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A Model Study of Ergot Alkaloid Biosynthesis[1]

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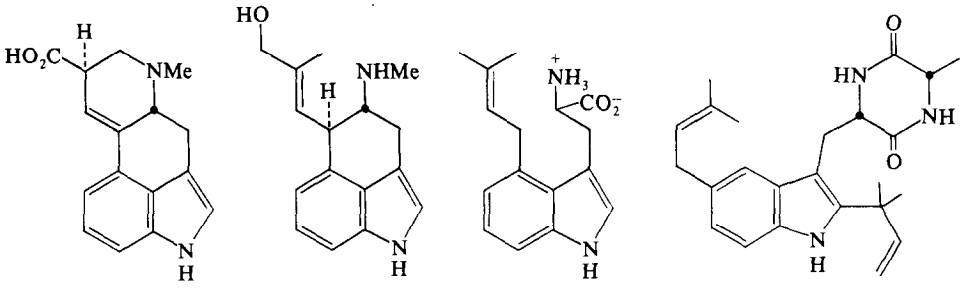
A hypothesis of the mechanistic mode of prenylation of tryptophan, an early phase of ergot alkaloid biosynthesis, occurring by way of 3-(α,α-dimethylallyl)indolenine and its ring-tautomer indoline intermediates and a Cope rearrangement of the latter has been tested in a model study. 3-(α,α-Dimethylallyl)indolines derived from tetrahydrocarbazole and its cyclopentano equivalent have been synthesized by a five-step procedure. The compounds are stable up to ca. 200°C and liberate no benz-prenylated products even on pyrolysis beyond this temperature, thus diminishing the viability of the above biosynthetic hypothesis. The chemistry of the thermolyses is described.

Recent views on the biosynthesis of the ergot alkaloids, e.g., *inter alia* lysergic acid (**I**) and chanoclavine-I (**II**), have held that prenylation of tryptophan leading to the alkylated tryptophan **III** is an early step along the complex, natural pathway (*1*). Since, however, the prenylating reagent, presumably dimethylallyl pyrophosphate, is an electrophile and electrophilic substitution of a β-alkylindole nucleus is expected to take place at C(3), C(5), or C(7), the site of the dimethylallyl group of **III** is most unusual. Although the preference of C(4) as the position of substitution of tryptophan might reflect special, enzymically controlled, steric and/or electronic constraints on the amino acid during the course of the alkylation of the generally activated benzene ring or a prior *N*- or *O*-prenylation of the tryptophan sidechain, followed by intramolecular delivery of the alkyl group to C(4) in an internal, electrophilic substitution process, yet other routes required consideration. One alternate path became apparent from an analysis of the possible biosynthetic origin of echinulin (**IV**), another prenylated tryptophan derivative.



I **II** **III** **IV**

[1] In memory of Professor Morris S. Kupchan whose premature death robbed natural products chemistry of a major, outstanding contributor.

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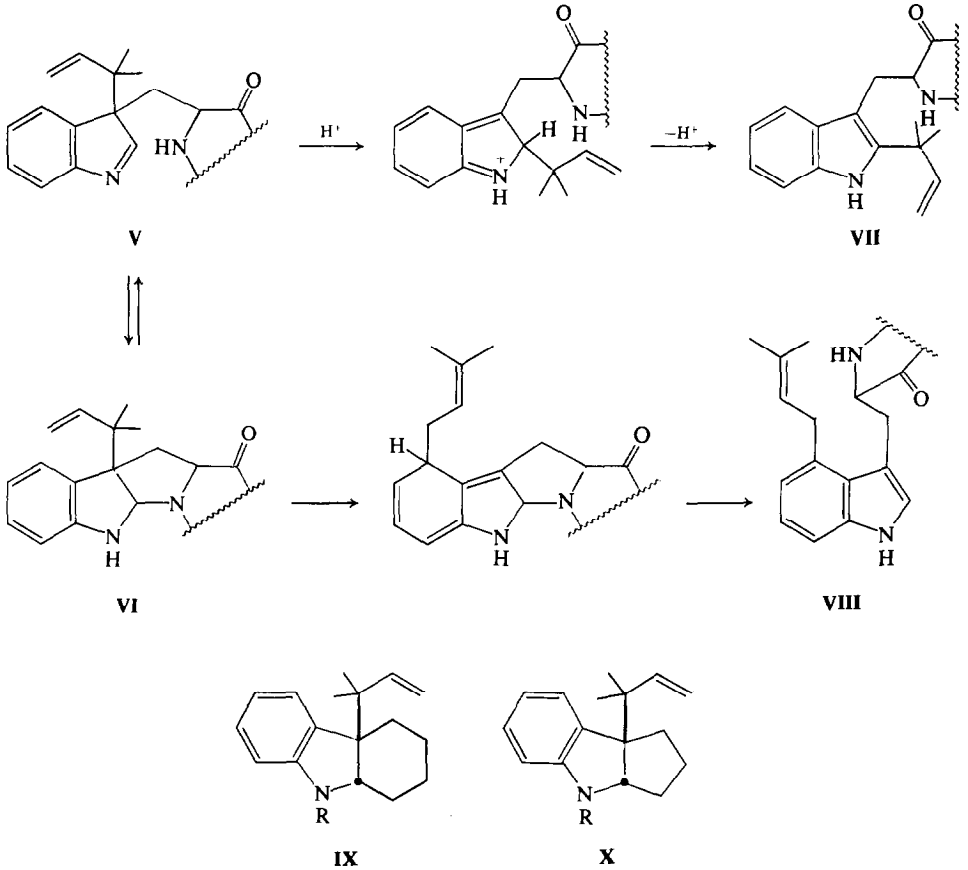
If it be assumed that *C*-prenylation of tryptophan or one of its peptides either directly or via *N*- or *O*-prenyl precursors occurs at the most nucleophilic indole center and introduces preferentially an α,α-dimethylallyl unit, indolenine **V** and/or indoline **VI** are the products of the reaction. The indolenine is ideally suited for a Wagner–Meerwein rearrangement en route to the indole substitution pattern (**VII**) characteristic of echinulin (**IV**) and the indoline might be ripe for a Cope rearrangement into a 4-(γ,γ-dimethylallyl)tryptophan system (**VIII**) representative of the ergot alkaloid precursor **III**. In order to gain some insight into the latter path, a study of the Cope rearrangement of models **IX** and **X** was undertaken.



