds of which the nitrogen atom is separated from the benzene nucleus by one carbon atom are also dopanomimetic agents [3]. Besides it was reported that the dopaminergic pharmacophore of the ergolines is the rigid pyrrolylethylamine moiety [4], whereas in another report there is evidence that the active pharmacophore is the benzenethylamine or indolylethylamine partial structure [5]. Thus, in view of the above pharmacological properties of the ergolines and the controversy about their pharmacophore moiety, we thought it would be of interest if we could synthesize aza-transposed ergolines, that is with nitrogen atom in the 9-position instead.
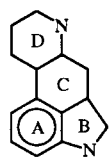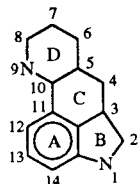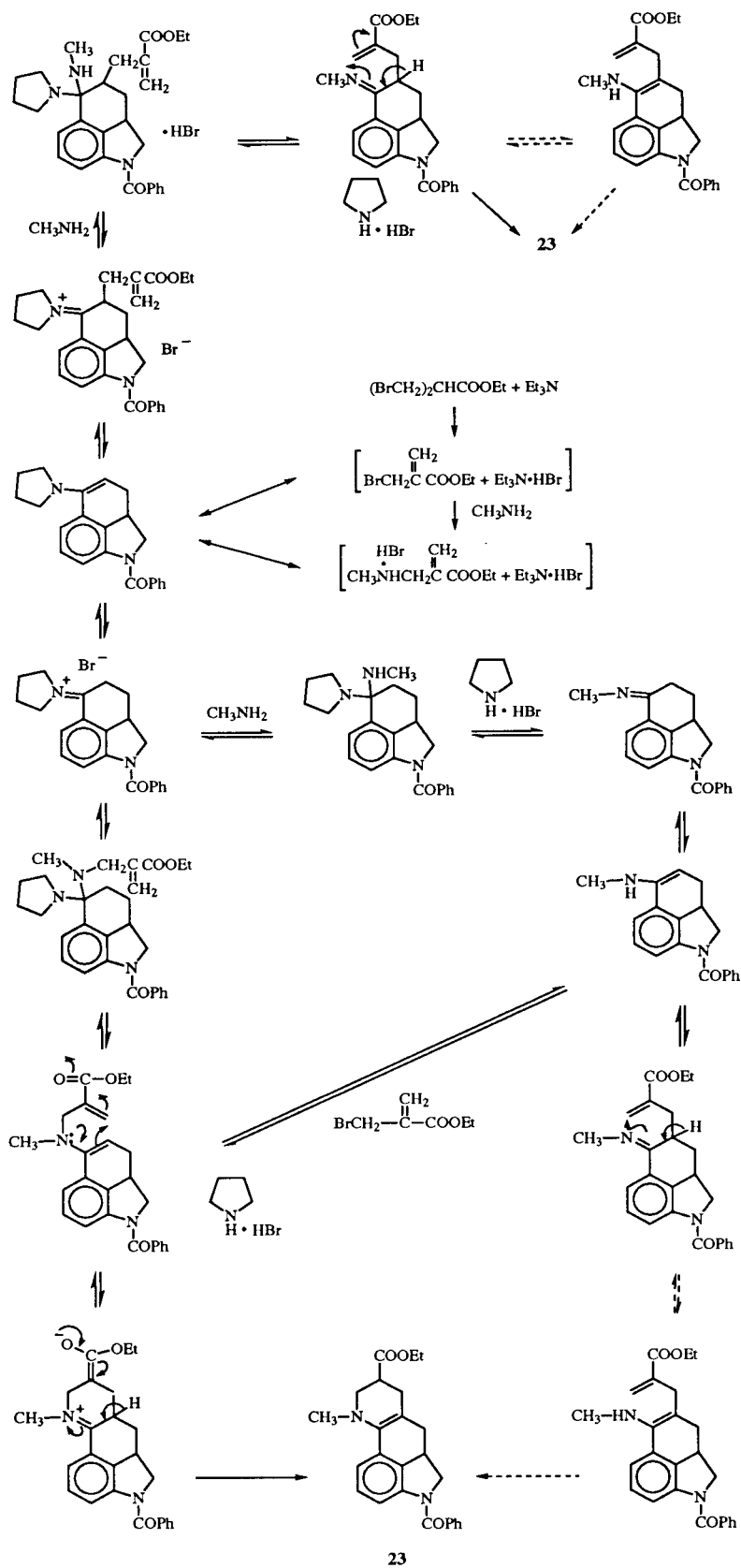

Normal Ergoline   Aza-Transposed Ergoline

Consequently such a total synthesis was undertaken and herewith we report our results. As a starting point the known ketone 1 was used [6] to prepare the corresponding pyrrolidine enamine under modified Dean-Stark conditions, which was used in the next step without purification. The crude enamine, in the presence of ethyl α,α-bis-(dibromomethyl)acetate, triethylamine, and methylamine

Scheme 1
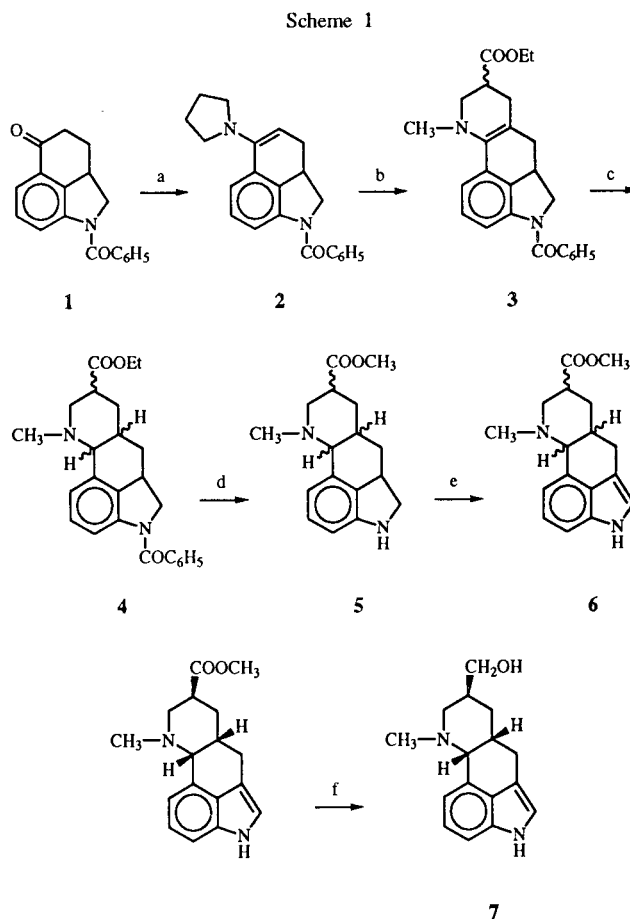
(a) pyrrolidine (b) (BrCH₂)₂CHCOOEt, Et₃N, CH₃NH₂ (c) NaCNBH₃, AcOH
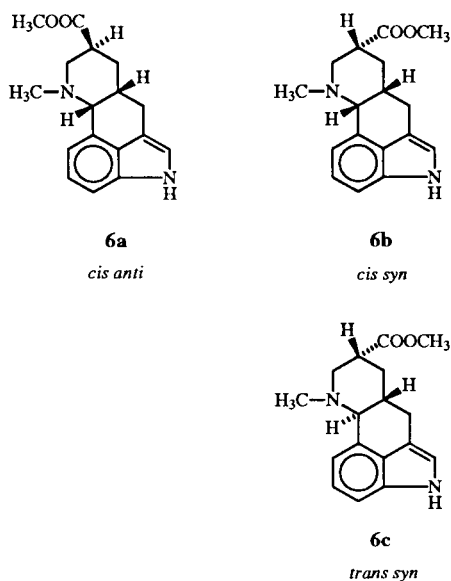(d) KOH, CH₃OH (e) MnO₂ (f) LiAlH₄

underwent an alkylation-amination reaction with concomitant expulsion of a molecule of pyrrolidine succeeding in the construction of the D-ring [7]. This one pot reaction, apparently involving a chain of reactions during which a molecule of methylamine replaces a mol-