V **VII**

VI **VIII**

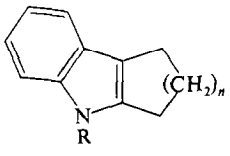
IX **X**

a, R = H

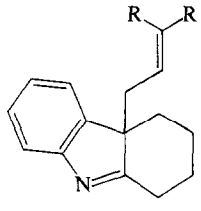
b, R = COC_6H_5

The synthesis of the model indolines was carried out in the following manner. Tetrahydrocarbazole (**XIa**) and its cyclopentano equivalent (**XIb**) (*2*) were allylated by the interaction of their magnesio salts with allyl bromides (*3*). The use of allyl bromide itself led to the formation of indolenine **XIIa** in the case of the former starting material and carbinolamine **XIII** in the case of the latter. The dissimilarity of behavior of the indoles may reflect the enhanced ease of hydration of the indolenine from **XIb** during aqueous, acidic work-up due to the strain inherent in the azahydropentalene system.

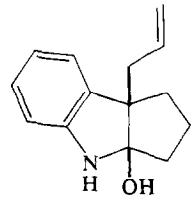
For similar reasons of strain the bridgehead substituents of the carbinolamine (**XIII**) are assumed to be *cis*-oriented toward each other. In the hope of possibly developing a two-step synthesis of **IXa**, the magnesio salt of tetrahydrocarbazole (**XIa**) was exposed to dimethylallyl bromide. Unfortunately, this reaction led only to the undesired indolenine isomer **XIIb**.



XIa, R = H, $n = 2$
b, R = H, $n = 1$
c, R = COC_6H_5, $n = 2$

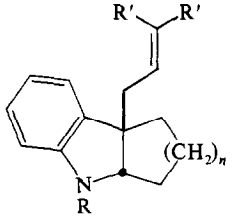


XIIa, R = H
b, R = Me



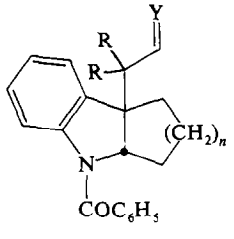
XIII

Reduction of compounds **XIIa**, **XIIb**, and **XIII** with sodium borohydride yielded indolines **XIVa**,, **b**, and **c**, respectively, whose benzoylation produced the benzamides **XIVd, e,** and **f,** respectively. By analogy with the stereochemical consequence of the hydride reduction of dehydroaspidospermidine, a pentacyclic indolenine related structurally to **XIIa** (*4*), compounds **XIV** and all substances derived therefrom are designated as *cis*-tricycles. Even though a direct proof of stereochemistry is desirable, its lack has little effect on the arguments for the Cope rearrangement of the final compounds **IX** and **X** (*vide infra*), since both *cis* and *trans* isomers can generate conformations containing dimethylallyl units *quasi*-axially and hence well disposed to the indoline rings for the Cope rearrangement.



XIVa, R = R′ = H, $n = 2$
b, R = H, R′ = Me, $n = 2$
c, R = R′ = H, $n = 1$
d, R = COC_6H_5, R′ = H, $n = 2$
e, R = COC_6H_5, R′ = Me, $n = 2$
f, R = COC_6H_5, R′ = H, $n = 1$

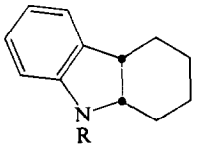
Oxidation of the amides **XIVd** and **f** by the Lemieux–Johnson procedure (*5*) afforded aldehydes **XVc** and **d,** respectively. Treatment of the oxidation products with ethanol during work-up led to the hemiacetals **XVa** and **b**, respectively, which on heating yielded the aldehydes. Alkylation of the latter with methyl iodide and potassium t-butoxide gave the methylated aldehydoamides **XVe** and **f,** respectively.