Scheme 2. Proposed Reaction Pathway

Scheme 3

Diastereomers of Aza Transposed Ergolines

6a

cis anti

6b

cis syn

6c

trans syn

Scheme 4

Bohlmann Bands

2900   2700   2900   2700   2900   2700 cm^{-1}

β-*cis*   *trans*   α-*cis*

ecule of pyrrolidine from its position, gave the desired product **3** in 74% overall yield from the ketone **1**, (Scheme 1). The proposed pathway for the formation of the D-ring, *via* this alkylation-amination reaction of the enamine, is outlined in the Scheme 2. Reduction of the enamine **3**, was accomplished with sodium cyanoboro-hydride and acetic acid [8]. Removal of the protecting group on the indoline nitrogen by basic hydrolysis and reesterification gave the indoline ester **4**. Oxidation with activated manganese dioxide [9] produced the desired ergoline ester **6**.
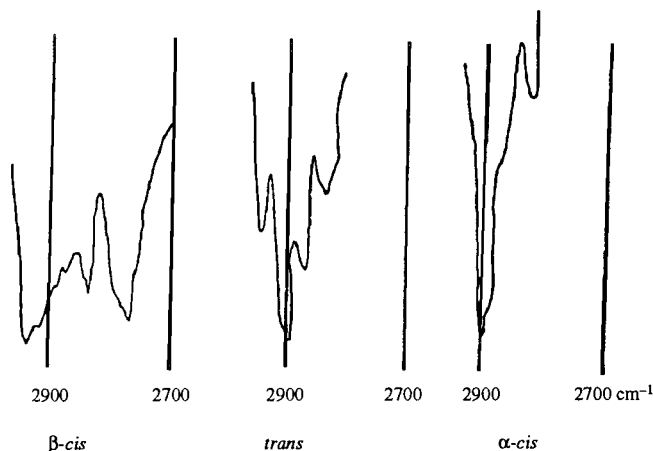
Analysis.

This product showed three major van Urk's positive spots on tlc which were separated by preparative layer chromatography on silica gel (chloroform:ethanol, 99:1) in a chamber of ammonia vapors, and crystallized from benzene-hexane. High resolution mass spectrometry revealed that these three compounds had identical masses indicating that they were stereoisomers which differed in configuration at C_5 and C_{10} (the C, D ring fusion) and C7. There are four possible structures among which these three compounds should have. Three of them are illustrated in the Scheme 3, in which *cis* and *trans* refers to the C, D ring fusion and *syn* and *anti* specifies the relationship between the protons at C_5 and C_7. Furthermore each structure gives rise to two possible conformers at N-9 depending on whether the *N*-methyl is α or β.

It is reported in the literature that catalytic reduction of tricyclic octahydrobenzo[*f*]quinolines, yielded only

two *cis* isomers, and hydride reduction gave two *cis* isomers and one *trans* [8a]. By analogy compound **3** was subjected to catalytic hydrogenation. After hydrolysis, reesterification and oxidation in the same manner as the original reactions, two major products were obtained and these co-chromatographed in two systems with two of the isolated isomers, which suggests that these two isomers have a *cis* ring fusion **6a**, **6b**, and that the third is a *trans* fused isomer, like **6c** (Scheme 3). The nmr spectrum of the *trans* isomer gave a doublet at 4.1 δ (J = 12 Hz) integrating for one proton which has been assigned as the proton at C_{10} by comparison with the spectra of some chelidonines [10]. The coupling constant for the chelidonine proton also suggests a *trans* configuration since the J value of 12 Hz compares well to that of 12.5 Hz found for the *trans* chelidonine. The value of the coupling constant of 12 Hz is in agreement with the vicinal Karplus correlation which predicts a value of ~10 for protons of *trans* fused rings [11].

For the *trans* isomer there are four possible diastereomers and in order to determine which of the isomers is the isolated *trans* compound, its ir spectrum was examined. It is reported that, in a given heterocyclic system, with at least one hydrogen antiparallel to the lone electron pair on nitrogen on a carbon next to the nitrogen there is an absorption in the ir spectrum called the Bohlmann *trans* band (2700-2900 cm^{-1}) which is proportional to the number of these *trans* diaxial hydrogens [12]. The ir of the *trans* isomer shows absorption in the Bohlmann band region (Scheme 4). From the models only two configurations have hydrogen *trans* diaxial to the *N*-lone pair, those of the *N*-methyl α pair (Scheme 5).

Of these two the *trans syn* **6c** is likely to be favored since the carbomethoxy substituent is equatorial. The carbomethoxy group can assume an equatorial position in the *trans anti* but only with the ring in a boat configuration.