XVa, R = H, Y = OH, OEt, $n = 2$
b, R = H, Y = OH, OEt, $n = 1$
c, R = H, Y = O, $n = 2$
d, R = H, Y = O, $n = 1$
e, R = Me, Y = O, $n = 2$
f, R = Me, Y = O, $n = 1$

Treatment of aldehydes **XVe** and **f** with triphenylmethylenephosphorane produced the desired amides **IXb** and **Xb**, respectively, whose mild reduction with lithium aluminum hydride (*6*) yielded indolines **IXa** and **Xa**, respectively.

The four indolines **IX** and **X** were stable at ambient temperature and only underwent chemical change at elevated temperatures. Thus pyrolysis of indoline **IXa** in pyridine solution in the presence of a minute quantity of the antioxidant hydroquinone for 4 hr at 200°C furnished tetrahydrocarbazole (**XIa**), the rearranged indoline **XIVb**, and hexahydrocarbazole (**XVIa**) (*7*) in 63, 20, and 10% yields, respectively. A similar pyrolysis of **IXb** proceeded more slowly (222°C for 15 hr), but gave related products, i.e., the *N*-benzoyl derivative of tetrahydrocarbazole (**XIc**) (*2*), of the rearranged indoline (**XIVe**), and of hexahydrocarbazole (**XVIb**) (*8*) in 22, 47, and 19% yields, respectively. The indolines **X**, however, were much less reactive, heating of the *N*-unsubstituted compound (**Xa**) even at 235°C for 11 hr resulting in the recovery of 45% of starting material and the formation of indole **XIb** in 37% yield and thermolysis of the *N*-benzoyl derivative **Xb** at either 245°C for 42 hr or 290°C for 5 hr leading only to recovery of 80% of starting compound.



XVIa, R = H
b, R = COC_6H_5

These results are interpreted most readily on the basis of the intermediacy of a benzyl–allyl radical pair whose recombination leads to the sterically less encumbered and hence more stable indoline (**IXa** →**XIVb**; **IXb** → **XIVe**), whose hydrogen transfer from the allyl to the benzyl moiety produces unobserved isoprene and 2,3-dihydroindole (**IXa** → **XVIa**; **IXb** → **XVIb**) and whose alternate hydrogen transfer from the benzyl to the allyl unit affords trimethylethylene and indole (**IXa** → **XIa**; **IXb** → **XIc**; **Xa** → **XIb**). The loss of the dimethylallyl substituent and indole formation is reminiscent of the pyrolysis of 2-allyl-2-phenylcyclohexanone yielding 2-phenyl-2-cyclohexenone and propylene (*9*) and may have an alternate explanation. If the stereochemistry of the starting compounds of the pyrolyses is as depicted on formulas **IX** and **X**, a point strengthened by the liberation of only *cis*-hexahydrocarbazoles (**XVI**) from the same reactions, the production of indoles **XI** may reflect a concerted, *retro*-ene process.

The lack of formation of any benz-isopentenyl products from the indolines **IX** and **X** even on thermolysis bodes ill for the hypothesis of the **VI** → **VIII** transformation or its equivalent being involved in ergot alkaloid biosynthesis (*vide supra*).

EXPERIMENTAL SECTION

Melting points were recorded on a Reichert micro hot stage and were uncorrected. Infrared spectra were determined on Perkin–Elmer 137 and 621 spectrophotometers and ultraviolet spectra on a Carey 14 instrument. ^1H nmr spectra of carbon tetrachloride solutions, containing tetramethylsilane ($\delta = 0$ ppm) as internal standard, were taken on a Varian A-60 spectrometer. Mass spectra were recorded on an Atlas CH-7 gc-ms instrument.

4a-Allyl-1,2,3,4-tetrahydro-4a-H-carbazole (**XIIa**). A solution of 42.8 g of tetrahydrocarbazole (**XIa**) in 180 ml of dry benzene was added dropwise to an ice-cold, stirring solution of methylmagnesium iodide (from 6.08 g of magnesium, 39.0 g of methyl iodide, and 150 ml of anhydrous ether), and the mixture was then refluxed under nitrogen for 15 min. It was cooled in an icebath, 30.5 g of freshly distilled allyl bromide was added dropwise, and the mixture was stirred at room temperature under nitrogen for 24 hr. It was then poured into a mixture of 50 ml of concentrated hydrochloric acid, 350 ml of water, and ice. The precipitated indolenine hydrochloride was filtered and both it and the aqueous phase were washed with ether. The precipitate was resuspended in the aqueous solution, an equal volume of ether was added, and the mixture was neutralized with 2 *N* sodium hydroxide. The aqueous phase was washed with ether and the combined organic solutions were dried (K_2CO_3) and evaporated. Crystallization of the residue from hexane gave 42.3 g of crystalline **XIIa** (80%); ^{1}H nmr δ 0.8–3.0 [*m*, 10, $(CH_2)_5$], 4.6–5.4 (*m*, 3, olefinic Hs), 6.9–7.6 (*m*, 4, aromatic Hs); *m/e* 211 (M^+), 170 (base).

Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.52; H, 8.20; N, 6.47.

4a-(γ,γ-Dimethylallyl-)1,2,3,4-tetrahydro-4a-H-carbazole (**XIIb**). The reaction between a solution of 8.55 g of **XIa** in 50 ml of benzene and a methylmagnesium iodide solution (from 1.22 g of magnesium, 7.80 g of methyl iodide, and 50 ml of ether) and subsequently with a solution of 7.50 g of γ,γ-dimethylallyl bromide in 15 ml of ether followed the above procedure. Chromatography of the oily product on basic alumina, activity I, and elution with hexane and ether yielded 5.10 g of colorless liquid **XIIb** (43%) which solidified on cooling (mp ca. 39–41°), but was difficult to crystallize from hexane; ^{1}H nmr δ 0.8–3.0 [*m*, 10, $(CH_2)_5$], 1.50 (broad *s*, 6, Me_2), 4.50 (*tm*, 1, $J = 7$ Hz, olefinic H), 6.9–7.6 (*m*, 4, aromatic Hs); *m/e* 239 (M^+), 171 (base, 122.3*), 143 (119.5*).

Anal. Calcd for $C_{17}H_{21}N$: C, 85.31; H, 8.84; N, 5.85. Found: C, 85.07; H, 9.05; N, 5.88.

3-Allyl-2-hydroxy-2,3-trimethyleneindoline (**XIII**). The reaction between a solution of 78.5 g of **XIb** (*2*) in 350 ml of benzene and a methylmagnesium iodide solution (from 12.2 g of magnesium, 78.0 g of methyl iodide, and 300 ml of ether) and subsequently with a solution of 71.0 g of allyl bromide in 100 ml of ether followed the above procedure. Crystallization of the crude solid product from hexane yielded 71.5 g of crystalline **XIII** (67%), mp 51–52°, uv (MeOH), λ_{max} 245, 300 nm; ^{1}H nmr ($CDCl_3$) δ 1.2–2.2 [*m*, 6, $(CH_2)_3$], 2.3–2.6 (*m*, 2, allyl CH_2), 4.8–6.1 (*m*, 3, olefinic Hs), 6.3–7.1 (*m*, 4, aromatic Hs); *m/e* 215 (M^+), 197, 174, 156 (base), 146, 128.

Anal. Calcd for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.04; H, 7.80; N, 6.45.

4a-Allyl-1,2,3,4,4a,9a-hexahydrocarbazole (**XIVa**). A solution of 28.5 g of sodium borohydride and 30 ml of water in 240 ml of ethanol was added dropwise to a stirring solution of 63.3 g of indolenine **XIIa** in 400 ml of ethanol at 60°C, and the mixture was refluxed for 4 hr. Water, 700 ml, was added and the mixture was extracted with methylene chloride. The extract was dried (K_2CO_3) and evaporated. Distillation of the residue yielded 56.4 g of colorless liquid **XIVa** (88%), bp 119°/0.5 Torr; ^{1}H nmr δ 1.2–1.8 [*m*, 8, $(CH_2)_4$], 2.31 (*dm*, 2, $J = 7$ Hz, allyl CH_2), 3.99 [*t* (after NH–D_2O exchange),

1, J = 5 Hz, NCH], 4.7–6.1 (*m*, 3, olefinic Hs), 6.3–7.1 (*m*, 4, aromatic Hs); *m/e* 213 (M^+), 172 (base), 130.

Anal. Calcd for $C_{15}H_{19}N$: C, 84.45; H, 8.98; N, 6.57. Found: C, 84.56; H, 8.88; N, 6.64.

4a-(γ,γ-Dimethylallyl-)1,2,3,4,4a,9a-hexahydrocarbazole (**XIVb**). The same procedure for a solution of 2.80 g of sodium borohydride and 3 ml of water in 25 ml of ethanol and a solution of 4.20 g of indolenine **XIIb** in 50 ml of ethanol, followed by distillation of the oily product, yielded 2.65 g of colorless, liquid **XIVb** (64%), which solidified on cooling; bp 114°/0.15 Torr; mp 48° (crystallized from hexane); ^{1}H nmr δ 1.2–2.0 [*m*, 8, $(CH_2)_4$], 1.45 (broad *s*, 3, Me), 1.65 (broad *s*, 3 Me), 2.1–2.5 (*m*, 2, allyl CH_2), 3.36 (*t*, 1, J = 5 Hz, NCH), 5.10 (*tm*, 1, J = 7 Hz, olefinic H), 6.4–7.0 (*m*, 4, aromatic Hs); *m/e* 241 (M^+), 172 (base), 130 (98.3*).

Anal. Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.43; H, 9.44; N, 5.83.

3-Allyl-2,3-trimethyleneindoline (**XIVc**). The same procedure for a solution of 39.8 g of sodium borohydride and 40 ml of water in 360 ml of ethanol and a solution of 68.8 g of **XIII** in 400 ml of ethanol, followed by distillation of the oily product, gave 37.7 g of colorless, liquid **XIVc** (59%), bp 102°/0.5 Torr; ^{1}H nmr δ 1.5–2.0 [*m*, 6, $(CH_2)_3$], 2.3–2.5 (*m*, 2, allyl CH_2), 3.85 (*t*, 1, J = 3 Hz, NCH), 4.7–6.1 (*m*, 3, olefinic Hs), 6.2–7.0 (*m*, 4, aromatic Hs); *m/e* 199 (M^+), 158 (base, 125.4*), 130 (106.9*).

Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.34; H, 8.91; N, 6.79.

4a-Allyl-9-benzoyl-1,2,3,4,4a,9a-hexahydrocarbazole (**XIVd**). A solution of 53.4 g of indoline **XIVa** and 35 ml of benzoyl chloride in 300 ml of pyridine was kept in an icebath for 12 hr. It was poured into 100 ml of ice water, acidified with 10% sulfuric acid, and extracted with chloroform. The extract was washed with water, 10% sodium hydroxide solution, and again with water, dried (Na_2SO_4), and evaporated. Crystallization of the residue from hexane yielded 68.0 g of amide **XIVd** (86%), mp 76°; ^{1}H nmr δ 0.9–2.7 [*m*, 8, $(CH_2)_4$], 2.0–2.4 (*m*, 2, allyl CH_2), 4.07 (*t*, 1, J = 6 Hz, NCH), 4.7–6.0 (*m*, 3, olefinic Hs), 6.8–7.1 (*m*, 4, aromatic Hs), 7.3–7.6 (*m*, 5, benzoyl Hs); *m/e* 317 (M^+), 276, 105 (base), 77.

Anal. Calcd for $C_{22}H_{23}ON$: N, 4.41. Found: N, 4.22.

9-Benzoyl-4a-(γ,γ-dimethylallyl-)1,2,3,4,4a,9a-hexhydrocarbazole (**XIVe**). The same procedure applied to 964 mg of indoline **XIVb** and 0.6 ml of benzoyl chloride in 5 ml of pyridine, chromatography of the crude, oily product on neutral alumina, activity I, and elution with hexane and ether yielded 1.24 g of **XIVe** (88%) as viscous, colorless oil; ^{1}H nmr δ 0.9–1.8 [*m*, 8, $(CH_2)_4$], 1.37 (broad *s*, 3, Me), 1.67 (broad *s*, 3, Me), 2.0–2.4 (*m*, 2, allyl CH_2), 4.15 (*t*, 1, J = 6 Hz, NCH), 5.08 (*tm*, 1, J = 7 Hz, olefinic H), 6.8–7.1 (*m*, 4, aromatic Hs), 7.2–7.5 (*m*, 5, benzoyl Hs); *m/e* 345 (M^+), 276, 105 (base), 77.

Anal. Calcd for $C_{24}H_{27}ON$: N, 4.05. Found: N, 4.14.

3-Allyl-1-benzoyl-2,3-trimethyleneindoline (**XIVf**). The same procedure for 35.8 g of indoline **XIVc** and 26 ml of benzoyl chloride in 200 ml of pyridine and crystallization of the crude product from hexane gave 51.5 g of **XIVe** (94%), mp 83°; ^{1}H nmr δ 1.3–2.2 [*m*, 6, $(CH_2)_3$], 2.3–2.6 (*m*, 2, allyl CH_2), 4.40 (*t*, 1, J = 6 Hz, NCH), 4.8–5.8 (*m*, 3, olefinic Hs), 6.9–7.1 (*m*, 4, aromatic Hs), 7.39 (*s*, 5, benzoyl Hs); *m/e* 303 (M^+), 262 (226.5*), 167, 149, 105 (base), 77.

Anal. Calcd for $C_{21}H_{21}ON$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.12; H, 7.02; N, 4.72.

9-Benzoyl-4a-[β-hydroxy-β-ethoxyethyl-)1,2,3,4,4a,9a-hexahydrocarbazole (**XVa**). Osmium tetraoxide, 500 mg, and thereafter 89.8 g of finely divided sodium metaperiodate in 5-g portions were added over a 2-hr period to a stirring solution of 63.4 g of **XIVd** in 200 ml of water and 600 ml of dioxane maintained at 23°C, and the stirring continued for 3 hr. The precipitate was filtered and rinsed with ether, and the filtrate was saturated with sodium chloride and extracted with ether. The combined organic extracts were dried (Na_2SO_4) and evaporated. A chloroform solution of the black residue was passed through 100 g of Florosil and the column was eluted with chloroform. Evaporation of the eluants and refrigeration of an ethanol solution of the residue for 12 hr yielded 42.0 g of crystalline hemiacetal **XVa** (58%), mp 98°; ir (KBr) OH 3.05 (m), C=O, C=C 6.18 (*s*), 6.29 (*s*), 6.37 (*m*) μm; ^{1}H nmr ($CDCl_3$) representative of an equilibrium mixture of **XVa** and **XVc** (*vide infra*); mass spectrum (135°) identical with that of **XVc**.

Anal. Calcd for $C_{23}H_{27}O_3N$: C, 79.59; H, 7.45; N, 3.83. Found: C, 75.63; H, 7.34; N, 3.78.

1-Benzoyl-3-(β-hydroxy-β-ethoxyethyl-)2,3-trimethyleneindoline (**XVb**). The same procedure was applied to 500 mg of osmium tetraoxide, 69.1 g of sodium metaperiodate, and a solution of 46.6 g of **XIVf**, yielding 31.8 g of colorless, crystalline hemiacetal **XVb**, mp 108°; ir (KBr) OH 3.01 (*m*), C=O, C=C 6.18 (*s*), 6.23 (*s*) μm; ^{1}H nmr ($CDCl_3$) representative of an equilibrium mixture of **XVb** and **XVd**; *m/e* 351 (M^+), 305, 105 (base) 77.