Scheme 5

Chair Conformations of D Ring of *cis* Isomers and of *trans* Isomer

α-*cis syn*

β-*cis anti*

α-*trans syn*
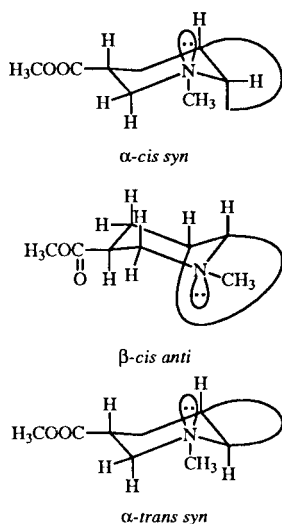
Examining the models in the *cis* series (Scheme 5) the *N*-methyl in the α pair lies approximately in the plane of the aromatic A ring, while the *N*-methyl in the β pair lies below the plane of the ring. One would expect the *N*-methyl to be deshielded when it is in the same plane as the aromatic ring and, conversely, to be shielded when it is below the plane of the ring in the influence of the pi cloud. This deshielding-shielding difference is evident from the nmr spectra of the *cis* isomers. The *N*-methyl signals of these isomers occur at 2.8 δ and 2.21 δ. In the normal ergoline series the N_6 methyl is not influenced by the aromatic ring and its signal appears at 2.45 δ [13]. Therefore, the isomer whose *N*-methyl signal is at 2.8 δ belongs to the α pair and the one with the signal at 2.21 δ belongs to the β pair.

The Bohlmann band absorption in the ir supports this assignment. The β pair of the *cis* isomers have two hydrogens which are *trans* diaxial to the one electron pair on nitrogen while the α pair only has one. Scheme 4 illustrates the obvious intensity difference in the Bohlmann bands between the α-*cis* and β-*cis* isomers.

In each of these pairs the configuration in which the ester substituent is equatorial is again likely to be favored *i.e.* α-*cis syn* and β-*cis anti*.

Finally the β-*cis anti* isomer was reduced to the corresponding alcohol 7 (Scheme 2) using lithium aluminum hydride. The nmr spectrum confirms an alcohol showing a doublet corresponding to the two methylene protons of the alcohol at 3.59 δ, and a singlet corresponding to the hydroxy proton (disappears in deuterium oxide) at 1.69 δ.

EXPERIMENTAL

General Procedures.

Melting points were determined on a Thomas-Hoover Uni-Melt with open capillary tubes and are uncorrected. Spectra were obtained as follows: ir on a Beckman Model 33 or Model 4230; uv on a Cary 17 Model using Baker Chemical Co. "Photoorex" reagent grade absolute methanol; nmr on a FT-80 spectrometer, using TMS as an internal standard and deuteriochloroform as a solvent, unless otherwise noted; high resolution Mass on a Consolidated Electronics Corporation Model 21-110.

Thin and preparative layer chromatography were performed using EM Labs silica gel 60 F-254 or aluminum oxide F-254 plates as noted, using for visualization an ultraviolet lamp and van Urk's spray reagent. Elemental analyses were performed by the Department of Chemistry Microanalysis Laboratory at Purdue University. All reactions were performed under a nitrogen atmosphere, unless otherwise noted.

4-Benzoyl-8-carbethoxy-10-methyl-4,5a,6,7,9,10a-dodecahydro-$\Delta^{6\alpha}\Delta^{10\beta}$-didehydroindolo[3,4-*gh*]quinoline (3).