Anal. Calcd for $C_{22}H_{25}O_3N$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.20; H, 7.33; N, 4.22.

Heating of the hemiacetal near its mp for a few seconds gave aldehyde **XVd**; ^{1}H nmr δ 1.3–2.2 [*m*, 6, $(CH_2)_3$], 2.80 (*m*, 2, $COCH_2$), 4.58 (*t*, 1, J = 7 Hz, NCH), 6.9–7.2 (*m*, 4, aromatic Hs), 7.43 (*s*, 5, benzoyl Hs), 9.53 (*t*, 1, J = 7 Hz, CHO).

9-Benzoyl-4a-formylmethyl-1,2,3,4,4a,9a-hexahydrocarbazole (**XVc**). A solution of 39.6 g of **XVa** and 5 ml of conc. hydrochloric acid in 95 ml of water and 300 ml of tetrahydrofuran was stirred under nitrogen at room temperature for 2 hr and then saturated with sodium chloride and neutralized with 10% potassium carbonate solution. The mixture was resaturated with sodium chloride and extracted exhaustively with ether. The extract was dried (Na_2SO_4) and evaporated. Crystallization of the residue from benzene yielded 29.2 g of aldehyde **XVc** (84%), mp 121°; ir (KBr) aldehyde CH 3.71 (*w*), C=O 5.84 (*s*), 6.13 (*s*), C=C 6.23 (*m*), 6.30 (*m*), 6.38 (*m*) μm; ^{1}H nmr ($CDCl_3$) δ0.9–2.4 [*m*, 8, $(CH_2)_4$], 2.60 (*m*, 2, $COCH_2$), 4.28 (*t*, 1, J = 7 Hz, NCH), 7.0–8.4 (*m*, 4, aromatic Hs), 7.50 (broad *s*, 5, benzoyl Hs), 9.57 (*t*, 1, J = 7 Hz, CHO); *m/e* 319 (M^+), 276 (238.7*), 105, 77 (base, 56.5*).

Anal. Calcd for $C_{21}H_{21}O_2N$: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.22; H, 6.77; N, 4.62.

9-Benzoyl-4a-(α-formylisopropyl-)1,2,3,4,4a,9a-hexahydrocarbazole (**XVe**). A solution of 28.0 g of aldehyde **XVc** in 75 ml of dry benzene was mixed with a solution of 37.2 g of potassium t-butoxide in 250 ml of freshly distilled (from calcium oxide) t-butyl alcohol under nitrogen, and the mixture was stirred at room temperature for 5 min. It was then cooled by an icebath, 40 ml of methyliodide was added, and the mixture was

kept under nitrogen for 12 hr. It was poured into 200 ml of water and the alcohol was evaporated under vacuum. The aqueous solution was extracted with ether and the extract was dried (Na_2SO_4) and evaporated. ^1H nmr ($CDCl_3$) spectral inspection of the residue revealed it to be a mixture of ca. 45% of desired *C,C*-dimethylated product [9.30 (*s*, 1, CHO)], ca 30% of *O*-monomethylated compound [3.38 or 3.40 (*s*, 3, OMe), 4.86, 5.76 (*d* each, 1 each, J = 13 Hz, olefinic Hs)], and ca. 25% of *C,O*-dimethylated substance [3.38 or 3.40 (*s*, 3, OMe), 5.25 (*s*, 1, olefinic H)]. Hence a solution of the product mixture and 10 ml of concentrated hydrochloric acid in 90 ml of water and 250 ml of tetrahydrofuran was heated at 65° under nitrogen for 3 hr and then saturated with sodium chloride and neutralized with 10% potassium carbonate solution. The mixture was extracted with ether, and the extract was dried (Na_2SO_4) and evaporated under vacuum. A solution of the residue in 100 ml of benzene was poured into a solution of 13.8 g of potassium t-butoxide in 150 ml of t-butyl alcohol, and the mixture was stirred under nitrogen for 5 min. It was then cooled in an icebath, 14.8 ml of methyl iodide was added, and the mixture was kept at room temperature under nitrogen for 12 hr. It was extracted and exposed to acid hydrolysis as before. A solution of the resultant product in 75 ml of ether was poured into a column of 112 g of basic alumina, activity I, and eluted with 250 ml of ether. Evaporation of the eluates furnished 24.8 g of colorless, liquid **XVe** (81%); ^1H nmr δ 0.98, 1.13 (*s*, 3 each, Me_2), 0.8–2.3 [*m*, 8, $(CH_2)_4$], 4.52 (*m*, 1, NCH), 6.8–7.2 (*m*, 4, aromatic Hs), 7.40 (*s*, 5, benzoyl Hs), 9.23 (*s*, 1, CHO); *m/e* 347 (M^+), 276 (219.5*), 105 (base), 77 (56.5*).

Anal. Calcd for $C_{23}H_{25}O_2N$: C, 79.50; H, 7.25; N, 4.03. Found: C, 79.23; H, 7.27; N, 4.10.

1-Benzoyl-3-(α-formylisopropyl-)2,3-trimethyleneindoline (**XVf**). The aldehyde **XVd** was liberated from its hemiacetal **XVb** by a solution of 29.8 g of the latter and 5 ml of conc. hydrochloric acid in 70 ml of water and 200 ml of tetrahydrofuran being stirred under nitrogen at room temperature for 2 hr. Work-up as for aldehyde **XVc** (*vide supra*) gave crude **XVd** whose solution in 60 ml of dry benzene was poured into a solution of 27.2 g of potassium t-butoxide in 200 ml of t-butyl alcohol and the mixture was stirred under nitrogen for 5 min. It then was cooled in an icebath, 32.3 ml of methyl iodide was added, and the mixture was kept at room temperature for 12 hr. Work-up, aqueous acid hydrolysis of the *O*-alkylation products, remethylation, and second work-up followed the procedure developed for the preparation of **XVe** (*vide supra*). Chromatography of the crude product on basic alumina, activity I, and elution with ether gave 21.3 g of an oil whose crystallization from ether yielded aldehyde **XVf** (76%), 132–133°; ^1H nmr ($CDCl_3$) δ 1.0–2.2 [*m*, 6, $(CH_2)_3$], 1.10, 1.15 (*s*, 3 each, Me_2), 4.75 (*m*, 1, NCH), 6.9–7.2 (*m*, 4, aromatic Hs), 7.43 (*s*, 5, benzoyl Hs), 9.58 (*s*, 1, CHO); *m/e* 333 (M^+), 262 (206.1*), 105 (base), 77 (56.5*).

Anal. Calcd for $C_{22}H_{23}O_2N$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.41; H, 7.14; N, 4.20.

9-Benzoyl-4a-(α,α-dimethylallyl-)1,2,3,4,4a,9a-hexahydrocarbazole (**IXb**). A mixture of 1.95 g of sodium hydride and 40 ml of anhydrous dimethylsulfoxide was heated at 80°C under nitrogen for 45 min and brought to room temperature. A solution of 28.9 g of triphenylmethylphosphonium bromide in 95 ml of dimethylsulfoxide was added and the mixture was stirred for 15 min. A solution of 20.8 g of aldehyde **XVe** in 30 ml of dimethylsulfoxide was added dropwise and the mixture was stirred under nitrogen at

room temperature for 12 hr. It then was poured into 200 ml of water and ice and extracted with 1 liter of pentane. The extract was washed with 200 ml of 1:1 DMSO–water and with 100 ml of concentrated brine solution, dried (Na_2SO_4), and evaporated. Chromatography of the residue on 100 g of neutral alumina, activity I, elution with cyclohexane and ether, and crystallization of the resultant solid from hexane yielded 13.0 g of amide **IXb** (63%), mp 114°; 1H nmr δ 0.8–2.2 [*m*, 8, $(CH_2)_4$], 1.02, 1.05 (*s*, 3 each, Me_2), 4.62 (*t*, 1, J = 7 Hz, NCH), 4.8–6.2 (*m*, 3, olefinic Hs), 6.8–7.1 (*m*, 4 aromatic Hs), 7.41 (*s*, 5, benzoyl Hs); *m/e* 345 (M^+), 276, 105 (base), 77.

Anal. Calcd for $C_{24}H_{27}ON$: N, 4.05. Found: N, 3.99.

1-Benzoyl-3-(α,α-dimethylallyl-)2,3-trimethyleneindoline (**Xb**). The same procedure was used for 1.07 g of sodium hydride in 23 ml of DMSO, 15.9 g of triphenylmethylphosphonium bromide in 50 ml of DMSO, and 10.5 g of aldehyde **XVf** in 50 ml of DMSO. Crystallization of the chromatographed product from hexane yielded 6.60 g of amide **Xb** (63%), mp 102°; 1H nmr δ 1.01, 1.08 (*s*, 3 each, Me_2), 1.0–2.1 [*m*, 6, $(CH_2)_3$], 4.54 (*t*, 1, J = 7 Hz, NCH), 4.8–6.2 (*m*, 3, olefinic Hs), 6.8–7.2 (*m*, 4, aromatic Hs), 7.40 (*s*, 5, benzoyl Hs); *m/e* 331 (M^+), 262, 105 (base), 77.

Anal. Calcd for $C_{23}H_{25}ON$: N, 4.23. Found: N, 4.16.