Into a 200 ml round bottomed flask fitted with a Dean-Stark type water trap (passing the distillate through a thimble of molecular sieves 4A, covered with 40 ml of dry benzene-toluene 1:1) was placed 5.5 g (20 mmoles) of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (provided by Lilly Research Laboratories), 50 ml of benzene, 50 ml of toluene, 5.5 g (77.3 mmoles) distilled pyrrolidine, and 30 mg of *p*-toluenesulfonic acid. The mixture was refluxed for 96 hours after which time the solvent and excess pyrrolidine were removed under vacuum. The solid remaining in the flask was dissolved in 20 ml of anhydrous dimethylformamide and cooled to 0°. To this solution was added 11 g (40 mmoles) ethyl α,α-bis(dibromomethyl)acetate [14] and 4.05 g (40 mmoles) anhydrous triethylamine. This mixture was stirred for 0.5 hours at 0°, and three hours at room temperature. It was then cooled to -15° using an ice-salt bath and excess dry methylamine was condensed into the solution. The mixture was stirred overnight and allowed to rise to room temperature slowly, heated on a steam bath for twelve hours, and stirred overnight at room temperature. The reaction was stopped by pouring the solution into ice-cold dilute hydrochloric acid and the water layer was extracted with ethyl acetate. The ice-cold aqueous layer was then basified slowly in the presence of chloroform with solid sodium carbonate with stirring and, while cooling, extracted thoroughly with chloroform. This chloroform layer was separated, dried (sodium sulfate), filtered and concentrated on a rotary evaporator. Filtration through Florisil (Sigma) using ether-hexane (1:1) and concentration of the solution gave white crystals (2.73 g). The mother liquor was chromatographed on silica gel using ether-hexane mixtures to give 3.07 g of additional product. The total yield was 5.8 g (74%), mp 127-129°; ir (potassium bromide): 1720 (-O-C=O), 1630 (-N-C=O), 1595 (C=C) cm⁻¹; nmr: δ 7.3-7.8 (m, 6H), 7.0 (bs, 2H), 4.2 (q, 2H), 2.7-4.0 (m, 6H), 2.7 (s, 3H), 2.15-2.6 (m, 4H), 1.3 (t, 3H).

Anal. Calcd. for $C_{25}H_{26}N_2O_3$: C, 74.62; H, 6.46; N, 6.96. Found: C, 74.4; H, 6.35; N, 6.67.

4-Benzoyl-8-carbethoxy-10-methyl-4,5a,6,7,9,10a-dodecahydro-$\Delta^{10\beta}$-dehydroindolo[3,4-*gh*]quinoline (4).

To a cold (0°) solution of 1.552 g (3.86 mmoles) of **3**, thirty ml of tetrahydrofuran and ten ml of glacial acetic acid was added 277 mg (4.4 mmoles) of sodium cyanoborohydride. The mixture was stirred at room temperature for two hours, then water was added and the aqueous solution was basified with solid sodium carbonate and extracted with chloroform. The chloroform layer was washed with water, dried (sodium sulfate), filtered and evaporated *in vacuo*. The residue was filtered through a column of silica gel using chloroform. Evaporation of the solvent gave 1.52 g (98% yield) of a colorless amorphous solid.

8-Carbethoxy-10-methyl-4,5a,6,7,9,10a-dodecahydro-$\Delta^5,\Delta^{10\beta}$-didehydro-4*H*-indolo[3,4-*gh*]quinoline (**6**).

To a solution of 1.52 g (3.76 mmoles) of **4** in 30 ml of methanol was added 30 ml of 10% potassium hydroxide solution. The mixture was refluxed for 24 hours. After cooling the solution was evaporated to dryness at ambient temperature. The residue was dissolved in 50 ml of anhydrous methanol, acidified slowly with concentrated sulfuric acid and stirred at room temperature for three days. The solution was basified with solid sodium carbonate, poured into a flask containing chloroform and washed with cold water. The chloroform layer was dried (sodium sulfate), concentrated and filtered through Florisil using chloroform. The solvent was evaporated to give a syrup which was partially crystalline. The crystals isolated from the syrup melted at 147-149°. Evaporation under high vacuum gave 1 g of an amorphous solid which was dissolved in 50 ml of chloroform and stirred with 3 g of activated manganese dioxide at room temperature for 24 hours. The mixture was filtered through Celite and washed with hot chloroform. The solvent was evaporated on a rotary evaporator and the residue was filtered through silica gel using benzene. Further purification and separation was achieved by preparative layer chromatography (silica, chloroform:ethanol 99:1 in an atmosphere saturated with vapor from concentrated ammonia) giving three isomeric compounds in yields of 160 mg, 370 mg, and 240 mg, total = 770 mg or 72% yield from **4**. The three products separated were recrystallized from benzene-hexane.

Isomer **6**-α-*cis syn*.

This compound had mp 158.5-159°; ir (potassium bromide): 1720 (C=O) cm^{-1}; nmr: δ 7.84 (bs, 1H, NH), 6.82-7.35 (m, 4H, Ar), 4.2 (bs, 1H), 3.54 (s, 3H, CH$_3$), 2.8 (s, 3H, NCH$_3$); uv: λ_{max} = 225 nm (E = 31,600), 285 nm, 293 mn; ms: exact mass Calcd. for $C_{17}H_{20}N_2O_2$: 284.153. Found: 284.154.

Isomer **6**-β-*cis anti*.

This compound had mp 96-97°; ir (potassium bromide): 1730 (C=O) cm^{-1}; nmr: δ 7.9 (bs, 1H, NH), 6.85-7.35 (m, 4H, Ar), 3.72 (s, 3H, OCH$_3$), 2.21 (s, 3H, N-CH$_3$); uv: λ_{max} = 225 nm (E = 32,800), 285 nm, 293 nm; ms: exact mass Calcd. for $C_{17}H_{20}N_2O_2$: 284.153. Found: 284.154.
Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.86; H, 7.34; N, 9.60.

Isomer **6**-α-*trans syn*.

This compound had mp 172.5-173°; ir (potassium bromide): 1725 (C=O) cm^{-1}; nmr: δ 7.9 (bs, 1H, NH), 6.8-7.35 (m, 4H, Ar), 4.1 (d, 1H, C-D ring junction proton, J = 12 Hz), 3.71 (s, 3H, OCH$_3$), 2.42 (s, 3H, N-CH$_3$); uv: λ_{max} 225 nm (E = 34,500), 285 nm, 293 nm; ms: exact mass Calcd. for

$C_{17}H_{20}N_2O_2$: 284.153. Found: 284.154.

Reduction of 4-Benzoyl-8-carbethoxy-10-methyl-4,5a,6,7,9,10a-dodecahydro-$\Delta^{6\alpha},\Delta^{10\beta}$-didehydroindolo[3,4-*gh*]quinoline (**3**) with Hydrogen over Platinum.

A solution of 60 mg of **3** (0.15 mmoles) in ethyl acetate was hydrogenated over Adam's catalyst at 1 atmosphere of hydrogen for seven hours. The solution was then suction filtered through Celite and the Celite washed with ethyl acetate. The combined ethyl acetate solution was evaporated on the rotary evaporator to give 80 mg of a brown residue. This residue was then carried through hydrolysis, esterification and oxidation in a procedure analogous to that previously described for 4-benzoyl-8-carbethoxy-10-methyl-4,5a,6,7,9,10a-dodecahydro-$\Delta^{10\beta}$-dehydroindolo[3,4-*gh*]quinoline (**4**).

The final residue (32.9 mg) was chromatographed on silica gel plates using chloroform with ammonia vapors and showed six spots, two of which were van Urk's active. The major indole spot corresponded to isomer **6**-β-*cis anti* and the minor spot co-chromatographed with isomer **6**-α-*cis syn*.

8-Hydroxymethyl-10-methyl-4,5a,6,7,9,10a-dodecahydro-$\Delta^5,\Delta^{10\beta}$-didehydro-4*H*-indolo[3,4-*gh*]quinoline (**7**).

A solution of 24.1 mg (0.085 mmole) of isomer **6**-β-*cis anti* in a small amount of dry tetrahydrofuran (refluxed over LAH and distilled) was added to a stirred solution of excess lithium aluminum hydride in tetrahydrofuran, and stirred for one hour at room temperature. The reaction mixture was then poured into a saturated aqueous sodium sulfate solution and thoroughly extracted with methylene chloride. The combined methylene chloride layers were dried (magnesium sulfate), filtered and evaporated on a rotary evaporator followed by vacuum drying to yield 20.4 mg (94%) of a slightly yellow solid, which chromatographed as one spot on silica using chloroform:methanol, 95:1, with NH$_3$, as a solvent or alumina using chloroform:methanol, 95:5, mp 196-198°; nmr: δ 7.89 (bs, 1H, NH), 6.85-7.25 (m, 4H, Ar), 3.6 (d, 2H, C*H$_2$*OH), 2.24 (s, 3H, N-.CH$_3$), 1.69 (s, 1H, CH$_2$O*H*); ms: exact mass Calcd. for $C_{16}H_{20}N_2O$: 256.158. Found: 256.159.

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