4a-(α,α-Dimethylallyl-)1,2,3,4,4a,9a-hexahydrocarbazole (**IXa**). A solution of 2.07 g of amide **IXb** in 30 ml of tetrahydrofuran was added dropwise to an ice-cold, stirring solution of 400 mg of lithium aluminum hydride in 40 ml of anhydrous ether and the stirring was continued at 0°C for 1 hr and at room temperature for 30 min. Then 0.3 ml of water, 0.3 ml of 15% sodium hydroxide solution, and 0.9 ml of water were added successively and the mixture was stirred for 15 min and filtered. The precipitate was washed with ether and the washings were extracted exhaustively with 10% hydrochloric acid. The extract was neutralized with 5 *N* sodium hydroxide solution and extracted with ether. The extract was dried (K_2CO_3) and evaporated. Chromatography of the residue on 25 g of basic alumina, activity I, and elution with hexane and ether yielded 795 mg of liquid **IXa** (55%); ir (neat) NH 2.92 (*w*), C=C 6.10 (*w*), Ar C=C, 6.20 (*m*), C=CH 10.92 (*m*) μm; uv (MeOH), λ_{max} 248, 304 nm; 1H nmr δ 0.93, 0.97 (*s*, 3 each, Me_2), 1.0–2.0 [*m*, 8, $(CH_2)_4$], 3.78 (*t*, 1, J = 4 Hz, NCH), 4.7–6.1 (*m*, 3, olefinic Hs), 6.2–7.1 (*m*, 4, aromatic Hs); *m/e* 241 (M^+), 172 (base), 130.

Anal. Calcd for $C_{17}H_{23}N$: N, 5.80. Found: N, 5.73.

3-(α,α-Dimethylallyl-)2,3-trimethyleneindoline (**Xa**). The same procedure was applied to 1.99 g of amide **Xb** in 25 ml of dry tetrahydrofuran and 372 mg of lithium aluminum hydride in 25 ml of anhydrous ether. The chromatographed oil amounted to 905 mg of colorless, liquid indoline **Xa** (66%); ir (neat) NH 2.91 (*w*), C=C 6.10 (*w*), Ar C=C 6.20 (*m*), C=CH 10.92 (*m*) μm; uv (MeOH), λ_{max} 246, 302 nm; 1H nmr δ 0.94, 1.06 (*s*, 3 each, Me_2), 1.2–1.9 [*m*, 6, $(CH_2)_3$], 3.92 (*t*, 1, J = 4 Hz, NCH), 4.7–6.1 (*m*, 3, olefinic Hs), 6.2–7.1 (*m*, 4, aromatic Hs); *m/e* 227 (M^+), 158 (base), 130.

Anal. Calcd for $C_{16}H_{21}N$: N, 6.16. Found: N, 6.47.

Pyrolyses. (*a*) **IXa**. A solution of 461 mg of indoline **IXa** and 20 mg of hydroquinone in 3 ml of pyridine was heated in a sealed tube at 200°C for 4 hr. Upon opening of the cooled tube and evaporation of the solution under vacuum the products were chromatographed on 15 g of neutral alumina, activity I. Elution with combinations of hexane, benzene, ether, and chloroform yielded 207 mg of tetrahydrocarbazole (**XIa**) (63%) (mp 118–119°, spectrally identical with an authentic sample), 47 mg of indoline

XIVb (20%) (mp 48°C, spectrally identical with the sample above), and 32 mg of *cis*-1,2,3,4,4a,9a-hexahydrocarbazole (**XVIa**) (10%) [mp 97–98°; *m/e* 173 (M^+), 130 (base); spectrally identical with an authentic specimen (*7*)].

[*b*) **IXb**. A solution of 2.00 g of amide **IXb** and 100 mg of hydroquinone in 6.5 ml of pyridine was heated in a sealed ampule at 222°C for 15 hr. Work-up as above, chromatography of the products on 75 g of neutral alumina, activity I, and elution as above gave 372 mg of *N*-benzoyltetrahydrocarbazole (**XIc**) (22%) [mp 85°; ^{1}H nmr δ 1.6–1.9 (*m*, 4, 2 × CH_2), 2.5–2.8 (*m*, 4, 2 × allyl CH_2), 6.8–7.2 (*m*, 4, aromatic Hs), 7.2–7.7 (*m*, 5 benzoyl Hs); spectrally identical with an authentic sample (*2*)], 930 mg of amide **XIVe** (47%) (spectrally identical with the sample above), and 303 mg of *cis*-9-benzoyl-1,2,3,4,4a,9a-hexahydrocarbazole (**XVIb**) (19%) [mp 106°C; ^{1}H nmr δ 0.9–2.3 (*m*, 8, 4 × CH_2), 3.3–3.6 (*m*, 1, benzyl H), 4.2–4.5 (*m*, 1, NCH), 6.8–7.1 (*m*, 4, aromatic Hs), 7.2–7.5 (*m*, 5, benzoyl Hs); spectrally identical with an authentic sample (*2*)].

(*c*) **Xa**. A solution of 829 mg of indoline **Xa** and 50 mg of hydroquinone in 5 ml of pyridine was heated in a sealed tube at 235°C for 11 hr. Work-up as before, chromatography of the products on 30 g of neutral alumina, activity I, and elution as before led to 376 mg of recovered starting material (45%) and 235 mg of indole **XIb** (37%) [mp 108°; spectrally identical with an authentic sample (*2*)].

(*d*) **Xb**. A solution of 2.00 g of amide **Xb** and 100 mg of hydroquinone in 6 ml of pyridine was heated in a sealed ampule at 245°C for 42 hr. Work-up as above, chromatography of the product on 75 g of neutral alumina, activity I, and elution as above led only to the recovery of 1.60 g of starting material (80%). A similar reaction with 1.48 g of **Xb** at 290°C for 5 hr gave back 1.17 g of starting amide (80%).

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